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Progress Report:

(a) Abstract:

The goal of this proposal is to investigate the roles of heparan sulfate proteoglycans (HSPGs) in regulating stem cell development. HSPGs are macromolecules on the cell surface and within extracellular matrix (ECM). Previous studies showed that HSPGs are involved in various developmental signaling pathways including Wnt, Hedgehog, BMP, Jak/Stat pathways in various developmental contexts. However, the roles of HSPGs in stem cell development are less understood.

During development, stem cells are usually maintained within a specialized microenvironment which termed as niche, for its normal retention, proliferation, and multipotency. Niches could be composed of cells together with their associated extracellular matrix (ECM). Recently with the discovery of more and more niches, functions of diverse types of cells in niches have been intensively studied. The roles of ECM in niche functions and stem cell regulation are poorly understood.

In this grant, we have utilized *Drosophila* adult midgut intestinal stem cell (ISC) as a model system to examine the roles of HSPGs in stem cell development. Using genetic and cell biology approaches, we show that Perlecan, the highly conserved basement membrane-specific heparan sulfate proteoglycan, controls stem cell activities and stem cell-niche attachment in *Drosophila* adult posterior midgut. Perlecan deficient intestinal stem cells (ISCs) detach from underlying ECM, lose their identity, and are no longer able to proliferate. JAK/STAT and EGFR signaling pathways are

two major signaling pathways required for maintaining ISCs proliferation activities. Interestingly, we found that both JAK/STAT and EGFR signaling pathways are not reduced. However, we observed impairment of integrin signaling activity in perlecan deficiency ISCs. Moreover, in perlecan deficiency midgut, activation of integrin signaling ISCs can partially rescue the proliferation deficiency, but is not able to restore the attachment of ISCs to basement membrane.

Together, our results demonstrated the critical roles of perlecan in the stem cell development, and suggest that perlecan may help stem cell to create an “activated ECM” for the maintenance of stem cell identity, activity, and anchorage. These findings may provide insights into basic stem cell researches as well as stem cell based tissue engineering.