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Jekyll and Hyde: the role of heme oxygenase-1 in erythroid biology

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There is currently a great deal of excitement regarding the role of stem cell niches that regulate hematopoietic stem cell self-renewal and differentiation. It should be noted, however, that the original description of a hematopoietic niche actually occurred in 1958 when the French hematologist, Marcel Bessis, described erythroblastic islands.[1] The island was characterized by developing erythroblasts surrounding a central macrophage and, based on careful structural observations, Bessis and colleagues made a number of interesting inferences about the role of central macrophages in erythropoiesis. It was suggested that the macrophage functions as a "nurse" cell, providing iron to developing erythroblasts for heme synthesis and, furthermore, that the extruded nuclei produced at the end of erythroid differentiation are phagocytized by these central macrophages.[2] These concepts proved prescient as they have been supported by a number of recent findings which have shown that the macrophage-erythroblast interactions mediated by a large number of adhesion molecules are essential for the highly regulated process of erythroblast proliferation and survival which is necessary for the production of two million reticulocytes per second.[3-6] In this context the recent findings that *in vivo* depletion of erythroblastic island macrophages blocks erythroblast proliferation and maturation fully validates the central role of macrophages in regulating erythropoiesis.[7]

Apart from playing an important role in the genesis of red blood cells within the bone marrow, macrophages of the reticulocyte endothelial system in general and spleen in particular play a critical role in quality control by removing senescent and damaged red cells from the circulation.[8-10] Thus different macrophage subsets play a dual role in both the production of red cells and in the elimination of senescent normal red cells and pathological red cells. This important symbiotic interrelationship between erythroid and macrophage biology is receiving increasing attention in hematology research since the findings of the studies have direct relevance to our understanding of both normal and disordered erythropoiesis.

In this issue of Haematologica, Fraser and colleagues describe exciting new findings regarding a key role for heme-oxygenase-1 in both regulating erythroid differentiation and in mediating clearance of circulating red cells through its effect on macrophages.[11] The work of Fraser *et al.* documents that heme-oxygenase-1 deficiency adversely affects steady-state erythropoiesis in murine bone marrow due to a diminished ability of erythroblasts to form erythroblastic islands. The reduction in erythroblastic islands was the result of decreased numbers of the subtype of bone marrow macrophages involved in island formation. These observations reinforce the concept of an essential requirement of a specific subset of macrophages for the formation of bone marrow erythroblastic islands and that island formation is necessary to sustain normal bone marrow erythropoiesis. Interestingly, the decreased erythropoiesis in the bone marrow led to increased erythropoiesis in the spleen, a common compensatory response in the murine system in which the spleen is the major erythropoietic organ that responds to stress erythropoiesis.

While heme-oxygenase-1 deficiency had a negative effect on bone marrow erythropoiesis, it had a positive effect on red cell life span in circulation as a result of compromised ability of the macrophages of the reticuloendothelial system to remove senescent red cells. It thus

appears that heme-oxygenase-1 plays the role of Dr. Jekyll by increasing red cell life span in circulation and also plays the part of Mr. Hyde by decreasing bone marrow erythropoiesis.

The work of Fraser *et al.* represents an important step in our understanding of the complex interplay between erythroid and macrophage biology in the regulation of red cell production and destruction. In particular, it brings to our attention the previously unsuspected and distinct roles of heme-oxygenase-1 in murine erythroid biology through its action on macrophages. However, many questions remain. How does heme-oxygenase-1 deficiency account for the observed microcytosis and decreased hemoglobin content of red cells? Is there perturbation of iron homeostasis due to dysregulation of hepcidin production?[12] Importantly, do the reported findings using the murine system account for the hematologic phenotype noted in the very rare cases of human heme-oxygenase-1 deficiency?[13,14]

What then are the implications of these current findings? One is that heme-oxygenase-1 may play a much broader role in erythroid biology than previously suspected and likely plays a role in a number of human red cell disorders. A second implication is that there is clearly a complex interplay of cell-cell interactions in regulating various biological functions. Finally, the work of Fraser *et al.* gives us a valuable impetus to further explore the complex role of macrophages in various aspects of erythroid biology.

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Personalized medicine in myelodysplastic syndromes: wishful thinking or already clinical reality?

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General concepts of managing patients with myelodysplastic syndromes

This editorial will start with the important (and true) premise that the term myelodysplastic syndromes (MDS) covers a group of heterogeneous and complex hematologic disorders primarily found within the older population. In fact, its diversity makes the disease challenging and "truly personalized", not only in terms of diagnostics but also in carrying out clinical decision-making. The heterogeneity of MDS manifests in the individual patient as a disease ranging from an indolent condition with a considerable life expectancy to forms approaching the aggressiveness of acute myeloid leukemia (AML). A risk-adapted treatment strategy is, therefore, mandatory for a disease showing such a highly variable clinical course. Prognostic factors may be subdivided into those related to the patient's general characteristics and health condition and those related to the MDS disease itself. During the past 15 years, treatment has been stratified according to the International Prognostic Scoring System (IPSS) risk score; i.e. into "lower-risk" MDS (low/int-1, LR-MDS), where correction of cytopenia was the main objective, and "higher-risk" MDS (int-2/high, HR-MDS), where the reduction or delay of progression or AML evolution and prolonged survival was the objective. More recently, a revised version of the IPSS has been introduced (IPSS-R) subdividing patients into 5 risk groups with different outcomes in terms of AML evolution and survival. Using this new IPSS-R, one-quarter of LR-MDS per classical IPSS were re-classified as having a higher risk, and may potentially require more intensive treatment, while on the other hand a substantial subset of HR-MDS patients per classical IPSS were re-classified as lower risk suggesting that IPSS-R can refine the scoring of an individual MDS patient. Nevertheless, it is still a subject of controversy as to how