UPDATE OF THE
CANCER EPIGENETICS and
BIOLOGY PROGRAM (PEBC)

PEBC
Cancer Epigenetics and Biology Program
Programa d’Epigenètica i Biologia del Càncer
Programa de Epigenética y Biología del Cáncer
www.pebc.cat
Introduction

It seems like yesterday, but it was January 2008 when the opening of the Cancer Epigenetics and Biology program (PEBC) was officially announced at the Catalan Parliament and it was October 2008 when I moved to take the position as PEBC Director. One year later in May 2009, we had the international opening symposium of the PEBC with the assistance of our scientific advisory board and now, two years later, I thought that it was a good time to update our status. The current report summarizes the activities and accomplishments of the PEBC from the period May 2009-May 2011. I am delighted to admit that the PEBC has thrived not only in the Bellvitge Biomedical Research Institute (IDIBELL), but also in the biomedical community of Barcelona, Catalonia and Spain and it is starting to emerge at the international level. I would like to thank all the PEBC principal investigators for their great work in attracting new personnel, being resourceful to find sources of funding at many different levels; and for their growing publication excellence (Mol Cell, Nat Genet, Genome Res, Cell Stem Cell, Cancer Cell, PNAS, Genes & Dev…). I am also pleased to see that the IDIBELL Cancer Conferences that we organize (ICC on Sirtuins, ICC on Cell Cycle, ICC-EMBO on Tumor suppressor genes, ICC on Mice Models of Cancer, ICC on Metastasis and Angiogenesis…) are able to gather excellent speakers and are extremely well attended. I would also like to thank the Health Department of the Catalan Government (Generalitat de Catalunya) for its continuous support to our work, to the research funding agencies of Catalonia (ICREA), Spain (MCYCT) and Europe (FP7 and European Research Council) for their funding and to many non-profit foundations (Fundació Cellex, Fundacion Lilly, Fundacion Marcelino Botín, Fundacion Sandra Ibarra, Fundación Científica AECC and Junta de Barcelona…).

Finally, please be so kind to enjoy the lecture of this update of the PEBC activities for the period May 2009-May 2011. It reflects the superb work of many young scientists that try to understand the biology of the cells and help in the therapy of human diseases.

Yours,

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ICREA Research Professor
Genetics Professor, School of Medicine, University of Barcelona
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<tr>
<td>Dori Huertas Ruz</td>
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<td>Sònia Guil Domenech</td>
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<td>Maria Illiou</td>
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### Update of the Cancer Epigenetics and Biology Program (PEBC)

#### GROUP NAME: GENES AND CANCER

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<tr>
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<tr>
<td>Montse Sánchez Céspedes</td>
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<td>GENES AND CANCER</td>
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<tr>
<td>Albert Coll Manzano</td>
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#### GROUP NAME: CHROMATIN BIOLOGY

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<tr>
<td>Alejandro Vaquero García</td>
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### GROUP NAME: CELL CYCLE

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<tr>
<td>Ethelvina Queralt Badia</td>
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<td>Vanesa Marfil Vives</td>
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<td>Nuria Russiñol Coll</td>
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<td>Hans Van Uden</td>
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<td>Inés Calabria Torres</td>
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<td>Jose A. Rodriguez Rodriguez</td>
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<td>Barbara Baró Sastre</td>
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### GROUP NAME: GENOMIC IMPRINT AND CANCER

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<td>Dave Monk</td>
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<td>Cristina Camprubí Sanchez</td>
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<td>Franck Court</td>
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<td>Amy Guillaumet Adkins</td>
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<td>Alejandro Martín Trujillo</td>
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<tr>
<td>Puri Muñoz Moruno</td>
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<td>Mª Victoria Da Silva Diz</td>
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<td>Sonia Colé Sánchez</td>
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### GROUP NAME: TRANSFORMATION AND METASTASIS

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<tr>
<td>Eva González Suárez</td>
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<td>Irene Ferrer Sánchez</td>
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### GROUP NAME: CHROMATIN AND DISEASE

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<td>Lorenzo de la Rica</td>
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### GROUP NAME: CELL DIFFERENTIATION

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<tr>
<td>Maribel Parra Bola</td>
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<td>Olga Mª Collazo Otero</td>
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<td>Bruna Barneda Zahonero</td>
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<td>Lidia Román González</td>
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ADMINISTRATION

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<tr>
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<tr>
<td>Anne Legrand</td>
<td>Administrative</td>
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<td>Anna Vergés Colominas</td>
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<td>Helena Díaz López</td>
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<tr>
<td>Verónica Padial Melián</td>
<td>National Project Manager</td>
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<tr>
<td>Anaïs Desclos</td>
<td>International Project Manager</td>
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GENOMICS AND BIOINFORMATICS

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<td>Sebastián Morán Salana</td>
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<td>Antonio Gómez Moruno</td>
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# PEBC Research Groups

## TRAINING AND MASTER STUDENTS

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<tr>
<th>Student</th>
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<tr>
<td>Max Carbonell Ballestero</td>
<td>Mònica Guixé Costa</td>
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<td>Yaiza Nuñez Alvarez</td>
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<td>Anna Palau de Miguel</td>
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<tr>
<td>Elena Fonalleras Lozano</td>
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## TECHNICAL SUPPORT GROUP

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<td>Olga Jorge López</td>
<td>Diana García Latorre</td>
<td>Elisabet Cañete Ortiz</td>
<td>Jemina Moretó Elias</td>
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<td>Sonia Del Oro Rivera</td>
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<tr>
<td>Laura Roa García</td>
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Update of the Cancer Epigenetics and Biology Program (PEBC)

GROUP NAME: CANCER EPIGENETICS

Biography PI and Research Interests:

Manel Esteller (Sant Boi de Llobregat, Barcelona, Catalonia, Spain, 1968) graduated in Medicine with Honours from the Universidad de Barcelona in 1992, where he also obtained his Ph.D. degree specialising in molecular genetics of endometrial carcinoma, in 1996. He was an Invited Researcher at the School of Biological and Medical Sciences at the University of St. Andrews, (Scotland, UK) during which time his research interests focused on the molecular genetics of inherited breast cancer.

From 1997 to 2001, Esteller was a Postdoctoral Fellow and a Research Associate at the Johns Hopkins University and School of Medicine, (Baltimore, USA) where he studied DNA methylation and human cancer. His work was decisive in establishing promoter hypermethylation of tumour suppressor genes as a common hallmark of all human tumours. From October 2001 to September 2008 Manel Esteller was the Leader of the CNIO Cancer Epigenetics Laboratory, where his principal area of research were the alterations in DNA methylation, histone modifications and chromatin in human cancer. Since October 2008, Dr Esteller is the Director of the Cancer Epigenetics and Biology Program of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona and leader of the Cancer Epigenetics Group. His current research is devoted to the establishment of the epigenome maps of normal and transformed cells, the study of the interactions between epigenetic modifications and non-coding RNAs, and the development of new epigenetic drugs for cancer therapy.

Author of more than two hundred-seventy original peer-reviewed manuscripts in biomedical sciences, he is also a Member of numerous international scientific societies, Editorial Boards and reviewer for many journals and funding agencies. Dr Esteller is also Associate Editor for Cancer Research, The Lancet Oncology and Carcinogenesis, Editor-in-Chief of Epigenetics and Advisor of the Human Epigenome Project, Associate Member of the Epigenome Network of Excellence and President of the Epigenetics Society. His numerous awards include: Best Young Cancer Researcher Award bestowed by the European School of Medical Oncology (1999), First Prize in Basic Research at the Johns Hopkins University and Medical Institution (1999), Best Young Investigator Award from the European Association for Cancer Research (2000), Young Investigator Award from the American Association for Cancer Research-AFLAC (2001), Carcinogenesis Award (2005), Beckman-Coulter Award (2006), Francisco Cobos Biomedical Research Award (2006), Fondazione Piemontese per la Ricerca sul Cancro (FPRC) Award (2006), Swiss Bridge Award (2006). National Research Award in Oncology “Maria Julia Castillo” (2007), “Dr Josep Trueta” Award by the Academy of Medical Sciences of Catalonia (2007), Innovation Award from the Commonwealth of Massachusetts (2007), Human Frontier Science Program Award (2007) “Dr. Jacint Vilardell” Foundation Award (2008), DEbiopharm-EPFL Award (2009), Dr. Josef Steiner Cancer Research Award (2009), Lilly Foundation Preclinical Biomedical Research Award (2009), World Health Summit Award (2010) and European Research Council Advanced Grant (2011).

Dr Manel Esteller is the Director of the Cancer Epigenetics and Biology Program of the Bellvitge Institute for Biomedical Research (IDIBELL), Leader of the Cancer Epigenetics Group, Professor of Genetics in the School of Medicine of the University of Barcelona, and an ICREA Research Professor.

Our main interests are:


- Study of the Epigenetics Machinery and Mechanisms: Role and function of DNA methyltransferases (enzymes that maintain DNA methylation), specificity of methyl-CpG binding domain proteins (the nuclear
factors that recognize DNA methylation), analysis of biological properties of histone deacetylases and methyltransferases (enzymes that modify histones).

- Study of Mutations in the Epigenetic Machinery: The mechanisms underlying the disruption of the epigenetic landscape in transformed cells are unknown. It is possible that the enzymes that epigenetically modify DNA and histone are themselves targets of genetic disruption. Mutational analysis of “epigenetic modifier genes”.

- Testing of Epigenetic Drugs: Study of the biological effects in cell lines and mouse models of different small epigenetic drugs directed against DNA methyltransferases, histone deacetylases and other enzymes of the epigenetic machinery. Analysis of their use as anticancer drugs.

Selected Recent Publications:


GROUP NAME: GENES AND CANCER

Biography PI and Research Interests:

Montse Sanchez-Cespedes was born in Badalona (Barcelona) in 1968. She graduated in Biology from the Universidad de Barcelona and carried out her Ph.D. work at the Hospital “Germans Trias i Pujol”. From 1997 to 2001 was a Postdoctoral Researcher at the Johns Hopkins University School of Medicine in Baltimore, USA. From 2001 to 2008 she was the Leader of the Lung Cancer Group at the Spanish National Cancer Centre (CNIO). In October 2008, Sanchez-Cespedes was appointed as the leader of the Genes and Cancer Group at the PEBC-IDIBELL.

Her research has focused on the identification and characterization of novel genetic and molecular alterations in cancer, mainly in lung cancer. Among her most important achievements was the discovery of frequent genetic inactivation at the LKB1 tumor suppressor gene in lung adenocarcinomas. She has also worked on the characterization of known gene alterations in lung tumors and in the analysis of gene expression and DNA copy number profiles of lung tumors. Another relevant discovery made by her group has been the identification of frequent mutations at BRG1, a tumor suppressor and a main component of a chromatin remodeling complex. She is a reviewer for many journals and funding agencies, serves in different Scientific Committees and is a member of the Editorial Board of the Journal of Pathology. Her list of over 70 peer-reviewed manuscripts and reviews in international journals of prestige serves as a testament of the experience she has already accumulated in the field of cancer research.

Scientific Interests:

The complete genetic characterization of tumors is important not only to understand tumor biology, but also to the development of new drugs and to the selection of patients that may benefit of a given targeted cancer therapy. The promise of using proteins encoded by mutant cancer genes as molecular targets for the development of novel therapies drives endeavors to identify novel mutated cancer genes as well as to create catalogues with the complete set of gene altered in cancer. This is now possible with the new high throughput technologies. Our current projects in the laboratory focus in this direction. Thus, the main goals of the group include:

- To identify and characterize novel genes altered, at a genetic level, in cancer.
- To understand how these abnormalities contribute to cancer development.
- To identify molecular markers that determine intrinsic and acquired sensitivity to novel targeted cancer drugs.

Selected Recent Publications:


GROUP NAME: CHROMATIN BIOLOGY

Biography PI and Research Interests:

Alejandro Vaquero (Barcelona, Catalonia, Spain, 1971) graduated in Biochemistry in 1994 from the University of Barcelona (UB), and received his PhD “Cum Laude” from the same University in 2000 for his work on the Characterization of the Drosophila GAGA factor on transcription. During his Predoctoral period, Dr Vaquero’s work contributed to the understanding of the mechanisms underlying gene transcription. In particular, Dr Vaquero elucidated the role of GAGA factor, involved in development and chromatin regulation, as an activator of RNA-polynmerase II transcription. In other studies, he also determined the effect of certain anti-tumor DNA-intercalating drugs on transcription. In 2000, Dr Vaquero joined the laboratory of Dr Danny Reinberg (HHMI, Piscataway, NJ, USA), as a postdoctoral fellow. In Dr Reinberg’s lab, Dr Vaquero made significant contributions to the chromatin epigenetics field, through the study of the role of Sir2, a group of NAD+-dependent deacetylases homologues of the yeast silencing factor Sir2, on chromatin function. Dr Vaquero’s work demonstrated a key role for SirT1 in global chromatin organization through the formation of compacted chromatin and described for the first time a direct link between Sir2 and cancer processes. Another significant contribution of his work was the identification of SirT2 as a cell-cycle dependent regulator of the global levels of Acetylation in Lys 16 of histone H4 (H4K16Ac), a modification involved in epigenetic phenomena through evolution with a unique role in chromatin structure, gene regulation, and cancer. In 2001, he became Howard Hughes Research associate, position he held until the end of 2005, when he returned to Spain as an I3P Researcher (CSIC) in the Institut de Biologia Molecular de Barcelona (IBMB-CSIC, Barcelona, Spain) where he was appointed Icrea Researcher in Dec 2006. During this time, in addition to follow up on his work on Sir2, he participated in the identification and functional characterization of linker Histone H1 post-translational modifications in chromatin structure. In January 2008, Dr Vaquero became group leader of the Chromatin Biology Laboratory in the Cancer Epigenetics and Biology Program of the Bellvitge Biomedical Research Institute (IDIBELL), in Barcelona (Spain) where he currently studies the epigenetic mechanisms that control chromatin dynamics and transcription.

