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REVIEW

Lipid Metabolism Reprogramming of Immune Cells in Acne: An Update

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Abstract: Acne vulgaris is one of the most widespread skin conditions and the main reason for visiting a dermatologist. Inflammatory response and abnormal infiltrations of immune cells are the main pathogenesis of acne. The increased lipid is the prerequisite for the acne, and the perturbation of lipid composition and content is consistent with the severity of acne. Furthermore, the increased lipid production not only contributes to the occurrence and development of acne, but also sensitizes the function of immune cells. The lipid metabolic dysfunction aggravates the severity of local tissue and provides pro-inflammatory-cytokine cues, which indicates the crucial roles of lipid metabolism on immune cells. Recent advances have demonstrated the lipid metabolism reprogramming of various immune cells in acne lesion. The abnormal lipid accumulation, lipolysis, and fatty acid oxidation lead to the activation and differentiation of immune cells, which promotes the pro-inflammatory cytokines production. Thus, this review discusses the emerging role of lipid metabolism reprogramming of immune cells in the progress of acne and aims to constitute food for others' projects involved in acne research.

Keywords: acne vulgaris, inflammatory response, lipid, reprogramming

Introduction

Acne vulgaris (acne) is a chronic inflammatory skin disease of the sebaceous glands characterized by papules, nodulocystic lesions, and inflammation of the pilosebaceous follicles.[1] As the eighth most prevalent disease, acne affects an estimated 9.4% population of the world and 8.1% of China. Acne patients suffer from increased risk of psychiatric comorbidities specifically depression and suicidality.[2] The pathogenesis of acne is closely related to endocrine, hyperkeratinization, microorganisms and the overcolonization of pilosebaceous units. The upregulated androgens, especially testosterone and dihydrotestosterone, and hyperinsulinemia caused by insulin resistance induce sebocyte activation, leading to the increased sebum production.[3] The sebum accumulation creates a new environment that foster microorganisms putatively *Cutibacterium acnes* (*C. acnes*) proliferation.[4] The ensuring immune infiltration is triggered by the infections of *C. acnes*, accompanied with inflammatory factor secretion. These changes drive pilosebaceous follicles from homeostasis into an inflammatory state, which results in the form of microcomedone. Then the microcomedone evolves into a comedone contributing to the acne.

Inflammatory response throughout acne is the hallmark of acne, and multiplied in large quantities by microorganisms especially *C. acnes*. Abnormal infiltrations of innate immune cells, such as, monocytes, dendritic cells, neutrophils, macrophages, and adaptive immune cells, such as T lymphocytes and B lymphocytes, are thought to be crucial in the pathogenesis of acne.[5] Besides the effect of inflammation of immune cells, the lipid metabolism reprogramming of immune cells has been implied in the development of acne. Metabolic reprogramming first recognized a century ago is an approach for cells to support the requirements of growth and proliferation by altering the metabolic patterns including glucose, lipid, amino acid metabolism and so on.[6] Lipid metabolic dysfunction is considered to be the prerequisite in the progress of acne. Skin surface lipids (also called sebum) are comprised of triglycerides, waxy, squalene, free fatty acids and cholesterol.[7] The emerging insights arising from advanced techniques in metabolic analysis indicated that glycerophospholipids, fatty acyls, and sterol lipids were significant

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increased and prenol lipids, saccharolipids were decreased in the cases with acne compared to their normal counterparts.[8] In addition, the average level of triglycerides, unsaturated free fatty acids and cholesterol showed an increase trend from mild to moderate adolescent acne, which suggested the perturbation of lipid composition and content was consistent with the severity of acne.[9] The lipid metabolic dysfunction impaired the skin barrier function and provided several pro-inflammatory-cytokine cues. Recent advances have highlighted the lipid metabolic reprogramming in the immune cells, which is critical for the immune response and lipid metabolism. Lipid metabolic reprogramming interfered with immune responses by not only promoting immune cells proliferation and differentiation, but also modulating the immunological activity in acne. Accordingly, the lipid metabolic reprogramming in immune cells promote sebocytes to activate sebum synthesis and secretion, which further aggravate the acne lesions. Therefore, this review mainly discusses the reprogrammed lipid metabolic activities and the possible pathways in immune cells in the progress of acne, with the aim of providing a comprehensive foundation for the development of novel therapies.

