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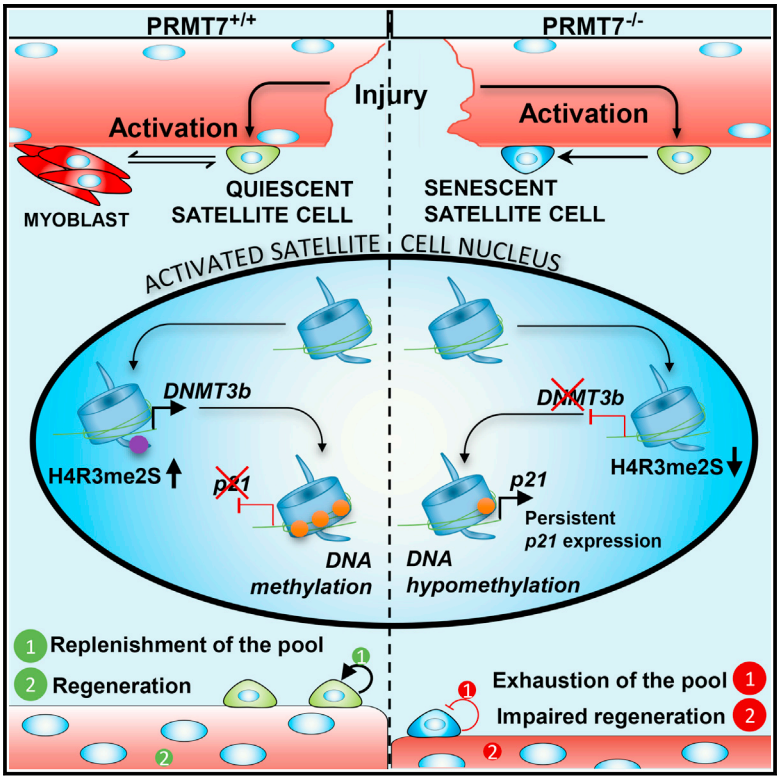
Cell Reports

PRMT7 Preserves Satellite Cell Regenerative Capacity

Graphical Abstract



Highlights

- PRMT7 is required for muscle stem cell self-renewal and regenerative capacity in vivo
- PRMT7 deletion causes senescence of activated muscle stem cells
- This entry into senescence is associated with persistent expression of p21

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In Brief

Decline of muscle stem cell function is associated with both intrinsic and extrinsic factors. Blanc et al. show that the protein arginine methyltransferase PRMT7 regulates the p21/DNMT3b axis in muscle stem cells to preserve their intrinsic capacity to self-renew and to fully regenerate muscles in adult mice.

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PRMT7 Preserves Satellite Cell Regenerative Capacity

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SUMMARY

Regeneration of skeletal muscle requires the continued presence of quiescent muscle stem cells (satellite cells), which become activated in response to injury. Here, we report that whole-body protein arginine methyltransferase PRMT7$^{-/-}$ adult mice and mice conditionally lacking PRMT7 in satellite cells using *Pax7-CreERT2* both display a significant reduction in satellite cell function, leading to defects in regenerative capacity upon muscle injury. We show that PRMT7 is preferentially expressed in activated satellite cells and, interestingly, PRMT7-deficient satellite cells undergo cell-cycle arrest and premature cellular senescence. These defects underlie poor satellite cell stem cell capacity to regenerate muscle and self-renew after injury. PRMT7-deficient satellite cells express elevated levels of the CDK inhibitor p21CIP1 and low levels of its repressor, DNMT3b. Restoration of DNMT3b in PRMT7-deficient cells rescues PRMT7-mediated senescence. Our findings define PRMT7 as a regulator of the DNMT3b/p21 axis required to maintain muscle stem cell regenerative capacity.

INTRODUCTION

Robust tissue regeneration requires the presence of somatic stem cells capable of differentiation and self-renewal, such that they are present throughout the lifetime of the individual. These properties are illustrated by the activity of the quiescent muscle stem cell, named the satellite cell for its normal anatomical position underneath the basal lamina of the myofiber, which is the sole cell responsible for regeneration of muscle (Lepper et al., 2011; Sambasivan et al., 2011). Quiescent satellite cells are marked by transcription factors of the paired homeodomain family *Pax7*, and in a subset of muscles, *Pax3*. Following injury, satellite cells re-enter the cell cycle and activate the myogenic program, marked by the expression of myogenic regulatory factors *Myf5*, *MyoD*, and *Myogenin*, as they differentiate to repair muscle fibers.

A critical role for epigenetic regulation of satellite cell function is emerging as methyltransferase EZH2 and DNMT3b were found to be necessary to repress Pax7 and Notch1 during satellite cell activation and differentiation (Acharyya et al., 2010; Palacios et al., 2010). Maintenance of satellite cell function is directly dependent on histone modifications, including a switch between H3K4 and H3K27 methylation, such that the epigenetic mark H3K27me3 can accumulate and spread with age in quiescent satellite cells (Liu et al., 2013).

Satellite cell aging and the associated functional decline have previously been demonstrated. Satellite cells enter senescence with age driven by the accumulation of DNA damage (Sousa-Victor et al., 2014). The CDK inhibitors p16 and p21CIP1 (p21), critical modulators of senescence, were identified along with p38α to induce a senescent state and a decrease of the self-renewal capacity, respectively, leading ultimately to the incapacity of the satellite cells to repair skeletal muscles (Bernet et al., 2014; Cosgrove et al., 2014). Despite the identification of these well-characterized senescence-related protein markers in geriatric mice, the underlying signaling and epigenetic mechanisms leading to satellite cell aging are still poorly understood. Questions regarding satellite cell function in muscle aging remain, since the inducible depletion of the satellite cell pool does not accelerate sarcopenia but may participate in muscle fibrosis (Fry et al., 2015). Moreover, the molecular mechanisms ensuring the integrity of the satellite cell pool during aging are unknown.

Protein arginine methylation is a common post-translational modification carried out by the nine members of the protein arginine methyltransferase (PRMT) family (Bedford and Richard, 2005). PRMTs have been classified in three types according to their catalytic activities: type I (PRMT1, 2, 3, 4, 6, and 8) and type II enzymes (PRMT5 and 9) carry out the formation of monomethylarginine as an intermediate before the establishment of asymmetric or symmetric arginine methylation, respectively (Yang and Bedford, 2013; Yang et al., 2015); PRMT7 has been shown to be a type III enzyme able to catalyze only the formation of stable monomethylarginines, and thus far, histones are its only known substrates (Feng et al., 2013; Zurita-Lopez et al., 2012).