Stem cells: from biomedical research towards clinical applications

Martin Zenke^{1,2,3}

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Over the past several years, our knowledge on stem cells has advanced to encompass stem cell applications that are far beyond stem cell use in traditional cell replacement therapy. This includes recent advances in engineering stem cells with desired properties from somatic cells by reprogramming and precision genome engineering. So what is unique to stem cells and why are they important? What are the most recent developments in stem cell research and what challenges remain ahead? This special issue summarizes recent advances in stem cell research and their implications for stem cell applications in biomedical research and in the clinic.

Stem cells combine two unique properties in one cell: a high self-renewal activity and a broad differentiation potential, which puts stem cells aside from most other somatic cells. Stem cells are required during embryonic development to build up the various tissues and organs and in the adult organism, for maintenance and repair of tissues and organs. We know various stem cell types, referred to as totipotent stem cells, embryonic stem cells, and adult (or somatic or tissue specific) stem cells, which occur during specific stages of embryogenesis and development of the organism. Totipotent stem cells, such as the fertilized oocyte, give rise to both embryonic and extraembryonic cells. Embryonic stem cells (ES

cells) occur as a transient cell population during early stages of embryonic development and are pluripotent, giving rise to cells of all three germ layers of the embryo. Adult (somatic or tissue specific) stem cells occur in the adult organism and are confined to a specific organ or tissue. Adult stem cells give rise to cells of their cognate organ/tissue, e.g., neuronal stem cells develop into neurons and cell types of the nervous system but not into cells of other organs or tissues.

More recently, procedures were developed to artificially engineer stem cells from somatic cells, a process referred to as reprogramming. For example, fibroblasts or blood cells can be reprogrammed into pluripotent stem cells by expression of a specific set of transcription factors, including Oct4, Sox2, Klf4, and c-Myc and are referred to as induced pluripotent stem cells (iPS cells [1, 2]). iPS cells exhibit properties very similar to ES cells and can give rise to an entire organism. Similarly, fibroblasts are readily reprogrammed into neural cells and neural stem cells by expression of yet another sets of transcription factors [3–5]. Furthermore, procedures were developed that allow the development of three-dimensional organ-like structures in vitro from tissue-resident adult stem cells or pluripotent stem cells, referred to as organoids [6, 7].

Hematopoietic stem cells represent one of the most extensively studied stem cell systems and are routinely used in the clinic in stem cell transplantation. Now, other stem cell types, such as mesenchymal stem cells, are rapidly moving into the clinic and also ES cell and iPS cell-derived cells are being tested in clinical trials [8, 9].

The impact of stem cells on medicine goes far beyond their direct application in patients. For example, patient-specific iPS cells harboring specific mutations are differentiated into mature fully functional cells, such as neurons, for toxicity studies and pharmacological testing [10]. Such

✉ Martin Zenke
martin.zenke@rwth-aachen.de

¹ Institute for Biomedical Engineering, Department of Cell Biology, RWTH Aachen University Medical School, Pauwelsstrasse 30, 52074 Aachen, Germany

² Helmholtz Institute for Biomedical Engineering, RWTH Aachen University, Pauwelsstrasse 20, 52074 Aachen, Germany

³ Interdisciplinary Research Group Gene Technology Report, Berlin-Brandenburg Academy of Sciences and Humanities, Jaegerstr. 22/23, 10117 Berlin, Germany

studies combined with advanced organoid cultures [6, 7] offer unprecedented opportunities for drug discovery and personalized medicine [10–12]. Further to this, stem cell growth and/or development can be aberrantly deregulated and thereby give rise to cancer stem cells [13].

In this special issue, we review our current understanding of some selected stem cell types and report on new developments in stem cell research.

In mammals, the fertilized oocyte, referred to as zygote, represents the ultimate totipotent cell. Upon fertilization, oocyte maternal factors induce epigenetic reprogramming of oocyte and spermatozoon genomes to establish totipotency. How this occurs mechanistically and which factors are involved is currently subject of intense research. The review by G. Wu, L. Lei, and H. R. Schöler summarizes the current knowledge on the early events in induction and establishment of totipotency, the molecular signatures of totipotency, and the exit from totipotency upon progression of embryonic development [14].

Advances in our understanding of stem cells, in particular of ES cells and of the molecular signature of pluripotency [15], have allowed induction of pluripotency artificially in fully differentiated somatic cells [1]. These groundbreaking studies caused a burst of reprogramming studies, including reprogramming towards pluripotency and transdifferentiation of somatic cells across all three germ layers (also referred to as lineage conversion [16]). The review by M. Mall and M. Wernig summarizes these in vitro and in vivo reprogramming studies and also the mechanisms, mediators, and road blocks of reprogramming [17].

The development of reprogramming strategies, such as iPS cell technology and transdifferentiation, had a particular impact on modeling of neuronal disorders, since neuronal cells can now be obtained in high cell numbers and high purity. Genome editing of iPS cells, e.g., by CRISPR/Cas for generating isogenic pairs of mutated and unmutated iPS cells, added further to this. The review by J. Jungverdorben, A. Till, and O. Brüstle provides a comprehensive survey on iPS cells for modeling neurodegenerative diseases with a particular focus on autophagy [18].

Hematopoietic stem cells have been particularly well studied, which includes a comprehensive understanding of the gene regulatory networks driving hematopoiesis. This comes along with a detailed knowledge of specific mutations, which cause and/or contribute to hematopoietic cell dysfunction in leukemia. The review by S. Basilico and B. Göttgens describes the advances and concepts in leukemic transformation with a focus on acute myeloid leukemia (AML) [19].

Finally, the review by S. Bartfeld and H. Clevers extends disease modeling by stem cells to three-dimensional (3D) organ-like structures (organoids). Such organoids more

appropriately recapitulate aspects of the in vivo situation and are being applied in basic research, disease modeling, drug development, and personalized medicine [20].

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