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The Erythroid Niche: Molecular Processes Occurring within Erythroblastic Islands

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Abstract

Erythroblasts terminally differentiate within specialized niches composed of erythroblast islands nesting in extracellular matrix proteins. A number of adhesion molecules active in erythroid island attachments have been identified. We have recently observed a receptor/counterreceptor interaction that appears to maintain island integrity: erythroid ICAM-4 interacting with macrophage αV integrin. When ICAM-4/ αV binding is blocked, a 70% decrease in islands is observed. Moreover, erythroblastic islands are markedly decreased in ICAM-4 null mice. Using erythropoietin to examine whether ICAM-4/ αV binding plays a role in stress erythropoiesis, we found that the reticulocyte response is different in ICAM-4 null mice compared to control mice. We speculate that this may be a reflection of the baseline decrease in island number in the ICAM-4 null mice. Erythroblast enucleation also occurs within the erythroid niche. Earlier, we examined whether abnormal protein sorting during nuclear extrusion creates the deficiencies of membrane proteins that are well described in hereditary spherocytosis (HS) and hereditary elliptocytosis (HE). We observed that whereas glycophorin C partitions to reticulocytes in normal mouse cells, it sorts to extruding nuclei in murine hereditary elliptocytosis cells. Additionally, in a murine model of hereditary spherocytosis, band 3, glycophorin A and RhAG partition to both nuclei and reticulocytes, while in normal cells these three proteins distribute predominantly to reticulocytes. Hence, it appears that abnormal protein sorting generates specific protein deficiencies in hereditary elliptocytosis and hereditary spherocytosis.

Keywords

Erythropoiesis; Erythroid niche; Erythroblastic island; ICAM-4; Protein sorting; Enucleation; Hereditary spherocytosis; Hereditary elliptocytosis

Terminal erythroid differentiation and enucleation take place within specialized niches composed of erythroblast islands nesting in extracellular matrix proteins. Erythroblast islands, first described by Bessis, contain erythroblasts of varying ages and multilobulated,

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young reticulocytes surrounding a central macrophage [1]. Within the erythroid niche, cell–cell and cell–extracellular matrix interactions serve as both positive and negative regulators of erythropoiesis. (recently reviewed [2]). A number of adhesion molecules active in erythroid island attachments have been identified. Emp (erythroblast macrophage protein), $\alpha 4\beta 1$ integrin and VCAM-1 contribute to erythroblast–macrophage binding while $\alpha 4\beta 1$ integrin and the blood group antigen Lutheran glycoprotein mediate erythroblast–extracellular matrix attachments to fibronectin and Laminin, respectively.

We have recently observed another receptor–counter receptor interaction that appears to maintain erythroid island integrity: erythroid ICAM-4 (intercellular adhesion molecule-4; blood group antigen LW) interacting with macrophage αV integrin [3]. When ICAM-4/ αV binding is blocked with αV synthetic peptides, a 70% decrease in islands is observed. Moreover, both islands formed in vivo or reconstituted in vitro are markedly decreased in ICAM-4 null mice. We recently began to examine whether ICAM-4/ αV binding plays a role in stress erythropoiesis. Using erythropoietin as a stress inducer, we found that the reticulocyte response is different in ICAM-4 null mice compared to control, wild type mice. We speculate that this may be a reflection of the baseline decrease in island number in the ICAM-4 null mice.

Expression of adhesion proteins varies dynamically over the course of erythroid differentiation. While proerythroblasts express an array of these receptors, normal mature red cell membranes are devoid of them. One process regulating the level of membrane protein expression in mature red cells is the partitioning of erythroblast membrane proteins during nuclear extrusion. At the time of enucleation, membrane proteins are sorted to either the plasma membrane of the nascent reticulocyte or to the plasma membrane surrounding the extruding nucleus. We have found that $\beta 1$ integrin sorts to both the extruding nucleus and the nascent reticulocyte [4]. Further, it appears that one molecular mechanism regulating protein sorting to reticulocytes is the degree of connectivity to the cytoskeleton.

To extend these studies, we have begun exploring whether abnormal protein sorting during nuclear extrusion creates the deficiencies of membrane proteins that are well described in hereditary spherocytosis (HS) and hereditary elliptocytosis (HE) [5]. For these investigations we have analyzed sorting patterns in bone marrow cells from mouse models of hereditary spherocytosis and hereditary elliptocytosis using immunofluorescent microscopy. We observed that whereas glycophorin C partitions to reticulocytes in normal cells, it sorts to extruding nuclei in 4.1R deficient HE cells. We also found that in an ankyrin-1 deficient murine model of hereditary spherocytosis, band 3, glycophorin A and RhAG partition to both nuclei and reticulocytes, while in normal cells these three proteins, distribute predominantly to reticulocytes. From these data it appears that altered protein sorting is a molecular mechanism generating specific membrane protein deficiencies in hereditary elliptocytosis and hereditary spherocytosis.

Despite extensive knowledge of hematopoiesis, less attention has been focused on processes occurring within the erythroid niche. Disordered erythropoiesis and/or altered structural organization of red cell membranes are features of multiple inherited and acquired anemias. Investigations of key mechanistic aspects of normal late stage erythropoiesis will lay critical groundwork for future studies examining whether perturbations in these processes contribute to the pathobiology of a number of prevalent hematologic diseases.

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