Are All Adult Stem Cells The Same?

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Abstract

Every adult tissue has its own resident committed progenitor or stem cell. In addition, there exists a class of adult stem cells that are multipotent and/or have injury-specific functions. Mesenchymal stem cells (MSCs) are quite different in comparison with neural stem cells (NSCs) when focusing on the range of different differentiated cell types that can develop from their progeny. These striking differences aside, MSCs, NSCs, and hematopoietic stem cells (HSC) have a very striking number of similarities. They are all dominant cells, multipotent, have a well-defined niche on or in contact with blood vessels, they all actively sense and respond to their local environment, they are all paracrine secretors, they are all immune-modulatory and trophic, and they all have a profound effect on site-specific regeneration following injury. These similarities, especially their unique interactions and association with vasculature, distinguish these adult cells from their embryonic progenitors and by virtue of these similarities define these unique adult stem cells.

Lay Summary

The adult body has many stem cells, at least one for every major tissue. These stem cells provide the basis for the maintenance, repair, and regeneration of these tissues. These stem cells can divide and differentiate into a specialized tissue like muscle or liver. However, stem cells from different tissues have a common core of properties that are similar in function. For example, the hematopoietic stem cell (HSC) produces all the cells in blood. The mesenchymal stem cell (MSC) can

produce fat or bone. The HSC and MSC function at tissue sites of injury to cause the tissue to regenerate. Thus, the HSC and MSC do the same injury function although they are uniquely different. Moreover, each stem cell establishes a unique habitat next to or in contact with blood vessels.

Keywords Neural stem cell (NSC) · Mesenchymal stem cell (MSC) · Hematopoietic stem cell (HSC) · Vasculature · Regeneration

Introduction

There are now a large number of human stem cells that are being studied and reported in both the scientific and lay literature. Clearly, the array of stem cells and their differences seem almost too complicated to grasp which may require simplifying groupings or new logics. This is even more complicated because there are both an array of tissue progenitors at various progressive stages of embryonic development and tissue-specific adult stem cells, which do different things and contribute to the changing biology of the organism in intricately different ways. Below, the focus of this treatise is only on adult human stem cells and their embryonic forefathers are left to others to discuss. The important distinction of this focus is the long and interesting list of cellular features that all adult stem cells have in common, not on the complex spectrum of distinctive phenotypes that the stem cells can become. The unexpected and simplifying conclusion is that all adult stem cells have a similar profound paracrine activity that is essential for the normal turnover and regeneration especially active and discernable at sites of injury [1–6].

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Adult Stem Cells

There are many adult stem cells, perhaps one or more for each tissue of the body. For the sake of brevity, the focus will be on the few that have been extensively studied. This is not to say that the liver stem cell [7, 8], the heart stem cell [9, 10], and the skeletal muscle stem cell [11, 12] which are not described here have not been studied or do not represent important examples to be seriously considered. The provocative use of the word ALL in the title and elsewhere is to suggest that all of these adult stem cells likewise fit in the simplifying, common categories considered herein.

HSCs The longest studied and most clinically relevant adult stem cell is the hematopoietic stem cell (HSC) and, indeed, until the earlier 1990s, it was reported to be the only stem cell that still functioned in the adult [13–15]. The focus of most studies on all stem cells is to trace where they reside and then where and into what they will differentiate. In the case of the HSCs, this not only involves tracing the lineage pathways for the 20–30 unique and individual blood cell types derived from the parental HSC but also the identification of the bioactive factors that control each step of the lineage differentiation process [16, 17]. Indeed, the biotechnology and pharmaceutical companies have used these basic lineage pathways and effector identification information to test and bring to market powerful drugs that can control the HSC differentiation to produce specific blood cells [18]. For example, erythropoietin (EPO) has long been on the market to control and accelerate the formation of red blood cells from HSCs. In this regard, the lay press has recently focused on the illegal use of EPO in competitive cycling and other sport activities emphasizing what the pharmaceutical management of HSCs can produce and their beneficial effects on human performance and physiology [19, 20]. Importantly, if all HSCs are extinguished in the body as can happen with some chemotherapy protocols, new blood cells will not arise to replenish those that naturally expire causing a life-threatening situation. In this case, HSCs must be provided from exogenous sources commonly referred to as bone marrow transplantation. Clearly, the adult HSC is absolutely necessary for life, because its descendants perform a complex array of life sustaining activities and tasks.

