Protein protects embryonic stem cells' versatility and self-renewal

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A protein known as REST blocks the expression of a microRNA that prevents embryonic stem cells from reproducing themselves and causes them to differentiate into specific cell types, scientists at The University of Texas M. D. Anderson Cancer Center report in the journal *Nature*.

Researchers show RE1-silencing transcription factor (REST) plays a dual role in embryonic stem cells, said senior author Sadhan Majumder, Ph.D., professor in M. D. Anderson's Department of Cancer Genetics. "It maintains self-renewal, or the cell's ability to make more and more cells of its own type, and it maintains pluripotency, meaning that the cells have the potential to become any type of cell in the body."

The paper posted online March 23 in advance of publication grew from M. D. Anderson research on the protein's role in medulloblastoma – an exceptionally aggressive pediatric brain cancer.

Embryonic stem cells are essentially blank slates. They have the unique ability to develop from identical, unspecialized cells and then differentiate into distinct types of cells with special functions. In the laboratory, scientists have been able to induce embryonic stem cells to develop into heart muscle cells or insulin-producing cells of the pancreas. The hope is that embryonic stem cells might one day be used to restore or replace failing cells in the human body and perhaps treat a wide range of diseases.

"Embryonic stem cells have a very high potential in medicine,"

Majumder said. "The critical thing is to learn the mechanisms that could be used to generate a lot of self-renewing embryonic stem cells and be able to differentiate them into various cell types." REST could play a key role in maintaining a steady supply of these cells and in preserving their differentiation capability.

Suppressing MicroRNA-21

In studies using mouse embryonic stem cells, the researchers found that REST disarms a specific microRNA called microRNA-21 or miR-21. MicroRNAs are tiny pieces of RNA that control gene expression by binding to the gene's messenger RNA.

The team found that MiR-21 suppresses embryonic stem cell self-renewal and is associated with a corresponding loss of expression of critical self-renewal regulators, such as Oct4, Nanog, Sox2 and c-Myc. REST counters this by suppressing miR-21 to preserve the cells' self-renewal and pluripotency.

The researchers discovered the roles of REST and miR-21 in a series of experiments using cultured mouse embryonic stem cells in either a self-renewal state or a differentiating state. They found that REST expression was significantly higher in the self-renewal state. Withdrawing REST reduced the stem cells' ability to reproduce themselves and started differentiation — even when the cells were grown under conditions conducive to self-renewal. Adding REST to differentiating cells maintained their self-renewal.

These experiments also revealed that REST is bound to the gene chromatin of a set of microRNAs with the potential to target self-renewal genes. REST controls transcription of 11 microRNAs.

REST Implicated in Pediatric Brain Cancer

Previous laboratory research suggests that the qualities that make REST beneficial in stem cell production and pluripotency may contribute to the development of medulloblastoma, an aggressive type of children's brain tumor. Medulloblastomas are believed to develop from undifferentiated neural stem cells in the external granule layer of the cerebellum.

In earlier research, Majumder's group at M. D. Anderson discovered that about half of these tumors overexpress REST, which is not found in most neural cells. "We found that REST is a critical factor in this group of children's brain tumors," Majumder said, "and that its major function is to keep a group of specific brain stem cells, or progenitor cells, in a state of stemness."

The researchers hypothesize that by maintaining the neural stem cells' 'stemness,' REST prevents their differentiation into normal and distinct types of cells, leading instead to tumor formation. The M. D. Anderson scientists are now exploring whether microRNAs might also play a role in medulloblastomas.

Understanding REST function has applications in both medulloblastoma and embryonic stem cell biology. "Just as blocking REST function has therapeutic potential in medulloblastoma, blocking REST function to allow for differentiation of embryonic stem cells is a potentially critical step in regenerative medicine," Majumder said.

Source: University of Texas M. D. Anderson Cancer Center