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Review Article

An Alternative and Cohesive View of Stem Cell Biology: Orderly Chaos

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Abstract

A recent intriguing publication summarizing various aspects of stem cell biology has pointed out many differences and inconsistencies within and between different stem cell systems [1]. We feel, in fact, that most stem cell systems can be viewed as coherent and consistent systems if viewed from a different perspective, that of continuum biologics [2-4]. Current thinking on stem cell systems considers hierarchies and differentiation cascades either uni- or bi-directionally. It was felt that these cells were characterized by the capacity to differentiate into multiple lineages and self-renewal. Based on our developed data on hematopoietic stem cells, we have established that this system is represented by continually dividing stem cells which constantly change phenotype as they transit cell cycle [5]. Thus the cells have a third basic characteristic, the capacity to change lineage potential, cell fate and phenotype reversibly over time that is tied to cell cycle status. This is responsible for the intrinsic heterogeneity seen with these cells. Thus we can add to the three models proposed by Dr. Goodell, et al [1] (hierarchical, consortium and speculative) a fourth model; the continuum model. This model is summarized in Figure 1.

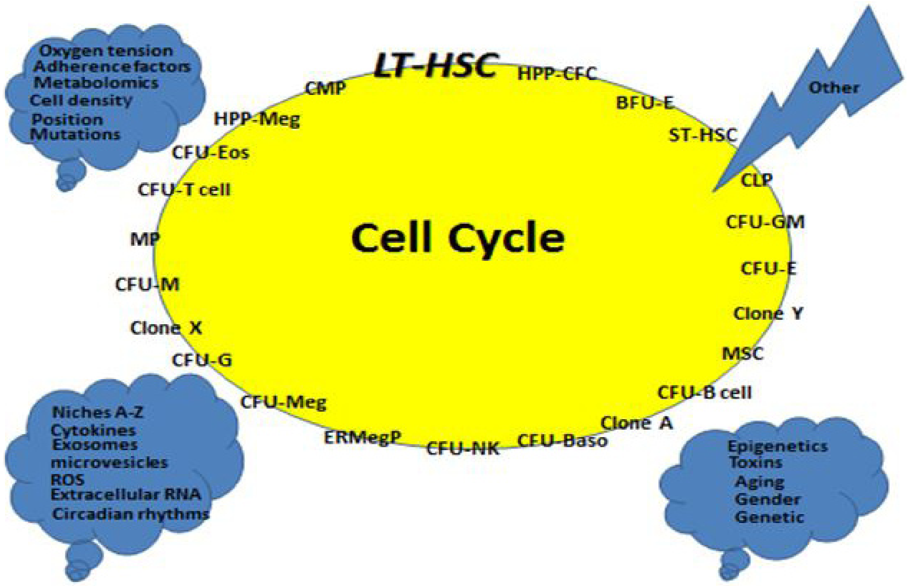


Figure 1: The phenotype of the “stem” cell continually and reversibly changes with passage through cell cycle.

Designations: LT-HSC Long-Term Multilineage Repopulating Hematopoietic Stem Cell; CLP, Common Lymphoid Progenitor; CMP, Common Multipotent Progenitor; LT-HSC, Long-Term Hematopoietic Stem Cell; ST-HSC, Short-Term Hematopoietic Stem Cell; GMP, Granulocyte-Macrophage Progenitor; ERMegP, Megakaryocyte Erythroid Progenitor; MP, Multipotent Progenitor; HPP-CFC, High Proliferative Potential Colony Forming Cell; HPP-meg, HPP-CFC megakaryocyte; CFU-meg, colony-Forming Cell Megakaryocyte; CFU-GM, Colony-Forming Cell Granulocyte-Macrophage; CFU-Eos, Colony-Forming Cell Eosinophil; CFU-baso, Colony-Forming Cell Basophil; CFU-M, Colonu-Forming Cell Macrophage; CFU-G, Colony-Forming Cell Granulocyte; BFU-E Burst-Forming Unit Erythroid, CFU-E, Colony-Forming Unit Erythroid; CFU-T cell, Colony-Forming Unit T Cell; CFU B cell, Colony-Forming Unit B Cell; CFU-NK, Colony-Forming Unit NK Cell, MSC, Mesenchymal Stem Cell; Clones X,Y and A represent possible other potentials. Clouds are influences on the phenotype and cell fate of hematopoietic progenitors and stem cells. ROS= Reactive Oxygen Species

