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EDITORIAL

Shedding light on hematopoietic stem cells: formation, regulation, and utilization

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Hematopoietic stem cells (HSCs) have been the focus of intense research since scientists introduced the 'stem cell' theory at the beginning of the 20th century. Major discoveries, sometimes serendipitous, have paved the way to our present concept of HSCs and blood formation. For instance, the successful transplantation of spleen and bone marrow cells to rescue people exposed to lethal doses of radiation during World War II and the following decades of fundamental research have established HSCs as the key cell type to restore damaged hematopoietic tissues. Indeed, their inherent multipotency and self-renewal properties confer them the capacity to reestablish the entire hematopoietic system and therefore to cure the thousands of patients affected with blood related diseases every year. HSC transplantations are widely performed in case of cancers of the hematopoietic system (e.g. leukemia, lymphoma), to replenish the cells lost after high doses of chemotherapy on solid tumors, or to resist autoimmune diseases. However, the shortage of HSCs available for the clinic has led to an increasing number of patients in long-term waiting list for compatible HSC transplant. This important limitation has warranted investigation aiming to either amplify HSCs *in vitro* or to find an alternative cell supply to donor HSCs. A very attractive solution would be to *de novo* produce large quantities of tailor-made HSCs. However, recapitulating all steps leading to HSC production *in vitro* has proven to be very challenging. A better understanding of HSC fate determination, generation, and regulation, as it occurs *in vivo* in the course of embryonic and adult life, represents a prerequisite to determine what a cell needs to become and to remain a transplantable HSC in a Petri dish.

We present in this Special Issue of FEBS Letters a collection of review articles authored by invited international experts in various fields. They discussed our current understanding of HSC generation as well as recent exciting fundamental and technical developments and also share their views on future research directions. The issue is divided into four main topics. The first topic covers hematopoietic stem and progenitor cell production during embryonic development. Parallel investigations in different animal models, including Drosophila [1], zebrafish [2], xenopus [3], mouse [4] as well as human embryos [5], have been instrumental in pushing the barriers of our understanding of developmental hematopoiesis. These reviews notably discussed the successive waves of hematopoietic development sustaining transient short-term and then stable long-term hematopoiesis [4,6]. They also highlight the key role of signaling pathways and transcription factors during the endothelial to hematopoietic transition, the crucial transdifferentiation process at the origin of HSCs [3]. The second topic covers the molecular control of hematopoietic specification and differentiation, embracing genetic programming, chromatin landscape regulation, epigenetic regulation, and the dynamics of enhancer landscape [7,8]. The third topic covers the recent progresses made toward developing new techniques (e.g. single-cell RNA sequencing, mass cytometry, integration site barcoding, cellular barcoding, and transposon barcoding [9]) and design computational models [10] to better understand, and sometimes revisit, our concepts of cell heterogeneity, cell lineage differentiation, and regulatory relationships. These reviews examined the capabilities, limitations, and promises of all these exciting new methods, that are still constantly improved and refined, and might lead in the future to the development of single-cell molecular profiling within the context of a complex 3D intact tissue. The fourth topic covers the recent progresses and future prospects for *in vitro* HSC production. The generation of tailor-made HSCs *in vitro* via directed differentiation

of pluripotent stem cells [11] (e.g. ES cells, iPS cells), or the reprogramming of somatic cells [12], represents the Holy Grail since decades. Although this field is in its infancy, tremendous progresses have been recently made. Further advances will be driven by more fundamental progresses in our understanding of the regulatory role of the endothelium, the gene regulatory networks and epigenetic mechanisms that control HSC self-renewal and differentiation. Finally, all the reviews highlight the importance to understand the fundamentals of the hematopoietic production and homeostasis under physiological condition to understand the deregulation occurring in pathological situation. Such knowledge will be increasingly exploited in the future for therapeutic purposes, drug testing, and discovery.

We would like to thank Prof. Dr. Wilhelm Just, Reviews Editor of the FEBS Letters for offering us the opportunity to edit this Special Issue on HSCs and also the journal Editorial Team, and particularly Anne Rougeaux (Editorial Assistant) for their help leading to the completion of the issue. We thank all the authors who dedicated their time to contribute to this Special Issue, to create a broad and in-depth overview of the blood system development. A particular thanks to Thierry Robin who accepted to provide the beautiful original picture of Antelope canyon that was used for the cover. It illustrates, with a little imagination, the hematopoietic tree with an intense light put on HSCs at the top, which however remain surrounded by a deep black that has yet to be explored. We hope that this Special Issue will be of interest for the scientific community working on HSCs and beyond.

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