On the Origin of the Term "Stem Cell"

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Stem cells have fascinated both biologists and clinicians for over a century. Here, we discuss the origin of the term "stem cell," which can be traced back to the late 19th century. The term stem cell originated in the context of two major embryological questions of that time: the continuity of the germ-plasm and the origin of the hematopoietic system. Theodor Boveri and Valentin Häcker used the term stem cell to describe cells committed to give rise to the germline. In parallel, Artur Pappenheim, Alexander Maximow, Ernst Neumann, and others used it to describe a proposed progenitor of the blood system. The original meanings of the term stem cell, rather than being historical relics, continue to capture important aspects of the biology of stem cells as we see them today.

Introduction

Stem cells are defined as having the capacity to both self-renew and give rise to differentiated cells (Morrison et al., 1997; Till and McCulloch, 1980; Weissman, 2000). Stem cells provide an opportunity to investigate the mechanisms that regulate embryonic development, cellular differentiation, and organ maintenance. Given their proliferation and differentiation capacities, stem cells have great potential for the development of novel cell-based therapies (Daley et al., 2003; Keller, 2005). In addition, recent studies suggest that dysregulation of stem cell properties may be the cause of certain types of cancer (Dalerba et al., 2007; Reya et al., 2001). Due to these widespread basic and clinical implications, it is of interest to put modern stem cell research into historical context. In this article, we briefly describe some of the earliest uses of the term stem cell and discuss the parallels that can be drawn between those early studies and current stem cell research.

"Stammzelle" and Germline Development

The term stem cell appears in the scientific literature as early as 1868 in the works of the eminent German biologist Ernst Haeckel (Haeckel, 1868). Haeckel, a major supporter of Darwin's theory of evolution, drew a number of phylogenetic trees to represent the evolution of organisms by descent from common ancestors and called these trees "Stammbäume" (German for family trees or "stem trees"). In this context, Haeckel used the term "Stammzelle" (German for stem cell) to describe the ancestor unicellular organism from which he presumed all multicellular organisms evolved (Haeckel, 1868, 1874). In the revised 3rd edition of his book *Anthropogenie* (Haeckel, 1877), Haeckel made one of his characteristic leaps from evolution (phylogeny) to embryology (ontogeny) and proposed that the fertilized egg also be called stem cell. That is, Haeckel used the term stem cell in two senses: as the unicellular ancestor of all multicellular organisms and as the fertilized egg that gives rise to all cells of the organism.

Uses of the term stem cell referring to a distinct cell in the embryo capable of giving rise to more specialized cells can be found later in that century. A central debate in embryology of the late 19th century revolved around August Weismann's theory of the continuity of the germ-plasm (Weismann, 1885). Weismann proposed that the germ-plasm, which was transmitted from one generation to the next, was segregated early during embryonic development to specialized cells (the germ cells) that would be distinct from the rest of the body (the somatic cells). Inspired by Weismann's theory, Theodor Boveri and Valentin Häcker set out to identify the earliest germ cells in animal embryos, which would presumably carry the germ-plasm. Boveri traced the cell lineages of the nematode *Ascaris* and depicted them as tree diagrams that he also called Stammbäume (Boveri, 1892a, 1892b). The *Ascaris* embryo displays a very unusual pattern of fragmentation and loss of chromatin in the earliest mitoses of cells destined to give rise to somatic cells. Only in the cell lineage that will give rise to germ cells is the full complement of chromatin initially present in the fertilized egg maintained (Boveri, 1887, 1892a, 1892b). Boveri concluded that these early germline cells maintained the full complement of chromatin so as to transmit the intact genetic material to the next generation, in support of Weissman's theory. In 1892, Boveri explicitly took Haeckel's definition of stem cell as the fertilized egg one step further: Boveri proposed that cells along the germline lineage between the fertilized egg and committed germ cells be called stem cells (Boveri, 1892b). Also in 1892, in a study of development of the crustacean *Cyclops*, Häcker identified a large cell that became internalized upon gastrulation (Figure 1A) (Häcker, 1892). He observed that this cell, which he also called stem cell, underwent asymmetric cell division and that one of the daughter cells of the stem cell gave rise to the mesoderm, whereas the

