CELL AND BODY: INDIVIDUALS IN STEM CELL BIOLOGY

Stem cells are much-discussed, yet poorly understood, both in popular culture and in biomedical research. This paper deals with stem cells as objects of biomedical research. Our incomplete understanding of these entities is glaringly obvious, as hoped-for stem cell-based therapies are not yet available. Most philosophical accounts of this situation approach it from a perspective of economics, policy, or research ethics (e.g., Robert et al 2006, Monroe 2008). These accounts locate stem cell research in a broader socio-political framework and highlight the diversity of values at work in biomedicine. This paper takes a different approach, focusing on conceptual and methodological challenges to studying stem cells experimentally. Successful stem cell therapies hinge on answers to three questions:

What are stem cells?
How are stem cells recognized?
What is required for stem cell function?

These are the central questions of stem cell biology today. Philosophers of science can help answer them, not by imposing extraneous concepts and standards on biomedical research, but by helping to explicate researchers' own concepts and standards. This paper examines the three questions above as concerns about individuation for a distinctive technical object: the stem cell.

This paper is in three parts. The first examines the question: what individuals are picked out by the stem cell concept? Stem cells are defined as cells with capacities for both self-renewal and differentiation (Melton and Cowan 2009). This functional definition problematizes the obvious answer, that stem cells are a kind of cell. Self-renewal is production of more cells like the parent, while differentiation is production of more from less specialized cells. Both are reproductive processes, defined in terms of comparison across cell generations.[1] Similarity and specialization are determined relative to a set of traits of interest. So the stem cell concept is relational and relative. Stem cells are defined by position in a reproductive hierarchy; the unique 'stem' of a cell lineage. Therefore, the individuals picked out by the stem cell concept are not single cells, but cell lineages. Depending on which cell traits are of interest, different lineages may be distinguished. This accounts for the diversity of stem cells in biomedical practice.

The second part of the paper examines how stem cells are individuated in experiments. Methods for identifying and characterizing stem cells share a basic pattern: remove cells from an organismal source, place them in a new context and measure traits, then move a subset to another context and measure stem cell capacities. Organismal sources differ in species, developmental stage, and site of extraction. Cells from a given source differ in their physical, molecular and morphological traits. Differentiation potential and self-renewal are measured indirectly, and correlated with measured cell traits. So the results of a stem cell experiment can be represented as a mapping between values of three sets of variables: traits of an organismal source, extracted cells, and differentiated cells to which the former give rise under controlled conditions. The diverse kinds of stem cell distinguished in practice differ with respect to one or more of these variables.

Stem cell experiments face a distinctive evidential challenge, because stem cell capacities are realized only in a stem cell's descendants. Measurements of self-renewal and differentiation potential are therefore necessarily indirect and retrospective. So a single cell cannot be

[1] Cells reproduce by binary division; a parent divides to produce two offspring cells.

experimentally shown to be capable of *both* self-renewal and differentiation. To establish its differentiation potential, a candidate stem cell must be placed in an environment conducive to differentiation, and its progeny observed. To establish its self-renewal capacity a cell must be maintained in an environment that is *not* conducive to differentiation, and its progeny observed. Stem cells can therefore be identified by experiment only at the population level. Given pure populations of identical stem cells, experiments can reveal self-renewal and differentiation potential. But the assumption of pure, homogeneous populations is at best provisional, and often empirically false. Stem cells are identified only relative to an experimental method (consisting of a specific organismal source, a set of traits measured, and manipulations of cells' environments) and a hypothesis of cell population homogeneity.

In light of these experimental limitations, researchers have become increasingly skeptical about the very existence of stem cells, proposing instead a state of stemness (e.g., Zipori 2004, Lander 2010). Stemness is defined as a state that cells may enter or leave, characterized by wide differentiation potential. The third part of my paper examines the "state or entity?" debate in terms of requirements for individuality. I show that the debate hinges on relation of molecular to cellular traits. 'Stemness' accounts aim to predict and explain cellular developmental pathways in terms of complex, dynamic arrangements of molecules (reference removed for blind review). That is, they aim to identify molecular criteria for individuating stem and other cell types, conceived as states with characteristic degrees of stability. However, diversity and context-dependence of molecular mechanisms in cell development undercuts this reductionist account of cell identity. The key to individuating stem cells, I argue, is not to replace the stem cell concept with a reductive simplification, but to make central their metaphysically transformative aspect. Stem cell biology is concerned with developmental processes linking cell and organism. Every organism begins as a single cell. In multicellular organisms, the originating cell gives rise to an organism composed of many cells. This 'interlevel' transformation is the core phenomenon stem cell researchers seek to understand. The stem cell concept picks out relations of single cells, cell lineages, and whole organisms. Stem cell experiments also highlight the interplay of developing entity and context: cell and niche, organism and environment. Stem cells can be conceived as drastically simplified organisms that represent less experimentally-tractable biological entities at early stages of development; 'non-classical' model organisms. But they function only in environments that are or represent organismal bodies. The engineered environments of stem cell experiments are model organisms, in another sense than pluripotent stem cell lines. The interplay of developing entity and context, cell and niche, is at the core of stem cell biology.

<u>Works Cited</u>

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