Research Program

Our laboratory is interested in determining the molecular mechanisms that regulate stem cell differentiation and de-differentiation and how these mechanisms become deregulated in cancer. We largely focus on post-transcriptional and epigenetic mechanisms of cell fate choice.

Post-transcriptional regulation of pluripotency

We have shown that a specific family of miRNAs, which we call the ESCC family, is a powerful inducer and stabilizer of the mammalian pluripotent embryonic stem cell (ESC) fate. We found that this family suppresses hundreds of downstream mRNA targets. By following a subset of these targets, we now know that the ESCC miRNAs function in part by directing the unique cell cycle structure, the epithelial state, and the epigenetic state of ESCs. More recently, we have used these miRNAs to more broadly probe the molecular mechanisms underlying pluripotency. We are now working to understand how these miRNAs function in the context of a broader network of post-transcriptional regulators including other miRNAs as well as RNA binding proteins. Furthermore, we are looking upstream of the miRNAs to understand how they are controlled.

Transcriptional/epigenetic regulation of pluripotency

Prior to forming all the germ layers of the mammalian body plan, differentiating ESCs initially pass through an alternative pluripotent state called the epiblast cell state (EpiC). EpiCs are very interesting as they are ?primed? to differentiate into all somatic cell types of the adult organism. At the molecular level, the primed state is associated with the poising of hundreds of developmental genes through multiple mechanisms. We have recently discovered one such mechanism, which appears to be much more common than the previously described mechanisms. This mechanism involves a new means of enhancer control where a single transcription factor simultaneously acts an activator and repressor thereby initiating enhancer activity while suppressing full blown gene activation. We are further dissecting this novel mechanism both in pluripotent stem cells as well as other more differentiated, yet multipotent cells. We also expect this mechanism to be important in cancer.

Post-transcriptional regulation of somatic stem and germ cells.

The lab is also studying the role of small RNAs in other stem cell types and in vivo developmental stages. In particular, we are studying miRNA roles in trophoblast stem cells, glial progenitor cells, endocrine cells, and oocytes. We made the surprising finding that miRNA function is globally suppressed in mammalian oocytes. We are following up this finding by trying to understand how and why all miRNA function is temporarily inactivated during this critical developmental time window. Simultaneously, we discovered that another
class of small RNAs, endogenous siRNA (endo-siRNAs) are essential for oocyte meiosis. We are currently dissecting the specific endo-siRNAs and targets responsible for meiotic progression. We are performing miRNA screens to dissect the molecular mechanisms underlying neural and endocrine cell fate choices, using approaches similar to those that have been so successful for us in ESCs.

**Post-transcriptonal regulation of in vivo embryonic development.**

We have developed knockout and reporter mice for a number of miRNAs highly expressed during the earliest stages of mammalian development. We are using these models to study the in vivo roles of these miRNAs both individually and in combination. We have uncovered interesting phenotypes both in the embryo proper during gastrulation and in the extra-embryonic tissues, specifically the placenta. We are dissecting these molecular mechanisms underlying these exciting phenotypes.

**Prostate Cancer**

Finally, we are studying the roles of miRNAs in cancer with a particular focus on prostate cancer. We have discovered that miRNAs are essential for the progression of prostate cancer from a hyperplastic to dysplastic lesion. Similar to our ESC work, we are using genomic approaches to uncover the miRNA-mRNA networks in order to dissect the molecular pathways required for progression. Furthermore, we have been analyzing miRNA signatures in the serum of prostate cancer patients, identifying miRNAs that prospectively identify patients at risk for progression and determine how they will respond to specific therapies.

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