Guest editorial: the seven wonders of erythropoiesis

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This month's issue introduces a special series of Progress in Hematology (PIH) reviews by seven outstanding scientists, providing comprehensive overviews of recent progress in seven aspects of erythropoiesis. A number of new findings in this rapidly evolving field are the focus this editorial feature, written by cutting-edge scientists invited to the 1st Annual International Symposium of The Japanese Society of Hematology (JSH) in Akita on 16–17 July 2010. The JSH International Symposium series focuses on outstanding scientific fields in each region of Japan, and encourages researchers to communicate and exchange knowledge and ideas, in the hope of contributing to advances in the selected field in both Japan and the rest of the world. This first year's Scientific Program included cutting-edge scientific presentations by an outstanding

group of speakers in seven sessions over a 2-day period. Oral and poster presentations by future leaders in the study of erythropoiesis were also a highlight of the meeting. The seven sessions were organized along the theme of “the Seven Wonders of Erythropoiesis”, acronymically titled Enucleation, Ribosomal proteins, Yield (of red cells), Transcription factors, Heme and iron, Red cell aplasia, and Oligodeoxynucleotide (ODN) and micro RNA, or “ERY-THRO”. There has been much progress in recent years toward developing a better understanding of these aspects of erythropoiesis, as well as applications at the frontiers of medical science. This International Symposium also represented the start of the 1st JSH-EHA Joint Educational Program. These seven reviews will appear in PIH across two volumes of the *International Journal of Hematology*.

1 Enucleation

Enucleation of mammalian erythroblasts is thought to involve a process similar to cytokinesis. The molecular bases of enucleation and erythroblastic islands, as well as the erythropoietic niches have been explored intensively in recent years [1, 2]. However, the structural organization of a number of additional transmembrane proteins has yet to be fully defined. In this issue, Mohandas et al. [3] throw new light on the evolution of unique features of the red cell membrane, and introduce a new strategy for distinguishing unambiguously between erythroblasts at successive developmental stages. These findings provide unique insights into the genesis of red cell membrane function during erythroblast differentiation, and offer a means of defining stage-specific defects in erythroid maturation in inherited and acquired red cell disorders and bone marrow failure syndromes.

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2 Ribosomal proteins

The finding that congenital mutations in ribosomal protein S19 and other genes encoding ribosomal proteins cause Diamond–Blackfan anemia, a disorder characterized by hypoplastic, macrocytic anemia [4] remains as exciting today as it was at the time of its discovery. Ribosomopathies compose a collection of disorders in which genetic abnormalities cause impaired ribosome biogenesis and function, resulting in specific clinical phenotypes, i.e., Schwachman–Diamond syndrome, dyskeratosis congenita, cartilage hair hypoplasia, and Treacher Collins syndrome [5]. The 5q– syndrome, a subtype of myelodysplastic syndrome, caused by a somatically acquired deletion of chromosome 5q, leads to haploinsufficiency of the ribosomal protein RPS14 and an erythroid phenotype highly similar to that seen in Diamond–Blackfan anemia [6]. In this issue, Narla et al. deepen our understanding both of ribosome defects in disorders of erythropoiesis and of acquired abnormalities in ribosome function, which have been implicated more broadly in human malignancies. The p53 pathway provides a surveillance mechanism for protein translation and genome integrity, and is activated by defects in ribosome biogenesis. This pathway appears to be a critical mediator of many of the clinical features of ribosomopathies.

3 Yield (of red cells)

The production of transfusable red blood cells (RBCs) in vitro remains something of a Holy Grail, as in many countries the supply of RBCs remains insufficient. Several teams of investigators have already taken up this challenge [7, 8], seeking to generate immortalized erythroid cell lines able to produce transfusable RBCs in vitro, which, were they to be established, would be an immensely valuable resource. Establishment of embryonic stem cell-derived erythroid progenitor cell lines represents one promising approach to the production of functional red blood cells [9]. In this issue, Nakamura surveys the possibilities of establishing useful cell lines committed to specific lineages other than hematopoietic progenitors from human ES cells.

