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Lipids as bioeffectors in the immune system

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Abstract

Lipids, in addition to serving as fuel stores and structural components of cell membranes, act as effectors and second messengers in a variety of biological processes including those associated with the immune system. These lipid mediators and regulators differ in structural composition and exert a diverse array of effects on cellular functional activities including those linked to homeostasis, immune responsiveness, and inflammation. They function as intercellular mediators and at the intracellular level act as critical conduits of external stimuli in signal transduction cascades. Lipid derived messengers and their receptors also may interact with other signaling molecules. Exogenous compounds such as cannabinoids share functionally relevant receptor binding domains with those for endogenous lipid signaling ligands and have the potential to alter transductional cascades linked to immune functional activities.

Keywords: Eicosanoids; Endocannabinoids; Leukotrienes; Lipids and immunity; Lipid bioeffectors; Lipoxins; Lysophospholipids; Prostaglandins

Introduction

The immune system in the mammalian host is comprised of an array of cell types that function in a coordinate fashion in immune cell maturation, responsiveness to microbial agents, and tissue damage and repair. This multiplicity of functional activities is operative within the framework of a complex network of cell contact-dependent interactions and cellular signaling mediated through a plethora of soluble factors. Many of these are products of genes that are inducibly expressed in response to a variety

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of stimuli. However, products of constitutively expressed genes also may play a role in immunoregulatory activities. The "cross-talk" between disparate cell types and extracellular signaling molecules does not occur in a disjunctive fashion but is operative contextual to a cascade regulation mode that maintains overall immune system homoeostatic balance. This complex array of cell types and cross-talking signaling factors is characterized by "built-in" redundancy so that failure in a given system often can be compensated. This interactive process comes into play during acute inflammation (Lawrence et al., 2002). Tissue release of vasoactive and chemotactic mediators in response to infection, cell injury, or damage results in local vasodilation, increased regional blood flow, and decreased velocity of blood flow. Consequent increase in vascular permeability leads to loss of plasma proteins and fluid into tissues, upregulation of adhesion molecules on endothelial cells, and release of chemotactic factors that facilitate extravasation. Exudation is followed by the influx of neutrophils to the site of pathogen invasion or tissue injury. A variety of pro-inflammatory mediators, representative of a diverse array of molecular classes, play a critical role at the onset of acute inflammation (Table 1). These include the amines histamine and bradykinin, the c3a and c5a components of complement, the cyclic nucleotide cGMP, a variety of adhesion molecules, pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin 1 (IL-1), and chemokines. This pro-inflammatory phase is marked by ingestion of necrotic cells and debris and is followed by non-inflammatory clearance of cells that have undergone apoptosis by macrophages and macrophage-like cells. During this latter phase, a shift in the balance of pro-inflammatory to anti-inflammatory factors occurs. Anti-inflammatory mediators include the amines adrenalin and noradrenalin, the c1q receptor of complement, the cyclic nucleotide cAMP, adhesion molecules such as the PS receptor, cytokines such as TGFβ and interleukin-10 (IL-10), and glucocorticoid steroid hormones.

Lipids play a critical role during the acute inflammatory process, both in a pro-inflammatory and anti-inflammatory capacity (Tables 2–5). Amides, such as ethanolamides, bind to and signal through cannabinoid receptors found in the central nervous system and on a variety of immune cells. These putative endogenous ligands of cannabinoid receptors have been linked to the modulation of gene expression of a spectrum of pro-inflammatory cytokines and immune regulatory factors. Lysophosphatidylcholine, an intermediate metabolite of phosphatidylcholine and the major phospholipid component of eukaryotic and prokaryotic cells, has been implicated as playing a role in cell proliferation, macrophage mitogenesis, activation of T-lymphocytes, and monocyte chemotaxis. Platelet-activating

Table 1
Mediators that regulate the acute inflammatory response

Mediator class	Pro-inflammatory	Anti-inflammatory
Amines	Histamine, bradykinin	Adrenalin, noradrenalin
Lipid mediators	PGE_2, PGI_2, LTB_4, LTC_4	PGJ_2, $PGA_{1/2}$, lipoxins
Complement	C3a, C5a	C1q receptor
Cyclic nucleotides	cGMP	cAMP
Adhesion molecules	E-selectin, P-selectin, ICAM-1, VCAM-1	$\alpha_v\beta_3$ integrin, TSP receptor, PS receptor
Cytokines	TNF, IL-1β, IL-6	TGF-β1, IL-10
Chemokines	IL-8 (CCL8), GRO/KC, MIP1α (CCL3), MCP1 (CCL2)	
Steroid hormones		Glucocorticoids