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Propionibacterium acnes and Sebaceous Lipogenesis: A Love–Hate Relationship?

Christos C. Zouboulis[1,2]

In this issue, Iinuma *et al.* show that *Propionibacterium acnes (P. acnes)*–conditioned medium and formalin-killed *P. acnes* augment intracellular lipid formation in hamster sebocytes by increasing the *de novo* synthesis of triacylglycerols. This commentary summarizes the current knowledge of the association of *P. acnes* with sebaceous lipogenesis, inflammation, and innate immunity, and points out the concurrent evidence that *P. acnes*–induced lipids may represent a recruitment of allies and/or enemies of the human skin.

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Dermatologists' understanding of the association of the gram-positive, anaerobic *Propionibacterium acnes* (*P. acnes*, formerly *Corynobacterium acnes*) with acne vulgaris has changed substantially over the past decade (Zouboulis *et al.*, 2005). *P. acnes* has successively been considered (i) a bacterium responsible for the development of acne lesions (Brown and Shalita, 1998), (ii) a microbial species with a role in aggravating acne but not in its initiation (Zouboulis, 2001), and (iii) a commensal bacterium whose presence may be skin protective and essential for innate immunity (Koreck *et al.*, 2003; Georgel *et al.*, 2005). Recent discoveries have transformed the concept of acne vulgaris from that of a simple temporary clinical problem to a model disease for investigating innate immunity.

The significance of the involvement of *P. acnes* in acne pathogenesis remains controversial, mainly owing to its presence in the resident microbiota of healthy skin (Leyden *et al.* 1998). The recent decoding of the *P. acnes* genome revived the possibility of a pathogenic role (Brüggemann *et al.*, 2004). This was further supported by the fact that *P. acnes* induces IL-12 and IL-8 protein production by primary human monocytes via a Toll-like receptor 2 (TLR2)-regulated pathway and that TLR2 is expressed on the cell surface of macrophages surrounding pilosebaceous follicles of acne lesions (Kim *et al.*, 2002). Moreover, functional TLR2 is also expressed in human keratinocytes and SZ95 sebocytes (Pivarcsi *et al.*, 2003; Oeff *et al.*, 2006). TLR2 and TLR4 expression was increased in the epidermis of acne lesions, and *P. acnes* was found to induce TLR expression in human keratinocytes *in vitro* (Jugeau *et al.*, 2005). On the other hand, *P. acnes* extracts have recently been implicated in the formation of microcomedones (Jarrousse *et al.*, 2007).

P. acnes and sebaceous lipids

In this issue, Iinuma *et al.* (2009) show that *P. acnes*-conditioned medium and formalin-killed *P. acnes* derived from several *P. acnes* strains augment intracellular formation of lipid droplets in hamster sebocytes by increasing the *de novo* synthesis of triacylglycerols *in vivo* and *in vitro*. *P. acnes* appears to participate directly in the augmentation of sebaceous lipogenesis through an increase in 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 (15d-PGJ2) production, leading to enhanced production of diacylglycerol acyltransferase 1–dependent triacylglycerol (Iwata *et al.*, 2005). These results indicate a direct role for *P. acnes* in the enhancement of sebaceous lipogenesis through *P. acnes*-derived soluble factor(s). The question of whether *P. acnes* and/or *P. acnes*-derived factors are largely responsible for the development of sebaceous lipids is considered below.

P. acnes, sebaceous lipogenesis, and inflammation

When applied directly to human sebocyte cultures *in vitro*, fatty acids such as arachidonic acid (AA), a long-chain, proinflammatory ω-6 fatty acid and precursor of leukotriene B_4 (LTB_4; Alestas *et al.*, 2006), and linoleic acid, an essential dietary fatty acid (Wróbel *et al.*, 2003), stimulate IL-6 and IL-8 synthesis and enhance the synthesis of sebaceous lipids. 5-Lipoxygenase (5-LOX) metabolizes AA to LTB_4, which induces recruitment and activation of neutrophils, monocytes, and eosinophils. It also stimulates the production of several proinflammatory

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cytokines and mediators that augment and prolong tissue inflammation. 5-LOX production is enhanced in the sebaceous glands of acne patients (Alestas *et al.*, 2006), and its *in vivo* inhibition reduces the production of proinflammatory sebaceous fatty acids as well as the number of inflammatory acne lesions (Zouboulis *et al.*, 2003). In addition, human sebocytes express functional platelet-activating factor receptors, which are involved in regulating the expression of inflammatory mediators, including cyclooxygenase-2 (COX-2), prostaglandin E_2 (PGE_2), and IL-8 (Zhang *et al.*, 2006c). COX-2 levels are enhanced in acne-involved sebaceous glands, where it augments sebaceous lipogenesis (Neufang *et al.*, 2001) and contributes to the high PGE_2 levels detected in AA-challenged human sebocytes *in vitro* (Alestas *et al.*, 2006).

