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Regulation and reversibility of muscle satellite cell function in tissue homeostasis and aging

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SUMMARY

Age-related muscle decline is associated with functional impairment of satellite cells (SC), although conflicting data suggest dysregulation of cell-extrinsic or –intrinsic factors can independently contribute to such impairment. Here, we emphasize the importance of identifying nodes that integrate these factors into feed-forward circuits, which could provide targets for therapeutic intervention.

Satellite cells (SC) are tissue-resident muscle stem cells required for postnatal tissue growth and repair through replacement of compromised myofibers. Recent studies have revealed that progressive impairment of satellite cells (SC) function correlates with the decline of muscle regenerative potential typically observed during mammalian aging. This functional exhaustion of regenerative potential has been proposed to arise from loss of integrity of the regulatory networks that maintain a quiescent pool of reserve SC and that ensure proper transitions between SC quiescence, activation, and progression into committed progenitors. Quiescent SC are poised to rapidly respond to microenvironmental cues, such as those provided by extracellular and cellular components of the SC niche, and SC activation occurs as a tightly regulated event in response to muscle injury. The coordinated temporospatial interplay between SC, differentiated myofibers and interstitial cellular components of the SC niche is therefore essential for maintaining SC number and function throughout life. Progressive dysregulation of this interplay during aging is emerging as a major cause of loss of SC quiescence.

Previous experiments utilizing parabiotic conjoining of mice showed that exposure of aged SC to a youthful environment is sufficient to restore their regenerative potential, indicating a critical role of systemic components in regulating SC function (Brack et al., 2007; Conboy et al., 2005). These experiments revealed a previously unappreciated reversibility of age-associated impairment of SC by restoring the physiological network of extrinsic cues present

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in young organisms. More recently, work has identified aberrant activation of several signaling pathways, such as STAT3, p38, FGF-2 and canonical Wnt signaling, and a reduction of Notch pathway, in aged muscles. Interestingly, all of these changes impacted on the transition of SC to a progenitor stage, leading to impaired control of quiescence and self-renewal (Bernet et al., 2014; Brack et al., 2007; Chakkalakal et al., 2012; Cosgrove et al., 2014; Price et al., 2014; Tierney et al., 2014). Elegant studies from the Brack group provided clear evidence that during aging, increased FGF2 signaling in the aged niche can cause SC to lose quiescence (Chakkalakal et al., 2012). Subsequent studies linked altered FGF2 signaling with constitutive, aberrant activation of the p38 MAPK pathway, leading to impaired self-renewal of aged SC (Bernet et al., 2014; Cosgrove et al., 2014). Intriguingly, the two studies utilized transplantation assays and showed that aged SC phenotype could not be rescued by a young environment – a finding seemingly in conflict with the conclusions from parabiosis experiments (Brack et al., 2007; Conboy et al., 2005). While this discrepancy may be due to the different experimental settings and assays utilized, we argue that transplanted SC might be “primed” by the aged organism of derivation and adopt a constitutive phenotype upon procedures, such as isolation and transplantation, which can artificially activate SC. Thus, the cell-autonomous resistance to youthful cues observed in transplanted aged SC could derive from changes that cannot be erased by the exposure to a recipient environment. Extensive genome modifications upon the exposure to extrinsic signals are typically mediated by epigenetic changes. In this regard, Liu et al. identified transcriptional and epigenetic signatures of SC aging, including loss of bivalency at promoters of developmental genes. Bivalent promoters are simultaneously marked by activatory and repressory marks (H3K4me3 and H3K27me3, respectively). Such promoters are associated with genes poised to be activated during lineage commitment in embryonic stem cells and correlate with stemness in quiescent SC (Liu et al., 2013). As such, it is possible that progressive loss of bivalent domains compromise quiescence in aging SC, but can be restored by the exposure to youthful cues when SC are in their native environment. By contrast, physical procedures, such as isolation and transplantation that notoriously lead to SC activation, might impose a resistance to external cues and render these epigenetic changes irreversible.

