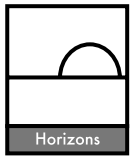


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# The evolutionary ecology of stem cells and their niches – the time is now

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Stem cells have the ability to both self-renew and to differentiate. Such cells are found as transient populations during development and growth of an organism and as stable populations in adult tissues. The niche of the stem cell is the local microenvironment that supports the maintenance, renewal, and differentiation of stem cells. Given our past experience intervening in biological systems, there is pressing necessity for the development of evolutionary theory associated with stem cells.

During the second set of clinical trials of penicillin in 1942, Howard Florey and his team administered the drug to 15 patients who were considered to be terminally ill with bacterial infections. Fourteen of those patients survived; the one who did not died because the microbe (*Streptococcus viridans*) causing bacterial endocarditis was thought to have become resistant to penicillin during the course of treatment (Florey and Florey 1943). From in vitro studies, Florey's team were aware that a range of microbes could be resistant to penicillin (Abraham et al. 1941). Alexander Fleming, the discoverer of penicillin, also knew from the use of other drugs how adaptable bacteria were and warned about the development of resistance during his Nobel Lecture in 1945 (Brown 2005, p. 223). To be sure, curing 14 of 15 previous hopeless cases is a great medical achievement. However, as evolutionary ecologists, our responsibility is to think about both short term and long term consequences of our interventions in natural systems.

Neither Fleming nor Florey had an evolutionary biologist in their group, but we can imagine that had there been one, the 15th case in which resistance developed would have been of considerable interest. At that time, the observation of Theodosius Dobzhansky that "nothing in biology makes sense except in the light of evolution" was 30 years in the future. But had an evolutionary biologist been there, the history of the last 60 years of development of resistance to antibiotics, herbicides and insecticides might have been very different (Bud 2007).

The current enthusiasm for regenerative medicine and associated interest in stem cells – both adult and embryonic – is based on the assumption that we can remove stem cells from their natural habitat, propagate them in culture, transplant them into a foreign environment and assume that the transplanted cells will do as we wish or that we can manipulate them in vivo with desired results (Fuchs et al. 2004). However, there may be enormous differences between what stem cells do in their original niche and what they can do when put into culture or when transplanted to a new location (Anderson 2001). Raff (2003, p. 16) noted that "perhaps the greatest challenge in stem cell biology is to uncover the ... mechanisms that determine whether a daughter of a stem cell division self-renews or commits to a particular pathway of differentiation. Cracking this problem for the adult mammalian stem cells of interest will be a crucial step for both developmental biology and cell therapy". In their classic study of the hematopoietic stem cell system, Till et al. (1964) observed great variability in the probability of renewal by a stem cell and that stem cells show remarkable quiescence relative to other cells of the body. For example stem cells of small rodents are estimated to replicate about once per four weeks, of cats about once per ten weeks, and in higher primates the frequency of stem cell division may be only once per 50 weeks (Lanza et al. 2006, p. 63).

In general, current thinking about stem cells (e.g. Lanza et al. 2006) is dominated by typological approaches (sensu Mayr 1982), although there are

examples of population thinking (for example, Watt and Hogan 2000). It is through population-level thinking about stem cells that evolutionary ecologists can make important, timely, and essential contributions.

Signals and feedback controls (both negative and positive) affect the pattern of behavior of the stem cells in their niche. Although there are a number of such cell behaviors that need to be accounted for in a full evolutionary theory, most simply stem cells: 1) maintain quiescence; 2) divide symmetrically - doubling and producing two stem cells; 3) divide asymmetrically - doubling and producing one stem cell and one cell that will be a progenitor of fully differentiated cell; or 4) undergo apoptosis (to maintain an error-free genome - Cairns 1975, Potten et al. 2002) or migrate out of the niche (Booth and Potten 2000). The progenitors of option 3) are often referred to as transit amplifying cells; they are the ones that generally multiply at a high rate and transform into the cells that are fully differentiated and that serve the various functions of the organism. We may thus envision characterizing the population dynamics of stem cells, transit amplifying cells, and fully differentiated cells through mechanisms of positive and negative feedback control and asking a variety of questions concerning their evolutionary ecology.

Till et al. (1964) also showed that the number of stem cells in clones of identical genetic origin was highly overdispersed. In a theoretical study originally motivated by this work, Vogel et al. (1969) confirmed that stem cells distributions are overdispersed and that clones differ in their probability risk of extinction. This suggests that the rate that determines the probability of a stem cell renewing itself has a compound distribution, in the same way that a Poisson process with a gamma density on the rate parameter of the Poisson leads to a negative binomial distribution (Mangel 2006). In addition to characterizing the distribution on the parameter of renewal, we must ask how natural selection has acted on the probability of renewal to generate such great variation. Adaptive dynamics (Metz et al. 1992, Diekmann 1997, Vincent and Brown 2005) and evolutionary invasion analyses (Pielou 1977, Mangel et al. 2007) are analytical deterministic tools for understanding the replacement and evolutionary dynamics that have shaped stem cell biology. Stochastic approaches such as state variable life history theory, implemented through dynamic programming (Mangel and Ludwig 1992, Houston and McNamara 1999, Clark and Mangel 2000), provide a natural means for predicting the decisions of a stem cell conditioned on its own resource state and the behavior of the other stem cells in its niche.

The number of stem cells in a tissue varies (Lanza et al. 2006, p. 20) from about 30% (tongue and epidermis) through 0.5% (bone marrow) to less than 0.1% (testis). A theory of the evolutionary ecology of stem cells will seek to understand the origins of these values in terms of the costs and benefits and associated fitness consequences.

We should also develop predictive models for the consequences of potential regenerative therapy. For example, we may ask what will happen when a stem cell with different life history properties is transplanted into a niche with a certain set of signaling properties and feedback controls – which set of stem, amplifying transit and differentiated cells will emerge as a result of the transplantation? Similarly, how will the hematopoietic system respond to challenges of different sorts – ranging from wounds that cause bleeding through attacks by pathogens. An evolutionary ecology of stem cells will complement the detailed ongoing molecular work by providing broad and deep qualitative understanding of the dynamics of these systems.

With the exception of stem cells associated with the germ line, stem cells may be seen as having unselfish genes, since their role is to support the success of the organism. It is thus an important question to sort out a meaningful definition of fitness for stem cells. In some cases, it may be more obvious than others. For example, one of the differentiated products of the stem cells of the hematopoietic system is erythrocytes and the connection between the level of red blood cells and fitness (at least at short-term level) is pretty obvious. In other cases, the connection is deeply hidden and we will have to work very hard to discover it.

In the 21st century, the great problems of biology are ones that cross different levels of biological organization. Stem cell therapy (Neff et al. 2006) offers the prospect of regenerative medicine and stem cells are a crucial feature of strategies for engineering negligible senescence (de Grey 2003). To embark on such endeavors without simultaneously investigating how natural selection has shaped stem cell behavior is a very risky trip (Woese 2004).

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