Dr Vaquero’s scientific contributions have been published in some of the most prestigious journals such as Nature, Cell, Molecular Cell and Genes & Development. He has written several invited reviews, two book chapters and is co-inventor of a Patent application on a new method to test Sir2 activity in cultured cells, which has been licensed by a pharmaceutical company, SIRTRIS Pharmaceuticals, Inc. (Boston, USA). Member of the Spanish Society of Biochemistry and the Catalan Society of Biology, Dr Vaquero has been awarded with a Ramon y Cajal position (2006), ICREA Researcher position (2006), European Union Marie Curie Reintegration Grant (2006) and senior group leader PEBC-IDIBELL position (2007).

Cell life regulation is determined by the information encoded in nuclear DNA. In Eukaryotic cells, DNA is associated with histones to form chromatin. Among the different regulatory levels that participate in the management of DNA information, post-translational modifications of the N-terminal tails of histones are important for ensuring a proper control of chromatin functions. These modifications are in part epigenetic, which means that they can be transmitted to its progeny and in many cases are vital for the maintenance of proper cell memory. Alteration of this epigenetic information has remarkable consequences in a wide number of human pathologies, such as cancer and others. Among these modifications, Acetylation and Methylation of Lysine residues are particularly important for the regulation of Chromatin structure and Gene expression.

The main goal of our laboratory is to understand the mechanisms that rule Chromatin dynamics and in particular how these post-translational modifications interplay with the rest of chromatin machinery to keep a healthy and efficient Chromatin organization. Because of that, we are also interested in the functional impli-
cations of these mechanisms in cancer and aging. For that purpose, our lab uses a combination of Biochemistry, Molecular and Cell Biology techniques to gain insight into Chromatin Biology.

In particular, our studies focus in a group of proteins, the Sir2 family or Sirtuins, that are homologues of the yeast silencing factor Sir2, a NAD+-dependent deacetylase involved in many aspects of chromatin regulation such as epigenetic silencing, DNA repair and replication, DNA recombination, etc... Two features make particularly interesting the Sir2 family: First, the requirement of the metabolic redox cofactor NAD+ for the enzymatic activity of the family, allows their members to act as sensors of cell metabolism.

Second, members of this family show a close link with the regulation of a specific modification, acetylation of lysine 16 in histone H4 (H4K16Ac), involved in many functions from Chromatin structure, gene expression and cancer to many epigenetic processes through evolution. However, not all Sirtuins are deacetylases, and in fact some show instead a mono-ADP-rybosyltransferase activity.

Sirtuins have been linked to many human pathologies such as cancer, neurological diseases like Alzheimer or Parkinson’s, malaria, leishmaniosis, and hormone-related pathologies. However, the mechanisms by which these proteins are involved in these processes are relatively unknown.

In our lab we aim to characterize the role of Sirtuins in chromatin regulation and the functional implications of this role on cancer, cell viability and genome integrity. From the seven mammalian Sirtuins (SirT1-7), only SirT1, 2, 6, 7 and possibly 3 seem to be functionally linked to Chromatin. Interestingly, each of them is involved in a particular aspect of chromatin regulation different from the others. Our main lines of research are actually defined by each of these Sirtuins and their corresponding specific role on chromatin:

- **SIRTUINS in Genome organization and Chromatin structure (SIRT1)**
- **SIRTUINS and Cell cycle control (SIRT2)**
- **SIRTUINS and DNA repair (SIRT6)**
- **SIRTUINS and Nucleolar function (SIRT7)**

**Recent Publications:**


GROUP NAME: CELL CYCLE

Biography PI and Research Interests:

Ethelvina Queralt (Benavites, Valencia, Spain, 1975) graduated in Biochemistry from the Universitat de Valencia in 1998, where she also obtained his Ph.D. degree in Biochemistry specialising in Cell Cycle, in 2003. During her PhD studies she acquired knowledge in molecular biology and genetics using yeast as a model organism. She was interested in the study of the regulation of the G1/S transition in the cell cycle. Ethel Queralt presented her thesis work in several national and international meeting and she had got the Innogenetics Diagnostics prize (for PhD degree) in the XXVII Conference of SEBBM (Lleida September 2004). From 2003 to 2007, Queralt was a Postdoctoral Fellow at the London Research Institute, Cancer Research UK where she studied others aspects of the cell cycle as genome stability and chromosome segregation. For her postdoctoral position she chose an internationally leading institution to carry out a cutting edge project in Dr. Frank Uhlmann’s laboratory. Dr. Uhlmann is an internationally recognised expert in the field of chromosome segregation. He has made key contributions to the current knowledge of genome inheritance during mitotic cell division.

During the postdoctoral work, Ethel Queralt studied the regulation of mitotic exit and cytokinesis in the model eukaryote Saccharomyces cerevisiae. Aneuploidy, i. e. missing or supernumerous chromosomes, is a near-ubiquitous feature of human cancer and is thought to promote tumour development. The regulation of mitosis is of particular importance in maintaining chromosome stability: Failure in cytokinesis initially leads to cells containing both sets of sister chromatids, and it is from these cells that most aneuploid tumour cells likely originate. Despite its importance, very little is known about mitotic exit regulation in any organism. Through her investigations, Ethel had made seminal contributions to our current understanding of the process in budding yeast. She published her postdoctoral work in leading international cell biology journals and presented her work in many international meeting. From 2007 to 2008, Queralt was in the Dra. Susana Rodriguez-Navarro’s laboratory, Instituto de Investigación Príncipe Felipe as a Ramon y Cajal researcher. Dra. Rodriguez-Navarro has made very important contributions to the current knowledge of the coupling between mRNA export and transcription in budding yeast. Since March 2008, Dr Queralt is leader of the Cell Cycle Group at the Cancer Epigenetics and Biology Program of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona. Her current research is focused in the mechanisms that ensure faithful chromosome maintenance during healthy cell growth, in particular the molecular framework that is responsible for the initiation of mitosis.

Mitosis is an intricately coordinated set of events that ensures the accurate inheritance of genetic information from one cell generation to the next. In metaphase the chromosomes are condensed, aligned in the metaphase plaque and attached to the mitotic spindle. Proper attachment of the chromosomes will lead to the activation of the anaphase-promoting complex (APC) by its co-activator Cdc20. APCCdc20 is an ubiquitin ligase that ubiquitiates securin, an inhibitor of the protease separase. Thereby, securin is degraded by the proteasome and separase is activated. Sister chromatid separation at anaphase onset is triggered when the Scc1 subunit of cohesin is cleaved by separase to destroy the cohesin complex. At this time, APCCdc20 also targets the cyclin Clb2 for degradation promoting the reduction of Cdk activity. However, cyclin destruction by APCCdc20 is not sufficient to completely remove all Cdk activity in order to exit from mitosis. For this reason, the activation of the mitotic phosphatase Cdc14 becomes essential. Cdc14 phosphatase directly counteracts the Cdk activity by dephosphorylating the Cdk targets. On the other hand, Cdc14 also contributes to the downregulation of the Cdk activity by dephosphorylating a second co-activator of APC, Cdh1, that complete destruction of all mitotic cyclins, and the Cdk inhibitor Sic1.

In metaphase, Cdc14 is kept inactive in the nucleolus by binding to the nucleolar protein Net1 (also called Cfi1). During anaphase, Cdk-dependent phosphorylation of Net1 release active Cdc14. Phosphorylated Net1
shows reduced affinity for Cdc14 and loose its ability to inhibit Cdc14 in vitro. Two different regulatory pathways are essentials for the Cdc14 release from the nucleolus. During early anaphase the FEAR pathway (Cdc14 early anaphase release) initiates the Cdc14 release and is kept active later in anaphase by a G protein signalling cascade, the mitotic exit network (MEN). A number of proteins including, Cdk, Slk19, Spo12, Fob1 and separase have been implicated in this early anaphase Cdc14 release. Several mutants in the FEAR show a delay in the Cdc14 release from the nucleolus. Nevertheless, an essential role in Cdc14 activation and mitotic exit for separase has been recently described (Queralt et al., 2006). The FEAR dependent Cdc14 release requires Net1 phosphorylation at Cdk consensus sites. PP2ACdc55 phosphatase keeps Net1 under-phosphorylated in metaphase (Queralt et al., 2006). Separase-dependent PP2ACdc55 downregulation initiates the Cdk-dependent Net1 phosphorylation specifically in anaphase, when mitotic kinase activity starts to decline. The mechanistic basis for separase-dependent PP2ACdc55 downregulation remains to be elucidated. Later in anaphase, when the Cdk activity is low, the MEN kinases maintain Net1 phosphorylated and Cdc14 release also contributes to the downregulation of the Cdk activity by dephosphorylating a second co-activator of APC, Cdh1, that complete destruction of all mitotic cyclins, and the Cdk inhibitor Sic1.

Related Publications:


GROUP NAME: GENOMIC IMPRINT AND CANCER

Biography PI and Research Interests:

David Monk graduated from Anglia Ruskin University, Cambridge with a B.Sc (Hons) in Biomedical science before undertaking an M.Sc in Human Reproductive Biology at Imperial College London. In 2001 he wrote his PhD thesis on the genetic aetiology of Silver-Russell syndrome, a project mentored by Professors Michael Preece and Gudrun Moore at Queen Charlotte’s and Chelsea Hospital (QCCH), Imperial College London. From 2001-2004 he was a Postdoctoral Researcher funded by the MRC to screen for novel imprinted genes using DNA methylation based technologies. This position was a multi-site collaborative project, which saw him spend time in the laboratories of Professor Moore, now at the Institute of Reproductive and Developmental Biology (IRDB) Imperial College London, Dr Gavin Kelsey at The Babraham Institute Cambridge, and with Professor Jo Peters at MRC Harwell. From 2005-2007, Dr Monk was a March of Dimes funded Postdoctoral Research Fellow at the IRDB, undertaking research into the epigenetic regulation of placental imprinting in the human, and the involvement of imprinted gene expression in human fetal growth. During this time he was awarded an EMBO short-term fellowship to spend time in the laboratory of Dr Robert Feil in CNRS, Montpellier France. In 2007, he was appointed as Lecturer in Molecular Epigenetics and Paediatric Oncology at the Institute of Child Health (ICH), University College London. Since the summer of 2008, Dr Monk is the Principal Investigator of the Genomic Imprinting and Cancer group within the Cancer Epigenetics and Biology Program (PEBC) of the Bellvitge Biomedical Research Institute (IDIBELL) in Barcelona. In 2010 he was awarded a Ramon Y Cajal Research Fellowship to for his studies of the aberrant epigenetic signatures associated with for loss-of-imprinting that occur in cancer and imprinting disorders.

One of the main interests of this group is Genomic Imprinting. Imprinted genes are expressed from only one parental allele, the other is silenced by epigenetic modifications, classically involving DNA methylation and asymmetric chromatin structure. Imprinted genes are typically involved in embryonic growth and development. Abnormal imprinted gene expression is one of the most frequent aberrations in carcinogenesis.

The current aims of this group include learning about the control mechanisms involved in genomic imprinting, and how genetic and epigenetic variation at imprinted genes is associated with cancer susceptibility and development. In addition, we are keen to assess the epigenetic profiles of babies born following assisted reproductive techniques, using HPLC, ChIP-seq and genome-wide DNA-methylation technologies, to ascertain epigenetic stability in these individuals. Lastly, we are currently determining the extent of DNA-methylation defects in imprinting syndromes, utilising custom DNA methylation array technologies, to determine the mechanisms that protect imprinted-DMRs from demethylation during early development.

Recent Publications:


GROUP NAME: AGING AND CANCER

Biography PI and Research Interests:

Purificación Muñoz Moruno was born in L’Hospitalet de Llobregat, Barcelona in 1965. She graduated in Biology from the Universitat de Barcelona in 1988, where she also obtained her masters degree in 1990. She studied the effects of vanadate, as an insulin-like agent, modulating the transport of amino acids in rat skeletal muscle. In 1995, she obtained her Ph.D. in Biology at the Universitat de Barcelona under the supervision of Dr. Antonio Zorzano Olarte. During her Ph.D. training she focused her studies on the characterization of the translocation of insulin-induced glucose transporters in skeletal muscle. In order to investigate different aspects of DNA repair and cell cycle control, she joined the laboratories of Dr. Jean Marie Blanchard and Dr. Jacques Piette at the Institut de Génétique Moléculaire de Montpellier (France) as a postdoctoral fellow in May 1995. In 1999, she returned to Barcelona to join Dr. José Luis Rosa’s laboratory in the Medical School of Barcelona from Universitat de Barcelona where her research work contributed to the analysis of p53 role in intracellular vesicular trafficking and cellular proliferation. In 2002 she obtained a Research Contract from the “Ramón y Cajal” Programme (funded by the Ministerio de Educación y Ciencia) and joined the laboratory of Dra. María A. Blasco at the Centro Nacional de Investigaciones Oncológicas (CNIO). There, her research interests focused on the role of DNA repair and homologous recombination proteins in telomere function and chromosomal stability. She also generated different mouse models that allowed the evaluation of the role of telomere binding proteins in telomere function and genome stability. Her studies revealed a genetic interaction between telomeres and the nucleotide excision repair machinery, which underlies susceptibility to cancer and aging. Her scientific achievements have given rise to several publications in high impact international journals.

Since June 2007, Dra. Muñoz is leader of the Aging and Cancer Group of the Cancer Epigenetic and Biology Program of Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona. Her current research is focused on studying genetic and epigenetic changes in adult stem cells during aging and cancer in order to understand the increased predisposition to cancer with age.

Scientific Interests:

1. Characterization of genetic and epigenetic changes in epidermal stem cells during aging. Despite their relevant role in tissue homeostasis, very little is known about the ability of adult stem cells to repair DNA lesions and signal through the DNA damage response (DDR) pathway or if these pathways are altered during normal aging. We are interested in analyzing if during aging epidermal stem cells accumulate DNA lesions and if these lesions result from failures in DDR and chromatin remodeling processes involved in DNA repair.

2. Isolation and characterization of tumor initiating cells from skin carcinomas. We aim to isolate and characterize tumor initiating cells from human and mouse skin carcinomas in order to identify genes responsible of the acquisition of their specific characteristics as well as to evaluate the impact of genomic instability during tumor growth. These studies offer the possibility to find new potential targets to suppress specifically the growth of these tumoral cells during cancer development.