In Dr. Goodell's speculative model [1] there are stem cells which are rare reserve cells that occasionally generate lineage restricted progenitors. The overall system, as described in transposon tagging studies [6], is composed of large numbers of lineage restricted progenitors which are the main sources of day-to-day hematopoiesis. Under stress these progenitors could revert to a primitive multi lineage stem cell phenotype. This is an interesting alternative speculative model. Dr Goodell emphasizes that recent data from studies on blood, skin and intestine indicate the concomitant action of multiple types of stem cells with distinct every day roles. This of course could be correct, it could be a semantic syllogism or it may not be correct. However, investigations in each system are compatible with the stem cell continuum model. It is worth noting that any point on a cell cycle related continuum could be considered a "new stem cell", all-be-it originating from the same originator cell in a reversible fashion. Thus multiple stem cells could fit in the continuum model but with a different cellular basis.

We would like to review the development of the continuum model in hematopoiesis and consider it in light of recent observations relating to the classical hierarchical systems. We will then consider the skin and intestinal stem cell systems and the distinction between transplant and baseline hematopoiesis.

Hematopoiesis

There never was much basis for considering early marrow stem cells as anything but heterogeneous [7,8]. From the initial studies of Colony-forming unit spleen, to our more recent examples, heterogeneity of stem cells has been apparent [9]. Our work has shown that the multi -lineage marrow renewal stem cell, as assayed in lethally irradiated hosts, is cycling [5] and thus always changing its phenotype as to surface epitopes, metabolic characteristics, differentiation and renewal potential, homing, senescence and autophagy potential, size and death potential [10-20]. We have shown that engraftable stem cells are in active cell cycle, the vast majority transiting cycle within 48 hours [5]. This means they cannot be reliably purified by epitope selection. We believe a major limitation in the bulk of stem cell studies over the past 30 years has been the reliance, almost total, on antibody based FACS separations to purify the stem cell before study. Unfortunately, almost all of the true renewal stem cells are discarded with the purification and these are actively cycling, thus the stem cells, such as lineage negative c-kit+Sca-1+CD150+ (21) are not fully representative of the total population of true stem cells.

Back to Heterogeneity

The above picture, of course indicates that these cells would be totally heterogenous on a continuum of change. Dr. Goodell has summarized heterogeneity studies nicely, but most were based on purified stem cells. We showed heterogeneity of highly purified Lineage negative/Rhodamine low/Hoechst low (LRH) stem cells in 1997 [20] and subsequently a number of publications have confirmed such heterogeneity. Perhaps most telling was work on LRH stem cells synchronized as to cell cycle and clonally grown in culture [9]. We demonstrated virtually total heterogeneity as to colony size, shape and differentiated cell content. However, the key issue is not that of heterogeneity, but the actual origin of the different stem cell types. We have previously shown that as stem cells transit cycle the following characteristics are altered mostly in a reversible fashion: engraftment, homing to marrow, differentiation, surface epitope expression, general gene expression, susceptibility to exosome modulation and capacity to modulate lung cells [10-20]. The wide variety of cytokine and niche modulators which have been described are best considered as differentially acting on stem cells as they continually change with cycle transit. In a similar vein, the gradual and continuous alteration of cell phenotype and surface molecules probably underlies the wide variety of stem cell descriptions. The lineage negative c-kit+ Sca-1-+CD150+ murine stem cell has now been divided into stem cells with differing expression of CD150 [22]. Put this on a continuum and it makes sense. Niches have received a great deal of attention recently and these have mostly been defined using purified stem cells. We would suggest that both the nesting stem cells and the nurturing niche are probably continually changing explaining the wide variety of niche cells which have been described. These include osteoblasts [23], endothelial cells [24,25], Schwann cells [26], adventitial reticular cells [27] and megakaryocytes [28].