Interestingly, LTB_4 binds and activates peroxisome proliferator–activated receptor-α (PPARα), which can modulate inflammatory responses in several cell types by inhibiting the expression of proinflammatory genes that regulate the production of cytokines, metalloproteinases, and acute-phase proteins (Delerive *et al.*, 2001). In addition, squalene peroxides—proinflammatory products of sebaceous lipid oxidation detected in acne—induce an initial upregulation of IL-6 production and secretion in cultured human keratinocytes that is counteracted by PPARα (Ottaviani *et al.*, 2006). On the other hand, COX-2 expression and PGE_2 production are enhanced by PPARγ agonists (Zhang *et al.*, 2006b). Moreover, 15d-PGJ2 has been reported to be an endogenous activator of PPARγ (Kliewer *et al.*, 1995; Ma *et al.*, 1998), and PPARγ agonists have been shown to augment lipogenesis (Trivedi *et al.*, 2006). PPARs are expressed in rat and human sebocytes *in vivo* and *in vitro* (Rosenfield *et al.*, 1999; Chen *et al.*, 2003; Alestas *et al.*, 2006; Trivedi *et al.*, 2006). They are regulated by fatty acid derivatives, control lipid and lipoprotein metabolism, and negatively regulate the transcription of inflammatory response genes. This is accomplished by antagonizing the AP-1, NF-κB, signal transducer and activator of transcription, and nuclear factor of activated T-cell signaling pathways and by stimulating the catabolism of proinflammatory eicosanoids (Weindl *et al.*, 2005).

Stearoyl coenzyme A desaturase, an enzyme responsible for the biosynthesis of monounsaturated fatty acids, is expressed by human sebocytes *in vivo* and *in vitro* (Georgel *et al.*, 2005; Harrison *et al.*, 2007). Monounsaturated fatty acids—mainly palmitic acid (C16:1) and oleic acid (C18:1), both of which are bactericidal against gram-positive organisms (Georgel *et al.*, 2005)—are produced by sebaceous glands, as is sapienic acid, another important antimicrobial lipid. Palmitic acid, oleic acid, and lauric acid have been proposed as active agents in an alternative natural antibiotic therapy for acne vulgaris (Georgel *et al.*, 2005; Nakatsuji *et al.*, 2009). Interestingly, the TLR2 ligand, bacteria-derived macrophage-activating lipopeptide-2, stimulates both stearoyl coenzyme A desaturase and fatty acid desaturase-2 mRNA expression in SZ95 sebocytes (Georgel *et al.*, 2005). Furthermore, free fatty acids in sebum are not likely to be solely bacterial products because cultured human sebocytes are able to produce free fatty acids in the absence of bacteria (Zouboulis *et al.*, 1999).

> The roles of *P. acnes* in sebaceous gland function remain uncertain.

Expression of liver X receptors (LXRs) α and β has been detected in SZ95 sebocytes (Russell *et al.*, 2007), and LXR ligands enhance the expression of LXRα, inhibit cell proliferation, and stimulate lipid synthesis (Russell *et al.*, 2007; Hong *et al.*, 2008). LXRs are members of the nuclear receptor superfamily, which plays a critical role in cholesterol homeostasis and lipid metabolism. They also decrease the expression of COX-2 and inducible nitric oxide synthase upregulated by treatment with polysaccharides, a function that indicates an important role for LXRα in the differentiation and inflammatory signaling in sebaceous glands (Hong *et al.*, 2008).

Neuropeptides are pilosebaceous stressors that enhance sebaceous lipogenesis. Corticotropin-releasing hormone (CRH) augments the synthesis of sebaceous lipids *in vitro* (Zouboulis *et al.*, 2002) and induces IL-6 and IL-8 release by human sebocytes, mediated by the CRH receptor 1 (Krause *et al.*, 2007). The CRH product adrenocorticotropic hormone causes the production of adrenal dehydroepiandrosterone to further induce skin inflammation (Alesci and Bornstein, 2000). CRH is expressed in human sebocytes *in vivo* and *in vitro* and is upregulated in acne-involved sebaceous glands (Ganceviciene *et al.*, 2009). These findings indicate that stress (Slominski *et al.*, 1999) may influence the development of clinical inflammation in early acne lesions.

Moreover, adrenocorticotropic hormone and the potent melanocyte-stimulating hormone (MSH) analog [Nle4, D-Phe7]-α-MSH increase squalene synthesis in primary human sebocytes (Zhang *et al.*, 2003). In line with the immunoregulatory actions of α-MSH, this peptide was also found to suppress basal and IL-1β–induced secretion of IL-8 in SZ95 sebocytes (Böhm *et al.*, 2002). Human sebocytes concomitantly express melanocortin (MC)-1 receptor and MC-5 receptor (Böhm *et al.*, 2002; Thiboutot *et al.*, 2001), but the MC-1 receptor is involved in pilosebaceous immunoregulation and inflammation (Ganceviciene *et al.*, 2007), whereas the MC-5 receptor is involved in sebocyte differentiation and lipogenesis (Zhang *et al.*, 2006a).