In this context, the re-establishment of the adult HSC niche following ablative chemotherapy and bone marrow or hematopoietic progenitor transplant does not simply involve re-engraftment in the repairing marrow. The HSC and early progenitors home to the spleen and liver and set up colonies of multiplying cells. Eventually, there is a migration of some of these cells back to the bone marrow. The sequence and timing

of re-engraftment and the re-establishment of the HSC niche with the identification of the controlling elements are yet to be described [21–26].

NSCs The same very complex set of differentiation and life-giving descendants can be established for almost all of the other adult stem cells. For example, the neuro-stem cells (NSCs) can differentiate into an amazing array of neurons and neural-support cells such as oligodendrocytes and astrocytes [27, 28]. Again, the central theme of such studies is to determine what bioactive factors control each step in the complex, multi-legged differentiation lineage pathways and the gain of function resulting from these differentiated descendants of NSCs when they come on-line in the nervous system. In this case, the intrinsic NSCs are available to replenish neurons which expire or to produce new neurons for gain-of-function situation. In addition, the NSCs give rise to neural-support cells that turnover or to oligodendrocytes that wrap axons with myelin. Importantly, if NSCs could be stimulated to form functional oligodendrocytes for neurons denuded of myelin (as is the case, in MS), function could be restored in the newly myelinated axons [27, 29, 30].

Again, in this case, the NSCs are found in intimate association with blood vessels [31–33]. In addition, there are NSC niches in different sectors of the brain and elsewhere in the nervous system. The prediction that although these wide-spread NSCs will have many features in common, their chemistry and default differentiation pathway could be expected to be different since their niches have different microchemistries.

MSCs The multipotent mesenchymal stem cells (MSCs) have been studied since the 1970s [34], and purified preparations were first commercialized as a reagent for research and development in the 1990s [35]. The proposal was that, like the HSCs found in bone marrow, the MSCs found in marrow could be separately induced into several mesenchymal lineage differentiation pathways to form bone, cartilage, muscle, fat, bone marrow stroma, etc. The marrow MSCs were shown to be capable of such differentiation in vitro into the complete spectrum of mesenchymal phenotypes and in the case of bone, also in vivo studies directly traced the MSCs into cells that fabricate bone [34–38].

That said, in the mid-1990s, it was recognized that marrow MSCs in culture could strongly inhibit the classical mixed lymphocyte reaction (MLR) and, thus, were immune-modulatory. Since these initial findings, MSCs have been shown to secrete bioactive factors that have been shown to affect almost all of immune systems' cells and functions when assayed in the proper context [39, 40]. The original claims were that

allogeneic MSCs were so powerfully regulatory that they could be “universally” (i.e., allogeneically) used without immunosuppression in all cell therapy applications [39–42]. This claim turns out to be mostly correct but for reasons quite different from originally envisioned. In this regard, MSCs are not immune-privileged but are rather immune-evasive [43]; this evasive function can have profound therapeutic implications including tuning down the host’s immune system when used as chaperons for organ transplantation [44] or when supplied to patients with graft-versus-host disease [45].

One other capacity of MSCs that is important to delineate is their trophic capacity. In studies of NSCs [46], Miller and his colleagues used human marrow-derived, MSCs conditioned medium and found that it had a profound effect on the differentiation of NSCs in culture. The MSCs 3-day growth medium was able to affect in vitro NSC differentiation by decreasing the number of glial cells that formed by a factor of 10 and increasing the number of oligodendrocytes that formed by a factor of four [27, 32]. These startling observations lead Miller and colleagues to test human MSCs in the mouse EAE model for MS [47]. A single dose of MSCs in the tail vein halted the destructive immunologic activity and completely cured the mouse of all symptoms of MS. When the central nervous system was studied histologically, it was clear that host-derived oligodendrocytes had formed and were rewrapping the axons previously denuded by the immune system.

In the same time-frame as the studies above, the trophic activities of MSCs [48] were established by a number of independent laboratories. In summary of these studies, MSCs produced molecules that (A) inhibited scar formation, (B) inhibited ischemia-caused apoptosis, (C) stimulated tissue-specific stem cell mitosis, and (D) stimulated rapid revascularization of injury sites [48–50]. These diverse capabilities have been summarily referred to as trophic activities which can be seen in the regenerative repair of injury sites in vivo. All of the adult stem cells [51] exhibit this paracrine trophic capacity in different manners at different sites and to different extents but usually containing these four activities.