3. Study of role of tumor initiating cells in the response to chemotherapy in human colorectal carcinoma. The aim of this project is to identify genes and mechanisms involved in chemotherapy resistance and generation of distant metastasis in colon cancer that could be used as predictive markers of chemotherapy response. Different immunodeficient mouse models, harboring human colorectal carcinomas grafts, have been generated. They allow us to immortalize colorectal carcinomas and to evaluate the role of tumor initiating cells in tumor progression and in response to chemotherapeutic treatments. This characterization will allow us
to identify molecular markers with predictive value in response to treatment that could be useful in the selection of the more personalized anti-tumor treatment and with better clinical response.

Recent Publications:


**GROUP NAME: TRANSFORMATION AND METASTASIS**

**Biography PI and Research Interests:**

Eva Gonzalez Suarez (1975, Oviedo, Asturias, Spain) got her bachelor degree in Chemistry and her master degree in Biochemistry in the Universidad de Oviedo. Her college graduation work (1998) consisted in the study of the effects of melatonin in the apoptosis induced by glucocorticoids in thymocytes.

She is a PhD in Molecular Biology and Extraordinary Award by the Universidad Autónoma de Madrid (2003). Dra. Eva Gonzalez Suarez scientific career has been focused in the cancer field. Her doctoral work at the laboratory of Dr. Maria Blasco, in the department of Immunology and Oncology at the CNB, in Madrid aimed to elucidate the role of telomerase in tumorigenesis and aging. The results of this work can be summarized in two main discoveries: 1) in the absence of telomerase, when telomeres are strikingly short, tumors are abolished or dramatically reduced (González-Suárez et al., Nat Genetics, 2000 and Can Res, 2003) and 2) telomerase overexpression, even in the presence of long telomeres, results in a higher incidence of spontaneous and induced tumors (González-Suárez et al. EMBO J, 2001, Mol Cel Biol, 2002) but extends maximum longevity due to a lower incidence of senile lesions (González-Suárez et al., Oncogene, 2005). She received several awards for this work including Young Investigator 2003 “Severo Ochoa” Award, Best Doctorate Thesis 2003 and Juan Abelló Pascual II Award 2003.

From 2003 until 2007 Dr Eva Gonzalez worked as a postdoctoral scientist at the Oncology department at Amgen, WA, USA. The main project developed by Dra Gonzalez Suarez in Amgen was the characterization of the role of RANK and RANKL in mammary gland development and tumorigenesis. Her results demonstrated that RANK signaling activation in MECs promotes proliferation, impairs terminal differentiation (Gonzalez-Suarez et al., MCB, 2007) and increases the susceptibility to mammary tumors in the transgenic mouse model, MMTV-RANK (González-Suárez et al., Nature, 2010).

She has designed the experiments to test the efficiency of RANK-Fc in blocking the progression of mammary tumors in both, preventive and therapeutic settings. The corresponding results have a big impact within Amgen, as they have developed a monoclonal antibody that blocks RANK/RANKL interaction (Denosumab), that is currently effective for the treatment of osteoporosis and bone metastasis. In 2008 Dra Eva Gonzalez Suarez joined the Cancer Epigenetics and Biology Program of the Bellvitge Institute of Biomedical Research (IDIBELL) in Barcelona as a Junior Group Leader. Her current research lines are within the mammary gland biology and breast cancer field, particularly in understanding the events that drive transformation of the mammary epithelial cells and metastasis and the stem cell pathways that become deregulated during carcinogenesis. Recently the group of Eva Gonzalez Suarez together with her collaborators in Amgen has demonstrated that pharmacological inhibition of RANKL attenuates tumors intiation in MMTV-RANK mice, and prevents mammaritumorigenesis in WT mice treated with progesterin and carcinogen. Moreover, inhibition of RANK signaling attenuates tumor initiation and importantly lung metastasis in the spontaneous model of mammary tumorigenesis MMTV-neu.

The main areas of research of her laboratory include: mammary gland development, mammary stem cells, breast cancer, metastasis and chemoresistance. Our goal is the identification of the main proteins and pathways that drive mammary epithelial cell transformation and metastasis in order to find targets for future therapeutics and response or prognosis markers. Further applications of Denosumab within the primary breast cancer site are expected based on the work of Dra. Gonzalez Suarez.
Recent Publications:


GROUP NAME: CHROMATIN AND DISEASE

Biography PI and Research Interests:

Esteban Ballestar (Valencia, Spain, 1969) graduated in Biology with First Class Honours from the Universitat de València in 1992, where he also obtained his Ph.D. degree under the supervision of Prof. Luis Franco, specialising in chromatin and histone modifications, in 1997. During this period, Ballestar identified and characterized a novel histone modification. From 1997 to 2000, Ballestar was a Postdoctoral Fellow at the Laboratory of Molecular Embryology led by Dr Alan Wolffe at the National Institutes of Health, (Bethesda, MD, USA) where he investigated associations between elements of the chromatin machinery and methylated DNA. There, Dr Ballestar contributed to demonstrate that methyl-CpG binding domain (MBD) proteins—an family of nuclear factors that associate with methylated DNA-establish mechanistic links between DNA methylation, chromatin remodelling and the histone modification machinery to silence genes. In addition, his work with MBD proteins demonstrated the ability of these proteins to associate with specific genes and their implications in epigenetic deregulation in Rett syndrome. From 2001 to 2008, Esteban Ballestar has worked at the CNIO Cancer Epigenetics Laboratory, in association with Dr Manel Esteller, where his principal area of research has been the study of the implication of chromatin factors in epigenetic alterations in human cancer. He has demonstrated the role of MBDs in the epigenetic deregulation in cancer and Rett syndrome. Also at the CNIO, he has contributed in seminal publications regarding specific alterations in the histone modification profile associated with hypomethylation in cancer and the age-dependent accumulation of epigenetic changes. Since 2002, Ballestar has coordinated together with Esteller a graduate course in Cancer Epigenetics within the Molecular Biology Program of the Universidad Autonoma de Madrid. Since 2004, Ballestar has been awarded with various grants to develop an independent research line on epigenetics and chromatin alterations in disease at the CNIO.

As group leader of the Chromatin and Disease Group of the Cancer Epigenetics and Biology Program of the Bellvitge Biomedical Research Institute (IDIBELL) in Barcelona, his current research is devoted to the establishment of different mechanisms of epigenetic deregulation in the context of the hematopoietic system in autoimmune diseases and in differentiation processes.

Author of more than sixty five peer-reviewed manuscripts in biomedical sciences, he is also a member of numerous international scientific societies and reviewer for many journals and national and international funding agencies.

The Chromatin and Epigenetics fields have experienced a spectacular development in the last few years. Key breakthroughs include the identification of a code of histone modifications associated with specific functions, the finding of mechanistic links between DNA methylation and histone modifications or the recognition that epigenetic modifications and chromatin organization not only define cell identity but also constitutes a dynamic readout of environment. But most importantly, the identification of alterations in chromatin structure and epigenetic regulation in diseases including cancer, autoimmune disease, and a variety of syndromes, have added a clinical dimension to studies in chromatin and epigenetics, since these alterations are potentially reversible. Rapid progress in understanding epigenetic alterations in cancer has enabled us to determine the general mechanisms of epigenetic misregulation, identify clinical markers of epigenetic change, and embark on the development of novel therapeutic drugs. By contrast, advances in understanding epigenetic mechanisms in the context of autoimmune diseases, as well as in other disorders, have been much slower, and studies remain confined to a small number of laboratories. Nevertheless, evidence of important roles for these types of alterations in autoimmune diseases is increasing. Furthermore, novel technologies that facilitate gene identification and the systematic search for novel epigenetically deregulated genes support the investment of research in this area.
Our research lines include:

- Epigenetic Deregulation in Autoimmune Disease.
- Epigenetic Mechanisms involved in Lymphocyte Differentiation.
- Epigenetic Deregulation Processes involved in Haematopoietic Malignancies.

**Selected Recent Publications:**


GROUP NAME: CELL DIFFERENTIATION

Biography PI and Research Interests:

Maribel Parra (Granollers, Catalonia, Spain, 1972) graduated in Chemistry in 1998 from the University Autonomous of Barcelona (UAB), and received her PhD from the University of Barcelona (UB) in 2003 under the supervision of Dr. Pura Muñoz Cánoves. Her PhD project was focused on the investigation of the molecular mechanisms regulating urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) gene expression during the cellular response to genotoxic stress.

In 2003, Dr. Parra joined the laboratory of Dr. Eric Verdin (Gladstone Institute of Virology and Immunology, UCSF) as a postdoctoral fellow. Dr. Maribel Parra made fundamental contributions in the field of class IIa HDACs. She elucidated the signal transduction mechanisms responsible for HDAC7 nucleo-cytoplasmic shuttling in response to T cell receptor (TCR) activation. First, Dr. Parra identified PKD1 as the specific kinase responsible for the phosphorylation of HDAC7 after TCR activation. Notably, at that stage, a major question remained to be addressed in the class IIa HDAC field was whether a phosphatase could dephosphorylate class IIa HDACs in the cytoplasm thereby resulting in their nuclear relocalization and de novo repression of their target genes. Dr. Parra was the first to identify “the” class IIa HDAC phosphatase. Indeed, she demonstrated that Myosin Phosphatase is critical in the regulation of negative selection of T cells by dephosphorylating HDAC7.

After her postdoctoral training period, Dr Parra decided to focus her initial research career as an independent investigator on studying the role of class IIa HDACs in the decisions occurring during hematopoiesis. To do so, she was granted a Ramon y Cajal Investigator Contract from the Spanish Ministry of Science and Innovation (MICINN) and a Marie Curie International Reintegration Grant from the European Comission. In July 2007, Dr. Parra joined for a brief stage the laboratory of Dr. Thomas Graf, coordinator of the Cancer and Differentiation Program at the Centre for Genomic Regulation (CRG) in Barcelona and a pioneer scientist in the hematopoietic field. Since February 2009, Dr. Maribel Parra leads the Cellular Differentiation Group at the Cancer Epigenetics and Biology Program (PEBC), where she currently studies the role of class IIa HDACs in the lineage commitment and differentiation of hematopoietic cells.

Adult hematopoiesis is characterized by the generation of all blood cell types. To achieve this, hematopoietic stem cells (HSCs) differentiate into common myeloid progenitors (CMPs) and lymphoid-primed multipotent progenitors (LMPPs). CMPs give rise to megakaryocyte/erythrocyte progenitors (MEPs) and granulocyte/macrophage progenitors (GMPs), whereas LMPPs still have the capacity to choose between the myelomonocytic and lymphoid lineages. Common lymphoid progenitors (CLPs) have the potential to differentiate into B and T lymphocytes, as well as natural killer (NK) cells. Since the stability of every differentiation step is critical, each transition is tightly regulated at the transcriptional level through the action of lineage-restricted transcription factors that induce genes characteristic of particular cellular states. Importantly, deregulation of particular transcriptional programs leads to the development of hematological malignancies such as leukemias and lymphomas. Surprisingly, very little is known on the role of gene transcriptional repressors, such as histone deacetylases (HDACs), in the lineage specification and differentiation of hematopoietic cells. Once a progenitor has chosen to become a particular cell type, it will both up-regulate lineage specific genes, and repress inappropriate genes characteristic of other cellular lineages.

The main goals of our laboratory are:

1. To investigate the role of class IIa HDACs in the lineage commitment and differentiation of B lymphocytes.
2. To investigate the potential role of class IIa HDACs in the development of hematological malignancies.
Recent Publications


SELECTED ORIGINAL ARTICLES, PERSPECTIVES AND REVIEWS
A TARBP2 mutation in human cancer impairs microRNA processing and Dicer1 function

Sonia A Melo1, Santiago Ropero1, Catia Moutinho1, Lauri A Aaltonen2, Hiroyuki Yamamoto3, George A Calin4, Simona Rossi4, Agustin F Fernandez1, Fatima Carneiro5, Carla Oliveira6, Bibiana Ferreira1, Chang-Gong Liu4, Alberto Villanueva5, Gabriel Capella5, Simo Schwartz Jr7, Ramin Shiekhattar5,8 & Manel Esteller1,9,10

microRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by targeting messenger RNA (mRNA) transcripts. Recently, a miRNA expression profile of human tumors has been characterized by an overall miRNA downregulation3–5. Explanations for this observation include a failure of miRNA post-transcriptional regulation4, transcriptional silencing associated with hypermethylation of CpG island promoters6,7 and miRNA transcriptional repression by oncogenic factors8. Another possibility is that the enzymes and cofactors involved in miRNA processing pathways may themselves be targets of genetic disruption, further enhancing cellular transformation9. However, no loss-of-function genetic alterations in the genes encoding these proteins have been reported. Here we have identified truncating mutations in TARBP2 (TAR RNA-binding protein 2), encoding an integral component of a Dicer1-containing complex10,11, in sporadic and hereditary carcinomas with microsatellite instability12–14. The presence of TARBP2 frameshift mutations causes diminished TRBP protein expression and a defect in the processing of miRNAs. The reintroduction of TRBP in the deficient cells restores the efficient production of miRNAs and inhibits tumor growth. Most important, the TRBP impairment is associated with a destabilization of the Dicer1 protein. These results provide, for a subset of human tumors, an explanation for the observed defects in the expression of mature miRNAs.

In order to explore the presence of inactivating mutations in the so-called ‘miRNA processing machinery genes’ it is useful to consider tumors that show microsatellite instability, both in the context of hereditary nonpolyposis colon cancer (HNPCC) associated with germline mutations in the mismatch repair genes15 and in sporadic cancers associated with hMLH1 inactivation by promoter CpG island methylation16,17. Tumors with microsatellite instability progress along a genetic pathway with a high rate of insertion and deletion mutations in mononucleotide repeats, which often results in the generation of premature stop codons. Illustrative target genes include the gene-control gene TGFBR2 (ref. 18) and the p53-dependent gene BAX19.