Skin Epithelial Stem Cells

The skin is another system which has been extensively studied as to stem cell phenotype and heterogeneity. A number of studies have indicated that a variety of stem cells can repopulate; these can have different phenotypes and locate in different areas, the basal layer, the intermolecular epidermis, the infundibulum, the junction zone, the isthmus and the Bulge [1]. The complexity is startling, but could simply be explained by a general population of cycling stem cells influenced by different microenvironments. There is interesting data that many of these stem cell classes show marked proliferation in vitro but not in vivo. However the in vivo studies were carried out measuring label retaining cells and assuming that label retention meant that the cell was not dividing [29-32]. While admittedly controversial, the immortal strand concept fits with this data [33-35]. In the immortal strand theory, which is backed up with significant data, the stem cell in a population does not randomly segregate its DNA but rather retains the original parental strands. If this is correct then these cells could be rapidly proliferating but retain the BrdU label. The wide variety of cell markers and locations for skin stem cells could indicate a larger number of separate stem cells but could also be consistent with a proliferating stem cell population on a continuum. The numerous cell types described as possible stem cell niches including dermal papilla, adiposities, nerves and arrestor pill muscle could also be on a continuum interacting with a changing population of stem cells [36-40].

Intestinal Stem Cells

Intestinal stem cells are the other stem cell population which has been extensively studied. They are confined to the crypts of Lieberkuhn. They function to replace the intestinal lining every 3-5 days. Proliferating progenitor cells are fed by proliferating intestinal stem cells located near the base of the crypts. So this from the start is a proliferating stem/progenitor cell system which then differentiates into enterocytes, goblet cells, and entero endocrine cells in the villus. A population of quiescent intestinal stem cells also known as +4 cells are felt to reside just above the zone that contains the crypt base stem cells and the Paneth stem cells [40-43]. Again different cell classes have a variety of cell surface markers and putative niche cells, but once again one can envision a system of stem cells modulating on a continuum and expressing a wide variety of phenotype based on their position in cell cycle and micro environmental cues.

Stem Cell Systems

The above suggests that the default position of stem cells, marrow, skin or intestine, is proliferation which, in turn would indicate a continuously changing population of cells and would explain the apparent large number of phenotypes and markers.

We propose a general model of stem cell biology based on these three classic systems. The stem cells continually change as they transit cell cycle and interact with micro environmental niches which are also modulating. This determines the phenotype of the stem cell as to surface markers, differentiation, homing, metabolic status, apoptosis, senescence and regulatory pathways.

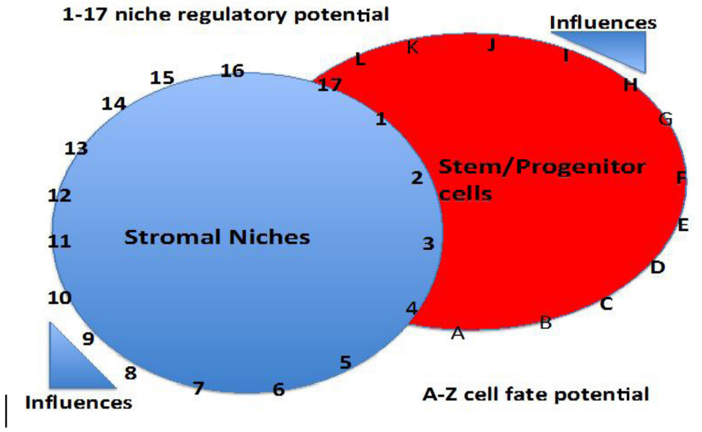


Figure 2: General Stem Cell Model.

