Scientists identify genes capable of regulating stem cell function

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Scientists from The Forsyth Institute, Boston, MA, and the Howard Hughes Medical Institute at the University of Utah School of Medicine have developed a new system in which to study known mammalian adult stem cell disorders. This research, conducted with the flatworm planaria, highlights the genetic similarity between these invertebrates and mammals in the mechanisms by which stem cell regulatory pathways are used during adult tissue maintenance and regeneration. It is expected that this work may help scientists pursue pharmacological, genetic, and physiological approaches to develop potential therapeutic targets that could repair or prevent abnormal stem cell growth which can lead to cancer.

In recent years, planarians have been recognized as a powerful model system in which to molecularly dissect conserved stem cell regulatory mechanisms in vivo. This research reveals that planaria are also a great model in which to study the molecular relationship between stem cells and cancer. The gene characterized in this study (PTEN) is one of the most commonly mutated genes in human cancers. As in human beings, genetic disturbance of the gene in planarians led to mis-regulation of cell proliferation resulting in cancer-like characteristics. These results indicate that some of the pattern control mechanisms that enable regeneration of complex structures may go awry in cancer.

Abnormal stem cell proliferation in planarians is induced by genetic manipulation of conserved cellular signaling pathways. These abnormal cells can be specifically targeted without disturbing normal stem cell

functions that support adult tissue homeostasis and regeneration. Importantly, this type of analysis could not be achieved in more traditional adult invertebrate model systems such as the fruit fly Drosophila and the nematode C. elegans. This research will be published in the journal Disease Models & Mechanisms available online on August 30. According to the paper's lead author, Dr. Néstor J. Oviedo, an Assistant Research Investigator in the Forsyth Center for Regenerative and Developmental Biology, this work provides new opportunities to expand knowledge of this regulatory molecule and the role it plays in cancer and tissue regeneration. "Our findings demonstrate that important signaling pathways regulating adult stem cell proliferation, migration and differentiation are evolutionarily and functionally conserved between planarians and mammals. Planarians are poised to not only advance the understanding of how diverse adult tissues are functionally maintained in vivo, but also will enhance our capabilities to identify, prevent, and remediate abnormal stem cell proliferation."

Summary of Study

The scientists have identified two genes, Smed-PTEN-1 and Smed-PTEN-2, capable of regulating stem cell function in the planarian Schmidtea mediterranea. Both genes encode proteins homologous to the mammalian tumor suppressor, phosphatase and tensin homolog deleted on chromosome 10 (PTEN). Inactivation of Smed-PTEN-1and -2 by RNA interference (RNAi) in planarians disrupts regeneration, and leads to abnormal outgrowths in both cut and uncut animals followed soon after by death (lysis). The resulting phenotype is characterized by hyperproliferation of neoblasts (planarian stem cells), tissue disorganization and a significant accumulation of postmitotic cells with impaired differentiation capacity. Further analyses revealed that rapamycin selectively prevented such accumulation without affecting the normal neoblast proliferation associated with physiological turnover and regeneration. In animals in which PTEN function is abrogated, the HHMI/University of Utah and Forsyth researchers also detected a

significant increase in the number of cells expressing the planarian Akt gene homolog (Smed-Akt). However, functional abrogation of Smed-Akt in Smed-PTENRNAi-treated animals does not prevent cell overproliferation and lethality, indicating that functional abrogation of Smed-PTEN is sufficient to induce abnormal outgrowths. Altogether, the data reveal roles for PTEN in the regulation of planarian stem cells that are strikingly conserved to mammalian models. In addition, the results implicate this protein in the control of stem cell maintenance during the regeneration of complex structures in planarians.

The PTEN molecules were originally identified and characterized in the laboratory of Dr. Alejandro Sanchez Alvarado, HHMI investigator and Professor of Neurobiology and Anatomy at the University of Utah School of Medicine. Dr. Sánchez Alvarado's is the paper's senior author. His laboratory is engaged in the identification of the molecular and cellular basis of animal regeneration. His laboratory's work on planarians has led to the establishment of this organism as an important model system to study stem cells, regeneration and tissue homeostasis.

The Forsyth research team is led by Michael Levin, Ph.D., Senior Member of the Staff in The Forsyth Institute and the Director of the Forsyth Center for Regenerative and Developmental Biology. Through experimental approaches and mathematical modeling, Dr. Levin and his group examine the processes governing large-scale pattern formation and biological information storage during animal embryogenesis. The lab investigates mechanisms of signaling between cells and tissues that allow a living system to reliably generate and maintain a complex morphology. The Levin team studies these processes in the context of embryonic development and regeneration, with a particular focus on the biophysics of cell behavior.

Source: Forsyth Institute