The in vivo regulation of erythropoiesis involves the integration of a range of intrinsic and extrinsic cues. The macrophage that sits at the heart of the erythroblastic island is known to be centrally important to normal differentiation and the support of erythroid development [1]. However, the contributions of other cell types found within the local bone marrow microenvironment, including osteoblasts, osteoclasts [10], adipocytes [11], and endothelial cells [12], and developing hematopoietic cells, remain largely unclear. The

dynamic interaction and coordination between erythroid development and skeletal homeostasis, particularly in the setting of erythroid demand, remains a particularly stimulating discovery. In this issue, Walkley elucidates a centrally regulated axis with roles in physiology, pharmacology, and the pathology of anemia states.

4 Transcription factors

Considerable effort has been put into understanding the regulation of erythroid differentiation, and recent discoveries have clearly shown that lineage-specific transcription factor networks are essential for the proper differentiation of erythroid cells, and that erythropoiesis is largely mediated by a relatively small number of lineage-restricted transcription factors, including GATA-1, SCL/TAL1, LMO2, LDB1, and KLF1 [13]. The transcription factors GATA1 and GATA2 are involved in regulatory networks controlling erythroid gene expression, and importantly, expression of the *Gata1* and *Gata2* genes is itself under the control of such regulatory networks [14]. In this issue, Suzuki et al. provide an overview of the mechanisms underlying *Gata1* and *Gata2* gene regulation during erythropoiesis, and the physiological significance of their dynamic transcriptional control.

5 Heme and iron

Mammalian iron homeostasis must be regulated closely to ensure that this essential element is available for use, but at the same time prevented from promoting the formation of toxic radicals [15]. Over the last decade, a number of central players in iron homeostasis have been introduced, helping to tie together previously discrete threads of knowledge. Typical examples of these include transferrin receptor 2 (TFR2) (2000) [16], a homolog of TFR1 that mediates cellular uptake of transferrin-bound iron in most cells; hepcidin (2001) [17, 18], a secreted peptide synthesized mainly by the liver that is a major regulator of iron metabolism; ferroportin (2004) [19], the only known vertebrate iron exporter; and hemojuvelin (2005) [20], a co-receptor of the bone morphogenetic protein (BMP) ligand, BMP-6, which is associated with a robust activation of hepcidin transcription. In this issue, Kaplan et al. explain the role of hepcidin and ferroportin in association with human disorders, involving either overloads or deficiencies of iron, while Camaschella and Pagani shine a light on the dual relationship between iron and erythropoiesis through the lens of spontaneous and engineered animal models of iron disorders.

6 Red cell aplasia and oligodeoxynucleotide (ODN) and micro RNA

Pure red cell aplasia (PRCA) is a syndrome characterized by a severe normocytic anemia, reticulocytopenia, and an absence of erythroblasts in otherwise normal bone marrow. Primary PRCA, and secondary PRCA that has proven unresponsive to treatment of the underlying disease, is treated as an immunologically mediated disease. Although vigorous immunosuppressive treatments induce and maintain remissions in a majority of patients, these carry an increased risk of serious complications. In this symposium, based on a nationwide survey in Japan, current strategies for the treatment of PRCA were introduced in a presidential lecture. Although this issue is not reviewed in this PIH series, relevant articles can be found elsewhere [21, 22] as can focused articles on idiopathic [23], thymoma-associated [24], large granular lymphocyte leukemia-associated [25] and lymphoma-associated PRCA [26].

Oligodeoxynucleotides (ODN) are another deserving wonder that does not appear in this PIH series. One of the highlights of the meeting was the oral and poster presentations by promising young researchers in the field of erythropoiesis. In this symposium, Guo et al. made the case for the selective inhibition of erythroid growth and down-regulation of the expression of erythropoietin receptor mRNA in human CD34+ cells by CpG (cytosine linked to guanine by a phosphate bound) ODN-2006, a toll-like receptor-9 (TLR9) ligand that shares a consensus sequence with the parvovirus (PV) B19 genome [27]. This report was highly evaluated and has been introduced in Hematology 2010, the American Society of Hematology Education Program Book (30th edition, p. 283) as an experimental result that provided insight into the mechanisms of PV B19 inhibition of erythropoiesis.

The search for Wonders in Erythropoiesis goes on, and our work in introducing them will continue necessarily to reflect a number of factors, such as the state of the science, clinical demand, and the sheer appeal of scientific curiosity. Scientific advances may also reveal new wonders to the field of erythropoiesis, and so although the content of the Seven Wonders of Erythropoiesis series may change over time, I believe these will continue to stand at the forefront of medical science.

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