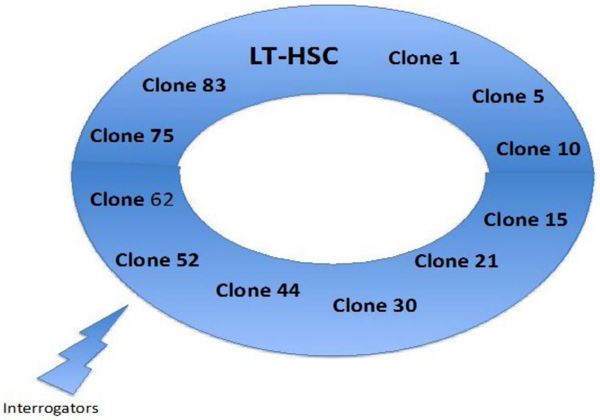
This demonstrates the continuously changing potential of both stem/progenitor cells and niche /stoma elements. In the case of stem/progenitor cells this is tied to cell cycle transit, while in the case of niches the relationship to cell cycle status is unclear. Influences are myriad as described in the text.

Environmental Influence is another important variable. This relates to known impact of the hematopoietic system of external cytokines, extracellular vesicles, hormones, metabolic influences, circadian variables, mutational frequencies and other myriad influences.

Transplantation Hematopoietic Stem Cell Regulation And Baseline Hematopoietic Stem Cell Regulation

Recent studies utilizing an elegant bar-coding approach to identify individual hematopoietic clones indicate that baseline hematopoiesis may be quite different from transplant hematopoiesis. Sun and colleagues [6] employing clonal marking by transposon tagging have presented data indicating that steady state hematopoiesis is maintained by successive recruitment of thousands of clones. This is as opposed to hematopoiesis occurring in the transplant setting which is the basis for much of our insights into hematopoiesis. These data indicate that rather than classically defined hematopoietic stem cells, a larger number of short-lived progenitors are responsible for baseline hematopoiesis (Figure 3). This is consistent with the "myelocyte sink theory" put forth by Patt and colleagues decades ago [44], and with the continuum model of hematopoiesis outlined above. Here the repopulating HSC is simply one cell phenotype on a cell cycle related continuum of change. The myriad of progenitor clones fits with the bar-coding data.

Thus we propose that, in general, stem cell systems represent proliferating systems in which the potential of the stem /progenitors cells is constantly changing with cycle transit. The changes may be miniscule at very short intervals of time, but represent significant shifts on eventual cell fate at longer time intervals. This would fit with the bar-coding experiments. It would provide a very elegant flexible system attuned to a multitude of adjustments which would be necessary with stresses upon the hematopoietic system such as inflammation, infection, trauma, hemorrhage, anemia, toxins, circadian influences, aging and a variety of disease states.



