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Publication Date	2012

COMMENTARY

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Abstract

Ageing is a biological certainty for all living organisms, and is due to the loss of tissue homeostasis and regenerative capacity (except for newts) in which somatic stem cells are thought to play an important role. Many ageing-associated dysfunctions in stem cells have been described, but it remains ambiguous whether these are merely an outcome of ageing or are causal. Parabiotic animal studies suggest there are factors in the systemic environment that can influence the regenerative capacity of tissues. These factors can be altered by ageing, but it is not clear where these age-dependent factors are derived. A recent provocative study on muscle stem cells, in a mouse model of human progeria, proposes a mechanism that might provide answers to these fundamental ageing questions.

The biology of ageing is the result of an inability to maintain tissue homeostasis and to repair damaged or pathological tissues due to injury or disease. The lack of tissue homeostasis and diminished capacity to regenerate with age (except for newts who magnificently defy the latter [1]) have been attributed to reductions in adult stem/progenitor cell numbers and/or inherent defects in stem cells. Whether these traits associated with old stem cells contribute to ageing, or are merely a consequence of the degenerative process, has not been well established. A recent study by Lavasani and colleagues attempts to address this issue, comparing a genetic mouse model of a human progeria called XFE progeroid syndrome and normal aged mice [2]. The progeroid mice lack the DNA repair enzyme excision repair cross-complementation group 1 (ERCC1), and exemplify accelerated ageing with pathological and genome-wide expression changes of

normal aged mice [3]. The ERCC1-deficient mice (*Ercc1*^{-/-}) die prematurely at about 21 days, compared with a normal lifespan of two years.

Lavasani and colleagues focused on the musculoskeletal system, isolating stem/progenitor cells from mouse skeletal muscle, using a method developed by the group [4]. A muscle single-cell suspension is pre-plated on collagen-coated flasks, such that highly differentiated cells adhere and separate from a less adherent cell fraction, which with repeated plating becomes enriched with myogenic stem/progenitor cells. The group has been studying these muscle-derived stem/progenitor cells (MDSPCs) for a decade, and they are one of several heterogeneous populations of adult muscle stem cells described to date, including side-population cells, mesoangioblasts, perivascular cells and satellite cells [5]. MDSPCs, although derived from muscle, are multipotent and have the potential to differentiate into other lineages: osteogenic cells, chondrogenic cells, adipogenic cells, neural cells, endothelial cells and hematopoietic cells [4]. MDSPCs isolated from both *Ercc1*^{-/-} and aged mice were shown to proliferate slowly, and did not differentiate as well, compared with young wild-type MDSPCs. The authors then tested whether young MDSPCs delivered into the intraperitoneal cavity of progeroid mice could extend their lifespan. Surprisingly, *Ercc1*^{-/-} mice with young MDSPCs lived three times longer, until 60 to 70 days.

Lavasani and colleagues' study indicates that MDSPCs from progeroid and aged mice are inherently and similarly defective, but can be partially compensated for by young MDSPCs. To explore the mechanism, the authors tracked the donor cells. *Ercc1*^{-/-} mice were injected with MDSPCs transduced with a β -galactosidase reporter. The donor cells were later detected in various tissues, but surprisingly not in tissues where signs of repair were evident, including skeletal muscle and brain. Given that the tissues which showed signs of regeneration were not subject to MDSPC engraftment, the authors examined whether the benefits of the donor cells were conferred by secreted factors. To this end, they exposed progeroid MDSPCs to conditioned media from young wild-type MDSPCs. Within days of exposure, proliferation

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and muscle differentiation capacity was almost normalised in the *Ercc1*^{-/-} MDSPCs. Closer analysis of the *in vivo* effects of young MDSPCs on the *Ercc1*^{-/-} mice revealed a profound increase in muscle fibre sizes, indicative of the preservation of muscle mass. Furthermore, there appeared to be a striking normalisation of the vasculature in both skeletal muscle and the cerebral cortex as detected by CD31 immunostaining, despite the absence of donor cells in these ameliorated tissues (see Figure 7 and Supplemental Figure S3 in [2]). The authors conclude that MDSPCs defective in proliferation and differentiation contribute to the ageing process, but these can be revived by the delivery of young MDSPCs resulting in an extended lifespan. They propose that the young MDSPCs rejuvenate ageing animals, by stimulating muscle and vascular repair, via secretion of a protein or molecule into the systemic milieu.

