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A Possible Role of Aquaporin Water Channels in Blood Cell Migration in Spleen; Interaction with Cluster of Differentiation Molecules

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ABSTRACT: Aquaporins (AQPs) are molecular water channels that play important physiological roles in fluid transporting organs. The expression and function of AQPs in the immune system are largely unknown. CD11(a—d)/CD18 integrins are adhesion molecules expressed on leukocytes, which play a critical role in leukocyte adhesion, migration and host defense. In the present study, we suggest that the expression of aquaporin water channels on spleen CD positive cells, and the content of CD positive splenocytes in aquaporin may regulate the migration of blood cells. Recent studies and their analysis suggested remarkably decreased monocyte/macrophage subpopulation and significantly decreased granulocyte subpopulation. This is the first hypothetical report suggesting an important role of AQP in the trafficking of hemapoietic cells.

Key words: Aquaporin, Spleen, Lymphocytes, CD147, Erythrocytes

The compartments of human spleen are ill defined and the location of T-cell regions with respect to the so-called "central arterioles" is especially controversial. The splenic red pulp cords are formed by fibroblasts and reticular fibers (1,2). They represent the open part of the splenic circulation that receives blood from terminal arterioles and lacks endothelia. The closed part of the splenic circulation consists of the rest of the vascular tree including the splenic red pulp sinuses. Despite this classification, the sinuses have an unusual discontinuous endothelium and basement membrane, which permit erythrocytes to enter from the open circulation of the surrounding cords. Recent results show, that the border between the splenic white and red pulp is more sophisticated in humans than in rats or mice (3,4). They provoke the interpretation that the region where red and white blood cells enter the spleen is species-specific. Recirculating mouse and rat lymphocytes are imagined to enter the white pulp by adherence to the endothelium of the marginal sinus and by migration across the marginal zone (MZ). Thus, they have to cross the wall of a vessel belonging to the closed splenic circulation.

We speculate that in humans the entry of white blood cells into the splenic white and red pulp is different in that it occurs primarily via the open splenic circulation in the perifollicular zone (5). Thus, the white cells need not cross an endothelium, because terminal vessels directly open into this site. Vascular structures similar to the rodent marginal sinus do definitively not exist in humans. We can, however, not exclude that the few capillaries in the perifollicular zone that express CD31 and/or CD34 serve the exit of white blood cells. These vessels are, however, only sparsely distributed. in autopsy specimens. The fact that blood cells are contained in an open part of the splenic circulation in the perifollicular zone is not only demonstrated by the distribution pattern of CD31, CD34, and CD141, but is supported by additional evidence coming from adhesion molecules involved in lymphocyte recirculation.

The spleen is equipped with a unique type of microcirculation permitting lymphocytes to exit from blood under conditions of low shear stress and in absence of high endothelial venules. In addition to erythrocytes, granulocytes, and monocytes, in some specimens with full blown germinal centers large numbers of CD-20 and CD-79 positive B lymphocytes, which are negative or weakly positive for IgD extend from the MZ into the perifollicular zone. On the other hand CD147 has been described as a potential adhesion molecule, which binds to endothelial cells and fibroblasts. For instance, CD147, like CD47, may be part of the recognition of erythrocytes as self, and that blockade of this molecule may prevent erythrocytes from escaping the splenic reticuloendothelial system. Aquaporin water channel CHIP28 is expressed on the erythrocytes and may contribute to distinct physiological functions in the presence of CD147. Alternatively, it is possible that ligation of CD147 alters erythrocyte deformability, leading to their mechanical trapping in the spleen. Taken together, these data strongly suggested that blockade of CD147 on erythrocytes was directly responsible for their trapping in the spleen (6).

Aquaporin water channels are expressed in the spleen but their precise function is not known (7,8). It is quite possible that aquaporin water channels may be requlating the trafficking of blood cells across spleen and in and out of spleen. A role of cluster of differentiation cells is speculated in this entire physiological process. A further possibility is that ligation of CD147 may alter erythrocyte adhesion through an intracellular signaling mechanism. This speculation is based on some recent studies although comprehensive studies need to be conducted (9). The identification of the ligand(s) for CD147 and the cell type expressing it should help elucidate mechanisms involved in CD147-mediated erythrocyte trafficking. The adhesion molecule $\alpha_4\beta_1$-integrin (VLA-4) has been previously shown to play a major role in the trafficking of hematopoietic precursors and their homing to the spleen and liver (10). However, other explanations cannot be ruled out. There may, in fact, be conditions in which the perifollicular zone harbors major numbers of B lymphocytes making a distinction between outer MZ and perifollicular zone rather difficult. These findings clearly suggest that the interpretations by Hsu and colleagues in that we definitively show the human MZ as a B lymphocyte region with a variable content of CD4-positive T lymphocytes. Apart from these two studies, the majority of other immunohistological reports on the human splenic white pulp correspond to our results. With exception of the study by van Krieken and te Velde, the existence of the perifollicular zone went, however, undetected in all these investigations (11). This is also true for other studies, who investigated the distribution of macrophages and dendritic cells in human spleens and described accumulations of monocytes or granulocytes around the follicles. CD147 is a member of the immunoglobulin superfamily and is a highly glycosylated cell surface protein. CD147 is considered an adhesion molecule and has been shown to induce matrix metalloprotease expression by neighboring epithelial cells. It is expressed in various tissues, including brain, leukocytes, endothelial cells, and most tumor cell lines (12,13). In addition, CD147 is expressed on erythrocyte lineage cells throughout erythroid development, including in mature erythrocytes. Apparently, the interaction of CD147 on erythrocytes and its potential ligand expressed on splenic vasculature is likely to be critical in the recirculation of mature erythrocytes from spleen into the general circulation. We postulate that the role of CD147 in erythrocyte circulation may be in its capacity as an inducer of matrix-degrading metalloproteases, thus actively participating in the exit of circulating erythrocytes from the spleen. Indeed, it was shown that CD147 increases the expression of interstitial collagenase, stromelysin, and gelatinase in stromal fibroblasts (14). However, other explanations cannot be ruled out. For instance, CD147, like CD47, may be part of the recognition of erythrocytes as self, and that blockade of this molecule may prevent erythrocytes from escaping the splenic reticuloendothelial system and possibly aquaporin water channels may contribute in

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this mechanism. Alternatively, it is possible that ligation of CD147 alters erythrocyte deformability, leading to their mechanical trapping in the spleen. A further possibility is that ligation of CD147 may alter erythrocyte adhesion through an intracellular signaling mechanism. CD147 increases the expression of interstitial collagenase, strome- lysin, and gelatinase in stromal fibroblasts. For e.g Aquaporin-1 (AQP-1), the universal water channel, is responsible for rapid response of cell volume to changes in plasma tonicity. In the membrane of the red cell the concentration of the protein is tightly controlled. It has been shown that AQP-1 is partially lost during *in vitro* maturation of mouse reticulocytes and that it is associated with exosomes, released throughout this process. AQP-1 in young reticulocytes localizes to the plasma membrane and also in endosomal compartments and exosomes, formed both *in vitro* and *in vivo* thus strongly suggesting the role of aquaporins in blood cell cyclization.Recent studies also show that aquaporin water channels are expressed on the CD cells and CD cell population in the spleen is remarkably decreased in aquaporin null mice thus further suggesting their role in immunogenicity and blood cell trafficking (15).

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