References

1. Goodell MA, Nguyen H, Shroyer N (2015) Somatic stem cell heterogeneity: diversity in the blood, skin and intestinal stem cell compartments. Nature Reviews Molecular Cell Biology 16: 299-309.
2. Quesenberry PJ, Colvin GA, Lambert JF, Frimberger AE, Dooner MS, et al. (2002) mingTrans Am Clin Climatol Assoc 113: 182-206.
3. Colvin GA, Lambert JF, Abedi M, Dooner MS, Demers D, et al. (2004) Differentiation hotspots: the deterioration of hierarchy and stochasm. Blood Cells Mol Dis 32: 34-41.
4. Quesenberry PJ, Goldberg L, Aliotta J, Dooner M (2004) Marrow Hematopoietic Stem Cells Revisited: They Exist in a Continuum and are Not Defined by Standard Purification Approaches; Then There are the Microvesicles. Front Oncol 4: 56.
5. Goldberg LR, Dooner MS, Johnson KW, Papa EF, Pereira MG, et al. (2014) The murine long-term multilineage renewal marrow stem cell is a cycling cell. Leukemia 28: 813-822.
6. Sun J, Ramos A, Chapman B, Johnnidia JB, Le L, et al. (2014) Clonal dynamics of native haematopoiesis. Nature 514: 322-327.
7. Till JE, McCulloch EA (1961) A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res 14: 213-222.
8. Till JE, McCulloch EA, Siminovitch L (1964) A stochastic model of stem cell proliferation, based on the growth of spleen colony-forming cells. Proc Natl Acad Sci 51: 29-36.
9. Colvin GA, Berz D, Liu L, Dooner MS, Dooner G, et al. (2010) Heterogeneity of non-cycling and cycling synchronized murine hematopoietic stem/progenitor cells.J Cell Physiol 222: 57-65.
10. Habibian HK, Peters SO, Hsieh CC, Wuu J, Vergilis K, et al. (1998) The fluctuating phenotype of the lymph hematopoietic stem cell with cell cycle transit. J Exp Med 188: 393-810.
11. Peters SO, Habibian HK, Vergilis K, Quesenberry PJ (1999) Effects of cytokines on stem cell engraftment depends on time of evaluation post-marrow-infusion. Int J Hematol 70: 112-118
12. Colvin GA, Lambert JF, Moore BE, Carlson JE, Dooner MS, et al. (2004) Intrinsic hematopoietic stem cell/progenitor plasticity: inversions. J Cell Physiol 199: 20-31.
13. Cerny J, Dooner M, McAuliffe C, Habibian H, Stencil K, et al. (2002) Homing of purified murine lymphohematopoietic stem cells: a cytokine-induced defect. J Hematother Stem Cell Res 11: 913-922.
14. Dooner MS, Aliotta JM, Pimentel J, Dooner GJ, Abedi M, et al. (2008) Conversion potential of marrow cells into lung cells fluctuates with cytokine-induced cell cycle. Stem Cells Dev 17: 207-210
15. Becker PS, Nilsson SK, Li Z, Berrios VM, Dooner MS, et al. (1999) Adhesion receptor expression by hematopoietic cell lines and murine progenitors: modulation by cytokines and cell cycle status. Exp Hematol 27: 533-541.
16. Berrios VM, Dooner GJ, Nowakowski G, Frimberger A, Valinski H, et al. (2001) The molecular basis for the cytokine-induced defect in homing and engraftment of hematopoietic stem cells. Exp Hematol 29: 1326-1335.
17. Dooner GJ, Colvin GA, Dooner MS, Johnson KW, Quesenberry PJ (2008) Gene expression fluctuations in murine hematopoietic stem cells with cell cycle progression. J Cell Physiol 214: 786-799.
18. Reddy GP, McAuliffe CI, Pang L, Quesenberry PJ, Bertoncello I (2002) Cytokine receptor repertoire and cytokine responsiveness of Ho(dull)/Rh(dull) stem cells with differing potentials for G1/S phase progression. Exp Hematol 30: 792-800.
19. Quesenberry PJ, Dooner GJ, Tatto MD, Colvin GA, Johnson K, et al. (2010) Expression of cell cycle-related genes with cytokine-induced cell cycle progression of primitive hematopoietic stem cells. Stem Cells Dev 19: 453-460.
20. Nilsson SK, Dooner MS, Tiarks CY, Weier HU, Quesenberry PJ (1997) Potential and distribution of transplanted hematopoietic stem cells in a nonablated mouse model. Blood 89: 4013-4020.
21. Kiel MJ, Yilmaz OH, Iwashita T, Yilmaz OH, Terhorst C, et al. (2005) SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. Cell 121: 1109-1121.
22. Chen J,Ellison FM,Keyvanfar K, Omokaro SO, Desierto MJ, et al. (2008) Young NS Enrichment of hematopoietic stem cells with Slam and LSK markers for the detection of hematopoietic stem cell function in normal andTrp53 null mice. Exp Hematol 36: 1236-1243.
23. Zhang J, Niu C, Ye L, Huang H, He X, Tong WG, et al. (2003) Identification of the haematopoietic stem cell niche and control of the niche size. Nature 425: 836-841.
24. Ding L, Saunders TL, Enikolopov G, Morrison SJ (2012) Endothelial and perivascular cells maintain haematopoietic stem cells.Nature.