We first screened six colorectal (Co113, RKO, SW48, LoVo, HCT-15 and HCT-116), four endometrial (SKUT-1, SKUT-1B, ANSCA and HEC1B) and two gastric (SNU-1 and SNU-638) cancer cell lines with established members of the miRNA processing machinery: the RNase III family of double-stranded RNAse (Dicer1 and DROSHA), RNA-binding proteins that act as catalytic partners (DGC8, TRBP and PACT) and Argonaut family members (AGO1, AGO2 and AGO4). The location of the corresponding repeats and the PCR primers used are shown in the Supplementary Table 1 online. We detected only wild-type sequences for all the genes described, with the single notable exception of TARBP2 (Fig. 1a). We found two frameshift mutations in TARBP2: the deletion of a C in a (C) coding microsatellite repeat of exon 5 in the colorectal cancer cell line Co113 and the insertion of a C in a (C) coding microsatellite repeat of exon 5 in the endometrial cancer cell line SKUT-1B (Fig. 1a). The TARBP2 mutations were present in 29 of 41 (71%) and 17 of 31 (55%) single-cluster sequences obtained from genomic DNA for Co113 and SKUT-1B respectively. The same proportion of mutant alleles was found when we used cDNA as starting material; thus, these are heterozygous mutations. The two alleles of TARBP2 were retained in both cell lines according to the FISH analysis (Supplementary Fig. 1 online). We analyzed TRBP
Epigenetic inactivation of the Sotos overgrowth syndrome gene histone methyltransferase NSD1 in human neuroblastoma and glioma


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Sotos syndrome is an autosomal dominant condition characterized by overgrowth resulting in tall stature and macrocephaly, together with an increased risk of tumors. The disease is caused by loss-of-function mutations and deletions of the nuclear receptor SET domain containing protein-1 (NSD1) gene, which encodes a histone methyltransferase involved in chromatin regulation. However, despite its causal role in Sotos syndrome and the typical accelerated growth of these patients, little is known about the putative contribution of NSD1 to human sporadic malignancies. Here, we report that NSD1 function is abrogated in human neuroblastoma and glioma cells by transcriptional silencing associated with CpG island promoter hypermethylation. We also demonstrate that the epigenetic inactivation of NSD1 in transformed cells leads to the specifically diminished methylation of the histone lysine residues H4-K20 and H3-K36. The described phenotype is also observed in Sotos syndrome patients with NSD1 genetic disruption. Expression microarray data from NSD1-depleted cells, followed by ChIP analysis, revealed that the oncogene MEIS1 is one of the main NSD1 targets in neuroblastoma. Furthermore, we show that the restoration of NSD1 expression induces tumor suppressor-like features, such as reduced colony formation density and inhibition of cellular growth. Screening a large collection of different tumor types revealed that NSD1 CpG island hypermethylation was a common event in neuroblastomas and gliomas. Most importantly, NSD1 hypermethylation was a predictor of poor outcome in high-risk neuroblastoma. These findings highlight the importance of NSD1 epigenetic inactivation in neuroblastoma and glioma that leads to a disrupted histone methylation landscape and might have a translational value as a prognostic marker.
RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis

Eva Gonzalez-Suarez, Allison P. Jacob*, Jon Jones, Robert Miller, Martine P. Roudier-Meyer, Ryan Erwert, Jan Pinkas* and Dan Branstetter & William C. Dougall

RANK ligand (RANKL), a TNF-related molecule, is essential for osteoclast formation, function and survival through interaction with its receptor RANK. Mammary glands of RANK- and RANKL-deficient mice develop normally during sexual maturation, but fail to form lobuloalveolar structures during pregnancy because of defective proliferation and increased apoptosis of mammary epithelium. It has been shown that RANKL is responsible for the major proliferative response of mouse mammary epithelium to progesterone during mammary lactational morphogenesis, and in mouse models, manipulated to induce activation of the RANK/RANKL pathway in the absence of strict hormonal control, inappropriate mammary proliferation is observed. However, there is no evidence so far of a functional contribution of RANKL to tumorigenesis. Here we show that RANK and RANKL are expressed within normal, pre-malignant and neoplastic mammary epithelium, and using complementary gain-of-function (mouse mammary tumour virus (MMTV)-RANK transgenic mice) and loss-of-function (pharmacological inhibition of RANKL) approaches, define a direct contribution of this pathway in mammary tumorigenesis. Accelerated pre-neoplasia and increased mammary tumour formation were observed in MMTV-RANK transgenic mice after multiparity or treatment with carcinogen and hormone (progesterone). Reciprocally, selective pharmacological inhibition of RANKL attenuated mammary tumour development not only in hormone- and carcinogen-treated MMTV-RANK and wild-type mice, but also in the MMTV-neu transgenic spontaneous tumour model. The reduction in tumorigenesis upon RANKL inhibition was preceded by a reduction in pre-neoplasias as well as rapid and sustained reductions in hormone- and carcinogen-induced mammary epithelial proliferation and cyclin D1 levels. Collectively, our results indicate that RANKL inhibition is acting directly on hormone-induced mammary epithelium at early stages in tumorigenesis, and the permissive contribution of progesterone to increased mammary cancer incidence is due to RANKL-dependent proliferative changes in the mammary epithelium. The current study highlights a potential role for RANKL inhibition in the management of proliferative breast disease.

Previously we reported that MMTV-RANK female transgenic mice show sustained proliferation and impaired alveolar secretory differentiation of the mammary epithelium upon pregnancy; however, spontaneous mammary tumours were not observed in aged virgin mice. In contrast, mammary glands from multiparous MMTV-RANK mice showed spontaneous tumour development (median onset 26.5 months) and exhibited a higher incidence of pre-neoplasias compared with wild-type mice; adenocarcinomas were only observed in MMTV-RANK mice (Supplementary Table 1).

To characterize more fully the role of the RANKL/RANK pathway in mammary tumorigenesis, we induced mammary carcinogenesis using combined treatment with the hormone medroxyprogesterone acetate (MPA) and a carcinogen (7,12-dimethylbenz(a)anthracene (DMBA)) (Supplementary Fig. 1). After MPA/DMBA treatment, MMTV-RANK transgenic mice showed a markedly enhanced susceptibility to mammary tumours compared with wild-type mice (Fig. 1a). Adenocarcinoma, adenosquamous carcinoma and adenosquamous carcinoma histotypes were observed in both strains (Supplementary Fig. 2). Pre-neoplastic mammary lesions were clearly more widely distributed in mammary tissues in MMTV-RANK mice than in wild-type mice (Fig. 1b). Multifocal ductal hyperplasias, multifocal and focally extensive mammary intraepithelial neoplasias (MIN), and multiple carcinomas were frequently present in a single involved MMTV-RANK mammary gland in contrast with focal lesions in the wild-type glands. Whole-mount analysis of mammary glands at a stage before detection of palpable tumours revealed a 100% incidence and high multiplicity of dense pre-neoplastic epithelial foci, consisting of a mix of hyperplasias and MIN, in MMTV-RANK mice (Fig. 1c). In the induced model, increased mammary proliferation was also evident in the MMTV-RANK versus wild-type glands as early as 2 days after the first DMBA treatment, and a significant increase in cyclin D1 immunohistochemistry signal was evident at 4 and 7 weeks after the last DMBA treatment (Fig. 1d).

RANK protein was clearly evident in luminal and abluminal cells of normal mammary epithelium and in the epithelial component of pre-neoplasias and carcinomas in both MPA/DMBA-treated wild-type and MMTV-RANK mice, and as expected, RANK was observed at higher levels in mammary tissue of MMTV-RANK mice (Supplementary Figs 3 and 4). Compared with ductal hyperplasias and adenoscarcinomas, RANK expression was relatively lower in MIN lesions from both wild-type and MMTV-RANK mice (Supplementary Figs 3 and 4). In mammary glands from tumour-bearing wild-type and MMTV-RANK mice, RANK protein was detected within the luminal cells of histopathologically normal mammary epithelium and in the epithelial component of pre-malignant lesions, with consistently higher levels detected in MIN lesions as compared to other pre-malignant tissues (Supplementary Figs 3 and 4). RANKL was also detected within the carcinoma element in the majority of duct histotype in wild-type and MMTV-RANK tumours. The lower level of RANK immunoreactivity within MIN may be explained by a ligand-dependent reduction of RANK protein or mRNA, as demonstrated in mammary tissues of MMTV-RANK mice or after treatment of mammary epithelial cells (MECs) with RANKL in vitro, respectively.

Given the potential importance of the RANK/RANKL pathway early in tumorigenesis, we confirmed that MPA pre-treatment resulted in an early and marked induction of RANKL (Supplementary Fig. 5). Expression of both RANK and RANKL proteins was also evident at the time of carcinogen administration (Supplementary Fig. 5). Dual immunostaining of samples from MPA/DMBA-treated mice indicated...
A Genetic Defect in Exportin-5 Traps Precursor MicroRNAs in the Nucleus of Cancer Cells

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SUMMARY

The global impairment of mature microRNAs (miRNAs) is emerging as a common feature of human tumors. One interesting scenario is that defects in the nuclear export of precursor miRNAs (pre-miRNAs) might occur in transformed cells. Exportin 5 (XPO5) mediates pre-miRNA nuclear export and herein we demonstrate the presence of XPO5-inactivating mutations in a subset of human tumors with microsatellite instability. The XPO5 genetic defect traps pre-miRNAs in the nucleus, reduces miRNA processing, and diminishes miRNA-target inhibition. The XPO5 mutant form lacks a C-terminal region that contributes to the formation of the pre-miRNA:XPO5:Ran-GTP ternary complex and pre-miRNAs accumulate in the nucleus. Most importantly, the restoration of XPO5 functions reverses the impaired export of pre-miRNAs and has tumor-suppressor features.

INTRODUCTION

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by targeting messenger RNA (mRNA) transcripts. miRNAs play important roles in several cellular processes by simultaneously controlling the expression levels of hundreds of genes (He and Hannon, 2004; Bartel, 2004; Chang and Mendell, 2007). In human cancer, miRNA expression profiles differ between normal tissues and derived tumors and between tumor types (Lu et al., 2005; Voinova et al., 2006), and it has been shown that miRNAs can act as oncogenes or tumor suppressors (Esquela-Kerscher and Slack, 2006; Hammond, 2007). Importantly, an miRNA expression profile of human tumors has emerged that is characterized by a defect in miRNA production and global miRNA downregulation (Lu et al., 2005; Calin and Croce, 2006; Gaur et al., 2007). Recent studies have provided possible mechanisms that could explain this miRNA deregulation in cancer: failure of miRNA posttranscriptional regulation (Thomson et al., 2006), CpG island promoter hypermethylation-associated transcriptional silencing (Salot et al., 2006; Lujambio et al., 2007), transcriptional repression by oncogenic factors (Chang et al., 2008), and mutational impairment of

Significance

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by inhibiting target messenger RNA (mRNA). Data from numerous studies indicate that miRNAs play a critical role in tumorigenesis. The production of mature miRNAs is accomplished via an enzymatic pathway that can go awry at various steps. These defects can explain the reported downregulation of miRNAs in human cancer. Herein, we show that a subset of tumors from the colon, stomach, and endometrium harbor inactivating mutations of XPO5, a gene critical to the export of the immature precursor miRNAs (pre-miRNAs) from the nucleus to the cytosol. The re-expression of the wild-type protein rescues the aberrant phenotype and has tumor-suppressor properties. This last finding might also have therapeutic applications.
Small molecule enoxacin is a cancer-specific growth inhibitor that acts by enhancing TAR RNA-binding protein 2-mediated microRNA processing

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MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression at the posttranscriptional level and are critical for many cellular pathways. The disruption of miRNAs and their processing machinery also contributes to the development of human tumors. A common scenario for miRNA expression in human cancers is the loss of expression that impaired miRNA production and/or down-regulation of these transcripts occurs in many neoplasms. Several of these lost miRNAs have tumor-suppressor features, so strategies to restore their expression globally in malignancies would be a welcome addition to the current therapeutic arsenal against cancer. Herein, we show that the small molecule enoxacin, a fluoroquinolone used as an antibacterial compound, enhances the production of miRNAs with tumor suppressor functions by binding to the miRNA biosynthesis protein TAR RNA-binding protein 2 (TRBP). The use of enoxacin in human cell cultures and xenografts, orthotopic, and metastatic mouse models reveals a TRBP-dependent and cancer-specific growth-inhibitory effect of the drug. These results highlight the key role of disrupted miRNA expression patterns in tumorigenesis, and suggest a unique strategy for restoring the distorted miRNAome of cancer cells to a more physiological setting.

miRNAs play important roles in several cellular processes, by simultaneously controlling the expression levels of hundreds of genes (1, 2). In human cancer, miRNA expression profiles differ between normal tissues, derived tumors, and tumor types (5, 6), and it has been shown that miRNAs can act as oncogenes or tumor suppressors (7, 8). Importantly, an miRNA expression profile of human tumors has emerged that is characterized by a deficit in miRNA production and global miRNA down-regulation (5, 6, 9–11). Several mechanisms explain this miRNA deregulation in cancer, such as the failure of miRNA posttranscriptional regulation (12), CpG island promoter hypermethylation-associated transcriptional silencing (13–16), transcriptional repression by oncogenic factors (17), mutational impairment of the TARBP2 miRNA processing gene that codes for the TAR RNA-binding protein 2 (TRBP) protein (18), and down-regulation of the Dicer1 miRNA biosynthesis gene (19–21). Consistent with these observations, experimental knockdown and genetic defects in miRNA-processing machinery genes, such as Dicer1 and TRBP, cause miRNA global depletion and stimulate tumorigenesis (18, 22–25), suggesting that miRNA impairment actively contributes to cancer development.

Despite the impact of miRNAs on cancer biology, miRNA-based cancer therapy is still in its early stages and mostly limited to target a single miRNA (26, 27). However, because most tumors show a global down-regulation of miRNA expression (5, 6, 9–11), restoration of normal miRNA levels might represent an attractive approach in cancer therapy. Herein, we present an miRNA-based treatment of malignancies in which enoxacin, a small molecule proposed to promote RNA interference and miRNA processing (28), has a powerful cancer-specific growth-inhibitory effect mediated by a TRBP-dependent restoration of the expression of tumor suppressor miRNAs.

