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Human monocytes stimulated by Shiga toxin 1a via globotriaosylceramide release proinflammatory molecules associated with hemolytic uremic syndrome

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ABSTRACT

The life-threatening sequela of hemorrhagic colitis induced by Shiga toxins (Stx)-producing *Escherichia coli* (STEC) infections in humans is hemolytic uremic syndrome (HUS), the main cause of acute renal failure in early childhood. The key step in the pathogenesis of HUS is the appearance of Stx in the blood of infected patients because these powerful virulence factors are capable of inducing severe microangiopathic lesions in the kidney. During precocious toxemia, which occurs in patients before the onset of HUS during the intestinal phase, Stx bind to several different circulating cells. An early response of these cells might include the release of proinflammatory mediators associated with the development of HUS. Here, we show that primary human monocytes stimulated with Shiga toxin 1a (Stx1a) through the glycolipid receptor globotriaosylceramide released larger amounts of proinflammatory molecules (IL-1β, TNFα, IL-6, G-CSF, CXCL8, CCL2, CCL4) than Stx1a-treated neutrophils. The mediators (except IL-1β) are among the top six proinflammatory mediators found in the sera from patients with HUS in different studies. The molecules appear to be involved in different pathogenetic steps of HUS, i.e. sensitization of renal endothelial cells to the toxin actions (IL-1β, TNF-α), activation of circulating monocytes and neutrophils (CXCL8, CCL2, CCL4) and increase in neutrophil counts in patients with poor prognosis (G-CSF). Hence, a role of circulating monocytes in the very early phases of the pathogenetic process culminating with HUS can be envisaged. Impairment of the events of precocious toxemia would prevent or reduce the risk of HUS in STEC-infected children.

Keywords:
Proinflammatory mediators
Hemolytic uremic syndrome
Human leukocytes
Shiga toxins
Monocytes

Abbreviations: Gb3Cer, globotriaosylceramide; HC, hemorrhagic colitis; HUS, hemolytic uremic syndrome, Stx, Shiga toxins; Stx1a, Shiga toxin 1a; Stx2a, Shiga toxin 2a; STEC, Shiga toxins-producing *Escherichia coli*; TLR4, Toll-like receptor 4.