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Opinion

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Starvation as an initiator of mesenchymal stem cell/ multipotent stromal cell differentiation

Abstract

The signals that trigger replacement of tissue by resident stem cells are unknown. Inductive factors can induce differentiation *in vitro*, and these no doubt play some role *in vivo*. However, in the presence of injury, the initiating event that precedes definitive differentiation is open to speculation. Here in, we propose that it is the disruption of tissue vitality that is key to this stem cell recruitment. Our foundational model has the disruption of the blood supply leading to mesenchymal stem cell/multipotent stromal cell (MSC) starvation, with glucose being the limiting nutrient. This triggers a stalled autophagy to recommence, allowing for eventual differentiation. Interestingly a prolonged anoxic phase may augment this tissue replacement. This model presents obvious implications for strategies aimed at intrinsic wound repair and therapeutic tissue regeneration.

Keywords: autophagy, hypoxia, glycolysis, starvation, mesenchymal stem cell, multipotent stromal cell

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Abbreviations: DAMP, damage associated molecular pattern molecules; MSC, mesenchymal stem cell/mutlipotent stromal cell; ROS, reactive oxygen species

Introduction

Stem cells are considered key element in tissue replacement and regeneration after wounding, and in the same vein of thought, as cellular therapy for missing tissue and organs. While evidence is strong that endogenous MSCs do contribute to normal repair,[1,2] their therapeutic implementation has been slowed by a number of issues. A key issue is the rapid destruction of the transplanted cells, but even as approaches are being developed to overcome this barrier,[3–8] a fundamental gap lies in the signals that trigger differentiation of such cells. For both endogenous and implanted stem cells, it is expected that the host environment would provide not only the guidance for the phenotypic outcome of cell differentiation but also the signals to differentiate. It is the latter, and the crucial impetus to regeneration that we will address in this opinion piece.

Somatic stem cells are recruited into tissue replacement after tissue loss and/or injury. In this situation, the normal homeostatic supports have been disrupted. The wounded tissue and its surrounding area are now characterized as a hostile microenvironment challenged both by death and inflammation signals in response to damage associated molecular pattern molecules (DAMPs)[9] and lack of nutrient support.[10,11] The MSC must survive the acute challenge of the various death signals, both cytokines and toxic metabolites such as reactive oxygen species (ROS)[12–14] to face an increasingly nutrient depleted environment over the longer term. One obvious protective mechanism would be for the cells to undergo a quiescent dormancy, minimizing metabolic requirement and downregulating intracellular signaling mechanisms. However, this would necessitate a subsequent trigger for differentiation. We propose that it is this hostile environment in itself, particularly the nutrient starvation, that serves to recruit the stem cells toward differentiation and subsequent tissue replacement.

MSC contain numerous autophagosomes[15,16] that are in a state of arrested autophagy.[17] The vesicles contain mitochondria, the only intracellular organelle other than the nucleus that contains the three key building blocks for cell replication - amino acids, lipids and nucleic acids. *Ex vivo* induction of differentiation activates the autophagic cascade leading to clearance of the autophagosomes and the decreasing the number of mitochondria.[17,18] Regulation of this autophagy is complex as acceleration or delay alters the efficiency of differentiation *ex vivo*.[17,19] Thus, the question arises as to the driver of this autophagy.

Autophagy is the most dramatic cell survival mechanism in the face of starvation. The self-catabolism provides nutrients until an external source can be found. The disruption of the vascular supply to wounded tissue establishes such an extreme and multi-day nutrient depletion situation if there is a limiting nutrient. The finding that MSC are glycolytic similar to embryonic stem cells,[20,21] led to the realization that glucose would be rapidly depleted *ex vivo* and likely *in vivo* as well once the blood supply was curtailed. This would trigger the autophagy but in a slightly delayed time scale, consistent with that noted during forced induction.

A second nutrient that would rapidly fall would be oxygen, particularly for allogeneic cell transplants out of culture expansions. As the MSC are overwhelmingly glycolytic, the oxygen consumption of these is minimal until after differentiation shifts them towards oxidative phosphorylation;[20] thus, a drop in oxygen would not be likely to compromise survival. This hypoxia could both promote limit as well as enhance differentiation efficiency. It has been reported that hypoxia increases the survival of stem cells while retaining their 'stemness';[8,22] this would render the MSC less likely to differentiate. On the other hand, MSC accelerate their phenotypic differentiation under hypoxic conditions *ex vivo*[6] as we have reported for osteogenic MSC differentiation.[17] Interestingly, hypoxia does not appear to affect the autophagic activities in these stem cells,[17] suggesting that the limited oxygen would not be a triggering event but merely augment both the initial induction trigger and the phenotypic signals.

That glucose could be the key rate-limiting trigger of recruitment of MSC into the differentiation cascade would have implications for diabetic wound healing. In addition to direct cellular damage done by hyperglycemia, the increased glucose levels also dramatically reduce the number autophagosomes in MSC. We predict that this would limit the ability of the MSC to respond to the starvation trigger, and be reflected in fewer MSC clones as identified after induction, as is commonly noted in specimens from diabetic patients. Additionally, the arteriolosclerosis of long-standing diabetes would subject tissue MSC to a chronic hypoxia further blunting any changes upon wounding. Combined, this would lead to limited regenerative potential, as is the hallmark of wounds in persons with diabetes.

Conclusion

In summary, these considerations ultimately direct us to propose a model in which the initial insult that requires stem cell contribution to replace damage and lost tissue is the also in itself the trigger to direct the stem cells to exit their stem niche and begin the differentiation process. This is elegantly simple in that a secondary signal or event is not necessary. It is fully appreciated that at present there is little experimental data to support or refute such a model; what information exists comes from contrived *in vitro* or *ex vivo* investigations, with all the obvious caveats. The *in vivo* information that leads to this model is extrapolated from observations. For this reason, the model remains at the level of hypothesis.

This model is a useful construct despite its lack of firm supportive data, in that it directs testable challenges. For instance, if a tissue is injured without disruption of the microvasculature, and thus not experience nutrient (glucose) deprivation or hypoxia, we would not expect stem cells to be recruited as replacement tissue (as a note, this is distinct from re-establishing normoxia or hyperoxia after the wound hypoxic challenge). Alternatively, an acute or local hyperglycemia would be expected to lead more towards scarring rather than replacement regeneration. This model being at least partially validated would have implications for the delivery of exogenous MSC for regenerative tissue replacement, in that the cells would need to be introduced within the delivery time of nutrient deprivation for recruitment into the tissue make-up rather than merely as a paracrine factor factory, as is presently the situation. Thus, we propose this model as much to stimulate investigations into a novel concept of cellular starvation triggering stem cell recruitment and initiating the differentiation process.

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Conflict of interest

The author declares no conflict of interest.

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