There are some limitations to the study that need to be considered. Although the life expectancy of the progeroid mice was extended from 21 to 60 days, this is still far short of a normal 2-year lifespan. Clearly the MDSPCs, although regenerating some muscular and vascular defects, are not able to overcome the multitude of tissue defects in the *Ercc1* null mice [6]. Caution is therefore required in interpreting these findings, until the effects of MDSPCs on normal ageing animals and other models of ageing are examined. Furthermore, the study would be enhanced by examining whether the conditioned media *per se*, delivered into the progeroid mice, could recapitulate the effects of young MDSPCs systemically and/or locally.

Relevant to Lavasani and colleagues' study is previous work showing the importance of the systemic milieu in governing tissue regeneration. This has been powerfully demonstrated using an old classic surgical technique of heterochronic parabiosis, involving the linkage of two animals' circulation, such that an old animal can be exposed to a young animal's circulatory milieu and *vice versa*. Studies using this technique have shown that a young systemic milieu can stimulate the regenerative capacity of neural cells [7] and muscle cells [8] in aged animals, respectively. These types of studies collectively imply that there are soluble factors in the young animals' circulation that can enhance and rescue the defective regenerative potential of aged animals. Lavasani and colleagues' study further suggests that select populations of young somatic stem cells are involved in this process, secreting stimulatory factors targeting the regeneration of specific tissues. A major determinant for successful tissue repair by multipotent stem cells may therefore reside in their paracrine actions rather than in their capacity for multi-lineage differentiation. Paracrine effects have been a highly evident mode of action for other stem cells, including mesenchymal stem cells [9].

A pertinent point from this study is that although ageing MDSPCs have an intrinsic defect of diminished proliferation and differentiation potential, these changes are in fact reversible by placing the aged MDSPCs in the conditioned media from young MDSPCs [2]. Others have suggested that reversible stem cell defects are probably due to epigenetic changes, as opposed to cumulative mutations, which would be irreversible [10]. It will be interesting to examine whether the MDSPC effects are mediated by known or novel secreted factor(s) affecting epigenetic pathways. Trophic factors reported to promote muscle and/or vascular regeneration are obvious candidates to examine in the MDSPCs, including insulin-like growth factor 1 [11], vascular endothelial growth factor [12], and Wnt factors [13]. Proteomic analysis of the MDSPC milieu, to decipher the secretome of young versus aged MDSPCs, will be an interesting challenge in the search for these age-dependent trophic factor(s). The established regulatory importance of the stem cell niche (its microenvironment) [14], however, suggests that there will be a need to profile the secretome *in vivo*, which will probably require the development of new technologies [9]. Gene profile analyses of the MDSPCs for RNA, miRNA and epigenetic alterations using widely available methods may also deliver an insight into the MDSPC mechanism of action.

In conclusion, a population of muscle stem cells are seen to prolong the life of a specific mouse model of premature ageing; whether such effects can be observed in normal ageing mice and other diseases, however, remains to be determined. Furthermore, whether these provocative findings can be translated into the human condition is always the question, and insights are sure to be gained by the recent isolation of human muscle-derived stem cells [15].

Abbreviations

ERCC1, excision repair cross-complementation group 1; MDSPC, muscle-derived stem/progenitor cell; miRNA, microRNA.

Competing interests

The author declares that he has no competing interests.

Acknowledgements

This work was supported by funding from the Health Research Board Ireland (Grant HRA/2009/79).

Published: 28 May 2012

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doi:10.1186/scrt110

Cite this article as: McCullagh KJA: **Can a young muscle's stem cell secretome prolong our lives?** *Stem Cell Research & Therapy* 2012, **3**:19.