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Commentary OMICS International

Neutrophil Adhesion and Migration: Another Role of the Glucose-6-Phosphate Transporter

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Commentary

Glycogen storage disease type Ib (GSD-Ib) is caused by a deficiency in a glucose-6-phosphate transporter (G6PT) that belongs to the solute-carrier-37 family of endoplasmic reticulum (ER)-associated sugar-phosphate/phosphate exchangers [1,2]. The primary *in vivo* function of the ubiquitously expressed G6PT protein is to translocate G6P from the cytoplasm into the ER lumen where it couples with either the liver/kidney/intestine-restricted glucose-6-phosphatase-α (G6Pase-α) or the ubiquitously expressed G6Pase-ß to hydrolyze G6P to glucose and phosphate [3,4]. The G6PT/G6Pase-α complex maintains interprandial glucose homeostasis and the G6PT/G6Pase-ß complex maintains neutrophil energy homeostasis and functionality. Therefore, GSD-Ib is an autosomal recessive metabolic and immune disorder characterized by impaired glucose homeostasis, neutropenia and neutrophil dysfunction [3,4]. Recently, we showed that G6PT-deficient neutrophils from GSD-Ib patients receiving granulocyte-colony stimulating factor (G-CSF) therapy exhibited impaired energy homeostasis and function [5], suggesting that G6PT-regulated G6P metabolism is important for neutrophil function. However, G-CSF failed to correct impaired neutrophil energy homeostasis in GSD-Ib [5].

Neutrophils are the most abundant leukocytes in peripheral blood that play a critical role in host defence by eliminating invading pathogens. Upon infections, neutrophils migrate from peripheral blood stream into inflammatory sites which is a tightly regulated process involving three distinct steps, selectin-mediated rolling, firm adhesion via integrins and transmigration into infected tissues [6]. Neutrophil adhesion is mediated by lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1), members of the ß2 integrin family that are predominantly expressed on neutrophils [6,7]. LFA-1 and Mac-1 are heterodimers composed of a distinct α subunit (CD11a for LFA-1 and CD11b for Mac-1) and a ß subunit (CD18). Studies have shown that mutations in CD18 cause leukocyte adhesion deficiency syndrome type I, characterized by life-threatening recurrent bacterial infections resulting from severe defects in neutrophil/monocyte emigration to extravascular sites of inflammation [8]. However, genetic mutations in CD11a and CD11b have not been reported.

More recently, our research group demonstrated that GSD-Ib ($G6pt^{-/-}$) mice exhibited neutropenia in both blood and bone marrow, and G-CSF treatment increased both the frequency and the absolute neutrophil counts in the peripheral bloodstream [9]. However, neutrophil recruitment into the peritoneal cavity during peritonitis remains impaired in G-CSF-treated $G6pt^{-/-}$ mice [9]; suggesting G-CSF therapy cannot rescue impairment in neutrophil adhesion and migration. We also provided evidence showing that the decrease in the expression of CD11a and CD11b on $G6pt^{-/-}$ neutrophils underlies, at least in part, the impairment in neutrophil recruitment to the inflammation sites. Both CD11a and CD11b are glycoproteins [10]. While the glycosylated CD11b (170 kDa) was the primary species identified in wild-type neutrophils, both glycosylated and unglycosylated (~130 kDa) CD11b were found in G6PT-deficient neutrophils [9]. We have shown that impaired neutrophil recruitment into the peritoneal cavity is a characteristic of G6Pase-ß deficiency [11]. Moreover, G6Pase-ß deficiency is associated with a major defect of protein glycosylation [12]. The G6PT/G6Pase-ß complex regulates glucose homeostasis in the ER of neutrophils and the ER lumen serves as a critical site in protein maturation and its biochemical environment is uniquely designed to facilitate optimal post-translational modifications [13]. Therefore, G6PT may regulate protein glycosylation.

G-CSF is widely used to treat neutropenia patients including GSD-Ib and G6Pase-ß deficiency [14,15]. We have shown that G-CSF cannot correct impaired energy homeostasis in G6PT-deficient neutrophils in human GSD-Ib patients [5]. We recently showed that this growth factor also fails to rescue impaired neutrophil recruitment in $G6pt^{-/-}$ mice [9], highlighting the limitations of G-CSF in treating patients exhibiting neutrophil dysfunction. Understanding the functional roles of G6PT and/or G6Pase-ß in neutrophils would facilitate the development of novel therapeutic approaches to address neutrophil dysfunction.

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