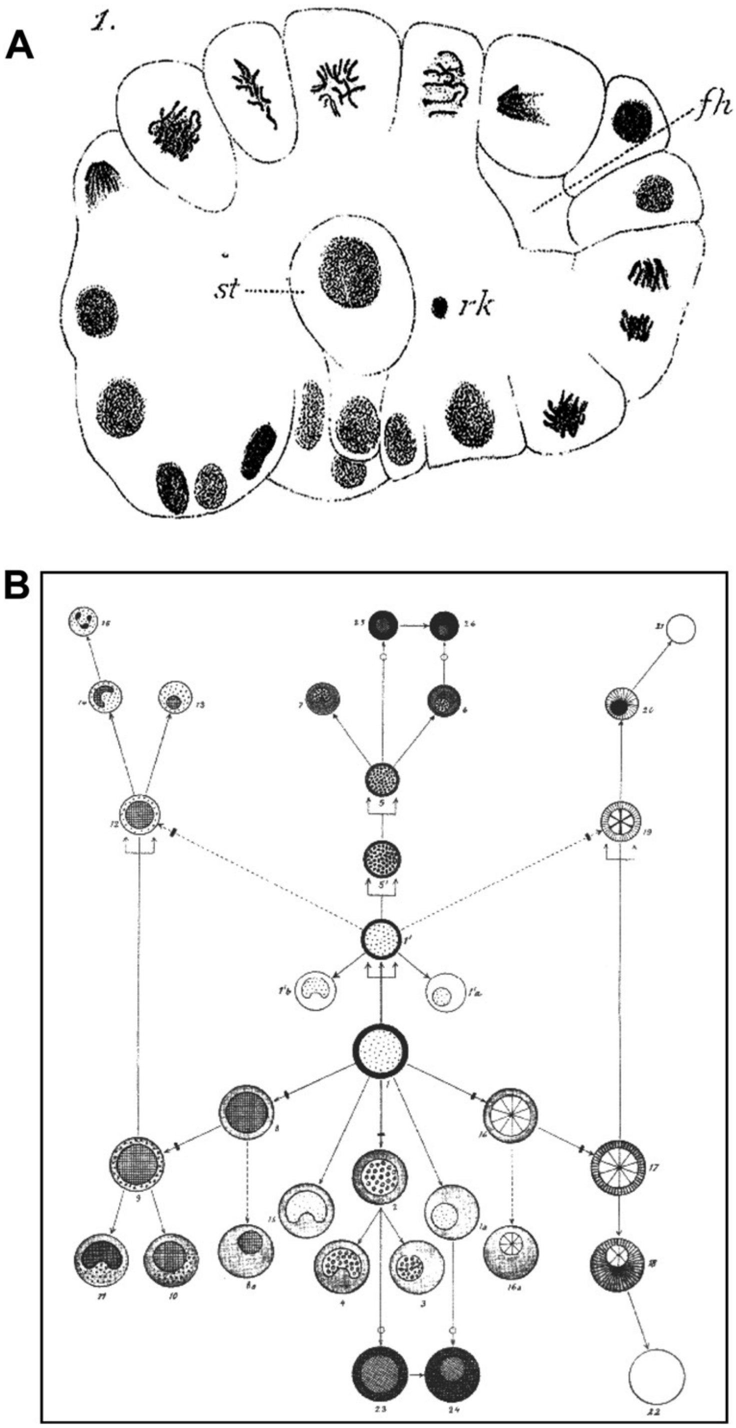

Figure 1. Early Uses of the Term "Stem Cell"
(A) Valentin Häcker's 1892 diagram of the stem cell in the *Cyclops* embryo. According to Häcker, the stem cell (st) has just migrated to the inside of the embryo and is about to undergo asymmetric cell division. One daughter cell will give rise to the germline; the other will give rise to mesodermal tissue.
(B) Artur Pappenheim's view of hematopoiesis from 1905. The cell in the center is the hypothesized common progenitor of the entire blood system. Pappenheim called this cell, among other terms, the stem cell.

other gave rise to the germ cells. In that same article, Häcker describes stem cells as cells that later in development produce oocytes in the gonad (Häcker, 1892). Thus, in these early studies, the term stem cell referred to what we today call the germline lineage, primordial germ cells, and germline stem cells.

Four years later, Edmund B. Wilson popularized the term stem cell in the English language by reviewing Häcker's and Boveri's work in his book *The Cell in Development and Inheritance* (Wilson, 1896). Wilson's book was inspirational to a generation of turn-of-the-century embryologists and geneticists, particularly in the United States. Given the wide readership and influence of Wilson's book, he is generally credited as having coined the term stem cell (Maienschein, 2003; Shostak, 2006). However, Wilson used the term stem cell in the same sense as in the earlier studies of Boveri and Häcker, that is, it referred to the unspecialized mother cell of the germline. Interestingly, although Weismann's theory was the great stimulus for these studies, current knowledge indicates that most organisms, including mammals, do not segregate the germline at the earliest cleavage stages (Extavour and Akam, 2003) and may therefore have other mechanisms of protecting the integrity of the genetic material in their germline.