Results

Enoxacin Treatment Has a Cancer-Specific Growth-Inhibitory Effect

Despite the enormous potential that a small molecule that enhances RNA interference might have for cancer therapeutic purposes, the effects of enoxacin in tumor proliferation have not been characterized. Thus, we first analyzed whether enoxacin could potentially act as a cancer growth inhibitor by examining the effects of the drug in a panel of 12 cancer cell lines from seven common malignancies. The transformed cell lines studied included colorectal (RKO and HCT-116), gastric (SNU-1 and SNU-638), lung (H1299 and A549), breast (MCF-7 and MDA-MB-231), liver ( HepG2, leukemia (KG1a), and lymphoma (RAJI). A


The authors declare no conflict of interest.

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Additional author information is available in the Supporting Information.
Stabilization of Suv39H1 by SirT1 Is Part of Oxidative Stress Response and Ensures Genome Protection

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SUMMARY
Sirtuins are NAD-dependent deacetylases that sense oxidative stress conditions and promote a protective cellular response. The sirtuin SirT1 is involved in facultative heterochromatin formation through an intimate functional relationship with the H3K9me3 methyltransferase Suv39h1, a chromatin organization protein. However, SirT1 also regulates Suv39h1-dependent constitutive heterochromatin (CH) through an unknown mechanism; interestingly, SirT1 does not significantly localize in these regions. Herein, we report that SirT1 controls global levels of Suv39h1 by increasing its half-life through inhibition of Suv39h1 lysine 87 polyubiquitination by the E3-ubiquitin ligase MDM2. This in turn increases Suv39h1 turnover in CH and ensures genome integrity. Stress conditions that lead to SirT1 up-regulation, such as calorie restriction, also induce higher levels of Suv39h1 in a SirT1-dependent manner in vivo. These observations reflect a direct link between oxidative stress response and Suv39h1 and support a dynamic view of heterochromatin, in which its structure adapts to cell physiology.

INTRODUCTION
All organisms must adapt to environmental changes, particularly those affecting metabolic, nutritional, or energy homeostasis. These conditions induce a coordinated protective response, which entails using available resources more efficiently and ensures genomic stability (Guarente and Ricardo, 2005). It encompasses two principal targets: mitochondria and chromatin, which are closely linked to aging and life span control (Vaquer and Reimberg, 2009). Chromatin is particularly important, owing to its functional duality: it is the signaling hub at which most of the response is coordinated, and is also the target itself of several protective measures activated during the response (Heydari et al., 2007).

Evidence discovered over the past decade has suggested that the members of the Sirtuin family are major players in sensing and coordinating the responses geared to chromatin and to mitochondria (Saunders and Verdine, 2007). Mammals have seven Sirtuins, denoted SirT1 to SirT7. These exhibit great functional diversity, encompassing two different enzymatic activities (deacetylation and ADP-ribosylation of proteins), myriads substrates, and a highly diverse pattern of cellular localization (Vaquer, 2009). Sirtuins help coordinate stress response by detecting changes in the NAD+/NADH ratio, which stems from the fact their enzymatic activity requires NAD+ (Kim et al., 2000). The role of Sirtuins in sensing, and promoting a response to, these fluctuations in the redox state of the cell is paramount in many processes, as reflected in their numerous functions, including gene expression, cell survival under stress, cell-cycle control, metabolic homeostasis, development, and cell differentiation, among others (Saunders and Verdine, 2007). The presence of Sirtuins in chromatin regulation is illustrated by the conservation of this relationship from early eukaryotes as well as by a conserved functional relationship with two histone post-translational modifications that have been crucial for regulating chromatin structure and epigenetic phenomena in evolution: H4K16Ac and H3K9Ac (Vaquer, 2009). Among Sirtuins, only SirT1-3 and 6 have been shown to participate in chromatin regulation through deacetylation of histone and non-histone proteins; of these, SirT1 is the best characterized. SirT1 promotes the formation of facultative heterochromatin (FH) by deacetylating H4K16Ac, H3K9Ac, and H1K26Ac (Vaquer, 2009). Among Sirtuins, only SirT1 promotes establishment of H3K9me3 via several mechanisms (Vaquer et al., 2007); deacetylation of H3K9Ac to enable methylation by Suv39h1, direct recruitment of Suv39h1, and
Gene amplification of the transcription factor DP1 and CTNNB1 in human lung cancer

Sandra D. Castillo, Barbara Angulo, Ana Suarez-Gauthier, Lorenzo Melchor, Pedro P. Medina, Lydia Sanchez Verde, Juan Torres-Lanzas, Guillermo Pita, Javier Benitez and Montse Sanchez-Cespedes

Abstract

The search for novel oncogenes is important because they could be the target of future specific anticancer therapies. In the present paper we report the identification of novel amplified genes in lung cancer by means of global gene expression analysis. To screen for amplics, we aligned the gene expression data according to the position of transcripts in the human genome and searched for clusters of over-expressed genes. We found several clusters with gene over-expression, suggesting an underlying genomic amplification. FISH and microarray analysis for DNA copy number in two clusters, at chromosomes 11q12 and 13q34, confirmed the presence of amplifications spanning about 0.4 and 1 Mb for 11q12 and 13q34, respectively. Amplification at these regions each occurred at a frequency of 3%. Moreover, quantitative PCR of each individual transcript within the amplics allowed us to verify the increased in gene expression of several genes. The p120ctn and DP1 proteins, encoded by two candidate oncogenes, CTNNB1 and TFDP1, at 11q12 and 13q amplics, respectively, showed very strong immunostaining in lung tumours with gene amplification. We then focused on the 13q34 amplon and in the TFDP1 candidate oncogene. To further determine the oncogenic properties of DP1, we searched for lung cancer cell lines carrying TFDP1 amplification. Depletion of TFDP1 expression by small interference RNA in a lung cancer cell line (HCC35) with TFDP1 amplification and protein over-expression reduced cell viability by 50%. In conclusion, we report the identification of two novel amplics, at 13q34 and 11q12, each occurring at a frequency of 3% of non-small cell lung cancers. TFDP1, which encodes the E2F-associated transcription factor DP1 is a candidate oncogene at 13q34. The data discussed in this publication have been deposited in NCBI Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/) and are accessible through GEO Series Accession No. GSE21148.

Keywords: oncogene; lung cancer; TFDP1; CTNNB1; p120ctn

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Introduction

The overwhelming benefit with respect to overall survival and quality of life that specific anticancer drugs offer for the treatment of some leukaemia cases exemplifies the power of the therapies designed to deal with proteins encoded by genetically altered genes. Tyrosine kinase inhibitors such as Imatinib, which acts against the BCR–ABL kinase fusion protein in chronic myeloid leukaemia or against gastrointestinal stromal tumours with activating mutations in the KIT or PDGFRα oncogenes, are the paradigm [1,2]. Thus, knowledge of the gene alteration profile in tumours has begun to guide drug design.

Lung cancer is among the types of tumour whose therapy has shown the least improvement in the last three decades. Although this is a highly preventable type of cancer, by cessation or non-initiation of the smoking habit, the absence of effective therapies, coupled with the lack of tools for early diagnosis, makes lung cancer the primary cause of death due to cancer in most developed countries. The only therapeutic improvement of note for this cancer is the use...
A Robust and Highly Efficient Immune Cell Reprogramming System

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SUMMARY

Here we describe a lineage reprogramming system consisting of a B cell line with an estradiol-inducible form of C/EBPα where cells can be converted into macrophage-like cells at 100% efficiency within 2 to 3 days. The reprogrammed cells are larger, contain altered organelle and cytoskeletal structures, are phagocytic, and exhibit an inflammatory response. Time-lapse experiments showed that the cells acquire a macrophage morphology and increased migratory activity as early as 10 hr. During induction, thousands of genes become up- or downregulated, including several dozen transcription and chromatin-remodeling factors. Time-limited exposure of cells to the inducer showed that the reprogrammed cells become transgene independent within 1 to 2 days. The reprogramming can be inhibited, at least partially, by perturbation experiments with B cell and macrophage transcription factors. The tightness, robustness, and speed of the system described make it a versatile tool to study biochemical and biological aspects of lineage reprogramming.

INTRODUCTION

Harold Weintraub’s laboratory showed that a single gene, encoding the transcription factor MyoD, can induce the differentiation of fibroblasts into myotubes (Davis et al., 1987). The subsequent finding that MyoD can also induce the expression of muscle genes in cell lines of ectodermal and endodermal origin (Weintraub et al., 1989) raised the possibility that fully specialized cells can be reprogrammed into other cell types. Indeed, experiments with avian myeloid leukemia cells showed that GATA-1 can convert the cells into megakaryocytic/erythroid cells. The cells not only activated genes of the megakaryocytic/erythroid lineage but also downregulated macrophage genes (Kulesza et al., 1999). Since then, transcription factors have been used to reprogram a number of other tissues, such as cultured astrocytes into neuronal cells by Pax6 (Heins et al., 2002); pancreatic cells into liver cells by activation of C/EBPβ (Shen et al., 2003); B cells into macrophages by C/EBPα (Kie et al., 2004); and embryonic stem cells into the trophectoderm by Cd2 (Niwa et al., 2008). Direct reprogramming of specialized cells has also been shown in vivo. Thus, an activated form of Pdx1 induces hepatic cells to turn into pancreatic beta islet cells in Xenopus (Horb et al., 2003). More recently, a combination of Pdx1 with Ngn1 and MafA was shown to reprogram exocrine cells into beta islet cells in the mouse pancreas (Zhou et al., 2008). Given enough knowledge about how lineages are reprogrammed, it might therefore one day become feasible to directly custom-make any desired cell type in cultures or in patients.

To unravel the molecular basis of lineage reprogramming, a cell system would be desirable where reprogramming can be induced with high efficiency and within a short time span and cell numbers are not limiting. Several of these requirements are met by the conversion of primary lymphoid cells into myeloid cells. For example, the enforced expression of C/EBPα by retroviral infection can convert more than 60% of B and T cell progenitors into macrophages (Kie et al., 2004; Lalosa et al., 2006). The frequency of induced lymphoid to macrophage conversions is therefore substantially higher compared to the reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) by embryonic stem cell-associated transcription factors (Takahashi and Yamanaka, 2006). However, even primary lymphoid cells are not ideal because an important fraction of the cells are resistant to reprogramming, the cultures require stromal cells, and cell numbers are limiting. In addition, for every experiment the starting population has to be freshly isolated from bone marrow and infected with retroviruses, and the infected cells have to be sorted before analyses.

Here we describe a pre-B cell line that can be converted by C/EBPα into macrophage-like cells at 100% efficiency within 2 to 3 days in the absence of stroma. The induced cells exhibit dramatic changes in gene expression within hours and acquire functional macrophage properties. Time-lapse experiments showed that all cells change in morphology and become highly motile. Furthermore, we showed that the system can be used to test for genes with the capacity to specifically perturb cell reprogramming.

RESULTS

Pre-B Cell Lines Containing C/EBPαER Can Be Induced to Reciprocally Regulate Lineage Marker Expression and to Change Cell Parameters at 100% Efficiency

To develop a reprogrammable cell line system, we screened two adult and one fetal pre-B cell lines for their ability to convert into...
Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus

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Monocytotoxic (MZ) twins are partially concordant for most complex diseases, including autoimmune disorders. Whereas phenotypic concordance can be used to study heritability, discordance suggests the role of non-genetic factors. In autoimmune diseases, environmentally driven epigenetic changes are thought to contribute to their etiology. Here we report the first high-throughput and candidate sequence analyses of DNA methylation to investigate discordance for autoimmune disease in twins. We used a cohort of MZ twins discordant for three diseases whose clinical signs often overlap: systemic lupus erythematosus (SLE), rheumatoid arthritis, and dermatomyositis. Only MZ twins discordant for SLE featured widespread changes in the DNA methylation status of a significant number of genes. Gene ontology analysis revealed enrichment in categories associated with immune function. Individual analysis confirmed the existence of DNA methylation and expression changes in genes relevant to SLE pathogenesis. These changes occurred in parallel with a global decrease in the methylcytosine content that was concomitantly accompanied with changes in DNA methylation and expression levels of ribosomal RNA genes, although no changes in repetitive sequences were found. Our findings not only identify potentially relevant DNA methylation markers for the clinical characterization of SLE patients but also support the notion that epigenetic changes may be critical in the clinical manifestations of autoimmune disease.

Supplemental material is available online at http://www.genome.org. The sequence data from this study have been submitted to the NCBI Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo) under accession no. GSE90333.

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Calorie restriction and the exercise of chromatin

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Since the earliest stages of evolution, organisms have faced the challenge of sensing and adapting to environmental changes for their survival under compromising conditions such as food depletion or stress. Implicit in these responses are mechanisms developed during evolution that include the targeting of chromatin to allow or prevent expression of fundamental genes and to protect genome integrity. Among the different approaches to study these mechanisms, the analysis of the response to a moderate reduction of energy intake, also known as calorie restriction (CR), has become one of the best sources of information regarding the factors and pathways involved in metabolic adaptation from lower to higher eukaryotes. Furthermore, responses to CR are involved in life span regulation—conserved from yeast to mammals—and therefore have garnered major research interest. Herein we review current knowledge of responses to CR at the molecular level and their functional link to chromatin.

“You’ll live longer and you’ll be healthier too,” he answered. ‘Because as we were saying today, there’s nothing in the world like eating moderately to live a long life.’ ‘If that’s the way things are,’ I thought to myself, ‘I never will die.’ ‘Because I’ve always been forced to keep that rule, and with my luck I’ll probably keep it all my life.’—Anonymous, The Life of Lazarillo de Tormes and of His Fortunes and Adversities (1554).

