Stem cell biology—from basic research to regenerative medicine

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Ever since the demonstration of stem cells in the hematopoietic system in the 1960s [1], researchers have been fascinated by the implications of such cells for questions of development, health, and disease. Stem cells can, on one hand, renew themselves throughout the lifespan of an organism and on the other differentiate into the specialized cell types needed in tissues and organs. Intense investigations have proven that many different processes determine the identity of stem cells, e.g., from the ability of embryonic stem cells to differentiate into all cells of the adult organism to hepatocytes that upon liver damage reactivate a tissue regeneration program. It is hoped that these insights will lead to new forms of therapy in which stem cells can be retrained to generate tissues damaged during a disease. In 2011, over 400 international scientists working in this very broad field gathered at a conference on state-of-the-art stem cell biology held at the Max Delbrück Center [2]. Much of what was discussed is covered in this special issue of the *Journal of Molecular Medicine*, in which leading experts review key facets of stem cell biology [2].

The article by James Adjaye and colleagues (Max Planck Institute (MPI) of Molecular Genetics, Berlin) describes novel findings in the field of induced pluripotent stem cells (iPSCs), including potential uses in clinical settings and drug screening [3]. In a landmark study in 2006, Shinya Yamanaka and colleagues established that somatic (differentiated) cells could be reprogrammed into pluripotent (stem-like) cells by only four transcription factors, i.e., Oct4, Sox2, Klf4, and c-Myc [4]. The review describes different methods to derive iPS cells as well as new

discoveries about the molecular mechanisms that permit reprogramming to take place. Two processes that play a key role are the switch from mitochondrial-based oxidative phosphorylation to glycolysis that they recently discovered [5] and the way cells undergo a mesenchymal to epithelial transition [6]. The authors provide a comprehensive list of human diseases studied involving in vitro uses of iPSCs and their application in drug development and toxicology studies. In addition, the article addresses the overall issue of the potential of iPSCs in therapies and the need to establish iPSC banks [7].

A new trend in stem cell research is a growing intersection with studies of microRNAs (miRNAs), the theme of the review by Tobias Cantz and coworkers (Hanover Medical School, Germany) [8]. It has been appreciated for some time now that miRNAs are important for fine-tuning differentiation processes and cell fate decisions in development [9]. However, their function in the control of pluripotency has been underestimated. The review highlights the important contributions of miRNAs in pluripotency, where their main function is to control the cell cycle and to block differentiation cues. These seem to be unique in pluripotent cells compared to other cell types. Moreover, miRNAs have been proven to be valuable tools in the reprogramming of somatic cells into a pluripotent state [10]. In elegant screening experiments, Cantz and his colleagues identified a miRNA-dependent mechanism involving the transcription factor Meox2 [11]. Further important findings regarding the function of miRNAs are sure to appear in the future.

Another theme of growing importance is the relationship between germ cell development and pluripotency, covered in the review by Mehdi Pirouz, Alexander Klimke, and Michael Kessel (MPI for Biophysical Chemistry, Göttingen) [12]. The unique epigenetic regulation in germ cells involving the factors Blimp-1 (Prdm1) and Prdm14 is discussed.

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The review highlights the reciprocal connection between germ cells and pluripotent stem cells [13] and introduces signaling pathways that control the biology of germ cells. The authors conclude that further efforts are required to harvest the potential and possibilities of human PGC-like cells in settings for reproductive medicine.

All of these insights are leading to practical applications for stem cells in research and, potentially, medicine. Allen Wang and Maïke Sander (University of California, San Diego) discuss the current state-of-the-art protocols in the derivation of cells of the definitive endoderm from pluripotent stem cells [14]. They begin by reviewing the signal transduction and gene regulatory networks that guide the differentiation of endodermal cells. The derivation of hepatocyte-like cells in vitro from human pluripotent stem cells is quite advanced [15], while it has not yet been possible to derive functional pancreatic β -cells. However, it has been shown that in vitro-derived pancreatic progenitors have the potential to give rise to functional insulin-producing cells after engraftment [16]. Regarding the differentiation of intestinal cells, the transcription factor CDX2 has been found to play a central role. Such in vitro-differentiated cells are becoming important tools to study human disease [3]. Leading scientists agree that the use of human pluripotent stem cells and their derivatives to model human diseases and conduct pharmaceutical screening will become routine well before cell-based therapies can be brought to clinical settings.

Our START-MSC consortium has extensively characterized the biologic properties of mesenchymal stromal/stem cells (MSCs). The review by Karen Bieback and colleagues (Medical Faculty Mannheim, Heidelberg University) summarizes the results generated in the consortium [17] as well as futile attempts to induce their “trans-differentiation” into cardiac and hepatic cell lineages [18]. Nevertheless, MSCs harbor important features that are crucial for novel approaches in regenerative medicine. They show robust osteo- and chondrogenic differentiation capacities, modulate immune reactivity, provide stromal support for cell engraftment in vivo, and supply factors that support the regenerative potential of resident cells in the body. Although MSCs have already found their way into a vast number of clinical trials within the emerging field of regenerative medicine, the physical, phenotypic, and functional properties of MSCs remain ill defined. There is an urgent need for the development of molecular markers as well as universal criteria for quality control in GMP settings for MSCs. The review discusses the potential of MSCs for future use in clinical therapies.

Salvador Aznar Benitah (Centre for Genomic Regulation, Barcelona) and Michaela Frye (Wellcome Trust Centre for Stem Cell Research, University of Cambridge, UK) debate the function of stem cells in ectodermal development

beginning at the early cell fate decisions in the developing embryo [19]. They provide an overview of the signaling network that determines the establishment of the ectoderm. A transcription factor network involving p63 and its homologues, the tumor suppressor p53, and p73 plays a central role in determining the identity of ectodermal cell types [20]. The review further highlights the process of epidermal stratification and the role of signaling in the development of the hair follicle, particularly of Wnt ligands. A better understanding of the basic processes underlying the generation of hair follicles and sweat glands should lead to novel strategies in the treatment of patients who require skin replacement [21].

In the final review, Lilian van Vlerken, Elaine Hurt, and Robert Hollingsworth (MedImmune, Gaithersburg) highlight the recent advances in the field of cancer stem cells and cancer-initiating cells [22]. They point out many similarities in pluripotent stem cells, tissue stem cells, and cancer stem cells (CSCs) in terms of the control of stem cell identity. This includes the epigenetic control of the genome, involving mechanisms such as DNA methylation and histone modifications. The function of the Polycomb group in stem cell identity is under intensive scrutiny in laboratories around the world [23]. Ultimately, understanding these processes in pluripotent stem cells, somatic stem cells, and in CSCs will undoubtedly lead to improvement in the treatment of a range of fatal diseases.

In summary, these reviews on the many aspects of stem cell research highlight the exciting possibilities that these cell types present for novel avenues of treatment in regenerative medicine as well as for the identification of new drugs. Nevertheless, the authors are unified in their opinion that harvesting the full potential of stem cells in clinical and pharmaceutical settings will require major research efforts into the highly complex mechanisms that control their behavior.

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