Editorial

New insights into stem cells

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Stem cells represent one of the most advanced areas in life science research today. The maintenance of pluripotency and differentiation in stem cells may involve a regulatory network with many factors and pathways. The timely developments reported in this issue might provide new clues for improving our understanding of many facets of stem cells and discovering the molecular mechanisms underlying the roles of stem cells in pluripotency maintenance and differentiation and new therapeutic targets for stem cell-related diseases.

In order to develop therapies for blood cell disorders, it is important to understand the molecular mechanism by which human pluripotent stem cells differentiate into hematopoietic stem/progenitor cells. However, the mechanisms behind the generation of hemogenic endothelial cells from the mesoderm are still unclear. Ma's laboratory reported that *RUNX1b/c*, two isoforms of human *RUNX1*, could inhibit early hematopoiesis from the mesoderm in human embryonic stem cells (hESCs). They demonstrated that *RUNX1b* overexpression at an early stage blocked early hematopoiesis from hESCs. This inhibition was partially rescued by an inhibitor of the TGF-β signaling pathway; in addition, D0-induced *RUNX1b* was shown to upregulate TGF-β signaling at an early stage. The study is the first to demonstrate the negative regulation of human early hematopoiesis by *RUNX1b/c* and may aid further research of its function in normal and diseased models.

Ca^{2+} signals play important roles in developmental processes, among which, inositol 1,4,5-trisphosphate receptors (IP3Rs)-mediated Ca^{2+} signals are known to be involved in early development. However, the underlying mechanisms of IP3R-regulated cell fate decision remain to be elucidated. Yang's research group reported that IP3Rs regulated hematopoietic and cardiac lineage divergence in mouse ESCs. The authors showed that the deletion of IP3Rs (IP3R-tKO) decreased hematopoietic mesoderm and hematopoietic progenitor cells whereas increased cardiac progenitor cardiomyocytes. Activation of the Ca^{2+}–calcineurin–NFATc3 pathway time-dependently rescued the phenotype of IP3R-tKO cells and the Ca^{2+}–calcineurin–NFATc3 pathway directly regulated the hematopoietic master gene *Etv2* expression. These results indicate that IP3Rs play an important role in hematopoietic and cardiac fate decision through the IP3R–Ca^{2+}–calcineurin–NFATc3–Etv2 pathway during early ESC differentiation and mesoderm-derivative selection.

Mesenchymal stem cells (MSCs) have been shown to have promising therapeutic benefits against neurological diseases, with compelling evidence for their neuroprotective effects in glaucoma. However, the underlying molecular mechanisms are not fully understood. Zheng and Zhuo's group studied the role of miRNA-21a-5p (miR-21) and its target, PDCD4, in MSC-mediated neuroprotection using a mouse model of acute glaucoma. They showed that intravitreal injection of MSCs promoted RGC survival in acute glaucoma, with significantly decreased microglial activation, TNF-α, IL-1β, and reactive oxygen species production, and caspase-8 and caspase-3 activation. *In vitro*, MSCs inhibited retinal ganglion cell apoptosis after oxygen-glucose deprivation and reperfusion and microglial activation by LPS stimulation. Therefore, modulation of the miR-21/PDCD4 axis might be a promising new method for clinical treatment of neurological and inflammatory diseases.

Cancer stem cells are believed to be responsible for tumor initiation, invasion, recurrence, and therapy resistance of aggressive brain tumors, such as glioblastoma and anaplastic meningioma. Although cancer stem cells differ from normal stem cells in many aspects, they are primarily controlled by stem cell maintenance factors. Zhou's laboratory reported that in glioma-initiating cells (GICs), paired related homeobox 1 transactivated dopamine D2 receptor and thus activated ERK and AKT to maintain GIC propagation and tumorigenicity. On the contrary, KLF4 was found to suppress proliferation, colonogenicity, and invasion of anaplastic meningioma stem-like cells by Zhang and Gong's group.