25;481(7382):457-62.

25. Kunisaki Y, Bruns I, Scheiermann C, Ahmed J, Pinho S, et al. (2013) Arteriolar niches maintain haematopoietic stem cell quiescence.Nature 502: 637-643.
26. Yamazaki S, Ema H, Karlsson G, Yamaguchi T, Miyoshi H, Shioda S, et al. (2011) Nakauchi H. Nonmyelinating Schwann cells maintain hematopoietic stem cell hibernation in the bone marrow niche. Cell 147: 1146-1158.
27. Quesenberry P, Song Z, Alberico T, Gualtieri R, Stewart M, et al. (1985) Bone marrow adherent cell hemopoietic growth factor production. Prog Clin Biol Res 184: 247-256.
28. Bruns I, Lucas D, Pinho S, Ahmed J, Lambert MP, et al. (2014) Megakaryocytes regulate hematopoietic stem cell quiescence through CXCL4 secretion. Nat Med 20: 1315-1320.
29. Morris RJ, Potten CS. (1994) Slowly cycling (label retaining) epidermal cells behave like clonogenic stem cells in vitro. Cell Prolif 27: 279-289.
30. Cotsarelis G, Sun TT, Lavker RM (1990) Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell 61: 1329-1337.
31. Taylor G, Lehrer MS, Jensen PJ, Sun TT, Lavker RM. (2000) Involvement of follicular stem cells in forming not only the follicle but also the epidermis. Cell 102: 451-461.
32. Tumbar T, Guasch G, Greco V, Blanpain C, Lowry WE, et al. (2004) Defining the epithelial stem cell niche in skin. Science 303: 359-363.
33. T Wakeman JA, Hmadcha A, Soria B, McFarlane RJ (2012) The immortal strand hypothesis: still non-randomly segregating opinions. Biomol Concepts 3: 203-211.
34. Cairns J (2006) Cancer and the immortal strand hypothesis. Genetics 174: 1069-1072.
35. Conboy MJ, Karasov AO, Rando TA (2007) High incidence of non-random template strand segregation and asymmetric fate determination in dividing stem cells and their progeny. PLoS Biol 5: e102.
36. Rompolas P, Deschene ER, Zito G, Gonzalez DG, Saotome I, et al. (2012) Live imaging of stem cell and progeny behaviour in physiological hair-follicle regeneration. Nature 487: 496-499.
37. Brownell I, Guevara E, Bai CB, Loomis CA, Joyner AL (2011) Nerve-derived sonic hedgehog defines a niche for hair follicle stem cells capable of becoming epidermal stem cells. Cell Stem Cell 8: 552-565.
38. Liao XH, Nguyen H (2014) Epidermal expression of Lgr6 is dependent on nerve endings and Schwann cells. Exp Dermatol 23: 195-198.
39. Fujiwara H, Ferreira M, Donati G, Marciano DK, Linton JM, et al. (2011) The basement membrane of hair follicle stem cells is a muscle cell niche. Cell 144: 577-589.
40. Mezoff E, Shroyer N (2014) in Pediatric Grastrointestinal and liver diseases. 5th edn eds Hyams, J.s. and Wylie, R. 324-336.
41. Potten CS Hume WJ, Reid P, Cairns J (1978) The segregation of DNA in epithelial stem cells. Cell 15: 899-906.
42. Potten CS, Owen G, Booth D (2002) Intestinal stem cells protect their genome by selective segregation of template DNA strands. J Cell Sci 115: 2381-2388.
43. Gracz AD, Magness ST (2014) Defining hierarchies of stemness in the intestine; evidence from biomarkers and regulatory pathways. Am J Physiol Gastrointest. Liver Physiol 307: G260-G273.
44. Patt HM (1966) Rates of Blood Formation and of Blood-Cell Depletion and Recovery after Irradiation. Effects of Ionizing Radiations on Tissue 45: 14-24.