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Research Interests

We study the mechanisms that regulate stem cell function in the nervous and hematopoietic systems. Two of the best characterized classes of stem cells are hematopoietic stem cells, which give rise to all blood and immune system cells, and neural stem cells, which give rise to the nervous system. Yet we are just beginning to understand how the functions of these cells are regulated. We are particularly interested in the mechanisms that regulate stem cell self-renewal, aging, and differentiation. By studying these mechanisms in stem cells from two different tissues we will assess the extent to which different types of stem cells employ similar mechanisms to regulate these critical functions.

The Regulation of Stem Cell Self-Renewal The ability of mammals to maintain their tissues throughout adult life is dependent on the persistence of stem cells. Stem cells persist throughout life by self-renewing (dividing to make more stem cells). We and our colleagues have found that the polycomb family transcriptional repressor Bmi-1 is required for the self-renewal but not for the differentiation of stem cells in the hematopoietic system (Nature 423: 302), and peripheral and central nervous systems (Nature 425:962). In each case, stem cells are formed in normal numbers during fetal development, but exhibit impaired self-renewal potential, and become depleted postnatally. In the absence of Bmi-1, stem cells express genes associated with senescence pathways (the cyclin dependent kinase inhibitors p16Ink4a and p19Arf) and their rate of proliferation is reduced (Genes & Development 19:1432). Bmi-1 therefore promotes the maintenance of neural stem cells throughout adult life by



preventing the premature senescence of these cells. By further elucidating the pathways that regulate stem cell self-renewal we may come to a molecular understanding of how cells replicate themselves and how this goes awry in cancer.

Stem Cell Aging Aging leads to a decreased capacity for repair, an increased incidence of degenerative disease, and an increased incidence of cancer in tissues that contain stem cells. These observations suggest a link between aging and stem cell function because stem cells drive growth and regeneration in most tissues, and because many cancers are thought to arise from the transformation of stem cells (Nature Reviews Cancer 3:895). One possibility is that much of age-related morbidity in mammals is determined by the influence of aging on stem cell function. We have found that both neural stem cells and hematopoietic stem cells undergo similar changes in properties as they age (Nature Medicine 2:1011; Neuron 35:657). We are currently testing whether there are conserved changes in gene expression within stem cells with age that cause age-related changes in stem cell function. We hypothesize that stem cell aging is influenced by genes that regulate the proliferation of stem cells during development as well as by genes that protect stem cells from the wear and tear of adult life. If we can identify genes that regulate aging in diverse stem cells, we might better understand the aging process and how the effects of aging on stem cells can be therapeutically ameliorated.

The generation of spatial diversity from stem cells The fundamental question in organogenesis is how do a small number of undifferentiated stem cells give rise to a complex three dimensional organ with different types of mature cells in different locations. The hematopoietic system goes out of its way to avoid regional specialization in stem cells. Hematopoietic stem cells are distributed in different compartments throughout the body, during fetal and adult life, and yet these spatially distinct stem cells have very similar phenotypes, functions, and gene expression profiles. This contrasts with the nervous system, where even small differences in position are associated with the acquisition of different fates by stem cells. We have found that intrinsic differences between stem cells play an important role in the generation of neural diversity. Neural crest stem cells from different regions of the developing peripheral nervous system exhibit cell-intrinsic differences in their response to the factors that regulate differentiation (Neuron 35:643). These differences bias the differentiation of neural crest stem cells in vivo even while these cells remain multipotent. Part of the reason why different types of cells are generated in different regions of the nervous system is that intrinsically different types of stem cells are present in different regions of the nervous system. We are currently studying how these intrinsic differences between stem cells are regulated so as to understand the role of stem cells in the generation of neural diversity.

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