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Cell Reports

The adhesion G-protein-coupled receptor *Gpr116* is essential to maintain the skeletal muscle stem cell pool

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In this paper, we focus on understanding the receptors on the exterior of cells that respond to changes in the muscle environment. We use genetic tools in a mouse model of Duchenne muscular dystrophy (DMD) to demonstrate that inactivation of these receptors exacerbates the progression of DMD. Furthermore, we use 'biosensors' to determine how these receptors communicate to the muscle stem cell and modify its behaviour. We expect our characterization of the receptor in MuSCs will provide a framework to manipulate stem cell behaviour in a therapeutic context.

Adult tissues with regenerative capacity harbor adult stem cells that are commonly quiescent but activate the cell cycle and a differentiation program to regenerate tissue after injury. These properties are highlighted by skeletal muscle stem cells (MuSCs), which are required for post-natal growth and regeneration of skeletal muscle.

In this study, we show that the adhesion G-protein-coupled receptor *Gpr116* is essential for long-term maintenance of the MuSC pool. Quiescent MuSCs express high levels of *Gpr116*, which is rapidly downregulated upon MuSC activation. MuSCs deficient for *Gpr116* exhibit progressive depletion over time and are defective in self-renewal. Adhesion G-protein-coupled receptors contain an agonistic peptide sequence, called the "Stachel" sequence, within their long N-terminal ectodomains. Stimulation of MuSCs with the GPR116 Stachel peptide delays MuSC activation and differentiation. Stachel peptide stimulation of GPR116 leads to strong interaction with β-arrestins. Stimulation of GPR116 increases the nuclear localization of β-arrestin1, where it interacts with cAMP response element binding protein to regulate gene expression. Altogether, we propose a model by which GPR116 maintains the MuSC pool via nuclear functions of β-arrestin.

Our study reveals the function of the GPR116 Stachel peptide to maintain MuSC quiescence, but it does not investigate the function of GPR116 adhesive domains. Further investigation will reveal the components of extracellular matrix that bind GPR116 and whether these adhesive interactions modulate GPR116 signaling.

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