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The stem state: the nature of normal stem cells and the relevance to cancer

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Stem cells are commonly defined as being undifferentiated and capable of self-renewal. Although indefinite self-renewal is often regarded as an intrinsic and unique stem cell trait, accumulating evidence, points to the possibility that stem cells also arise through processes of de-differentiation. Therefore, the classical presentation of cell populations as being organized in a hierarchical manner, topped by a stem cell that gradually differentiates in an irreversible mode, should be re-examined. If progenitor cells that have already begun to differentiate, may turn back and become stem cell, then stemness is a state rather than a cellular entity. Our recent studies on multipotent stromal cells (MSC), show that such cell populations do not differentiate in a hierarchical manner, and that their differentiation mode is compatible with a phase space model. One example is that the capacity of MSC to support hemopoiesis, which is regarded as one direction of MSC differentiation, may be either a property of the undifferentiated MSC itself, or alternatively a property of fully differentiated osteogenic products of the MSC. An additional issue which is a focus of intense controversy, is the finding that bone marrow-derived stem cells

may give rise to cells of other organs and tissues. The same is true for muscle-derived stem cells, neural stem cells and skin stem cells. I recently suggested that pluripotency that entails plasticity, rather than any other trait, is a hallmark of the stem state. Plasticity is thus a state in which the cells harbor a potential to give rise to a multitude of lineages and choose among the options available within the three germ layers. Several studies demonstrated the plastic nature of some adult tissue stem cells, such as the mesenchymal stem cells from the bone marrow, or the skin progenitor cell. These studies strongly suggest that the commonly accepted notion, that adult stem cells should be classified as entities distinct from pluripotent stem cells, is questionable. It is suggested that the underlying properties of cells in the stem state are: being undifferentiated, dependent on their niche for asymmetrical divisions and self-renewal and capable of differentiation into a wide range of cellular entities. These properties are not shared by cells within tumors that are capable of giving rise to new tumors upon transplantation, the tumor initiating cells (TIC). Indeed, unlike stem cells that depend on their niche and are lost

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following serial transplantation, TIC proliferate indefinitely. Most importantly, TIC have a very limited differentiation potential and are certainly not pluripotent. They therefore represent a biological entity that is biologically different from stem cells.

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