Stem Cells in a Vacuum: Probing Adult Stem Cell Regulation in Zebrafish

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This study examines the regulation of melanocyte stem cells (MSCs) in zebrafish, an important aspect of zebrafish development. These cells are significant targets for scientific inquiry due to their ability as adult stem cells to self-renew and to maintain their target cells over many years of turnover. The overall purpose of this study would be to shed light on the regulatory mechanisms for adult stem cells in mammals in vivo, a critical step in unlocking their therapeutic potential. As melanocyte stem cells (MSCs) have not yet been isolated, any inferences about them must be elucidated indirectly by counting the daughter cells, the melanocytes.

In zebrafish embryos, we can ablate the larval melanocyte pattern with a mutation in the mitf-ts gene, which causes ablation of these direct developing melanocytes at 32°C and allows for their replacement by cells arising from MSCs. We can also stop MSC establishment using AG1478, which blocks the ErbB signaling pathway essential to establishing stem cells. Applying submaximal concentrations of AG1478 allows the establishment of a small fraction of MSCs while significantly decreasing the MSC population in the zebrafish. This resultant reduction in MSC number results in a “stem cell in a vacuum” paradigm, in which we hope to determine if MSCs can fully regenerate after partial ablation by comparing the cell counts for each AG1478 concentration to determine the level of MSC regeneration.

Our experiments show that reducing the number of MSCs in embryos treated in 2.5 μM, 2.9 μM and 3.2 μM AG1478 plateau in melanocyte development compared to control embryos, indicating new MSCs are not being established in response to the ablation, reflecting an asymmetric division model for MSCs where the melanoblasts, not the MSCs, are flexible in number.