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State of the art

Mechanisms of sickle cell alloimmunization☆

Mécanismes de l'allo-immunisation anti-érythrocytaire au cours de la drépanocytose

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Abstract

Red blood cell (RBC) alloimmunization can be a life-threatening complication for patients with sickle cell disease (SCD) receiving therapeutic transfusions. Despite provision of extended antigen-matched donor RBCs, patients continue to develop antibodies due to high degree of polymorphisms in the immunogenic antigens in individuals of African ancestry. Identification of biomarkers of alloimmunization in this patient population is therefore of great interest and will help to identify in advance patients most likely to make antibodies in response to transfusion. We have recently identified altered T cell responses and innate immune abnormalities in alloimmunized SCD patients. In this paper, we summarize this work and propose our working model of how innate immune abnormalities can contribute to pathogenic T cell responses in alloimmunized SCD patients. We believe that unravelling the basis of such altered interactions at the cellular and molecular level will help future identification of biomarkers of alloimmunization with the goal that this information will ultimately help guide therapy in these patients.

Keywords: Sickle cell; Alloimmunization; Heme; Heme oxygenase; Tregs; Th1; Transfusions

Résumé

L'allo-immunisation vis-à-vis des antigènes de groupes sanguins peut représenter un risque majeur pour les patients drépanocytaires polytransfusés. Malgré la mise à disposition de CGR polyphénotypés étendus, les patients drépanocytaires ont un niveau élevé d'allo-immunisation en partie du fait du polymorpgisme des groupes sanguins entre donneurs et receveurs d'origine Africaine. Il est donc important de pouvoir déterminer chez ces patients des biomarqueurs associés à un risque élevé d'allo-immunisation. Nous avons récemment montré qu'il existait des altérations au niveau des T régulateurs chez les patients allo-immunisés, ainsi que des anomalies de l'immunité innée. Dans cette revue, nous proposons un modèle permettant d'expliquer comment l'altération de la réponse immune innée peut être impliquée dans la physiopathologie de la réponse T chez les patients immunisés. La mise en évidence de ces interactions pourra permettre dans le futur de caractériser les biomarqueurs associés à l'allo-immunisation et ouvrir la voie à de nouvelles thérapeutiques préventives vis-à-vis de l'allo-immunisation anti-érythrocytaire.

Mots clés : Drépanocytose ; Allo-immunisation ; Hème ; Hème oxygénase ; Tregs ; Th1 ; Transfusion

1. Introduction

SCD results from a mutation in the β-globin gene which causes hemoglobin (Hb) S to polymerize when deoxygenated, forming rigid polymers within RBCs. Hb S containing RBCs are deformed in sickle-prone conditions, resulting in chronic hemolytic anemia, shortened RBC survival in circulation, increased reticulocytosis, periodic painful vaso-occlusive crises (VOCs), and end organ damage due to persistent tissue hypoxia [1]. RBC transfusions remain a very important modality of treatment for patients with SCD with majority (60–90%) of patients receiving RBC transfusions in their lifetime [2]. Its use has been in primary and secondary stroke prophylaxis and treatment,

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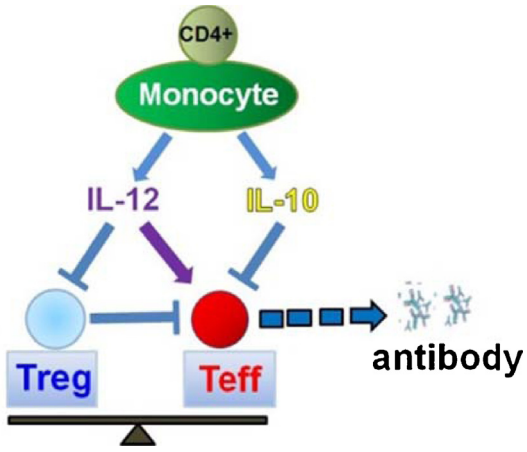

Fig. 1. Working model of monocyte control of T cells that leads to antibody production by B cells. Balance between Tregs and effector T cell (Teff) is dictated by cytokines secreted by T cell-monocyte interactions.