Pericytes Last, MSCs have been traced to originate from perivascular mesenchymal cells (pericytes) [52, 53]; these abluminal cells are embedded in the basement membrane of blood vessels. Experimental observations clearly document that both endogenous and exogenously supplied MSCs have the capacities to immune-modulate and protect injury sites from immune-destructive events and to provide a trophic microenvironment for the regeneration (not repair) of the injured tissue. These MSCs go to sites of vascular discontinuity or inflammation which is where released pericytes naturally function [24, 54]. The immune-modulatory and trophic functions are dominant and precede any differentiation of these MSCs. These

observations stimulated the proposal of a new name for medicinal signaling cells (MSC) since none of these paracrine regenerative activities are related to the multipotentiality of the cells (i.e., not true “stem” cells under these conditions) [55].

All Adult Stem Cells

Rather than focus on all of the separate and quite different differentiation lineage pathways of each of the uniquely different adult stem cells, it is quite striking to consider all of the activities that all adult stem cells have in common. For the sake of brevity, I abbreviate human adult stem cells (haSCs):

Mitotic All haSCs are mitotic and, in principle, at least one daughter cell remains as a stem cell [56].

Multipotent All haSCs are multipotent; in cell culture challenges with specific inductive factors, multiple phenotypes can be recognized to form [57–61].

Niche All haSCs are found in highly structured multicellular clusters in contact with blood vessels. This localization at vascular sites is quite striking and emphasizes the inter-dependence of haSCs and vascular components [21–23, 62–65]. The dependence of haSCs on their niches is in counter distinction to embryonic stem cells (ESCs) that are not niche dependent. For all of these haSCs, the niche is in intimate contact or association with vasculature (with endothelial cells) and is a special place where the stem cell can be quiescent but hooked in to the physiology of the tissue and, indeed, the entire organism through the circulating blood stream. Both the cells in the immediate vicinity and the vascular endothelial cells provide the local physiologic response team, the elements that impart a tissue or functional identity to the SC [31–33, 63]. For example, the HSC niche involves a cluster of cells that secrete informational molecules including nestin-positive MSCs/osteoblasts that can be, likewise, activated by injury or inflammation. Thus, the niche for haSCs is a special sanctuary physically and functionally connected to the whole organism. Its unique chemistry can provide the haSCs with “memory” by each location imparting an identity to the haSC. This niche dependence and imprinting is why iPs-MSCs [58, 59] are probably not functionally identical to native haSCs.

Dominant All haSCs are paracrine dominant in their in vivo activities. In clusters of diverse cells in tissues or at sites of injury, their secretory products control or are commanding in the tissue field compared to the other cells [65, 66].

Responsively Sensory All haSCs are exquisitely sensitive to the composite microenvironment in which they engraft or reside. Importantly, in injury microenvironments or implantations, the haSCs first deal with “fixing” the injury BEFORE responding to the differentiation needs of the site or organism [66–69]. This “sensory” activity is responsive to the dynamically changing microenvironment of an injury or regenerative site since an injury site clearly goes through substantial changes from its initiation to the final regenerative resolution. Yet to be determined is the issue of when, where, and how long do these powerful paracrine haSCs need to function at injury or regenerative sites. Indeed, the question can be asked: who makes the therapeutic molecules, the cells of injured tissue or haSCs? I would speculate in this regard that the haSCs help to stimulate and to manage the host tissues’ intrinsic regenerative capabilities and that such localized regeneration must be site and tissue specific (i.e., stimulated by the haSC and controlled by the local components.).

Immuno-Modulatory All haSCs secrete molecules that essentially provide a barrier or curtain to inhibit all of the interrogators of the immune system from entering an injury or developmental tissue field [69, 70]. This is not to say that the haSCs are not eventually rejected [71]. This curtain or modulatory activity is the first line of defense against the establishment of autoimmune conditions. This immune-modulatory capacity is clearly functioning in MSC treatment of graft-versus-host disease [45], organ transplantation [2, 44, 54], and animal models of MS [47] or asthma [54, 55].

Trophic All haSCs secrete bioactive factors that structure both physically and molecularly the injury or developmental (regenerative) field. This activity is not unique to neural element from which the term “trophic” is derived with regard to its biologic meaning (Greek meaning “feeding”). The secreted factors from motor neurons to the muscles they innervation which sustain or maintain the muscle units are referred to as trophic. Rather trophic for haSCs means contributing to a progressive and dynamically changing microenvironment that [48] supports regenerative activities (not the maintenance of the innervated muscle).

