Dr. Sang Min Project Results

Role of PIKFyve in platelet-mediated inflammation and thrombosis

During the first year of funding, Dr. Min's research focus was on determining how platelets promote inflammation and arterial thrombosis in mice lacking PIKfyve only in their platelets and megakaryocytes. She was able to demonstrate that the release of platelet lysosomes from PIKfyve-null platelets critically contributes to the platelet-mediated inflammatory responses found in PIKfyvefl/fl Pf4- Cre mice. Furthermore, she found that the genetic inhibition of platelet lysosomal secretion in PIKfyvefl/fl Pf4-Cre mice could rescue the prothrombotic phenotype in these mice. These results demonstrate the essential role of PIKfyve in the platelet lysosomal homeostasis. It further demonstrates that an abnormal release of platelet lysosomes could lead to the pathological inflammation and arterial thrombosis in mice. A manuscript describing the findings of this work was published in the September 2014 issue of *Nature Communications*.

During the second year of funding, Dr. Min's research was focused on understanding further the mechanisms by which PIKfyve regulates the lysosomal homeostasis in mammalian cells. To achieve this goal, she generated mice lacking PIKfyve in the myeloid-specific lineage (PIKfyvefl/fl LysM-Cre). PIKfyvefl/fl LysM-Cre mice exhibited hepatosplenomegaly due to tissue infiltration of neutrophils and macrophages. PIKfyve-null macrophages showed increased levels of lysosomal proteins and enlarged lysosomes. Nevertheless, the intralysosomal proteolysis was defective, suggesting that PIKfyve is essential for lysosomal biogenesis and degradative functions in macrophages. Intriguingly, PIKfyve deficiency was associated with active forms of the transcription factor TFEB, suggesting that PIKfyve may also modulate the transcriptional regulation of lysosomal gene expression.

Dr. Min's published work identifies PIKfyve as an essential regulator of platelet lysosome homeostasis, and demonstrates the previously unrecognized pathological contributions of platelet lysosomes to inflammation, arterial thrombosis, and macrophage biology. In addition, her recent study demonstrates that PIKfyve regulates not only the lysosome biogenesis and homeostasis, but also the intralysosomal degradative activity in vivo. Furthermore, the study also suggests that PIKfyve modulates the activation of the master transcription factor for lysosomal gene network. Together, her studies show the novel regulatory role of PIKfyve in lysosome biogenesis and functions in platelets as well as in macrophages.