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Perspective: Stem cells react! Cell lineages as complex adaptive systems

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It may be argued that adult stem cell processes or, more precisely, the cell lineages that arise from them, represent complex reactive or adaptive systems. Approaching hematopoietic and other stem cell lineages from this perspective has direct bearing on current debates regarding the plasticity of these lineage systems as well as on interpretation and modeling of clinical data regarding many diseases.

From three feet eight inches high (I was 6 years old), the line of ants stretching from food source to anthill just outside our back door looked like a thin, straight line. Kneeling down, the seemingly purposeful energy of hundreds of ants became apparent. Though I was delighted, my mother was not. When the occasional divergent ants at the margins of the line sometimes found their meandering way into her kitchen, we wound up in conflict: "Don't kill it!" I pleaded. By and large she let me rescue the hapless outlier, to return it to the outdoors. However, needless to say, she eventually trumped me by calling the exterminator.

Ants are perhaps the best known example of a *complex adaptive* or *reactive system* [1,2], but these self-organizing systems can be seen everywhere: in stock market bulls and bears, embryologic development, growth of cities, the rise and extinction of species, diversity of immune system responses, perhaps even consciousness arising from neuronal networks. What all these systems have in common is *emergent* self-organization arising on the macro scale from micro-scale interactions of the individuals that constitute the system. During discussions with Jane Prophet, a new media artist at the University of Westminster's Centre for Arts Research, Technology and Education, whose work sometimes focuses on modeling of biological systems, we became aware that adult stem cell processes—or, more precisely, the cell lineages that arise from them—can also be thought of as complex reactive systems. It also became apparent that approaching hematopoietic and other stem cell lineages from this perspective has direct bearing on current debates regarding the plasticity of these lineage systems [3] as well as on interpretation and modeling of clinical data regarding many diseases. This brief essay will discuss: the defining features of complex systems; the utility of mathematical modeling of cell lineages, some clinical implications of complexity in cell dynamics, and the implications for current controversies regarding "robustness" of stem cell plasticity events.

By way of introduction to these concepts, studies of complex adaptive systems reveal a variety of common defining traits, some of which, as summarized in *Emergence* by Steven Johnson [2], are:

- More is different. A few ants will not a colony make; a village is not a city. It is when the number of ants or people achieves a certain size that the simple rules of interaction give rise to self-organization.
- Ignorance is useful. Or: simple rules of *local* interaction between component individuals and their environments give rise to the adaptive stability of complex systems. The individuals are largely "unaware" of the larger organization or needs of the system. The complexity is thus at the macro level, not at the micro level.
- Randomness is encouraged, but not overly so. Self-organization fails to emerge in completely determined systems (planets in motion, billiard balls) and completely random ones (molecules in a gas). It is only with a distinct but low-level randomness, so called *quenched disorder*, that local interactions give rise to complexity (Fig. 1). Think of those random divergent ants that aren't following the line.
- Pay attention to your neighbors. Interactions between individuals and between individuals and their environments form homeostatic, negative feedback loops. These lead to adaptation and response, fueling complexity. Again: noninteractive billiard balls do not form communities; people—shopping, gossiping, watching, etc.—do.

Comparing stem cell lineage systems to ants is not simply argument by analogy. Cell lineages demonstrate many of

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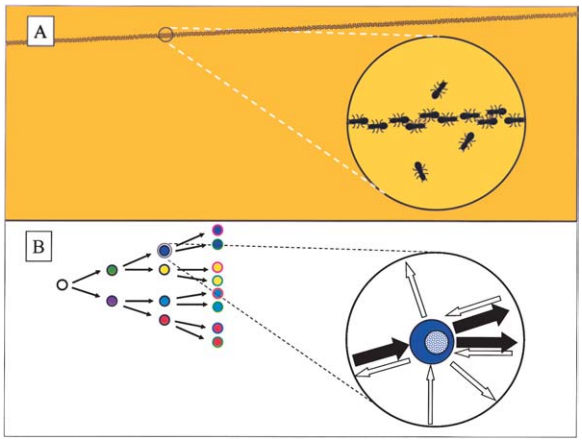

