Lgr5 Marks Adult Progenitor Cells Contributing to Skeletal Muscle Regeneration and Sarcoma Formation

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Abstract

Regeneration of adult skeletal muscle is driven largely by resident satellite cells, a stem cell population increasingly considered to display a high degree of molecular heterogeneity. In this study, we find that Lgr5, a receptor for Rspo and a potent mediator of Wnt/β-catenin signalling, marks a subset of activated satellite cells which contribute to muscle regeneration. Lgr5 is found to be rapidly upregulated in purified myogenic progenitors following acute cardiotoxin-induced injury. *In vivo* lineage tracing using our *Lgr5-2ACre*^{ERT2}*R26tdTomato*^{LSL} reporter mouse model shows that *Lgr5*$^{+}$ cells can reconstitute damaged muscle fibres following muscle injury, as well as replenish the quiescent satellite cell pool. Moreover, conditional mutation in *Lgr52ACre*^{ERT2}*;Kras*^{G12D}*;Trp53*$^{flox/flox}$ mice drove undifferentiated pleomorphic sarcoma formation in adult mice, thereby substantiating Lgr5^{+} cells as a cell-of-origin of sarcomas. Our findings provide the groundwork for developing Rspo/Wnt signalling-based therapeutics to potentially enhance regenerative outcomes of skeletal muscles in degenerative muscle diseases.

Figure

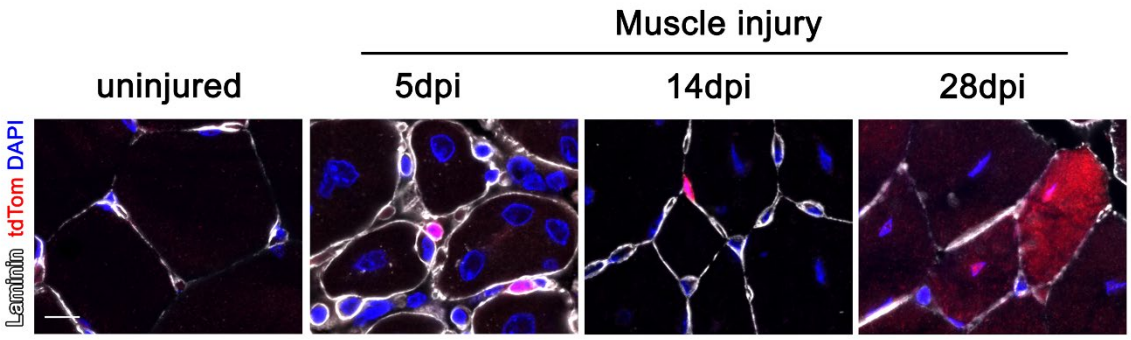

Figure legend: Lineage tracing reveals active contribution of Lgr5+ satellite cells to muscle regeneration in vivo.