Stammzelle and Hematopoiesis

Around the same time, research on the development and regeneration of the hematopoietic system raised the question of whether a common precursor of the various cell types of the blood existed. Paul Ehrlich's staining techniques (Ehrlich, 1879) had enabled the identification of different white blood cell lineages, splitting investigators of hematopoiesis into two camps. Dualists did not believe in the existence of a stem cell common to all hematopoietic lineages. Their understanding was that myeloid and lymphoid cells derived from committed precursor cells residing in distinct hematopoietic tissues, the bone marrow, and lymphatic glands/spleen, respectively. By contrast, according to the unitarian model of hematopoiesis, a cell existed that represented the common origin of erythrocytes, granulocytes, and lymphocytes. Thus, unitarians were naturally poised to introduce a term that captured the developmental potential of such a cell. Various terms were used to describe the common precursor of the hematopoietic system. Although it was suggested in 1868 that most of hematopoiesis occurred in the bone marrow (Neumann, 1868), the lymphatic system had historically been the first tissue believed to harbor hematopoietic activity (Müller, 1844). Because lymphocytes differed from erythrocytes and granulocytes in size, color, or granularity and resembled immature cells with progenitor activity, the cells proposed as common precursors were variously described as polyvalent large lymphocytes (Pappenheim, 1908b), true large lymphocytes (Maximow, 1908), nongranular undifferentiated lymphocytes (Dantschakoff, 1908), or lymphoidocytes (Pappenheim, 1908a). Other terms used included primary wandering cells (Saxer, 1896), hemato- or hemogones (Mollier, 1909; Pappenheim, 1907), hemoblasts (Pappenheim and Ferrata, 1910), and hemocytoblasts (Zoja, 1910). Artur Pappenheim, in particular, exhibited great creativity in designating the cell positioned at the center of his evolving genealogy of hematopoiesis (Figure 1B). Alexander Maximow (Maximow, 1908), Wera Dantschakoff (Dantschakoff, 1908), Ernst Neumann (Neumann, 1912), and others began to use the term stem cell to refer to the common precursor of the blood system after the turn of the century. Indeed, Maximow is often credited (Fliedner, 1998; Lichtman and Williams, 2006) with coining the term in 1909 (Maximow, 1909). However, the term stem cell can be found in earlier publications of the hematopoietic field. As early as 1896, Pappenheim used stem cell to describe a precursor cell capable of giving rise to both red and white blood cells (Pappenheim, 1896). Due to limitations of the experimental methods available at the time, the debate about the existence of a common hematopoietic stem cell continued for several decades until definitive evidence was provided by the work of James Till, Ernest McCulloch, and others in the 1960s (Becker et al., 1963; Till and McCulloch, 1961; Till et al., 1964).

The Meristem

One would be tempted to assume that the term stem cell has some relation to the term "meristem," because meristems are the stem cell compartments of plants. The term meristem was first used by the Swiss botanist Karl Nägeli in 1858 to refer to the areas of continuing cell division in a plant (Nägeli, 1858). Nägeli derived the term meristem from the Greek "meristos" (divided/divisible) and the suffix "-em" (as in "phloem" or "xylem"). Hence, the terms stem cell and meristem, despite being similar and having overlapping meanings, were developed independently and are etymologically unrelated.

Concluding Remarks

In summary, the early uses of the term stem cell were made in the late 19th century in the context of fundamental questions in embryology: the continuity of the germ-plasm and the origin of the blood system. The demonstration of the existence of hematopoietic stem cells (Becker et al., 1963; Till and McCulloch, 1961; Till et al., 1964) established these cells as the prototypical stem cells: cells capable of proliferating nearly indefinitely (self-renewal) and of giving rise to specialized cells (differentiation). Using this current definition, it is possible to identify stem cells in other tissues such as the central nervous system, intestine, skin, etc. The term stem cell is not used to refer to primordial germ cells anymore. However, the term still applies to germline stem cells, such as spermatogonia in the testes. Interestingly, recent evidence suggests that embryonic stem cells may have similarities to primordial germ cells (Matsui and Okamura, 2005; Zwaka and Thomson, 2005). Today, as in the 19th century, stem cells are at the heart of some of the most fascinating questions in biology and medicine.