While cell non-autonomous changes in the aged SC niche may provide the initial trigger ultimately leading to epigenetic dysregulation and compromised SC function, identification of nodes which integrate these disparate signals to sustain the irreversibility of this process might reveal therapeutic targets for anti-aging interventions. The finding that pharmacological blockade of FGF2, p38 and STAT3 signaling, which are aberrantly activated in aged SC, can reverse SC impairment (Bernet et al., 2014; Brack et al., 2007; Chakkalakal et al., 2012; Cosgrove et al., 2014; Price et al., 2014; Tierney et al., 2014) indicate that these pathways control downstream feed-forward circuits that establish and maintain aging-associated changes in SC. Intriguingly, p38 and STAT3 signaling are essential activators of skeletal myogenesis and promote SC differentiation during regeneration (Palacios et al., 2010; Price et al., 2014; Tierney et al., 2014), thereby raising the question of how activation of these same signaling pathways can impair SC performance in aged muscles. One possibility could relate to the altered cellular distribution of activated pathway components. Presumably, activated signaling components are restricted to the

committed progeny of SC in young muscles, but become uniformly activated in all SC of old mice. Moreover, changes in the epigenetic landscape in aged SC might alter chromatin accessibility to downstream signaling pathway effectors, thereby modulating transcriptional output.

The cellular basis underlying the switch from physiological activation of the p38 and STAT3 pathways in young SC (i.e. by regeneration cues) to age-associated constitutive activation has not yet been conclusively demonstrated. One potential mechanism underlying this switch is the aberrant levels of inflammatory cytokines typically observed in aged organisms. Consistent with extrinsic changes (i.e. the cellular components of the niche, the related secretome and biomechanical cues) activating a feed-forward mechanism that amplifies age-related events in SC, exposure to biomaterials that mimic the biomechanical properties of young muscles can rescue the age-related defects of SC (Cosgrove et al., 2014). A second possibility lies in changes of the heterogeneity of the SC compartment during aging. Consistently, p38 inhibition and biomechanical cues may only target a subset of the aged SC compartment and change the cellular composition of the SC pool, rather than acting to reverse the aged phenotype per se.

As mentioned above, cellular senescence is one process associated with the functional decline of aged tissues. While the precise relationship between cellular senescence and aging has not been determined, increasing evidence suggests that senescence can be a ‘point of no return’ at which aging SC acquire a cell-autonomous phenotype that limits their functional capacity. Of interest, a recent breakthrough from the Munoz-Canoves group has identified a number of senescence-associated features in SC isolated from over two-year old (geriatric) mice. This phenomenon has been termed “geroconversion” and appears to be mediated by de-repression of the cell cycle inhibitor p16 (INK4a) – a typical hallmark of cellular senescence (Sousa-Victor et al., 2014). This evidence suggests that an altered nuclear landscape in SC from aged animals might deregulate gene expression and even bias chromatin accessibility to certain signaling pathways. In this regard, alterations of histone modifications (i.e. the reduction of genes marked by a “bivalent” chromatin) and histone variants detected in aged SC (Liu et al., 2013) might alter the physiological response to environmental signals. Thus, in addition to an elevated concentration of upstream extracellular signals in aged tissues, an increased or altered sensitivity to pro-differentiation cues can further contribute to the age-related functional exhaustion of SC. Interestingly, previous work has shown that p38 signaling can directly control chromatin structure by targeting key components of the chromatin-modifying machinery, including the Polycomb Repressive Complex (PRC2). Disruption of PRC2-mediated gene repression leads to constitutive de-repression of senescence hallmarks, such as p16, and conversion of aged SC into senescent cells in geriatric mice (Sousa-Victor et al., 2014).

It remains unclear how p38 inhibition could reverse the permanent cell cycle arrest associated with cellular senescence (Bernet et al., 2014; Cosgrove et al., 2014), which was previously considered irreversible. A potential explanation arises from the different ages of the mice used in these studies, with p38 inhibition restoring the cell cycle of pre-senescent, but not senescent, SC – an effect that has been widely reported in SC of young mice. The

emerging relationships between chromatin structure, signaling pathways and their potential impact on the irreversible impairment of SC in geriatric mice, deserve future studies.

Although the decline in the regenerative potential of aged SC is well documented, whether this contributes to reduced homeostatic maintenance and progressive reduction in muscle mass in aged individuals – known as sarcopenia – is still a matter of debate. By utilizing an inducible mouse model to selectively ablate Pax7+ SC, the Peterson team has recently shown that aging-associated sarcopenia is not affected by depletion of SC, thereby underscoring the low turnover nature of skeletal muscle and pointing to mature myofibers as the direct cellular targets of this chronic process (Fry et al., 2015). However, an increase in fibrosis in aged muscles was observed in these SC-depleted mice. Thus, while these findings indicate SC are not directly involved in aged-associated sarcopenia, they also reveal once again the contribution of SC to the niche/signaling network that regulates muscle homeostasis. This hypothesis is consistent with a function of SC not only in tissue repair, but also as sources and targets of secreted or cell contact–mediated signals for coordinated spatio-temporal regulation of the regenerative niche. Further elucidation of the reciprocal interactions between SC and the other cell types within the niche will improve our understanding of skeletal muscle homeostasis, and identify novel targets for the pharmacological interventions to counter age-related muscle loss.

