Our laboratory is interested in determining the molecular mechanisms that regulate stem cell self-renewal, differentiation, and de-differentiation and how these mechanisms become deregulated in cancer. When starting the lab in 2006, we largely focused on the role of post-transcriptional regulators including microRNAs (miRNAs) and RNA binding proteins (RBPs). However, in past five years, we have also added a focus on epigenetic mechanism associated with enhancer control. In addition, we have developed a strong interest in exosomes both as biomarkers and regulators of cancer progression.

**Post-transcriptional control of pluripotency and early mammalian development**

We have largely focused on the role of two miRNA families, the ESCC and let-7 families. We have shown that ESCC miRNAs promote embryonic stem cell (ESC) self-renewal, suppress the G1-S checkpoint of the cell cycle, and can dedifferentiate somatic cells into induced pluripotent stem cells (iPSC). Recently, we also showed that the ESCC miRNAs suppress phasic expression of genes during the different phases of the cell cycle. We have shown the let-7 miRNAs have the opposite effects. They promote ESC differentiation, inhibit dedifferentiation into iPSCs, promote a G1-S checkpoint, and induce phasic expression across the cell cycle. In the past few years, we have also studied the roles of the ESCC miRNAs in vivo. The ESCC miRNAs are expressed from two genetic loci: the miR-290 and miR-302 loci. By knocking in fluorescent proteins, we have been able to study the dynamic expression of these loci during normal development and de-differentiation toward iPSCs. These data show co-expression of the two loci in the early post-implantation embryo followed by separation of miR-302 to the embryo proper and miR-290 to the extra-embryonic tissues. Consistent with its expression, we have shown the knockout of miR-302 leads to embryonic specific defects including a neural tube closure defect secondary to precocious neural differentiation. Also consistent with its expression, the knockout of miR-290 leads to a placental defect associated with premature differentiation of trophoblast progenitors. Our current leading hypothesis is that the ESCC miRNAs suppress premature differentiation in vivo by suppressing premature phasic gene expression. This represents a novel link between cell cycle and cell differentiation.

**Transcriptional/Epigenetic control of pluripotency**

The miR-290 and miR-302 reporters have provided us with a powerful tool to study the molecular events during early mouse development as they enable purification of homogenous populations of developmentally staged specific cells. Using this tool, we have been studying epigenetic reprogramming of enhancers during early embryonic stem cell differentiation. Focusing on enhancers that transition between a primed and active epigenetic state, we discovered the transcription factor FOXD3 as an important regulator. Mechanistically, we discovered that FOXD3 binding opens chromatin at enhancers, while actively keeping the enhancer deacetylated and thus poised for future activation. Quite remarkably, it does this at a distinct set of enhancers at each developmental stage defining the developmental potential of the cells. Separately, by focusing on the movements of the chromatin structural protein complex Cohesin, we uncovered the role of another transcription factor GRHL2. Through our
studies on GRHL2, we discovered that the transcriptional networks of early pluripotent cells are subdivided prior to lineage diversification during gastrulation. We hypothesize that this subdividing enables pluripotent cells to distribute transcriptional networks differentially between their downstream lineages.

**Exosomes and Cancer**

Through our studies on the roles of miRNAs in cancer, we became interested in exosomes. Several years back, we discovered extracellular miRNA signatures in the plasma of patients that were predictive of pathological state of prostate cancer. Exosomes are thought to represent a major source of extracellular miRNAs. Therefore, we have become interested in how miRNAs are packaged in exosomes and what potential roles they have downstream. Serendipitously, we have recently discovered that exosomes can play a very important immunomodulatory role in cancer progression. By manipulating exosomes, we can either promote or block tumor growth in an immunocompetent host. We are now dissecting the mechanisms that provide exosomes with this remarkable property.

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