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REFERENCES

Becker, A.J., Mc, C.E., and Till, J.E. (1963). Nature *197*, 452–454.

Boveri, T. (1887). Anat. Anz. *2*, 688–693.

Boveri, T. (1892a). Befruchtung. In Ergebnisse der Anatomie und Entwicklungsgeschichte, F.S. Merkel and R. Bonnet, eds. (Wiesbaden: Joseph Friedrich Bergmann), pp. 386–485.

Boveri, T. (1892b). Sitzungsber. d. Gesellschaft f. Morphologie und Physiologie *8*, 114–225.

Dalerba, P., Cho, R.W., and Clarke, M.F. (2007). Annu. Rev. Med. *58*, 267–284.

Daley, G.Q., Goodell, M.A., and Snyder, E.Y. (2003). Hematology (Am Soc Hematol Educ Program), 398–418.

Dantschakoff, W. (1908). Anat. Hefte *37*, 472–589.

Ehrlich, P. (1879). Arch. Anat. u. Physiol. *3*, 571–579.

Extavour, C.G., and Akam, M. (2003). Development *130*, 5869–5884.

Fliedner, T.M. (1998). Stem Cells *16* (*Suppl. 1*), 357–360.

Häcker, V. (1892). Archiv f. mikr. Anat. *39*, 556–581.

Haeckel, E. (1868). Natürliche Schöpfungsgeschichte (Berlin: Georg Reimer).

Haeckel, E. (1874). Anthropogenie, 1st edn (Leipzig: Wilhelm Engelmann).

Haeckel, E. (1877). Anthropogenie, 3rd edn (Leipzig: Wilhelm Engelmann).

Keller, G. (2005). Genes Dev. *19*, 1129–1155.

Lichtman, M.A., and Williams, W.J. (2006). Williams Hematology, 7th edn (New York: McGraw-Hill).

Maienschein, J. (2003). Whose View of Life?: Embryos, Cloning, and Stem Cells (Cambridge, MA: Harvard University Press).

Matsui, Y., and Okamura, D. (2005). Bioessays *27*, 136–143.

Maximow, A. (1908). Anat. Anz. *32* (*Suppl.*), 65–72.

Maximow, A. (1909). Fol. Haematol. *8*, 125–134.

Mollier, S. (1909). Arch. f. mikr. Anat. *74*, 474–524.

Morrison, S.J., Shah, N.M., and Anderson, D.J. (1997). Cell *88*, 287–298.

Müller, J. (1844). Handbuch der Physiologie des Menschen (Coblenz: Jakob Hölscher).

Nägeli, K.W. (1858). Beiträge zur wissenschaftlichen Botanik (Leipzig: Wilhelm Engelmann).

Neumann, E. (1868). Zentralbl. f. d. mediz. Wiss. *44*, 689.

Neumann, E. (1912). Arch. f. Mikrosk. Anatomie und Entwicklungsgeschichte *207*, 480–520.

Pappenheim, A. (1896). Virchows Arch. *145*, 587–643.

Pappenheim, A. (1907). Fol. Haematol. (*Suppl. 4*), 301–308.

Pappenheim, A. (1908a). Fol. Haematol. *6*, 217–242.

Pappenheim, A. (1908b). Fol. Haematol. *5*, 511–524.

Pappenheim, A., and Ferrata, A. (1910). Fol. Haematol. *10*, 78–208.

Reya, T., Morrison, S.J., Clarke, M.F., and Weissman, I.L. (2001). Nature *414*, 105–111.

Saxer, F. (1896). Anat. Anz. *11*, 355–358.

Shostak, S. (2006). Bioessays *28*, 301–308.

Till, J.E., and McCulloch, E.A. (1961). Radiat. Res. *14*, 213–222.

Till, J.E., and McCulloch, E.A. (1980). Biochim. Biophys. Acta. *605*, 431–459.

Till, J.E., McCulloch, E.A., and Siminovitch, L. (1964). Proc. Natl. Acad. Sci. USA *51*, 29–36.

Weismann, A. (1885). Die Continuität des Keimplasmas als Grundlage einer Theorie der Vererbung (Jena: Gustav Fischer).

Weissman, I.L. (2000). Cell *100*, 157–168.

Wilson, E.B. (1896). The Cell in Development and Inheritance (New York: Macmillan).

Zoja, L. (1910). Fol. Clin. Chim. Micr. *2*, 370–372.

Zwaka, T.P., and Thomson, J.A. (2005). Development *132*, 227–233.