acute chest syndrome treatment and preoperative prophylaxis [3]. Despite its benefits, RBC transfusion results in alloimmunization in approximately 20–50% of patients with SCD [4]. Alloantibodies can cause delayed hemolytic transfusion reactions which in SCD patients can trigger hyperhemolysis, a life-threatening poorly understood phenomena in which the transfused and the patient's own RBCs are destroyed [4]. In addition, finding compatible units for patients with alloantibodies can be difficult and identifying and characterizing the antibodies can be costly, time-consuming and laborious, causing transfusion delays. As such, alloimmunization is associated with morbidity and mortality in chronically transfused SCD patients. However for the indications described above, few additional/alternative therapeutic options besides transfusion exist. Differences in minor (non-ABO) blood group antigens between mostly Caucasian blood donors and transfusion recipients who are of African descent are mainly responsible for formation of alloantibodies [5]. Even with provision of Rh-D, -C, and -E antigen-matched donor RBCs, patients continue to develop Rh antibodies, which may in part be due to genetic diversity of the *RH* locus in donors of African ancestry; many of these antibodies are considered clinically significant [6]. This highlights the need for better characterization of triggers of alloimmunization and identification of risk factors in this highly vulnerable population. Genetic as well as acquired patient-related factors are likely to influence the process of alloimmunization. In a small study of chronically transfused patients with SCD, we recently reported reduced peripheral regulatory T cell (Treg) suppressive function (in the absence of accessory cells) and altered Th responses with higher circulating IFN-α (Th1 cytokine) but lower IL-10 (anti-inflammatory) cytokine levels in antibody responders as compared to non-responders [7]. These data are consistent with a model in which a generalized immune dysregulation exists in SCD alloimmunized patients with an imbalance between the regulatory (Tregs) and effector (Th) cells, possibly due to an underlying inflammatory state [8]. As a result, the model predicts that the likelihood of antibody production is increased (Fig. 1) since Tregs can suppress B cells either directly [9,10] or indirectly through inhibition of activation/expansion of effector Th cells which in turn control IgG antibody responses. Understanding how Treg/Th differentiation and expansion are controlled is thus likely to provide an explanation of how alloimmunization may ensue.

2. Heme and heme oxygenase I

Heme oxygenase 1 (HO-1) is expressed in various cell types and its expression can be induced in response to its substrate heme as well as acute stress stimuli [11]. Through its enzymatic activity, HO-1 breaks down the pro-oxidant heme into iron, bilirubin and carbon monoxide, thereby conferring cytoprotective and anti-inflammatory effects via heme breakdown products as well as by reducing intracellular heme availability [12–17]. Deficiency of HO-1 in mice, and in the one reported case in human is associated with chronic inflammatory state [18]. HO-1 is upregulated in SCD [19–21]. Furthermore, modulation of HO-1 expression in mouse models appears to affect vascular inflammation and vaso-occlusion with high HO-1 levels increasing microvasculature blood flow whereas attenuated HO-1 levels associated with increased red blood stasis [12,15,22]. In non-SCD setting, HO-1 is considered immunosuppressive as it was shown to inhibit T lymphocyte proliferation [11], block maturation of dendritic cells (DCs) and inhibit proinflammatory and allogeneic immune responses [23,24]. In myeloid derived cells (specifically monocyte/macrophage/DCs), HO-1 expression inhibits inflammatory cytokine secretion (IL-6, IL-12, TNFα, IL-1β) and increases regulatory cytokine (IL-10) expression [25–27] HO-1 levels/activity in response to its substrate (e.g. hemin) can thus be thought of as a critical parameter to switch the proinflammatory activity of monocyte/macrophages into an immunoregulatory one.

3. T cell responses to hemin in SCD alloimmunization

Human monocytes which are generally regarded as precursors of tissue macrophages and dendritic cells (DCs) [28], are increasingly recognized for their ability to trigger and polarize Th responses [29,30] as well as to both stimulate and suppress T-cell responses [30,31]. Such T cell-monocyte interactions are likely to occur in secondary lymphoid organs such as the spleen, but also in inflamed tissues [30]. In a group of patients with or without a history of alloimmunization, we found differences in monocyte control of Treg/Th cells in alloimmunized vs non-alloimmunized SCD patients in part due to altered secretion/responsiveness to IL-12 [32]. Surprisingly, baseline HO-1 levels in CD16+ monocyte subset from alloimmunized patients were lower as compared to non-alloimmunized patients [32]. More importantly, in response to hemin, a surrogate marker for transfused RBC breakdown products, HO-1 levels were still lower and alloimmunized monocytes were unable to dampen Th1 proliferation and were less effective in increasing Treg expansion as compared to non-alloimmunized group [32]. Since the monocyte/macrophage system of the spleen and liver is responsible for extravascular clearance of transfused RBCs, as a working model, we hypothesize that inadequate