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Introduction

The biomedical field has been periodically revolutionized by major discoveries. A notable example was Evans and Kaufman's [1] observation that cells from the inner cell mass of the mouse blastocyst could be propagated indefinitely in vitro with maintenance of their totipotentiality. The enormous potential of this technology to elucidate and manipulate processes regulating the development of the mouse was thus very rapidly realized. The subsequent creation of human embryonic stem cell (ESC) lines with analogous properties [2] expanded these avenues of experimental study to previously inaccessible stages of human development. In addition, they introduced the exciting prospect of generating new types of human cells and tissues for therapy. Biology was delivered a third seismic jolt when Takahashi et al. demonstrated that mature somatic cells from both mice [3] and humans [4] could be reproducibly reprogrammed into a new type of "induced pluripotent stem cell" (iPSC) through the transient expression of only four factors. The rapid adoption of this methodology worldwide has now extended the reach of stem cell biology into patient-specific disease modeling and the production of HLA-identical tissues for clinical use.

Interestingly, an understanding of many aspects of hematopoietic stem cell (HSC) biology was already well advanced before the first mouse ESC (mESC) and human ESC (hESC) lines were generated. Mouse HSC transplants had become routine experimental models and clinical applications of HSC-containing transplants became established, albeit imperfect, treatment modalities. Transfusions of red blood cells, platelets, and neutrophils were also standardized procedures and the potential of adoptive transfer of T cells for immunotherapy was being explored. Likewise, the unusual stepwise development of primitive hematopoietic cells in the embryo was recognized, as was the greater output potential of fetal and neonatal hematopoietic cells from both mice and humans. However, differences between mouse and human development and the limited access to late stages of human fetal development continue to retard progress in this field.

Hematology was thus well primed to consider the use of ESCs and iPSCs for obtaining new insights and for developing new clinical applications for understanding and treating disease. However, since their discovery, ESC and iPSC technology has had an impact on the science of normal and malignant hematopoiesis

that has been at the same time dramatic, illuminating, and frustrating. A decade later, the advances made are closing outstanding gaps and make a collation of these a timely exercise. This Special Issue was thus created to provide a compilation of current advances and challenges.

The early accumulation of an extensive knowledge of HSC biology and its use in transplantation-based therapies initially led to the assumption that HSCs would likely be the first type of tissue-specific stem cells to be generated from ESCs and iPSCs and used clinically. However, the production from PSCs of long-term self-renewing HSCs with the properties of definitive HSCs has proven more difficult to realize than expected. Several groups have shown that the self-renewal capacity and durability of PSC-derived CD34⁺ hematopoietic cells can be enhanced by forced overexpression of certain transcription factors, but spontaneous production of cells with the properties of normal transplantable HSCs has to date eluded the field. Current evidence suggests that the differentiation of PSCs is often blocked at an embryonic stage of development, although recent findings have shown that mature functional lymphoid cells from the innate and adaptive immune system can be produced from PSCs.

In this Special Issue, we begin with a review by Slivkin and Uenishi [5] on the process of the normal development of definitive HSCs. This review focuses on the arterial identity of hemogenic endothelium from which definitive HSCs arise, anticipating that an improved understanding of how these cells develop will be critical to the future generation of definitive human HSCs from PSCs. This is then followed by a contribution by Bernarrgegi, Pouyanfar, and Kaufman [6] discussing the generation of natural killer (NK) cells and macrophages from PSCs and the clinical potential of PSC-derived NK cells armed with chimeric antigen receptors. Montel-Hagen and Crooks [7] then review the literature on the production of T cells from PSCs and discuss the recent development of "artificial thymic organoid" technology to allow positive selection and maturation of conventional T cells and genetic engineering approaches to arm these cells to kill tumor cells.

Significant progress has also been made recently in using PSCs to model hematopoietic diseases. Three articles describe examples of models for benign hematopoietic disease. Elbadry, Espinoza and Nakao [8] review the literature on the challenging field of bone marrow failure syndromes; Karagiannis, Yamana, and Saito [9] provide an overview of iPSCs and primary immune deficiency with a focus on specific

disorders of innate immune cells such as neutrophils and monocyte–macrophages; and Dannenmann et al. [10] present original findings using iPSCs from patients with congenital neutropenia.

The last trio of articles in this Special Issue summarize results from modeling hematopoietic malignancies using iPSCs. Turhan and colleagues [11] lay out the close biological relationship of cancer and cellular reprogramming, including the heterogeneity of cancers and the clonal development of certain cancers, findings that have led to the cancer stem cell hypothesis. The article by Chao and Majeti [12] then discusses the challenges presented by reprogramming the epigenome of malignant cells with retention of the original cancer phenotype. Finally, Papapetrou [13] reviews experience in using patient-derived iPSC to model several human myeloid malignancies.

As will be evident from these state-of-the-art articles by leaders in the field, current understanding of the challenges and potential of this fascinating biological system to affect hematology in particular has now reached a new turning point. Due to space limitations, we are unable to specifically recognize the many others who have facilitated this progress. However, we expect that the ongoing international effort to understand how human PSCs can be coaxed into the many disparate lineages of hematopoiesis will continue at full force and will now be joined by an exciting new phase of disease modeling and clinical translation.

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