Editorial

Stem Cell INVESTIGATION

eIF2α, a potential target for stem cell-based therapies

Ryo Fujita, Yusuke Ono

Department of Stem Cell Biology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
Correspondence to: Yusuke Ono. Department of Stem Cell Biology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan. Email: yusuke-ono@nagasaki-u.ac.jp.

Received: 20 June 2016; Accepted: 05 July 2016; Published: 22 July 2016.
doi: 10.21037/sci.2016.07.01
View this article at: http://dx.doi.org/10.21037/sci.2016.07.01

The vast majority of adult tissue stem cells exist in a "quiescent (sleeping) state" for prolonged periods of time (1). However, the molecular basis underlying how stem cell quiescence is maintained has been largely unexplored. A recent paper by Crist and colleagues has now reported that translation initiation factor eIF2α is a key to control the quiescent state of muscle stem cells (2).

Satellite cells, localized between the sarcolemma of myofibers and the basal lamina, are the residential muscle stem cells responsible for muscle regeneration in the adult. Normally, satellite cells persist in a quiescent state but are activated in response to injury. Following activation, satellite cells proliferate to generate myogenic progenitors that eventually undergo terminal differentiation into myofibers. During myogenic progression, the satellite cell population is maintained by asymmetrical or symmetrical cell-divisions, allowing the generation of daughter cells committed to self-renewal or differentiation. The fine-tuning of these satellite cell fate choices have been recently characterised (3-6). For example, distribution of cell polarity protein complexes asymmetrically activates the MAPK pathway that controls satellite cell fates (3,7-9).

Quiescent satellite cells express Pax7 in adult muscle. The majority of Pax7^{+ve} quiescent satellite cells also express a myogenic determination gene *Myf5*. Interestingly, expression of Myf5 protein is silenced by translational mechanisms that include microRNA silencing and sequestration of Myf5 transcripts in RNA granules (10,11). This unique post-transcriptional control mechanism reinforces the quiescent state of satellite cells by preventing myogenic progression. The RNA granules share feature with stress granules, which generally contain poly(A)+ mRNA, 40S ribosomal subunits, translation initiation factors (eIF4E, eIF4G, eIF4A, eIF4B, eIF3 and eIF2A) and RNA binding proteins for mRNA storage in the cytoplasm (12). Crist *et al.*, previously reported that, in quiescent satellite cells, miR-31 silences the translation of *Myf5* transcripts, and that both RNAs are sequestered in RNA granules (10). Following this work, they have focused on the role of a component of the RNA granule assembly in quiescent satellite cells. In a recent article published in *Cell Stem Cell*, 2016 (2), Crist and colleagues find that translation initiation factor eIF2α is highly phosphorylated by PKR-like endoplasmic reticulum kinase (Perk) in quiescent satellite cells and swiftly dephosphorylated after activation of myogenic program. Using transgenic mouse models, they demonstrated that satellite cells unable to phosphorylate eIF2α break quiescence, enter the cell cycle, and then commit to differentiation. Forcibly activated satellite cells with dephosphorylated eIF2α contributed to new myofiber formation but failed to self-renew, resulting in a reduction of satellite cell pool following muscle injury induced by cardiotoxin injection. Together, the authors concluded that phosphorylation of eIF2α is required for satellite cell quiescence and self-renewal but not muscle differentiation.

Generally, phosphorylation of eIF2α represses global translation. However, phosphorylation of eIF2α paradoxically causes the selective translation of specific transcripts, including those for the unfolded protein response (UPR)-related proteins Atf4, Chop and BiP, which contain upstream open reading frames (uORF) within their 5' untranslated region (UTR). Atf4, Chop and BiP were also highly translated in quiescent, but not activated satellite cells (2). The authors next compared genome-wide gene (13) and protein (14) expression profiles in quiescent satellite cells with transcripts selectively translated when

eIF2α is phosphorylated (15). They identified 35 transcripts including Usp9x and Chd4 that also have 5' UTRs with uORFs and go on to demonstrate that Usp9x transcripts are selectively translated in the quiescent state of satellite cells. In future analysis, it will be intriguing to determine whether eIF2α dependent selectively translated transcripts directly prevent activation of satellite cells.

Finally, the authors tested whether pharmacological manipulation of eIF2α modulates satellite cell quiescence using sal003, a potent inhibitor of the eIF2α phosphatase Gadd34/PP1. Treatment with sal003 resulted in an increase in the levels of phosphorylated eIF2α, preventing satellite cell entry into the myogenic program and promoting satellite cell self-renewal *ex vivo* in culture (2). In general, adult tissue stem cells, including satellite cells, lose their regenerative capacity *ex vivo* after a long period of culture due to their loss of ability to self-renew (16-18). Importantly, satellite cells cultured in the presence of sal003 retain their ability to self-renew and efficiently regenerate muscle after transplantation into the muscle of a mouse model of Duchenne muscular dystrophy (2). These findings clearly suggest that sal003 permits satellite cell *ex vivo* expansion without losing their regenerative capacity, and thus it could be a potential candidate to improve stem cell-based therapies for muscle-wasting diseases.

This study uncovered a novel function of eIF2α that maintains properties of somatic stem cells through the selective translation of transcripts, providing an insight into how stem cell quiescence and self-renewal are maintained. Pharmacological manipulation of eIF2α phosphorylation by sal003 may be a "sleeping pill" applicable to not only muscle stem cells but also other adult stem cells for the development of regenerative medicine.

Acknowledgements

Funding: This work was supported by grants from the Japan Society for the Promotion of Science (16K13046 and 15H05368).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Zismanov V, Chichkov V, Colangelo V, et al. Phosphorylation of eIF2α is a translational control mechanism regulating muscle stem cell quiescence and self-renewal. Cell Stem Cell 2016;18:79-90.

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doi: 10.21037/sci.2016.07.01
Cite this article as: Fujita R, Ono Y. eIF2α, a potential target for stem cell-based therapies. Stem Cell Investig 2016;3:30.

