Molecular Regulation of Muscle Stem Cell Function

Prof. Michael A Rudnicki

Director, Regenerative Medicine Program and Sprott Centre for Stem Cell Research, Ottawa Hospital Research Institute and University of Ottawa, Canada

Email: mrudnicki@ohri.ca

Satellite cells and their progenitors are thought to be organized hierarchically with functional heterogeneity existing withing different subsets of quiescent cells. How satellite cells balance the generation progenitors while maintaining self-renewal can be posited as either stochastic fate acquisition, or a hierarchical organization of asymmetric divisions with determined cell fates. Previously, we identified a putative stem cell within the satellite cell population using Cre-LoxP lineage tracing. We found committed satellite myogenic cells express high levels of Myf5-Cre (YFP+), whereas 8 % of satellite stem cells have never expressed Myf5-Cre (YFP-). Engraftment experiments established that satellite stem cells (Pax7+/Myf5low) reconstitute the self-renewing satellite cell population following transplantation whereas satellite myogenic cells cannot efficiently reconstitute this population. Satellite stem cells are multipotential and can generate both muscle and brown fat. Thus, this sub-compartment fulfill the defining criteria of adult stem cells in that they exhibit long-term self-renewal and are multipotential. Therefore, we performed single-cell RNA-seq and gene expression analysis on YFP- (Myf5low) populations enriched for the satellite stem cell population and defined a novel cluster. We identified unique cell surface markers that facilitate prospective isolation of a distinct subpopulation of Myf5low cells. Engraftment experiments demonstrate that this subset of MuSCs exhibits superior stem-like characteristics, enhanced self-renewal, and are deeply quiescent. They exhibit low metabolic activity, markedly reduced mitochondrial membrane potential (MMP), and smaller fragmented mitochondria with high levels of pDRP-1. We conclude that Myf5low MuSCs represent a distinct subpopulation of satellite cells with very low metabolic requirements, which represent long term self-renewing muscle stem cells (LT-MuSCs).