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IBT researchers learn about cardiac stem cell regulation

(HOUSTON) — Researchers at the Texas A&M Health Science Center (TAMHSC) Institute of Biosciences and Technology have found fibroblast growth factor (FGF) signaling suppresses cardiac progenitor cell differentiation through regulating autophagy activity.

Autophagy, or “self-eating,” is the way that cells in general internally recycle nutrients for one purpose to another. This is the first evidence autophagy plays a role in heart progenitor differentiation and a possible new venue for regulating stem/progenitor cell differentiation.

The study, led by Fen Wang, Ph.D., professor and associate director of the Center for Cancer and Stem Cell Biology, has been published online and will be in an upcoming issue of *Circulation Research*. The editors of the specialty journal *Autophagy* noted the work and invited the researchers to contribute a summary of their findings in their prestigious section *Autophagy Punctum*, which covers the most significant breakthroughs in the autophagy field.

“One of the major problems facing patients with heart disease is that the adult human heart lacks the ability to regenerate,” said Dr. Wang, who has a group in his laboratory focusing on the signaling pathway that regulates cardiac stem cells. “Stem cell therapies – including using embryonic stem cells (ESCs), induced pluripotent stem cells and cardiac progenitor cells – have potential for repairing damage to the heart.”

Though the FGF signaling axis has been implicated in the development, recruitment and differentiation of heart progenitors, disruption of FGF signaling leads to severe defects in heart development. But how FGF signaling regulates cardiac stem cells to differentiate into functional cardiomyocytes has not been clarified.

In the study, Dr. Wang and his colleagues determined that ablation of the FGF receptor β (FGFR1/2)-FGF receptor substrate 2 (Frs2) signaling axis in mouse heart progenitor cells led to premature differentiation of second heart field cells. By using embryoid bodies (EBs) derived from mouse ESCs and in vitro cultures of embryonic heart explants, they demonstrated FGF signaling promoted ESCs undergoing mesoderm differentiation in early stages but inhibited cardiomyocyte differentiation at late stages.

“To our surprise, inhibition of FGF signaling not only increases myocardial differentiation but also regulates autophagy in *ex vivo* cultured embryos,” said study author Jue Zhang, Ph.D., a former TAMHSC-Institute of Biosciences and Technology graduate student. “We did not suspect that autophagy would regulate cardiac stem cell differentiation and that FGF signaling was doing the regulation.”

Autophagy, controlled self-digestion, acts as a cellular garbage disposal and recycling system for dysfunctional aggregated proteins and worn-out organelles. It serves to break down cellular components into the basic building blocks to rebuild new organelles or recycle them for use in other essential cellular processes, such as cardiac stem cell development.

“It’s possible that cardiac progenitors may use the autophagy system to take the cellular waste and recycle and purify components for the next step in the process,” said study author Junchen Liu, TAMHSC-Institute of Biosciences and Technology graduate student.

Dr. Wang’s study helps understand the underlying mechanism of how cardiac stem cells are regulated to undergo differentiation. It also suggests that regulating FGF signaling and autophagy can be potential venues for improving cardiac stem cell therapy. Cheryl Lyn Walker, Ph.D., director of the TAMHSC-Institute of Biosciences and Technology and an autophagy expert, noted “it could have a major impact on cardiovascular disease.”

“There is urgent need to understand how cardiac stem cells contribute to the fully functional heart, and this finding could help us find new ways to win the battle against heart disease,” Dr. Wang said. “As a major mechanism for recycling nutrients, key cellular building blocks and damaged organelles, autophagy has emerged as a central player in cell biology that now includes stem cells.”

Other *Circulation Research* study contributors include Leyuan Liu, Ph.D., assistant professor in the Center for Cancer and Stem Cell Biology; Wallace McKeehan, Ph.D., J.S. Dunn Foundation Endowed Regents and Distinguished Professor and director of the Center for Cancer and Stem Cell Biology; and other collaborators. Research was supported by the National Cancer Institute and the American Heart Association.

The Texas A&M Health Science Center provides health education, outreach and research through its colleges and campuses in Bryan-College Station, Dallas, Temple,