Since antiquity, human beings have associated immoderate levels of eating with disease and a shortened life span. This intuition, exemplified by the Renaissance era quote above, is only now starting to be truly understood. One of the most important laboratory tools for studying the effects of energy intake on eukaryotes is the intervention known as calorie restriction (CR), which was originally defined in mice as a reduction in food intake of 30%–50% as compared with animals fed with no control (ad libitum)

[Keywords: Sirtuins; chromatin; calorie restriction; TOR; NAD+; metabolism]

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Selected Original Articles, Perspectives and Reviews

Regulatory signal transduction pathways for class Ila histone deacetylases
Maribel Parra¹ and Eric Verdin²,³

The class Ila histone deacetylases (HDACs), HDAC4, 5, 7, and 9, have crucial roles in the development of the immune system and other organs, including brain, heart, and muscle. In addition to their catalytic domain, they are characterized by a large amino-terminal extension. The amino-terminal domain is subject to reversible phosphorylation, which controls their nucleo-cytoplasmic distribution. Unphosphorylated, class Ila HDACs remain in the nucleus, bound to chromatin, and repress transcription. Upon phosphorylation, they shuttle out of the nucleus, allowing derepression of their target genes. Thus, the nucleo-cytoplasmic translocation is associated with derepression of target genes. Recent studies identified the kinases and phosphatases that regulate the nucleo-cytoplasmic shuttling of class Ila HDACs. Here we will summarize this rapidly evolving field with a particular focus on the immune system.

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Introduction
Histone deacetylases (HDACs) have emerged as crucial transcriptional co-repressors in highly diverse physiological systems. To date, 18 human HDACs have been identified and grouped into four classes, Class I HDACs (HDAC1, 2, and 8), class II HDACs (HDAC4, 5, 6, 7, 9, and 10), class III HDACs, also called sirtuins, (SIRT1, 2, 3, 4, 5, 6, 7), and class IV HDACs (HDAC11). Class II HDACs are further subdivided into class Ila (HDAC4, 5, 7, 9, and the HDAC5 splice variant MITR) and class Ilib (HDAC6 and 10) [1].

Class Ila HDACs have three unique features. First, they are expressed in a tissue-specific manner and exert their transcriptional repressive function in skeletal, cardiac, and smooth muscle, bone, the immune system, the vascular system, and the brain. Knockout mice for each class Ila HDACs show important defects in differentiation and developmental processes. Mice lacking HDAC5 and/or HDAC9 exhibit exacerbated cardiac hypertrophy in response to stress induced by aortic stenosis. Mice deficient in HDAC4 show premature bone calcification, and mice lacking HDAC7 show embryonic lethality resulting from a failure to form tight junctions in the developing circulatory system (see [2,3] for recent reviews). Second, class Ila HDACs contain a regulatory N-terminal domain that mediates their interactions with tissue-specific transcription factors and co-repressors. Third, they are signal-dependent co-repressors and become phosphorylated at two or three conserved serine residues in the regulatory N-terminal domain. Phosphorylation of class Ila HDACs is a crucial event that determines whether they are localized in the nucleus or cytoplasm and, therefore, their ability to act as transcriptional co-repressors in the nuclear compartment. By coupling the activity of the kinase or phosphatase with extracellular signals, developmental pathways can be triggered via extracellular signals.

Because the phosphorylation of class Ila HDACs is so important for regulating their transcriptional repressive capacity, identifying the signal transduction pathways and the kinase(s) responsible for such modification has been the focus of many recent studies. This review highlights those discoveries on the signal transduction pathways that govern class Ila HDACs nucleo-cytoplasmic shuttling.

Regulation of class Ila HDACs by nucleo-cytoplasmic shuttling

In the nucleus, class Ila HDACs bind to the co-repressors SMRT/N-CoR and are recruited to their target promoters via tissue-specific transcription factors, such as myocyte enhancer factor (MEF2), Runx2, and serum response factor (SRF). However, in response to a variety of physiologic stimuli and depending on the cell type, class Ila HDACs become phosphorylated at two (HDAC5) or three (HDAC5, 7, and 9) conserved serines in the N-terminal domain. This phosphorylation leads to their interaction with 14-3-3 proteins, their cytoplasmic localization and the derepression of their target genes [1,3]. The currently accepted model explaining class Ila HDACs regulation is that the phosphorylation occurs
MASSIVE PARALLEL DNA PYROSEQUENCING ANALYSIS OF THE TUMOR SUPPRESSOR BRG1/SMARCA4 IN LUNG PRIMARY TUMORS

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Communicated by Bruce R. Gottlieb

ABSTRACT: The tumor suppressor gene, SMARCA4 (or BRG1), which encodes the ATPase component of the chromatin remodeling complex SWI/SNF, is commonly inactivated by mutations and deletions in lung cancer cell lines. However, SMARCA4 alterations appear to be rare in lung primary tumors. Ultra-deep sequencing technologies provide a promising alternative to achieve a sensitivity superior to that of current sequencing strategies. Here we used ultra-deep pyrosequencing to screen for mutations over the entire SMARCA4 coding region in 12 lung tumors without detectable BRG1 protein. While automatic-fluorescence-based sequencing detected one somatic mutation (p.K586X), the pyrosequencing revealed additional variants, thus increasing the sensitivity. Of the variants, which affected a consensus splice site, was confirmed by individual cloning of PCR products, ruling out the possibility of PCR or pyrosequencing artifacts. This mutation, confirmed to be somatic, was present at a frequency of ten percent, suggesting normal cell contamination in the tumor. Our analysis also allows us to determine the sensitivity and to identify any limitations of the technology. In conclusion, in addition to cell lines, SMARCA4 is biallelically inactivated in a significant proportion of lung primary tumors, thereby constituting one of the most important genes contributing to the development of this type of cancer.

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KEY WORDS: Deep sequencing, SMARCA4, BRG1, lung cancer, tumor suppressor gene, 454-Roche

INTRODUCTION

The accurate identification of the complete set of genes mutated in cancer is becoming increasingly important.

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Dietary Restriction: Standing Up for Sirtuins

WE BELIEVE THAT L. FONTANA, L. PARTRIDGE, AND V. D. LONGO SHOULD HAVE INCLUDED A DISCUSSION OF SIRTUINS IN THEIR REVIEW “Extending healthy life span—From yeast to humans” (16 April, p. 321). We also believe that some of the references used are misleading.

The authors state that the purpose of their Review is to “consider the role of nutrient-sensing signaling pathways in mediating the beneficial effects of dietary restriction.” Yet there was no mention of the sirtuins, a family of critically important nutrient-sensing proteins that promote health span from yeast to mammals, as shown by more than 1000 peer-reviewed publications from labs around the world. The authors state that “[b]ecause [it] is unlikely that a single, linear pathway mediates the effects of dietary restriction in any organism,” and we agree. Indeed, the aging field now recognizes that healthy life span is under the influence of several nutrient-sensing pathways, and there is as much evidence for the involvement of sirtuins in the dietary restriction response as for any of the pathways discussed in the Review (1).

Numerous independent studies show that dietary restriction does not extend life span when sirtuins are deleted. This result has been shown in multiple organisms, from yeast to flies and even in mice (2). Moreover, deleting SIRT1, SIRT3, SIRT4, or SIRT5 abrogates various physiological aspects of dietary restriction and fasting, including longevity (3). SIRT1 activity in mice increases during dietary restriction, and enforced SIRT1 activity results in a dietary restriction–like physiology and protection from many of the same degenerative diseases that are protected by dietary restriction in mice, including cancer, neurodegeneration, inflammatory disorders, metabolic syndrome and type 2 diabetes, and cardiovascular disease (4). In humans, there is also evidence that sirtuins may be involved in mediating the response to dietary restriction and extending health span. For example, SIRT1 levels increase in humans practicing dietary restriction (5), and there are strong associations between alleles that increase SIRT1 expression and increased metabolic rate, as well as protection from type 2 diabetes (6).

Collectively, these studies provide strong support for a central role of sirtuins, as well as other nutrient-sensing proteins, as mediators of the effects of dietary restriction and the extension of healthy life span.

We also believe that the Review fails to assign due credit for major discoveries in the aging field, and not just from the sirtuin field. In some cases, credit is incorrectly attributed. For instance, the ablation of Drosophila germ line as it affects insulin-like peptides (dilp) and life span was performed by Flatt et al. (7). In another instance, data is selectively used to support the view that insulin signaling plays a role in dietary restriction, which is the opposite of what the original paper shows (8).

The Review shows dietary restriction works through insulin signaling in nematodes and flies, both of which are controversial. Studies indicate thatdaf-16/FoxO is not required for life-span extension by dietary restriction in nematodes (9) or in flies (8). Published data further demonstrate that dietary restriction robustly extends fly life span even when RNAi has suppressed diet-associated changes in insulin-like peptides.

JOSEPH A. BAUR,1 DANICA CHEN,1 EDUARDO N. CHINI,1 KATRIN CHUZ,1 HAIM Y. COHEN,1 RAFAEL DE CABO,1 CHUXIA DENG,1 STEFANIE DIMMELER,1 DAVID GIUS,1 LEONARD P. GUARANTE,1,* STEPHEN L.

27 AUGUST 2010 VOL 329 SCIENCE www.sciencemag.org
Cancer epigenetics reaches mainstream oncology

Manuel Rodriguez-Paredes1 & Manel Esteller1-3

Epigenetics is one of the most promising and expanding fields in the current biomedical research landscape. Since the inception of epigenetics in the 1940s, the discoveries regarding its implications in normal and disease biology have not stopped, compiling a vast amount of knowledge in the past decade. The field has moved from just one recognized marker, DNA methylation, to a variety of others, including a wide spectrum of histone modifications. From the methodological standpoint, the successful initial single gene candidate approaches have been complemented by the current comprehensive epigenomic approaches that allow the interrogation of genomes to search for translational applications in an unbiased manner. Most important, the discovery of mutations in the epigenetic machinery and the approval of the first epigenetic drugs for the treatment of subtypes of leukemias and lymphomas has been an eye-opener for many biomedical scientists and clinicians. Herein, we will summarize the progress in the field of cancer epigenetics research that has reached mainstream oncology in the development of new biomarkers of the disease and new pharmaceutical strategies.

Introduction to epigenetics and its biological roles

When Conrad Waddington coined the word ‘epigenetics’ (literally ‘over’ or ‘upon genetics’) in the early 1940s, the term was used to explain why genetic variations sometimes did not lead to phenotypic variations and how genes might interact with their environment to yield a phenotype1. But the word currently refers specifically to the study of mitotically and/or meiotically heritable changes in gene expression that occur without changes in the DNA sequence2. The disruption of such changes underlies a wide variety of pathologies, including cancer3-4. Epigenetic regulation includes DNA methylation (Fig. 1) and covalent histone modifications (Fig. 2), and we will discuss only these two epigenetic layers here.

DNA methylation usually takes place at the 5’ position of the cytosine ring within CpG dinucleotides, and its consequence is the silencing of genes and noncoding genomic regions. There are three main DNA methyltransferases (DNMTs): DNMT1, which maintains the existing methylation patterns following DNA replication, and DNMT3A and DNMT3B, de novo enzymes that target previously unmethylated CpGs5. CpG sites are concentrated either in CpG islands, short CpG-rich DNA regions located in approximately 60% of human gene promoters, or in regions of large repetitive sequences (for example, centromeres and retrotransposon elements)5-8. Although in the latter case most of the CpGs are methylated to prevent chromosome instability, the majority of CpG islands remain unmodified during development and in different tissues5. Nevertheless, naturally occurring CpG island methylation takes place during developmental phenomena such as X chromosome inactivation or genomic imprinting9. Further investigation will be needed to elucidate additional roles of DNA methylation in non-CpG island promoters and in the origin and maintenance of pluripotency9,10. Recent findings also suggest that extensive DNA methylation changes caused by differentiation take place at CpG island ‘shores’, regions of comparatively low CpG density close to CpG islands11,12. Additionally, almost one-quarter of all DNA methylation found in embryonic stem (ES) cells occurs in a non-CpG context12. Finally, 5-methylcytosine (5-mC) can be converted into 5-hydroxymethylcytosine (5-hmC) by the 2-oxoglutarate– and Fe(II)-dependent oxygenases TET1, TET2 and TET3 (ref. 13). It will be necessary to gain insight into the role of this recently described modification, detected in ES cells and Purkinje neurons and involved in ES cell self-renewal and embryonic inner cell mass specification14.

Histones can undergo multiple post-translational modifications15, which mainly occur along their N-terminal tails. The enzymes that add and remove such modifications are, respectively, histone acetyltransferases (HATs) and deacetylases (HDACs and sirtuins), methyltransferases (HMTs) and demethylases (HDMDs), kinases and phosphatases, ubiquitin ligases and deubiquitinases. SUMO ligases and proteases, and so on16,17. Genome-wide studies have revealed that various combinations of modifications in a specific genomic region can lead, like a ‘histone code’, to a more ‘open’ or ‘closed’ state of chromatin structure and, therefore, to the activation or repression of gene expression12. For instance, trimethylation of lysines (K) 4, 36 or 79 on H3 (H3K4me3, H3K36me3 and H3K79me3, respectively),
Aberrant Epigenetic Landscape in Cancer: How Cellular Identity Goes Awry

María Bardasco and Manel Esteller

Introduction
Normal development appears to take place through a unidirectional process characterized by a step-wise decrease in developmental potential and an activation of specific gene programs that trigger differentiation into specialized cell types. Once established, temporal and spatial activation and silencing of specific genes in a cell-type-specific pattern must be stable over many cell generations and long after inductive developmental signals have disappeared. Equally important, a cell must silence expression of genes specific to other cell types to secure its fate. Repression must be maintained throughout the life of the individual in normal development, and epigenetic mechanisms, which are defined as heritable changes in gene function that do not alter the primary DNA sequence, are ideal for regulating such events. The best-studied epigenetic modification is DNA methylation, which consists of the addition of a methyl group to carbon 5 of the cytosine within the dinucleotide CpG. It has been estimated that 3%-6% of cytosines are methylated in normal tissues and that this DNA methylation is necessary for controlling gene expression of tissue-specific, housekeeping or imprinted genes and also for maintaining genomic stability through silencing transposable elements of the genome (Esteller, 2007).

DNA methylation does not work alone and occurs in the context of other epigenetic modifications, such as histone modifications. Histone tails may undergo many post-translational chemical modifications, including acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation. For instance, the different statuses of acetylation and methylation of specific lysine residues are considered crucial histone marks affecting chromatin structure and gene expression (Kouzarides, 2007).

