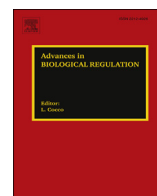




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Sphingolipids in neutrophil function and inflammatory responses: Mechanisms and implications for intestinal immunity and inflammation in ulcerative colitis

Mel Pilar Espaillat ^{a, b}, Richard R. Kew ^c, Lina M. Obeid ^{b, d, *}

^a Department of Molecular Genetics and Microbiology, Stony Brook University, Stony Brook, NY 11794, USA

^b Department of Medicine, Stony Brook University, Stony Brook, NY 11794, USA

^c Department of Pathology, Stony Brook University, Stony Brook, NY 11794, USA

^d Northport Veterans Affairs Medical Center, Northport, NY 11768, USA

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ABSTRACT

Bioactive sphingolipids are regulators of immune cell function and play critical roles in inflammatory conditions including ulcerative colitis. As one of the major forms of inflammatory bowel disease, ulcerative colitis pathophysiology is characterized by an aberrant intestinal inflammatory response that persists causing chronic inflammation and tissue injury. Innate immune cells play an integral role in normal intestinal homeostasis but their dysregulation is thought to contribute to the pathogenesis of ulcerative colitis. In particular, neutrophils are key effector cells and are first line defenders against invading pathogens. While the activity of neutrophils in the intestinal mucosa is required for homeostasis, regulatory mechanisms are equally important to prevent unnecessary activation. In ulcerative colitis, unregulated neutrophil inflammatory mechanisms promote tissue injury and loss of homeostasis. Aberrant neutrophil function represents an early checkpoint in the detrimental cycle of chronic intestinal inflammation; thus, dissecting the mechanisms by which these cells are regulated both before and during disease is essential for understanding the pathogenesis of ulcerative colitis. We present an analysis of the role of sphingolipids in the regulation of neutrophil function and the implication of this relationship in ulcerative colitis.

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* Corresponding author. Department of Medicine, Stony Brook University, Health Science Center, L-4, 179, Stony Brook, NY 11794-8430, USA.

E-mail address: lina.obeid@stonybrookmedicine.edu (L.M. Obeid).

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1. Introduction

In the last three decades, it has become evident that sphingolipids are essential and critical regulators in the cell. The focus on bioactive sphingolipid research in signaling mechanisms has expanded from its origin in PKC regulation to multiple biological processes in immunity, inflammation, cellular growth, differentiation, proliferation, apoptosis, metabolism, and related pathologies (Abdel Hadi et al., 2016; Hannun et al., 1986; Hannun and Obeid, 2008; Pyne et al., 2016). Sphingolipids comprise a large class of structural and bioactive lipids that are metabolized in an interconnected network regulated by a large family of enzymes. Among the biologically active sphingolipids, sphingosine-1-phosphate (S1P) is one of the most characterized in immune and inflammatory processes. S1P regulates the differentiation of immune cells, production of inflammatory mediators and is an established regulator of immune trafficking. S1P can bind and activate five G-protein coupled S1P receptors (S1PR1–5) to mediate intracellular signaling and regulate cell function. The critical role of S1P and other sphingolipids in inflammation is underscored by the approval of FTY720 for the treatment of multiple sclerosis. FTY720 is a sphingosine analogue that alters lymphocyte trafficking by sequestering cells in secondary lymphoid organs preventing their migration towards sites of inflammation and delaying their return to the circulation. Upon phosphorylation by sphingosine kinase 2 (SK2), FTY720-phosphate functions as an agonist and modulator of G-protein coupled S1PRs, primarily S1PR1 in lymphocytes (Blankenbach et al., 2016). Modulators of S1PR signaling can have implication for diseases characterized by excessive lymphocyte recruitment such as inflammatory bowel disease (IBD) (Izzo et al., 2016; Rivera-Nieves, 2015). In fact, promising results in current clinical studies support the notion that sphingosine-1-phosphate (S1P) signaling and other sphingolipid metabolites may be involved in regulating inflammation in ulcerative colitis (UC) (Kunkel et al., 2013). The pathogenesis of UC is characterized by disruption of the innate and adaptive immune mechanisms that maintain intestinal homeostasis (Dieleman et al., 1998; Neurath, 2014). As effectors of innate immunity that can direct adaptive immune function, neutrophils represent an important research area in homeostasis of the gut. Neutrophils require regulation at multiple points to avoid collateral tissue damage during intestinal inflammation. In diseases like UC, characterized by high number of neutrophils in the intestinal lamina propria, the persistence of these cells contributes to tissue injury and the cycle of chronic inflammation that ensues. This review will highlight the current and expanding role of bioactive sphingolipids in UC. We summarize the mechanisms of neutrophil regulation in health and intestinal inflammation. Finally, we present an analysis of the scientific evidence supporting bioactive sphingolipids in neutrophil inflammatory responses, and discuss the implication of this relationship in the pathogenesis of UC.

2. Sphingolipid metabolism

Ceramide is considered the central metabolite of the pathway and is generated either in a *de novo* fashion at the endoplasmic reticulum (ER) or through the metabolism of other sphingolipids in cellular compartments (Siow et al., 2015). Ceramide structure consists of a sphingoid backbone N-acylated by one of six ceramide synthases (CerS). *De novo* N-acylation first results in the generation of dihydroceramide species of varying acyl chain lengths before a desaturase catalyzes the final reaction in ceramide synthesis. Subsequently, ceramides are transported to the Golgi where ceramide is metabolized to sphingomyelin by sphingomyelin synthase (SMS), to ceramide-1-phosphate (C1P) by a ceramide kinase (CerK) or to glucosylceramide and complex glycosphingolipids by glucosylceramide synthase (Carroll et al., 2015). From here, these sphingolipid metabolites can be transported by membrane transport to different compartments to regulate cellular processes. The reverse reaction can also occur, where sphingomyelin, C1P and glycosphingolipids can be broken down by sphingomyelinase (SMase), ceramide phosphatase and glycosidases, respectively, to increase the pool of ceramide in the cell. Another axis of ceramide metabolism generates S1P, a critical regulator of immune function. In this pathway, ceramide is deacetylated by a ceramidase (CDase) to generate sphingosine. Sphingosine is rapidly phosphorylated by sphingosine kinases (SK1 and SK2) to

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