Figure 1. Quenched disorder in complex systems. **(A)** From a distance, the line of ants from anthill to food source has the appearance of a completely ordered, straight line. Closer view reveals that there is a small but relatively stable proportion of ants moving randomly in comparison to the rest of the line. This so-called "quenched disorder" is a necessary feature of the ant colony as a complex adaptive system. **(B)** Similar to observations of ant colonies, techniques that assess large-scale ordering of cell populations to determine physiologic cell lineages primarily reveal only dominant pathways. If investigators detect low-level variations, they often dismiss them as "contaminants" or "aberrations." However, more detailed investigations now show that alternate differentiative pathways are both reproducible and irreducible, possibly representing the "quenched disorder" of a complex adaptive system.

the above defining traits. Stem cells and their progeny are "ignorant" of the whole. They do not monitor the entire organism, but respond to locally detected cytokines, chemokines, adhesion factors, and other signaling molecules, from other cells and from matrix in the immediate microenvironment. In such manner, stem cells and their progeny (i.e., all of the cells in the body) respond to their neighbors and their environments through elaborate—though still finite—feedback loops.

It is not difficult to see the adaptive nature of stem cells and their progeny and the emergent organization that arises from them. Their mechanisms of action create the system by which the body maintains itself from day to day, despite minor and major injuries, from within and without. If these systems were not homeostatically adaptive, we wouldn't live past the earliest stages of embryonic development. The question isn't why they fail us in response to old age or overwhelming injury, but rather how is it that they work so well to keep us moving for so long.

Another characteristic of complex adaptive systems is that computer modeling of the simple, local interactions can duplicate many, if not all, of the emergent aspects of the actual systems. For example, computer modeling of the simple feedback loops of the ants' search for food leads to the virtual emergence of the same food line seen in nature. Moreover, the parallel processing represented by the thousands of moving virtual ants and their virtual pheromone trails solves other problems, from the classic Traveling Salesman Problem [4] to maintenance of circuit lines of our increasingly complex phone networks.

Likewise, mathematical modeling of stem cell lineage systems can be instructive [5,6]. For example, Markus Loeffler and Ingo Roeder (University of Leipzig) model hematopoietic stem cells on the basis of limited parameters—variable affinity for a growth environment within the marrow (the "stem cell niche") and cycling status of the cell (assumed to be G_0 if in the niche) [7]. With inclusion of a stochastic ability of cells to escape and re-enter the niche and to shuttle between high and low niche affinities (so-called "within-tissue plasticity"), this model produces clonal fluctuation patterns that are a precise match for those seen experimentally in culture, in animal models, and even in human leukemias. The larger patterns of organization emerge from these few rules governing variations in niche affinity and coordinated changes in cell cycle.

Another interesting feature of complex adaptive systems is that they often have multiple ground states or points of equilibrium. Transitions between these states, triggered sometimes by relatively small events, may also lead to small or large instabilities, even to system collapse, e.g., mass extinctions of species, collapse of stock markets, demise of cultures and civilizations. Paradoxically, these "mass extinctions" arise emergently from the very same lower-level interactions that result in self-organization and the system's relatively long-term, adaptive stability. Could failure of stem cell systems sometimes not merely be due to the size of the insult, but rather to a similar "mass extinction" event? Aplastic anemia, for example, a complete failure of the hematopoiesis system, may not have a specific precipitating event. Likewise, acute hepatitis A: usually benign and self-limited, but a very few infected people suffer massive hepatic necrosis leading to death or transplant. The unpredictability of these events may relate to our limited understanding of pathogenesis, but it might be inherent in the system, a necessary tradeoff for the long-term stability of our bodies. Mathematical modeling of these systems and careful statistical analysis of clinical events may shed a new and very different light on these dire occurrences.

