

Stemness Is Only a State of the Cell

M.N. Kagalwala^{*#}, S.K. Singh^{*} and S. Majumder^{*†‡§¶}

[+](#) Author Affiliations

Abstract

How the programming and reprogramming of stem/progenitor cells regulate normal cell development and cancer is still not well known. One of the tools that we have chosen to use to investigate stem cell regulation is the transcriptional repressor element 1-silencing transcription factor (REST). REST contains a DNA-binding domain and two repressor domains. Once bound to its target genes, REST can interact with several cellular corepressors to regulate epigenetic modifications. REST is expressed in most nonneural cells, including neural stem/progenitor cells (NSCs), but it is absent in most neuronal cells. REST was originally found to be a major transcriptional repressor of neural differentiation. Previously, we found that activation of REST target genes in NSCs was sufficient to cause neuronal differentiation. Furthermore, the activation of REST target genes in myoblasts was sufficient to override the muscle differentiation pathway and produce a physiologically active neuronal phenotype. Although REST is normally not expressed in most neural cells, we previously found that approximately 50% of human medulloblastomas, a malignant pediatric brain tumor, express REST and that abnormal expression of REST in NSCs causes medulloblastoma-like cerebellar tumors by blocking neuronal differentiation. Interestingly, REST is also expressed at high levels in mouse embryonic stem (mES) cells, but its role in these cells is not understood. Recently, we found that REST maintains self-renewal and pluripotency in mES cells through suppression of microRNA-21 (miRNA21). Thus, REST is a newly discovered element of the interconnected regulatory network that maintains the self-renewal and pluripotency of mES cells. Taken together, the results of several different studies indicate that stem/progenitor cells are more flexible than previously believed and that a simple alteration of transcriptional regulators in these cells can affect both normal cell development and cancer.

[↓](#) Present address: Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, California 92037.

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