Stem cells and pluripotency: emerging themes and tools

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The Minisymposium on Stem Cells and Pluripotency was broad in scope, covering a variety of mechanisms regulating stem cell behavior during regeneration, aging, and tumorigenesis, as well as factors involved in regulating the conversion of differentiated cells back to a pluripotent state (reprogramming). In addition, one talk described the development of tools to assay functionality of cells differentiated in vitro from pluripotent stem cells. Altogether, the session provided a broad overview of a number of active areas in the field of stem cell biology.

Leanne Jones (Salk Institute for Biological Studies) presented data describing a potential mechanism that regulates aging of the stem cell microenvironment, also known as the stem cell "niche." In the *Drosophila* testis, aging results in a decrease in self-renewal factors emanating from key niche support cells. The Jones laboratory has characterized an RNA-binding protein that binds to the mRNA for a key self-renewal factor and protects it from degradation. However, with age, expression of the RNA-binding protein also decreases, leaving the self-renewal factor unprotected, resulting in decreased signaling, loss of stem cells, and decreased tissue homeostasis.

Hebao Yuan (Yamashita laboratory, University of Michigan) proposed a model for how stem cells monitor spindle orientation to ensure an asymmetric division in the *Drosophila* male germ line. His work has demonstrated that germ-line stem cells (GSCs) possess a checkpoint ("the centrosome orientation checkpoint") that monitors correct centrosome orientation prior to mitosis to ensure an oriented spindle and thus asymmetric outcome of the division. Par-1, a serine/threonine kinase that regulates polarity in many systems, is involved in this checkpoint. Par-1 shows a cell cycle–dependent localization to a germ line–specific, endoplasmic reticulum–like organelle, which in turn leads to localization of cyclin A. He proposes that the regulation of cyclin A localization via Par-1 function plays a critical role in the centrosome orientation checkpoint.

Adam Cohen (Department of Chemistry and Chemical Biology, Harvard University) described experiments to incorporate fluorescent voltage-indicating proteins (VIPs), which are based on a modified microbial rhodopsin protein, into high-throughput assays to screen differentiated cells for functionality. The fluorescence of VIPs sensitively and accurately reflects membrane potential; therefore, VIPs would be very useful for detecting action potentials in neurons or membrane potential of cardiomyocytes differentiated in vitro from human pluripotent stem cells. Having such tools in place would greatly facilitate the use of such cell types in screens for drugs or small molecules that could be used to treat patients suffering from diseases that affect such tissues.

Jizhou Yan (College of Fisheries and Life Sciences, Shanghai Ocean University) is studying the cellular and molecular processes that underlie restoration of the lower jaw after amputation in zebrafish. Zebrafish possesses the remarkable ability to regenerate the complicated structures by formation of the characteristic blastema; however, the mechanism by which blastemal cells arise and reorganize is debated. Yan and colleagues characterized the stages of jaw regeneration and found that the blastema is formed from dedifferentiation of mesodermal cells and neural crest–derived pigment cells into two types of precursor cells to restore the original tissue structures, including bone, muscle, pigment, and connective tissue. Further time point–based RNA sequencing revealed that specific signaling pathways are spatiotemporally activated in response to successive steps of cell type conversions. These data indicate that epithelial–mesenchymal interactions and local microenvironmental cues induce transdifferentiation and dedifferentiation of preblastemal cells, and subsequent redifferentiation.

Jennifer Brady (Blau laboratory, Stanford University) described experiments aimed at uncovering the molecular mechanisms underlying the process by which induced pluripotent stem cells (iPS cells) can be generated from essentially any somatic cell. A synchronous, reprogramming approach consisting of heterokaryons (interspecies, multinucleate, fused cells) was developed in which activation of human pluripotency genes occurs rapidly (<24 h) and efficiently (70% of single heterokaryons), enabling early mechanistic studies. High-throughput RNA sequencing revealed transcriptome-wide changes during heterokaryon reprogramming, including the induction of key human pluripotency genes and chromatin remodelers, validating this approach as a discovery tool.

Fernando Camargo (Children's Hospital, Boston; Harvard Stem Cell Institute, Cambridge) is studying the function of the highly conserved Hippo signaling pathway and its effects on tissue size and development and cancer. Growth suppression by Hippo signaling occurs by the inactivation of the transcriptional coactivator YAP. Camargo described experiments in mice that demonstrate that YAP, a protein known for its powerful growth-inducing and oncogenic properties, has an unexpected tumor-suppressive function in the mammalian intestine. Consistent with these findings, Camargo also presented data that indicate YAP is silenced in a subset of highly aggressive and undifferentiated human colorectal carcinomas. Altogether, the data he presented describe a novel mechanistic paradigm for how stem cell expansion and proliferative signals are counterbalanced by the Hippo pathway during organ growth.

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