P. acnes, sebaceous lipogenesis, and innate immunity

The recent identification of phylogenetically distinct *P. acnes* clusters (McDowell *et al.*, 2005, 2008) challenges our understanding of the pathogenic nature of bacteria in acne pathogenesis and raises the possibility that certain *P. acnes* strains may cause opportunistic infection, exacerbating acne lesions. This latter possibility becomes more likely after a bacteria-protective biofilm is formed (Coenye *et al.*, 2008; Holmberg *et al.*, 2009). Indeed, phylogenetic clusters of *P. acnes* differ not only in their production of secreted proteins but also in their ability to induce different immune responses in the immunocompetent pilosebaceous unit. The major difference is the ability of *P. acnes* and its products to induce human β-defensin-2 (hBD2)

expression in keratinocytes and sebocytes (Nagy *et al.*, 2005, 2006), which may simulate immune cells by virtue of pathogen recognition and abnormal sebum lipid production (Koreck *et al.*, 2003), followed by inflammatory cytokine production. Although hBD2 has no direct antimicrobial effects on *P. acnes* (Nagy *et al.*, 2006), it does act synergistically with cathelicidin (Lee *et al.*, 2008). Psoriasin is also present in acne-involved sebaceous glands (Ganceviciene *et al.*, 2006). Thus, antimicrobial activity in pilosebaceous units is probably the result of several antimicrobial peptides—and antibacterial lipids (Georgel *et al.*, 2005)—acting together. In addition, only distinct strains of *P. acnes* can induce selective hBD2 and IL-8 expression in human keratinocytes through TLRs and induce keratinocyte cell growth *in vitro* (Nagy *et al.*, 2005). Finally, antibodies elicited by inactivated *P. acnes*–based vaccines exert protective immunity and attenuate IL-8 production in human sebocytes (Nakatsuji *et al.*, 2008).

P. acnes–induced lipids: recruitment of allies or enemies?

Although it is controversial whether *P. acnes* itself interacts with the sebaceous gland, Iinuma *et al.* (2009, this issue) conclude that an aggravation mechanism exists whereby soluble factor(s) released from hyperproliferated *P. acnes* diffuse through sebum in the sebaceous duct and reach the sebaceous glands and pilosebaceous units from a distance, allowing sebaceous lipogenesis and inflammatory reactions mediated by infiltrated immune cells to be enhanced.

Although lipogenesis and inflammation are induced by certain *P. acnes* strains, sebaceous glands also express proinflammatory cytokines and produce free fatty acids in the absence of bacteria. In addition, whereas topical and systemic antibiotics that reduce the number of follicular bacteria are successful anti-acne drugs, antibiotics effective in treating acne vulgaris also exhibit anti-inflammatory activity.

Various antimicrobial peptides are expressed in healthy skin without visible signs of inflammation, suggesting that (i) antimicrobial peptides may be induced in the absence of proinflammatory cytokines or chemokines and (ii) resident skin microbiota may facilitate antimicrobial peptide induction without inflammation. It was recently proposed that the beneficial effects of resident microbiota may be due to their ability to induce antimicrobial peptide expression, thereby supporting effective innate immunity (Georgel *et al.*, 2005; Schröder and Harder, 2006). The identification of *P. acnes* proteins that induce antimicrobial peptides without inducing proinflammatory cytokine/chemokine expression would promote healthy levels of antimicrobial peptides and, consequently, resistance to abnormal *P. acnes* colonization.

CONFLICT OF INTEREST

The author states no conflict of interest.

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An "Ice-Cold" TR(i)P to Skin Biology: The Role of TRPA1 in Human Epidermal Keratinocytes

Tamás Bíró[1] and László Kovács[1]

Recent studies have suggested the expression of numerous heat-sensitive transient receptor potential (TRP) ion channels in non-neuronal cell populations of the skin. In this issue, Atoyan *et al.* provide evidence that the noxious cold-activated TRPA1 is widely expressed in various human cutaneous cells and that it may be directly involved in the regulation of keratinocyte proliferation and differentiation and in cutaneous inflammatory responses.

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Thermosensitive transient receptor potential ion channels

Alteration in external temperature is a common challenge to homoeothermic organisms, initiating a coordinated response to maintain constant core temperature. Importantly, the sensory afferent as well as the majority of executive efferent mechanisms of the thermoregulatory response take place chiefly in the skin.

The key target molecules of temperature challenge are members of the large transient receptor potential (TRP)

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