The Dynamics of Niche-Signals and Autonomy in Stem Cell Development

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1 Project Proposal

Embryonic stem cells have recently acquired a quasi-mythical reputation for their potential to give rise to every organ in the body. Though such totipotent cells demonstrate this uniquely comprehensive capacity, adults possess thousands of pluripotent stem cells that are able to reconstitute entire tissues in the case of extreme damage. A single hematopoietic stem cell, for example, can produce a complete, functional immune system when injected into an immuno-deficient mouse (Lord et. al. 1997). As individuals age, bone marrow stem cells become less able to effectively perform the two definitive functions of a stem cell: to self-renew and to differentiate into specialized cells. Recent papers have explored the cell-intrinsic properties of aging, but few have adequately addressed the relationship between the aging hematopoietic stem cell and its bone marrow environment, or so-called niche. A strong understanding of this interaction is essential for both a practical application of stem cell science through the possibility of transplantation, and a more theoretical consideration of such dynamics from an evolutionary perspective. Several models of stem cell differentiation have been proposed, postulating stochastic determination and inductive differentiation (Furusawa and Kaneko 2000; Colijn and Mackey 2005). These papers, however, do not address the observed characteristics of an aging stem cell as it exists among simultaneously changing signals of an aging environment. This project seeks to explore new models for hematopoietic stem cell differentiation that account for recently discovered aging trends and predicts the behavior of individual stem cells in both age-similar and age-dissimilar environments. We consider a fundamental dichotomy in development whereby cells can specify their own fate through a programmed round of cell divisions (autonomy) or rely on niche specific signals to induce differentiation. This is an echo of the nature/nurture debate at the level of the cell.