Forever young: Differentiation blocked in tumor stem cells

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A new comparison of normal stem cells and cancer stem cells reveals that the cancer stem cells are abnormally trapped at an early stage of development. The research, published by Cell Press in the January issue of *Cancer Cell*, significantly advances the understanding of glioma pathophysiology and provides new directions for design of therapeutic strategies that are targeted to specific types of tumors.

Tumor-initiating cells with stem like properties (TICs) are thought to be a small population of tumor cells that have many characteristics in common with normal stem cells (NSCs) in that they are self-replicating and capable of giving rise to populations of differentiated cells. Previous research has demonstrated that TICs are present in different types of brain tumors, including glioblastomas. Although the TICs share many properties with NSCs, they are known to possess genetic aberrations that support a tumorigenic phenotype.

“Thus far, there have been few, if any, reports demonstrating exactly where along the developmental pathway of tissue-specific stem cell maturation and differentiation tumor stem cells arise, and which, if any, of the intrinsic stem cell signaling pathways are perturbed in tumor stem cells remains largely unknown,” explains Dr. Howard A. Fine from the National Cancer Institute in Bethesda, Maryland. To better understand the development and differentiation pathways that play a significant role in cancer stem cells, Dr. Fine and colleagues isolated TICs from primary human glioblastomas and compared them to human and mouse NSCs at various developmental stages.

The researchers found that the TICs isolated from an adult patient are more similar to early embryonic stem cells than to later embryonic or adult-derived stem cells. Specifically, the TICs appear to be stuck at this early developmental stage, at least in part, due to epigenetic repression of bone morphogenic protein receptor 1B (BMPR1B) expression mediated through a polycomb repressive complex. BMPs are known to mediate proliferation, differentiation and apoptosis in NSCs, depending on the stage of cell development and the local environment. Importantly, forced expression of the silenced BMPR1B restored normal differentiation capacity to the isolated TICs, halting further cell division and inducing terminal differentiation.

“Our research provides an example of a temporally deregulated and aberrantly fixed normal stem cell developmental block to differentiation contributing to the pathogenesis of a human tumor. Not only will such insights pave the way for a more thorough understanding of tumor stem cell biology, but they also identify BMPR1B as a promising molecular target and open the potential for targeted therapeutic approaches for agents that can induce terminal differentiation of tumor stem cells,” offers Dr. Fine.

Source: Cell Press