Additionally, recent advances in the rapidly evolving field of epigenetics have demonstrated the extensive role of noncoding RNAs, especially miRNA expression, in maintaining global expression patterns during normal development (Sharma et al., 2010). Although several small-scale studies of specific epigenetic marks have provided limited information about the regulation of genes from different pathways, there is a need for knowl-

dge in a broader perspective. A range of matters remains to be resolved, such as the relationships between the epigenetic players (the “epigenetic code”) and how the environment and/or aging modulate the epigenetic marks. Some of this could be achieved by analyzing patterns on a genome-wide scale, an approach that has at last become possible thanks to recent technological advances (Bernstein et al., 2007; Barski et al., 2007; Izzary et al., 2009).

It is clear that a comprehensive knowledge of the human epigenome will allow a fuller understanding of normal development, aging, abnormal gene control in cancer, and other diseases, as well as the role of the environment in human health. This is the main goal of the International Human Epigenome Consortium (IHEC) and the Roadmap Epigenomics Program at NIH Fund (http://nihroadmap.nih.gov/epigenomics/); however, we must bear in mind that there is no single epigenome but, rather, many different ones that are characteristic of normal and diverse pathological states. It is clear that the information extracted from the whole-genome assays will help us understand the role of epigenetic marks in normal development and in diseases such as cancer. The aim of the present review is to provide an overview of how epigenetic factors, including genomic DNA methylation, histone modifications, and microRNA regulation, contribute to normal development, paying special attention to their role in the establishment of cell identity. In the second part, we will focus on how tissue-specific epigenetic patterns go awry during human cancer development.

Epigenetic Changes during Normal Development
It is well described that DNA methylation patterns undergo genome-wide alterations that occur immediately after fertilization and during early preimplantation development (Mayer et al., 2000; Reik et al., 2001) and that enrichment of individual histone modifications (such as H3K9me, H3K4me and H3K27me3) also varies in a specific manner at different stages of development (Reik, 2007). Apart from the extensive chromatin remodeling that occurs during early differentiation, epigenetic factors must guarantee the activation and maintenance of
Epigenetic modifications and human disease

Anna Portela1 & Manel Esteller1,2

Epigenetics is one of the most rapidly expanding fields in biology. The recent characterization of a human DNA methylome at single nucleotide resolution, the discovery of the CpG island shores, the finding of new histone variants and modifications, and the unveiling of genome-wide nucleosome positioning maps highlight the accelerating speed of discovery over the past two years. Increasing interest in epigenetics has been accompanied by technological breakthroughs that now make it possible to undertake large-scale epigenomic studies. These allow the mapping of epigenetic marks, such as DNA methylation, histone modifications and nucleosome positioning, which are critical for regulating gene and noncoding RNA expression. In turn, we are learning how aberrant placement of these epigenetic marks and mutations in the epigenetic machinery is involved in disease. Thus, a comprehensive understanding of epigenetic mechanisms, their interactions and alterations in health and disease, has become a priority in biomedical research.

Even before DNA was identified as the molecule of inheritance, scientists knew that not every gene in an organism can be active in each cell at all times. Even so, all cells in an organism share the same genetic information. Conrad Waddington coined the term “epigenetic landscape” for the molecular mechanisms that convert this genetic information into observable traits or phenotypes. In many instances, epigenetic gene expression patterns and associated phenotypes persist through mitosis or even meiosis, although no change in the primary DNA sequence has occurred. Consequently, epigenetics is generally understood to be the study of mechanisms that control gene expression in a potentially heritable way.

Recent breakthroughs in the understanding of the mechanisms underlying epigenetic phenomena and their prevalence as contributors to the development of human disease have led to a greatly enhanced interest in epigenetic research.

On a molecular level, covalent modifications of cytosine bases and histones, and changes in the positioning of nucleosomes are commonly regarded as the driving epigenetic mechanisms. They are fundamental to the regulation of many cellular processes, including gene and microRNA expression, DNA-protein interactions, suppression of transposable element mobility, cellular differentiation, embryogenesis, X-chromosome inactivation and genomic imprinting.

In multicellular organisms, the ability of epigenetic marks to persist during development and potentially be transmitted to offspring may be necessary for generating the large range of different phenotypes that arise from the same genotype1,5,6. For instance, cloned animals generated from the same donor DNA are not identical to, and develop diseases with different penetrance from, their donor1,5,7. Human clones that arise spontaneously—monozygotic twins—are identical at the DNA sequence level, but have different DNA methylation1,8 and histone modification profiles1,9 that might affect the penetrance of several diseases, such as cancer10 or autoimmune disorders11. But this phenomenon is also observed at a single cell level: how can stem cells develop into any type of cell and how does a liver cell always give rise to two new liver cells after cell division? Again, epigenetics seems to be part of the answer as it has been described as one of the key factors in cellular differentiation5,8 (see the review by Weissman6 in this issue).

The importance of epigenetics in maintaining normal development and biology is reflected by the observation that many diseases develop when the wrong type of epigenetic marks are introduced or are added at the wrong time or at the wrong place10. For instance, a clear causality role for DNA methylation in cancer is suggested by hypermethylation of some genes (e.g., p1610,6, p1410,6, p1510,7 and MGMT) as an early event in tumorigenesis, as well as by tumor type-specific methylation landscape10. Here we summarize recent progress in the field of epigenetic research and its role in disease, preparing ourselves for the surprises that epigenetics might hold in the future.

Epigenetic modifications and their machineries

For didactic purposes, epigenetic modifications can be grouped into three main categories: DNA methylation, histone modifications and nucleosome positioning. It is important to keep in mind the interplay between epigenetic factors—as the observed outcome is always the sum of their interactions—and the many positive and negative feedback mechanisms.

DNA methylation. The most widely studied epigenetic modification in humans is cytosine methylation. DNA methylation occurs almost exclusively in the context of CpG dinucleotides. The CpG dinucleotides tend to cluster in regions called CpG islands, defined as regions of
IDIBELL CANCER CONFERENCES
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Cancer Epigenetics and Biology Symposium
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Chairman: Manel Esteller, PEBC Director

Genevieve Almouzni
CNRS/Institut Curie, Paris, France
"Chromatin assembly factors and the challenges of DNA replication and repair"

Peter Andrews
University of Sheffield, Sheffield, U.K.
"Population dynamics of human ES cell cultures: self-renewal, adaptation and cancer"

Alan Ashworth
The Breakthrough Breast Cancer Research Centre, London, U.K.
"Synthetic lethal approaches to the development of new therapies targeting DNA repair deficiencies in cancer"

Mariano Barbacid
Spanish National Cancer Research Centre (CNIO), Madrid, Spain
"Mouse tumor models and target validation"

Rene Bernards
NKI-AVL, Amsterdam, The Netherlands
"Finding mechanisms and biomarkers of drug resistance in cancer"

Mina Bissell
Lawrence Berkeley National Laboratory, Berkeley, USA
"Extracellular matrix and tissue architecture regulate epigenetics of tissue specificity and breast cancer"

Manel Esteller
Cancer Epigenetics and Biology Program (PEBC), IDIBELL-ICREA, Barcelona, Spain
"Human cancer epigenetics"

Andrew Feinberg
Johns Hopkins University School of Medicine, Baltimore, MD, USA
"The epigenetic progenitor model of cancer"

Peter Jones
USC Norris Comprehensive Cancer Center, Los Angeles, USA
"Reversing cancer epigenetic alterations"

Tony Kouzarides
The Gurdon Institute, Cambridge, U.K.
"Chromatin modifying enzymes: their function and role in cancer"

Pier Paolo Pandolfi
Harvard University, Boston, MA, USA
"Targeting the cancer initiating cell for therapy"

Frank Slack
Yale University, New Haven, CT, USA
"MicroRNAs in cancer and aging"

Michael Stratton
Wellcome Trust Sanger Institute, Hinxton, Cambridge, U.K.
"Patterns of somatic mutation in human cancer genomes"

Thea Tsly
UCSF, Helen Diller Family Comprehensive Cancer Center, San Francisco, USA
"Re-programming the epigenome in carcinogenesis"

Maarten van Lohuizen
MD-AVL, Amsterdam, The Netherlands
"Role of polycomb repression in cancer and development"

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Update of the Cancer Epigenetics and Biology Program (PEBC)

October 22-23, Barcelona, Spain

Invitation to Attend

As organisers, we invite you to attend the IDIBELL Cancer Conference on Sirtuins. The meeting will be held in the Bellvitge Institute for Biomedical Research, IDIBELL, Barcelona.

The ICC on Sirtuins meeting will begin on Thursday morning, October 22, 2009, and will conclude with lunch on Friday, October 23, 2009. The goal of this meeting is to highlight the latest advances in the Sirtuin field from a multidisciplinary point of view, from the molecular to the physiological level, and to create an exceptional framework for scientific discussion.

Applicants are encouraged to submit Poster presentations. A limited number of these abstracts will be selected for oral presentation.

For registration visit www.pebc.cat. All meeting questions should be directed to Anne Legrand, Meeting Manager, alegrand@iconcologia.net

Invited Speakers

Fred Alt
Harvard Medical School
Cambridge, MA, USA.

Johan Auwerx
Ecole Polytechnique Federale de Lausanne
Lausanne, Switzerland.

Antonio Badalov
Fred Hutchinson Cancer Research Center
Seattle, WA, USA.

Eva Bober
Max-Planck-Institute for Heart and Lung Research
Bad Nauheim, Germany.

Katrin Chua
Stanford University School of Medicine
Stanford, CA, USA.

John Denu
University of Wisconsin-Madison School of Medicine and Public Health
Madison, WI, USA.

Manel Esteller
Cancer Epigenetics and Biology Program PEBC-IDIBELL,
Barcelona, Spain.

Ingrid Grummt
German Cancer Research Center
Heidelberg, Germany.

Wei Gu
Columbia University
New York, NY, USA.

Pere Puigserver
Dana-Farber Cancer Institute
Boston, MA, USA.

Danny Reinberg
NYU School of Medicine
New York, NY, USA.

Ed Seto
H.Lee Moffitt Cancer Center
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Alejandro Vaquero
Cancer Epigenetics and Biology Program, PEBC-IDIBELL,
Barcelona, Spain.

Eric Verdin
Gladstone Institute of Virology and Immunology
San Francisco, CA, USA.

Francesc Villarroya
University of Barcelona (UB)
Barcelona, Spain.

Organisers

Alejandro Vaquero (Cancer Epigenetics and Biology Program (PEBC)/Bellvitge Institute for Biomedical Research, IDIBELL)
Manel Esteller (Cancer Epigenetics and Biology Program (PEBC)/Bellvitge Institute for Biomedical Research, IDIBELL)

Contact Meeting Management:
avaquero@iconcologia.net
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IDIBELL Cancer Conferences organized by the PEBC and PEBC Invited Lectures

**Invitation to Attend**

As organisers, we invite you to attend the IDIBELL Cancer Conference on the Cell Cycle (ICC on the Cell Cycle). The meeting will be held in the Bellvitge Institute for Biomedical Research, IDIBELL, Barcelona.

The ICC on the Cell Cycle will begin on Thursday morning, November 26, 2009, and will conclude with lunch on Friday, November 27, 2009. The goal of this meeting is to highlight the latest advances in cell cycle regulation in a broad spectrum of experimental organisms.

**Invited Speakers**

- **Tim Hunt**
  Cancer Research UK, Clare Hall Laboratories
  South Mimms, UK.
- **John Diffey**
  Cancer Research UK, Clare Hall Laboratories
  South Mimms, UK.
- **Etienne Schwoob**
  Institute of Molecular Genetics
  Centre National de la Recherche, Montpellier, France.
- **Martí Aldea**
  Dept. Ciències Mèdiques Bàsiques
  Universitat de Lleida, Lleida, Spain.
- **Christian Lehner**
  University of Zurich, Institute of Zoology
  Zurich, Switzerland.
- **Wolfgang Zachariae**
  Max Planck Institute of Molecular Cell Biology and Genetics
  Dresden, Germany.
- **Jan-Michael Peters**
  Research Institute of Molecular Pathology IMP
  Vienna, Austria.
- **Prasad Jallepalli**
  Memorial Sloan-Kettering Cancer Center
  New York, USA.
- **Karim Labib**
  Paterson Institute for Cancer Research
  Manchester, UK.
- **Erich Nigg**
  Max Planck Institute of Biochemistry
  Martinsried, Germany.
- **Bela Novak**
  Oxford Centre for Integrative Systems Biology
  Department of Biochemistry
  University of Oxford, Oxford, UK.
- **Angel Nebreda**
  Centro Nacional de Investigaciones Oncológicas CNIO, Madrid, Spain.
- **Sergio Moreno**
  Centro de Investigacion del Cancer Salamanca, Spain.
- **Marcos Malumbres**
  Centro Nacional de Investigaciones Oncológicas CNIO, Madrid, Spain.
- **Frank Uhmann**
  Cancer Research UK, London Research Institute
  London, UK.
- **Ethel Queralt**
  Cancer Epigenetics and Biology Program PEBC-IDIBELL, Barcelona, Spain.

**Applicants**

Applicants are encouraged to submit Poster presentations. A limited number of these abstracts will be selected for oral presentation.

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**Organisers**

Frank Uhmann (Cancer Research UK London Research Institute)
Ethel Queralt (Cancer Epigenetics and Biology program PEBC/Bellvitge Institute for Biomedical Research, IDIBELL)

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**ICC on the Cell Cycle 2009**

**November 26-27, Barcelona, Spain**
Update of the Cancer Epigenetics and Biology Program (PEBC)
IDIBELL Cancer Conferences organized by the PEBC and PEBC Invited Lectures

on Mouse Models of Cancer 2010

October 7-8, 2010, Barcelona, Spain

You are cordially invited to attend the IDIBELL Cancer Conference on Mouse Models of Cancer (ICC on Mouse Models of Cancer). The meeting will be held in the Bellvitge Institute for Biomedical Research, IDIBELL, Barcelona. The ICC on Mouse Models of Cancer will begin on Thursday morning October 7th, 2010 and will conclude on Friday afternoon October 8th, 2010. The goal of this meeting is to highlight the latest advances in cancer research using genetically modified and xenograft mouse models.