Future Perspectives

The interconnected nature of extrinsic and intrinsic changes occurring in SC during aging suggests that they are both integral components of a self-amplifying molecular network triggered by age-associated perturbations in the SC niche. It is likely that this network evolves into a cell-autonomous and irreversible cause of SC impairment. Whether this potential scenario corresponds to “geroconversion” will be an interesting matter for future investigation. Ultimately, the elucidation of the molecular and epigenetic determinants of the interplay between extrinsic and intrinsic changes in SC will reveal the nodal points in this network that can be targeted by interventions aimed at interrupting the vicious cycle underlying SC aging. In this context, a significant challenge is posed by the intrinsic heterogeneity of SC. As we move forward, the development of highly sensitive technologies for single cell analyses will enable to improve our understanding of SC heterogeneity, how it changes with age and what its physiological role is in the maintenance of tissue homeostasis. Intriguingly, SC heterogeneity could not only be an intrinsic property of the SC compartment, but may also arise from microenvironmental cues/gradients to which SC are locally exposed within the tissue. This critical spatial information is lost upon tissue enzymatic digestion and cell isolation, limiting our understanding of SC heterogeneity. The optimization of strategies to perform three-dimensional tissue imaging, would enable to monitor SC in native tissues, investigate the spatial heterogeneity and shed light on the relationship between anatomical proximity to specific cell types and establishment of reciprocal functional interactions. These approaches should be complemented with multicolor Cre reporters for clonal lineage tracing *in vivo*, in order to further clarify SC dynamics in living tissues. Finally, a major challenge we face is understanding the degree to which these animal models of aging and degenerative disease recapitulates human conditions. Translational efforts aimed at integrating basic research with patient-oriented

studies in the clinic could enable addressing these fundamental questions and further the development of treatments for aging-associated defects in muscle function.

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References

Bernet JD, Doles JD, Hall JK, Kelly Tanaka K, Carter TA, Olwin BB. p38 MAPK signaling underlies a cell-autonomous loss of stem cell self-renewal in skeletal muscle of aged mice. Nat Med. 2014; 20:265–271. [PubMed: 24531379]

Brack AS, Conboy MJ, Roy S, Lee M, Kuo CJ, Keller C, Rando TA. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science. 2007; 317:807–810. [PubMed: 17690295]

Chakkalakal JV, Jones KM, Basson MA, Brack AS. The aged niche disrupts muscle stem cell quiescence. Nature. 2012; 490:355–360. [PubMed: 23023126]

Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature. 2005; 433:760–764. [PubMed: 15716955]

Cosgrove BD, Gilbert PM, Porpiglia E, Mourkioti F, Lee SP, Corbel SY, Llewellyn ME, Delp SL, Blau HM. Rejuvenation of the muscle stem cell population restores strength to injured aged muscles. Nat Med. 2014; 20:255–264. [PubMed: 24531378]

Fry CS, Lee JD, Mula J, Kirby TJ, Jackson JR, Liu F, Yang L, Mendias CL, Dupont-Versteegden EE, McCarthy JJ, et al. Inducible depletion of satellite cells in adult, sedentary mice impairs muscle regenerative capacity without affecting sarcopenia. Nat Med. 2015; 21:76–80. [PubMed: 25501907]

Liu L, Cheung TH, Charville GW, Hurgo BM, Leavitt T, Shih J, Brunet A, Rando TA. Chromatin modifications as determinants of muscle stem cell quiescence and chronological aging. Cell reports. 2013; 4:189–204. [PubMed: 23810552]

Price FD, von Maltzahn J, Bentzinger CF, Dumont NA, Yin H, Chang NC, Wilson DH, Frenette J, Rudnicki MA. Inhibition of JAK-STAT signaling stimulates adult satellite cell function. Nat Med. 2014; 20:1174–1181. [PubMed: 25194569]

Sousa-Victor P, Gutarra S, Garcia-Prat L, Rodriguez-Ubreva J, Ortet L, Ruiz-Bonilla V, Jardi M, Ballestar E, Gonzalez S, Serrano AL, et al. Geriatric muscle stem cells switch reversible quiescence into senescence. Nature. 2014; 506:316–321. [PubMed: 24522534]

Tierney MT, Aydogdu T, Sala D, Malecova B, Gatto S, Puri PL, Latella L, Sacco A. STAT3 signaling controls satellite cell expansion and skeletal muscle repair. Nat Med. 2014