Conceptualizing cell lineages as complex adaptive systems bears on some of the current debates regarding adult stem cell research. There is, of course, the long-standing debate as to whether stem cell lineages are determined or stochastic systems [8]. The modeling of Loeffler and colleagues is successful by inclusion of stochastic elements. Indeed, if one takes into account the increasing literature on reversibility of gene restriction, stochasticity of lineage fate decisions becomes nearly unavoidable in conceptualizing issues of cell plasticity [9–11]. Moreover, accumulating data from clinical studies [9], single cell culture, and gene expression experiments [12,13] reveals greater variability of gene expression pathways than would be expected from completely determined systems. Detailed discussion of these

findings is beyond the scope of this brief review, but the evidence builds in favor of the stochastic element. If we conceive of cell lineages as complex and adaptive, then stochasticity is implicit because fluctuations are necessary for self-organizing systems to explore new states.

Another current controversy concerning adult stem cell lineages is that many of the data indicate low levels of engraftment from bone marrow into other organ systems, often less than five percent, sometimes less than one percent, in the absence of overt, severe injury [14,15]. Critics suggest that, even if bone marrow plasticity can be demonstrated, such low levels of engraftment from the blood are physiologically trivial, insufficiently "robust" to be of relevance to tissue maintenance [16]. But consideration of these alternate lineage phenomena as parts of a complex adaptive system reveals that the converse, in fact, is likely to be true.

The documented low level of apparently random fluctuation, this quenched disorder, is what allows the system to be adaptive. It is the small percentage of divergent ants that guarantees rapid formation of new paths to food in case the current line is interrupted or the food source runs out. (My mother was right: the divergent ants in her kitchen were just the beginning!) It may be argued, therefore, that not only are these low-level engraftment fluctuations not trivial, but they are in fact vital. Literally so. Without them, robust responses to injury might prove inefficient or even impossible. It is precisely this intermediate level of stochastic variation, somewhere between determined rigidity and literal chaos, that makes cell lineage systems—and our bodies—complex, adaptive, and alive.

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References

1. Lewin R. Complexity: Life at the Edge of Chaos. 2nd ed. Chicago IL: University of Chicago Press; 2002.
2. Johnson S. Emergence. New York NY: Scribner; 2001.
3. Theise ND, Wilmut I. Cell plasticity: Flexible arrangement. Nature. 2003;425:21.
4. Dorigo M, Gambardella LM. Ant colonies for the travelling salesman problem. Biosystems. 1997;43(2):73–81.
5. Viswanathan S, Zandstra PW. Toward predictive models of stem cell fate. Cytotech Rev. (in press).
6. Loeffler M, Roeder I. Tissue stem cells: definition, plasticity, heterogeneity, self-organization and models—a conceptual approach. Cells Tissues Organs. 2002;171:8–26.
7. Roeder I, Loeffler M. A novel dynamic model of hematopoietic stem cell organization based on the concept of within-tissue plasticity. Exp Hematol. 2002;30:853–861.
8. Ogawa M. Stochastic model revisited. Int J Hematol. 1999;69:2–5.
9. Theise ND, Krause DS. Toward a new paradigm of cell plasticity. Leukemia. 2002;16:542–548.
10. Theise ND. New principles of cell plasticity. C R Biol. 2003;325: 1039–1043.
11. Thornley I, Sutherland R, Wynn R, et al. Early hematopoietic reconstitution after clinical stem cell transplantation: evidence for stochastic stem cell behavior and limited acceleration in telomere loss. Blood. 2002;99:2387–2396.
12. Brady G, Billia F, Knox J, et al. Analysis of gene expression in a complex differentiation hierarchy by global amplification of cDNA from single cells. Curr Biol. 1995;5:909–922.
13. Madras N, Gibbs AL, Zhou Y, Zandstra PW, Aubin JE. Modeling stem cell development by retrospective analysis of gene expression profiles in single progenitor-derived colonies. Stem Cells. 2002;20:230–240.
14. Krause DS, Theise ND, Collector MI, et al. Multi-organ, multi-lineage engraftment by single bone marrow–derived stem cells. Cell. 2001; 105:369–377.
15. Wagers AJ, Sherwood RI, Christensen JL, Weissman IL. Little evidence for developmental plasticity of adult hematopoietic stem cells. Science. 2003;297:2256–2259.
16. Weissman IL, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and transdifferentiations. Annu Rev Cell Dev Biol. 2001;17:387–403.