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Patrolling Monocytes in Sick Cell hemolytic Conditions

Yunfeng Liu*, Hui Zhong, Francesca Vinchi, Avital Mendelson, and Karina Yazdanbakhsh
Lindsley F. Kimball Research Institute, New York Blood Center, 310 East 67th Street, New York, NY 10065

Abstract

Patients with sickle cell disease (SCD) suffer from intravascular hemolysis associated with vascular injury and dysfunction. Painful vaso-occlusive crisis (VOC) involving increased attachment of sickle erythrocytes and activated leukocytes to damaged vascular endothelium is a hallmark of SCD. Patrolling monocytes, which normally scavenge damaged cells and debris from the vasculature, express higher levels of anti-inflammatory heme oxygenase 1 (HO-1), a heme degrading enzyme with anti-cytotoxic and anti-inflammatory properties. Recent data show that patients with SCD have a novel subset of patrolling monocytes expressing very high levels of HO-1 (HO-1^{hi}) which are decreased in numbers in patients who had a recent VOC episode. This patrolling monocyte subset was responsible for protection of endothelium against sickle RBC stasis in an experimental model. This raises the possibility that patrolling monocytes may also offer protection against vascular endothelium damage in hyperhemolytic conditions in SCD.

Résumé

Les patients drépanocytaires présentent une hémolyse intravasculaire associée à un effet délétère sur les vaisseaux. Au cours des crises vaso-occlusives (CVO) caractéristiques de la maladie, les GR drépanocytaires et les leucocytes altèrent la paroi des vaisseaux. Les monocytes en circulation ont une expression augmentée de d'hème Oxygénase 1 (HO-1), qui dégrade les débris, avec des caractéristiques anti-inflammatoires. Des données récentes ont montré que les drépanocytaires ont des monocytes circulants avec un taux élevé de HO-1, qui diminue au cours des CVO. Ces monocytes sont responsables, dans un modèle murin, de la protection de l'endothélium vis-à-vis de la stase des globules rouges au cours de la drépanocytose. Ils pourraient aussi jouer un rôle de protection vis-à-vis des effets de l'hyperhémolyse post-transfusionnelle sur l'endothélium vasculaire.

Keywords

patrolling monocytes; HO-1; vaso-occlusion; sickle cell disease

*Corresponding author: Yunfeng Liu, PhD, yliu@nybc.org.

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Painful vaso-occlusive crisis (VOC) is the most common complication of sickle cell disease (SCD), and acute VOC is the main reason for emergency visits and hospitalization for patients with SCD.¹ Repeated episodes of VOC contribute to morbidity and multi-organ injury in patients with SCD.² Currently, the molecular mechanisms resulting in VOC remain incompletely understood. It is now commonly accepted that microvascular occlusion by rigid sickle RBCs and inflammatory cells contribute to VOC.^{3–5} Patients with SCD also suffer from intravascular hemolysis in which fragile sickle RBCs release hemoglobin and its product, heme, into the circulation. These products cause oxidative damage and an inflammatory cascade in the vasculature, further increasing the adherence of sickle RBC and inflammatory cells to the activated endothelium, and heightening the risk of VOC as indicated by the protective role of heme scavenging agent, hemopexin in this setting.^{6–8} It therefore follows that VOC preventive strategies should include ways to protect the endothelium against hemolysis-induced injury and to prevent attachment of sickle RBCs to the endothelium. Heme oxygenase 1 (HO-1) plays an important role in response to hemolysis by degrading heme into iron, carbon monoxide, and biliverdin, and further conferring cyto-protective, anti-inflammatory and anti-oxidant effects through its breakdown products.⁹ Induction of HO-1 plays an important role in the protection of endothelium and tissues against hemolysis and oxidative stress.^{10–12} In addition, HO-1 byproducts inhibit the adherence of sickle RBCs to endothelial cells (ECs).¹³ Increase HO-1 level through HO-1 gene delivery is beneficial in sickle mice by degrading pro-oxidative heme, releasing anti-inflammatory heme degradation products CO and biliverdin/bilirubin into circulation, activating cytoprotective pathways and inhibiting vascular stasis at sites distal to transgene expression.¹⁴ We and others have shown that circulating monocytes in humans express higher level of HO-1 than other blood leukocytes, with the highest expression in the so-called endothelial patrolling monocytes (PMo).^{15,16} Monocytes have long been considered as a developmental intermediate between bone marrow precursors and tissue macrophages and dendritic cells, and not as effector cells. However, more recent studies have found that PMo crawl on the luminal side of ECs and can be regarded as the “accessory cells” of the endothelium.¹⁷ They phagocytose cellular debris derived from damaged ECs,¹⁸ and play important roles in some diseases including atherosclerosis¹⁹ and Alzheimer’s disease,²⁰ where absence of endothelial protection by PMo renders ECs more susceptible to atherosclerotic plaque growth or amyloid β deposition in Alzheimer’s disease, respectively.

We recently reported that a novel circulating PMo subset expressing very high levels of HO-1 (HO-1^{hi}) is present exclusively in SCD patients and that patients with a recent VOC episode have reduced numbers of HO-1^{hi} PMo.²¹ We showed that PMo clear hemolysis-damaged ECs with a concomitant upregulation of HO-1. ICAM-1 and PS expression on ECs was shown to be required for induction of HO-1^{hi} expression in PMo when cultured with hemolysis-damaged ECs. We went on to show that mice lacking PMo were susceptible to hemolysis-induced EC activation. These mice presented with vascular stasis in the presence of sickle, but not wildtype (WT) RBCs and transfer of PMo partially ameliorated the stasis phenotype. These data have led to the proposal that along with hemopexin and haptoglobin, PMo are an important line of defense against hemolytic damage to the endothelium,²² highlighting the important role of PMo as housekeepers of vasculature in SCD. This also raises the possibility that perturbations in PMo numbers or function may also play a role in

hyperhemolytic conditions in SCD. It is interesting to note that many patients presenting with severe delayed hemolytic transfusion reactions (DHTR) present with painful episodes, mimicking VOC. We posit that patients with deficiency in PMo will be at a higher risk of not only VOC, but also in conditions where heme levels are elevated including DHTR. This raises the possibility that PMos may be a novel biomarker of disease severity and that low basal numbers/function of PMo may increase the risk of patients having more severe SCD complications. Longitudinal studies to follow patients as they develop SCD complications needs to be performed to confirm these hypotheses. We speculate that increasing numbers/function of PMo used either prophylactically or therapeutically afford protection against VOC and DHTRs. Ongoing studies in our group are focused on examining various approaches to manipulate PMo numbers and functions to probe these hypotheses with the goal that we may be able to identify a novel strategy that will be helpful to prevent and treat the vascular injury as a result of chronic hemolytic state in these patients.

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