Invited Speakers

Mariano Barbacid
Spanish National Cancer Research Center, CNIO
Madrid, Spain

Maria A. Blasco
Spanish National Cancer Research Center, CNIO
Madrid, Spain

Gerhard Christofori
Institute of Biochemistry and Genetics, University of Basel
Basel, Switzerland

Alan Clarke
Cardiff School of Biosciences
Cardiff, United Kingdom

Michael Clarke
Institute for Stem Cell Biology and Regenerative Medicine
Stanford University
Palo Alto, CA, USA

Lisa Coussens
Comprehensive Cancer Center, University of California
San Francisco, CA, USA

Gerard Evan
University of Cambridge
Cambridge, United Kingdom

Douglas Hanahan
School of Life Sciences, EPFL, ISREC
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Robert M. Hoffman
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University of California San Diego
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David Tuveson
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Cambridge, United Kingdom

Erwin Wagner
Spanish National Cancer Research Center, CNIO
Madrid, Spain

Fiona Watt
Cambridge Research Institute, Cancer Research UK
Cambridge, United Kingdom

Jos Jonkers
The Netherlands Cancer Institute, NKI
Amsterdam, The Netherlands

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Barcelona, Spain

Alberto Villanueva
Catalan Institute of Oncology, ICO
Barcelona, Spain

Applicants are encouraged to submit Poster presentations. A limited number of these abstracts will be selected for oral communications. More information can be found on the conference web site: http://iccmcc.idibell.cat
All meeting questions should be directed to the technical secretariat: info@tacticsmd.net

Organisers

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Update of the Cancer Epigenetics and Biology Program (PEBC)
IDIBELL Cancer Conferences organized by the PEBC and PEBC Invited Lectures

21st-23rd September 2011, Barcelona, Spain

Invitation to Attend

As organisers, we invite you to attend the IDIBELL Cancer Conference on Genomic Imprinting and Beyond "Monoallelic Expression in Health and Disease". The meeting will be held at Institut d’Estudis Catalans within the picturesque 14th century Santa Creu Hospital, Barcelona, Spain.

Registration begins in the evening of Wednesday 21st, with the plenary lecture Thursday morning. Each session will have two invited speakers and 2 short talks selected from abstract submissions. The meeting will conclude Friday evening. The goal of this meeting is to highlight the latest advances in the epigenetic fields with emphasis on allelic regulation and genomic imprinting from a mechanistic and clinical point of view.

Invited Speakers

Howard Cedar
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Robert Feil (CNRS Institute of Molecular Genetics, University of Montpellier, Montpellier, France)

Queries

Due to the limited capacity (130 participants) priority will be given to applicants submitting poster presentations. Several of these abstracts will be selected for oral presentations. For registration visit www.pebc.cat. All meeting queries should be directed to Anne Legrand, alegrand@idibell.cat

Meeting Organisers:
dmonk@idibell.cat
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Meeting sponsored by:
Update of the Cancer Epigenetics and Biology Program (PEBC)

October 30 2009
Jaume Bertranpetit
“Lessons from the evolutionary dynamics of molecular networks”
Institut de Biologia Evolutiva (UPF-CSIC), Departament de Ciències Experimentals i de Salut, Universitat Pompeu Fabra, Parc de Recerca Biomèdica de Barcelona, Barcelona

December 4 2009
Mara Dierssen
“The Mouse as a model to decipher the genetic code in down syndrome”
Centre for Genomic Regulation (CRG), Universitat Pompeu Fabra, Barcelona Biomedical Research Park (PRBB), Barcelona

December 18 2009
Xose Bustelo
“Implication of Vav family oncoproteins in pathological states”
Centro de Investigación del Cancer and Instituto de Biología Molecular y Celular del Cancer (IBMCC), CSIC - University of Salamanca, Salamanca

January 15 2010
Gines Morata
“Cell competition and tumour growth in Drosophila”
Centro de Biología Molecular, Universidad Autónoma de Madrid, Madrid

February 5 2010
Javier Benitez
“Searching for high penetrance genes in familial breast cancer”
Spanish National Cancer Research Centre (CNIO), Madrid

February 26 2010
Miguel Martin
“Chemotherapy drugs as targeted agents: tailoring adjuvant chemotherapy in early breast cancer”
Medical Oncology Department, Hospital Clínico San Carlos, Madrid

March 19 2010
Jose Lopez-Barneo
“The neurogenic niche in the carotid body and its applicability to cell therapy in Parkinson’s disease”
Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío (CSIC-Universidad de Sevilla, Sevilla, Sevilla

April 16 2010
Andres Aguilera
“Genome Instability: from transcription to nucleotide excision repair”
Centro Andaluz de Biologia Molecular y Medicina Regenerativa CABIMER, Universidad de Sevilla – CSIC, Sevilla

May 7 2010
Amparo Cano
“Epithelial-mesenchymal transition: in the road to metastasis”
Instituto de Investigaciones Biomedicas Alberto Sols, CSIC - Universidad Autónoma de Madrid, Madrid

May 14 2010
Oscar Marin
“Neuronal migration mechanisms in development and disease”
Instituto de Neurociencias de Alicante, CSIC-Universidad Miguel Hernández, Sant Joan d’Alacant, Alicante

June 4 2010
Alberto Muñoz
“Vitamin D and colon cancer: mechanisms of action”
Instituto de Investigaciones Biomédicas Alberto Sols, CSIC - Universidad Autónoma de Madrid, Madrid

June 11 2010
Angel Nebreda
“Signal Integration by p38 MAPKs”
Spanish National Cancer Research Centre (CNIO), Madrid

Location: Sala d’Actes, Planta Baixa, Hospital Duran i Reynals, Gran Via 199-203, 08027 L’Hospitalet, Barcelona. Time: 13.00h
www.pebc.cat
IDIBELL Cancer Conferences organized by the PEBC and PEBC Invited Lectures

Hosted by Dr. Manel Esteller

October 2010 - June 2011

1 de Octubre, 2010
Dr. Vivek Malik
Centro de Regulación Genómica (CRG), Barcelona.
"Mechanism of protein secretion: conventional and unconventional"

29 de Octubre, 2010
Dr. Pilar Santisteban
Instituto de Investigaciones Biomédicas Alberto Sols- Consejo Superior de Investigaciones Científicas y Universidad Autónoma de Madrid, Madrid.
"BRAF and TGFβ cooperate to increase malignancy in thyroid cancer"

12 de Noviembre, 2010
Dr. Jesus Avila
Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid, Campus Cantoblanco, Madrid.
"How to explain the loss of memory in Alzheimer disease"

10 de Diciembre, 2010
Dr. Vicente Rubio
Instituto de Biomedicina de Valencia (IBV), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER-ISCIII), Valencia.
"Structural bases of signaling in bacteria"

21 de Enero, 2011
Dr. Carlos Simon
Stem Cell Bank, Prince Felipe Research Center (CIPF), Valencia.
"Adult vs Embryonic vs Induced Pluripotent Stem Cells"

4 de Febrero, 2011
Dr. Carlos Martinez-Alonso
Department of Immunology and Oncology, Centro Nacional de Biotecnología (CNB-CSIC), Campus Cantoblanco, Madrid.
"DioD1, chromosomes and stem cells"

25 de Febrero 2011
Dr. Atanasio Pandiella
Centro de Investigación del Cancer, Instituto de Biología Molecular y Celular del Cancer, Centro de Superior de Investigaciones Científicas, Universidad de Salamanca, Salamanca.
"The Neuroretinal EFBB system in cancer"

18 de Marzo 2011
Dr. Alonso Valencia
Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid.
"Cancer genomes from a protein perspective"

29 de Abril, 2011
Dr. Joan Guix
Instituto de Investigaciones Biomédicas (IRB), University of Barcelona, Barcelona.
"Glycogen, the Good, the Bad and the Ugly"

3 de Mayo, 2011
Dr. Liisa Badimon
Cardiovascular Research Center (CSIC-CCRC), Hospital de la Santa Creu i Sant Pau.
"Early characterization of atherogenic plaques using genomics and proteomics"

3 de Junio, 2011
Dr. Francisco Sanchez-Madrid
Servicio de Immunología, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid.
"Mechanisms of intercellular communication through the immunological synapse"
Selected PEBC Ad Hoc Seminars
Selected PEBC Ad Hoc Seminars

Dr. Xavi Roca  
*Cold Spring Harbor Laboratories*  
“New mechanisms of silice-site recognition: Implications for human genetic disease and cancer”

Dr. Lluís Morey  
*Center of Genomic Regulation (CRG)*  
“Role of the NuRD complex in Acute Promyelocytic Leukemia”

Dr. Maria Jose Barrero  
*Centro de Medicina Regenerativa de Barcelona (CMRB)*  
“Histone-modifying enzymes control the balance between self renewal and differentiation in human embryonic stem cells”

Dr. Gerald Schock  
*Quiagen* - *Izasa*  
“Epigenetics & Pyromark”

Dr. Juan Barba  
*Applied Biosystems*  
“Novedades en expresión génica por PCR Real time y genotipado”

Dr. Jenny Wu  
*Laboratory of Yeast Genetics and Cell Biology of The Rockefeller University*  
“Establishing the S phase program of origin usage in fission yeast”

Dr. David de Semir  
*California Pacific Medical Center Research Institute (CPMCRI), San Francisco*  
“Identification and validation of melanoma progression gene”

Dr. Jorge Perez Valle  
*Instituto de Biología Molecular y Celular de Plantas de la Universidad Politécnica de Valencia*  
“Regulation of ion homeostasis: Physiological and transcriptomic analysis of the hal4hal5 mutant in Saccharomyces cerevisiae”

Dr. Maite Huarte  
*The Broad Institute, Cambridge, MA 02142, USA; Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA*  
“Epigenetic control of oncogenic pathways by large intergenic non-coding RNAs”

Dr. Beatriz Pérez-Cadahía  
*Toxicology Unit of the Psychobiology Area of the University of A Coruña*

Dr. Gloria Torrents  
*GE HEALTHCARE*  
“Protein solutions seminar”
Dr. Agustin Sanchez  
“hSprouty2: Binding to signalling proteins and its role in cancer”

Dr. Shahaf Peleg  
Gottinga University (Germany)  
“Altered Histone 4 K12 acetylation is associated with age-dependent memory impairment”

Dr. Marcel Dinger  
Institute for Molecular Bioscience The University of Queensland  
“long noncoding RNAs: impact on development and disease”

Dr. Franck Court  
CNRS – Montpellier  
“Higher-order organisation of the mammalian chromatin fiber: its basic dynamics and specific folding at the Igf2/H19 locus”

Dr. Irene Ferrer  
“Spinophilin, a novel p53-loss dependent tumour suppressor”

Dr. Diego Molina Serrano  
Post-doctoral fellow at the Biology Department of the University of Rochester, NY, USA  
“Histone demethylases and epigenetics in yeast”

Dr. Boris Rodríguez Porrata  
Grup de Recerca Biomèdica HJ23, Unitat de Recerca, Tarragona

Dr. Rolf Reist  
SEQUENOM  
“EpiTYPER a quantitative highthroughput approach for methylation analysis”

Dr. Heather Holemon  
R&D Manager for the Gene Regulation Group at Sigma Aldrich  
“Learn about the latest thecnologies transforming the field of epigenetics (Chip, Whole genome amplification and Zinc Finger nucleases technologies)”
Bellvitge abre la vía a nuevos fármacos contra el cáncer
Esteller propone restaurar la correcta actividad de los genes

Josep Corbella

El científico Miquel Esteller, del Instituto d’Investigació de Bellvitge (Idibell) y de la institución Arqna, ha demostrado que se puede frenar la progresión de un cáncer con fármacos que funcionan de modo diferente a cualquier tratamiento utilizado hoy día en oncología.

La estrategia que propone Esteller ha demostrado ser eficaz en cultivos de células tumorales y en ratones con cáncer, según resultados asociados a un trabajo en la revista PNAS. La logística que se abre ahora es el desarrollo por alguna compañía farmacéutica de un medicamento para que esta línea de investigación pueda convertirse en medicamentos útiles para los pacientes.

La estrategia se basa en bloquear al citocromo. En cualquier célula cancerosa, hay genes que funcionan mal. Pero también funcionan mal unos pequeños pedazos de ADN, llamados microARNas (¿miRNAs), que controlan la actividad de los genes. Si se bloquean las miRNAs, en teoría se podría restaurar la correcta actividad de los genes, lo que podría frenar la progresión del cáncer.

Oncología: Un nuevo cimiento terapéutico
RANKL participa en el inicio del tumor de mama

Esteller, en el institutd’Investigació de Bellvitge

Una proteína del metabolismo óseo está vinculada con el cáncer de mama

Una investigación subraya su incidencia en procesos de metástasis

En condiciones fisiológicas normales existe una conexión entre la actividad de la vía RANK en mama y en huesos...
Siete científicos de Catalunya, reconocidos por Europa

El ERC anuncia la financiación de los mejores proyectos

Los siete proyectos seleccionados

Emma Cabré
Dermatología. UAB
Estudiará los datos de maternidad de las 250 parejas de la diócesis de Barcelona desde 1481 a 1906.

Covia Esping-Anderson
Sociología. UPV
Su proyecto investigará la evolución de los comportamientos de formación de pareja y de paternidad.

Manel Esteller
Medicina. IEO
Estudiará cómo algunas moléculas de ARN alteran la actividad del ADN en los cánceres humanos.

Un nuevo marcador predice respuesta a l-PARP en mama

Trendline Information Systems, Inc.

Trends in Biopharmaceuticals

Twins Provide Clues to Lupus

Twins with lupus were found to have increased expression of genes that are related to multiple immune system functions.

Some cancer cells hijack micro-RNA

Researchers discover a substance against the 'dark genome' of cancer

A research study coordinated by Manel Esteller, researcher at Bellvitge Biomedical Research Institute (IDIBELL) has identified a substance that inhibits cancer growth by activating the so-called "dark genome" (or "non-coding" DNA) and microRNA molecules. The study appears in the journal Proceedings of the National Academy of Sciences (PNAS).