Prashanth Rangan
Biology

Sponsor: National Institute of General Medical Sciences
Dates: August 1, 2014 to July 31, 2019
Anticipated Amount: **$1,437,680**

Regulation of Stem Cell Differentiation During Drosophila Oogenesis

Loss of stem cell self-renewal results in failure to maintain organs, leading to diseases such as infertility and neurodegenerative disorders. In contrast, some cancers result from the inability of “cancer stem cells” to differentiate, while other cancers result from de-differentiation of terminally differentiated cells to a more stem cell like state. Therefore, the ability to prevent premature differentiation in degenerative diseases or to induce differentiation in case of cancer will have tremendous therapeutic impact. Identifying the factors that mediate the transition between stem cell self-renewal and differentiation will provide us with new targets for both class of diseases. Our long-term goal is to determine the key events that control the transition from stem cell self-renewal to differentiation using Drosophila germline stem cells (GSCs) as a model system. The germ line is both totipotent, capable of creating a whole new organism; and immortal, passed on through each generation and is therefore the ultimate stem cell. Thus, paradigms established in the germ line can be extended to other stem cell systems. Drosophila is a superior model system because of the availability of mutants, markers, RNAi technology and targeted expression methods. In Drosophila embryogenesis, conserved process of global transcriptional silencing, mediated by the gene polar granule component (pgc), plays a pivotal role in germ cell specification. In absence of pgc germ cells show precocious transcription that result in the transcription of somatic genes leading to their death. During oogenesis, an oocyte fate is being specified from a GSC fate during the process of differentiation. We have discovered that during oogenesis, Pgc is transiently expressed in the differentiating daughter of the GSC and loss of pgc results in differentiation defects. We propose that during oogenesis, Pgc mediated transcriptional silencing acts to suppress response to self-renewal signaling from the surrounding niche cells and promotes differentiation in the GSC daughter.To test this hypothesis we will (1) Determine how the transcriptional silencer, Pgc, promotes GSC differentiation; (2) Identify Pgc targets and the mechanism of action during GSC differentiation; (3) Investigate the role of translational control in regulating Pgc during oogenesis. Our work will establish a role for transient transcriptional silencing in reprogramming stem cell fate by demonstrating that Pgc in the GSC daughter is expressed in a cell cycle dependent manner and determining a requirement for pgc in promoting efficient differentiation. We favor the idea that transcriptional

silencing is needed to “clear” stem cell factors thereby reprogramming the GSC daughter prior to differentiation. Recently, it has been shown that Blimp 1, along with other transcription factors, can reprogram epiblast-like cells into a germ cell fate, demonstrating that transcriptional silencing is an important part of resetting cell fate. Loss of Blimp1 also results in an improper differentiation of somatic cells during development. Based on our preliminary data and proposed work, we predict that because transient transcriptional silencing “clears” a previous cell fate it is not instructive. Thus, it can also be used to efficiently reprogram somatic cells back to pluripotency.