

## Epigenetic Inactivation of the Groucho Homologue Gene in *TLE1* Hematologic Malignancies

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An undifferentiated status and the epigenetic inactivation of tumor-suppressor genes are hallmarks of transformed cells. Promoter CpG island hypermethylation of differentiating genes, however, has rarely been reported. The Groucho homologue Transducin-like Enhancer of Split 1 (*TLE1*) is a multitasked transcriptional corepressor that acts through the acute myelogenous leukemia 1, Wnt, and Notch signalling pathways. We have found that *TLE1* undergoes promoter CpG island hypermethylation-associated inactivation in hematologic malignancies, such as diffuse large B-cell lymphoma and AML. We also observed a mutual exclusivity of the epigenetic alteration of *TLE1* and the cytogenetic alteration of *AML1*. *TLE1* reintroduction in hypermethylated leukemia/lymphoma cells causes growth inhibition in colony assays and nude mice, whereas *TLE1*-short hairpin RNA depletion in unmethylated cells enhances tumor growth. We also show that these effects are mediated by *TLE1* transcriptional repressor activity on its target genes, such as *Cyclin D1*, *Colony-Stimulating Factor 1 receptor*, and *Hairy/Enhancer of Split 1*, and . These data suggest that *TLE1* epigenetic inactivation contributes to the development of hematologic malignancies by disrupting critical differentiation and growth-suppressing pathways.