Paracrine Secretor All haSCs have a powerful and dynamically sustained secretory capability that accounts from all or most of the prominent activities listed above [54, 55]. This secretory activity precedes any differentiation activity in the sense that the microenvironment must be managed to decrease the immune-intrusion and establish a regenerative *milieu*. Without such site

preparation, the haSCs cannot differentiate should that site require differentiated descendants of the haSCs. The emphasis here is to highlight both the high quantity and spectrum of bioactive agents secreted by these cells especially at sites of injury. These cells in culture, likewise, exhibit high secretory activity [67–72].

Regenerative All haSCs provide regenerative microenvironments and under the appropriate conditions; the end result may be the initiation of their intrinsic differentiation cascade. At sites of injury, the quick-fix is the formation of scar tissue since the regeneration of the tissue is a much slower process requiring anatomic integration of the newly regenerative tissue [73, 74]. This slower dynamic process of tissue regeneration requires that several “quick-fix” modalities be inhibited and the slower formative processes enhanced.

Hard-Wired All haSCs have the immune-modulatory and trophic activities in vivo that survive experimentalists’ attempts to culture expand these cells using complex media that is lab or company specific [72, 75, 76]. Long after the haSCs have lost their capacity to differentiate in vitro, the in vivo regenerative paracrine activities seem to survive these manipulation when the expended cells are implanted or exogenously supplied to injured tissue [77].

Homing All haSCs appear to “home” to sites of tissue injury, damage, or inflammation [24, 78]. The mechanism for this activity has yet to be delineated, but since the initiation of regenerative process involves the disruption of the haSC niche, it may be that such disruption releases or uncovers docking antigens that assist in the localization of the haSCs. The vascular endothelial cells may play a prominent role in attracting these regenerative cells to the injury site [31, 79].

Who Secretes the Therapeutic Factors?

The question needs to be asked: do the endogenous or exogenously supplied haSCs secrete the therapeutic molecules or do the host cells sitting near the haSCs secrete the key therapeutic bioactive molecules. The suggestion could be made that the paracrine activity of haSCs is stimulatory causing the host to secrete therapeutic factors which feedback on these responsive cells to provide host-driven regeneration. This logic further suggests that the haSCs help stimulate the tissue’s natural and intrinsic capacities to regenerate themselves. Taken to an extreme, there are reports that a preparation of bladder extracellular matrix (ECM) can stimulate the reformation of severed fingers [80]. This implies that the bioactive factors

in this ECM preparation cause the host to secrete factors that control the morphology of the composite tissues of the regenerated digits. Certainly, the regeneration of a severed digit cannot occur without the presence of additional control elements. Clearly, the host tissue must have or make these morphogenic bioactive molecules as an intrinsic capability that can be uncovered by the ECM factors. Can an entire arm or leg be regenerated? This is the challenge: to extend the reactions which successfully provided the stimulus for digit regeneration to reform entire appendages. This is both the goal of and dream of regenerative medicine.

Disclaimer Obviously, all haSCs are quite different in their cell-surface molecules, their innate chemistries, their embryonic origins, and functional capacities. Having stated the obvious, this short thesis focuses on some of the (also) very obvious similarities of these essential adult stem cells. The differences between a muscle progenitor cells (satellite cells) from fast and slow muscles [81, 82] are profound, thus, emphasizing that a spectrum of different properties should be expected even for adult muscle stem cells. Yet, these satellite cells have a huge number of responses and functional similarities. One of the most obvious but least emphasized characteristic of adult stem cells is that their niches are all intimately associated with blood vessels. This positioning connects them with the changing physiology of their home tissue and the entire organism. Thus, the response to injury, trauma, or cyclic changes ideally positions the stem cells to respond or remain quiescent. Perhaps, this relationship with the vasculature and the unique properties of the adult stem cell niche is the most important feature common to all adult stem cells.

The similarities, in the broadest sense, have been under-studied. With the availability of Panomics, the challenge will be to focus on BOTH the unique differences between haSCs and the profound similarities (which often are discarded or minimally identified). This treatise is provided as a provocative challenge to the regenerative medicine community to further identify the full spectrum of the complex capacities of haSCs. The research surrounding the medicinal properties of MSCs and their use in over 500 clinical trials (clinicaltrials.gov) with an amazing array of clinical maladies stimulated the logic to look for the common features of all haSCs.

Future Directions

Although implied in several instances above that culture-expanded cells will be used clinically in the future, the tuning of these therapeutic cells to be optimal for both the tissue site

and the genetics of the recipient has yet to be addressed. In this light, the management of the body's own haSC and the intrinsic developmental potential of each organ or tissue is also a formidable therapeutic frontier. Both exogenous and intrinsic haSC management will be required to cure a variety of complex diseases.

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