Progress in Lipid Research 52 (2013) 141–164

Contents lists available at SciVerse ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Bioactive lipid mediators in skin inflammation and immunity

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ARTICLE INFO

Article history:
Received 13 August 2012
Received in revised form 15 October 2012
Accepted 17 October 2012
Available online 1 November 2012

Keywords:
Skin
Eicosanoids
Endocannabinoids
Sphingolipids
Immunity
Inflammation

ABSTRACT

The skin is the primary barrier from the outside environment, protecting the host from injury, infectious pathogens, water loss and solar ultraviolet radiation. In this role, it is supported by a highly organized system comprising elements of innate and adaptive immunity, responsive to inflammatory stimuli. The cutaneous immune system is regulated by mediators such as cytokines and bioactive lipids that can initiate rapid immune responses with controlled inflammation, followed by efficient resolution. However, when immune responses are inadequate or mounted against non-infectious agents, these mediators contribute to skin pathologies involving unresolved or chronic inflammation. Skin is characterized by active lipid metabolism and fatty acids play crucial roles both in terms of structural integrity and functionality, in particular when transformed to bioactive mediators. Eicosanoids, endocannabinoids and sphingolipids are such key bioactive lipids, intimately involved in skin biology, inflammation and immunity. We discuss their origins, role and influence over various cells of the epidermis, dermis and cutaneous immune system and examine their function in examples of inflammatory skin conditions. We focus on psoriasis, atopic and contact dermatitis, acne vulgaris, wound healing and photodermatology that demonstrate dysregulation of bioactive lipid metabolism and examine ways of using this insight to inform novel therapeutics.

Contents

Abbreviations: AA, arachidonic acid; AEA, *N*-arachidonoyl ethanolamine; AG, arachidonoylglycerol; ALA, alpha-linolenic acid; BLT, leukotriene B receptor; C1P, ceramide-1-phosphate; CB, cannabinoid receptor; CER, ceramide; COX, cyclooxygenase; cPGES, cytosolic prostaglandin E synthase; $cPLA_2$, cytosolic phospholipase A_2; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; CYP, cytochrome P450; CysLT, cysteinyl leukotriene receptor; DAG, 1,2-diacylglycerol; DAGL, diacylglycerol lipase; DC, dendritic cells; DDC, dermal dendritic cells; DGLA, dihomo-gamma-linolenic acid; DHA, docosahexaenoic acid; DHET, dihydro-eicosatetraenoic acid; DNFB, 2,4-dinitrofluorobenzene; DS, dihydrosphingosine; EET, epoxyeicosatetraenoic acid; EO, ester-linked omega-hydroxy; EP, E prostanoid receptor; EPA, eicosapentaenoic acid; FAAH, fatty acid amide hydrolase; FLAP, 5-lipoxygenase-activating protein; GE, glycerol ester; GPCR, G protein-coupled receptor; H, 6-hydroxy-sphingosine; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HETrE, hydroxyeicosatrienoic acid; HODE, hydroxyoctadecadienoic acid; HPETE, hydroperoxyeicosatetraenoic acid; H-PGDS, haematopoetic prostaglandin D synthase; IFN, interferon; IL, interleukin; LA, linoleic acid; LC, Langerhans cell; LEA, linoleoyl ethanolamine; LG, linoleoylglycerol; LOX, lipoxygenase; L-PGDS, lipocalin-type prostaglandin D synthase; LT, leukotriene; LX, lipoxin; MAG, monoacylglycerol; MAGL, monoacylglycerol lipase; MaR, maresin; MCP, monocyte chemotactic protein; MMP, matrix metalloproteinase; mPGES, microsomal prostaglandin E synthase; N, non-hydroxy; NAE, *N*-acyl ethanolamine; NAPE, *N*-acyl-phosphatidylethanolamine; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; NAT, *N*-acyl transferase; NK, natural killer; OEA, oleoyl ethanolamine; P, phytosphingosine; PBMC, peripheral blood mononuclear cell; PC, phosphatidylcholine; PD, protectin; PE, phosphatidylethanolamine; PEA, palmitoylethanolamine; PG, prostaglandin; PGDH, hydroxyprostaglandin dehydrogenase; PG-EA, prostaglandin ethanolamide; PGFS, prostaglandin F synthase; PGI_2, prostacyclin; PGIS, prostacyclin synthase; PIP_2, phosphatidylinositol (4,5)-bisphosphate; PLA_2, phospholipase A_2; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; Rv, resolvin; S1P, sphingosine-1-phosphate; S, sphingosine; SEA, stearoyl ethanolamine; SM, sphingomyelin; $sPLA_2$, secretory phospholipase A_2; TGF, transforming growth factor; TRPV-1, transient receptor potential vanilloid-1; TX, thromboxane; UVR, ultraviolet radiation; VEA, vaccenoyl ethanolamine; VG, vaccenoylglycerol.

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0163-7827/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.plipres.2012.10.003

1. Introduction

The skin provides the principal barrier to the external environment. Because of this, it has a highly active immune system with which to control any entry by foreign antigens [1]. The cutaneous immune system is highly organised and regulated, encompassing aspects of both innate and adaptive immunity, as disruption of the skin barrier or alterations in the resident skin flora can present a serious hazard to the host's health [2]. The skin contains a varied profile of innate immune cells and mediators, including antimicrobial peptides, proteins of the complement system, and phagocytes such as neutrophils and macrophages that perform routine surveillance of cutaneous tissue in the pervading blood vessels [1,3]. Additionally, the skin is host to constituents of the adaptive immune system, and it is dysfunction of these that features prominently in pathological inflammatory skin conditions. These conditions can result from an inappropriate immune response to a non-infectious antigen, an excessive response to a minor threat, or failure to resolve an inflammatory response, leading to chronic inflammation, which is a feature of many pathological skin conditions [4].

Active within the cutaneous inflammatory and immune systems are a plethora of bioactive lipids. Of these, fatty acids have long been known to be important in human health [5] as components of structural lipids, precursors of bioactive mediators, signalling molecules and regulators of gene expression [6], activities reflected in the growing interest in the field of nutrigenomics (reviewed recently in [7]). The importance of fatty acids in the skin is widely acknowledged particularly in relation to the integrity of the epidermal barrier [8,9], where they also act as antimicrobial agents [10], whilst links between fluctuating lipid profiles and pathological skin conditions are constantly emerging [11]. Of particular interest in this review are the numerous bioactive metabolites of polyunsaturated fatty acids (PUFA), produced when, in response to various stimuli, PUFA are released from complex membrane or storage lipids and transformed to lipid mediators.

Eicosanoids, endocannabinoids and sphingolipids are potent bioactive lipids intimately involved in skin health through their considerable influence over skin inflammation and mediation of the cutaneous immune response by means of effecting both resident and infiltrating cells [11–13]. Importantly, the formation and actions of these lipid mediators depend to a great extent on the prevalence of precursor PUFA, and, as such, can be influenced by diet or manipulated by systemic supplementation and/or topical application [14–17]. This review addresses the involvement of members of these three families of lipids in cutaneous inflammation and immunity. In depth understanding of their functions in cutaneous cells will potentially enable manipulation of the lipid profile, and therefore metabolic pathways, in order to influence the inflammatory and immune processes that play key roles in skin health and pathology. Prevalence of skin disease remains high [18], and to date, there is still a lack of appropriate studies of bioactive lipid mediators in human tissue that would improve treatment modalities, assist biomarker discovery, and inform systems biology approaches, improving skin care and reducing the burden of skin conditions.