Lipid Metabolism Reprogramming of Immune Cells in Acne

Neutrophils

Neutrophils, as the most abundant leukocytes in the peripheral blood, are characterized by multi-lobulated or rod-shaped nucleus and granules, that is why neutrophils are also known as polymorphonuclear neutrophils.[10] Neutrophils derived from the myeloid progenitor cells are differentiated and recruited to sites of inflammation after certain triggers.[11] The granules of neutrophils are classified into primary, secondary, and tertiary granules, consisting of myeloperoxidase, defensins, proteinase 3, collagenase, gelatinase, lactoferrin, and sialidase.[12] Neutrophils phagocytose, release granular contents and produce the reactive oxygen species (ROS) to eliminate pathogenic agents.[13,14] In addition to phagocytosis and degranulation, they release neutrophil extracellular traps (NETs) that resemble a net composed largely of decondensed chromatin where various cytoplasmic proteins are attached.[15,16] NETs play a vital role in capturing and digesting pathogenic agents like bacteria, fungi and viruses at the infection site to prevent severe tissue damage and promote the tissue healing.[17,18] Whereas excessive NETs alter the homeostasis of immune and further exacerbate the release of pro-inflammatory cytokines, which aggravate the severity of local inflammation and are detrimental to the local tissue.[19,20]

A notable increased proportions of infiltrated neutrophils were observed around the acne lesions, less than 48 h after their development compared to the healthy individuals.[21] Consistently, neutrophil gelatinase-associated lipocalin, also named lipocalin 2 (LCN-2), were markedly upregulated in the sebaceous glands and hair follicles of patients with acne.[22] LCN-2 initially isolated from neutrophils, is a novel adipocytokine responsible for the transportation of small lipophilic molecules, such as steroids, fatty acids, lipopolysaccharides, etc.[23] As a vital regulator of lipid metabolism, LCN-2 causes a wide spectrum of biological effects, including infections, cell differentiation, apoptosis, liver injury, and even tumorigenesis.[24–26] The level of LCN-2 was reported to be positive correlation with obesity and hypertriglyceridemia.[23] What is more, the expression of LCN-2 was obviously upregulated in patients with fatty liver diseases or atherosclerotic diseases, which indicated the considerable role of LCN-2 in lipid metabolism.[27–29] The transcription and secretion of LCN-2 were enhanced after the activation of toll-like receptors (TLRs) combined with the gram-positive bacteria (*C. acnes*) peptides on neutrophils.[30] On the one hand, the overexpression of LCN-2 was implicated to promote the production of pro-inflammatory mediators IL-6, IL-12, IL-8 and attenuate the secretion of anti-inflammatory mediators IL-10.[31,32] The upregulated pro-inflammatory cytokines such as IL-8 and IL-6 were elucidated to be involved in the form of NETs, which further amplified the inflammatory response and contributed to the local damage.[15,33,34] Moreover, the NETs formation was enhanced in patients with pyogenic arthritis, pyoderma gangrenosum and acne syndrome compared to the healthy individuals.[35] Thus, LCN-2 was confirmed to be a sensitive biomarker for inflammation.[36,37] On the other hand, as a vital regulator of lipid metabolism, LCN-2 deficiency attenuated the expression of Fasn, Srebp2, and Pparγ gene, LCN-2 deficiency disrupted the mammalian target of rapamycin (mTOR) signaling regulation of lipid metabolism.[38]

Monocytes/Macrophages

Monocytes, originating from bone marrow, are recruited and differentiated into macrophages with the stimulus of macrophage colony-stimulating factor to in response to homeostasis and inflammatory signals.[39] According to the active

state, macrophages are mainly classified as either classically activated M1 macrophages or alternatively activated M2 macrophages.[40] M1 macrophages predominantly generate the pro-inflammatory cytokines to promote inflammation, contrarily, M2 macrophages produce anti-inflammatory cytokines to dampen inflammation.[40] Interestingly, the high proportions of infiltrated macrophages were readily detected in the acne lesions,[21] the number of macrophages especially the M1 macrophages was increased as the acne progressed.[41]

Toll-like receptors (TLRs), a kind of pattern recognition receptors, are expressed on macrophages.[42] Pathogen-associated molecular patterns, such as lipase, hyaluronidase, and proteases produced by *C. acne*, were identified by TLRs on macrophages to initiate the innate immune.[43] In a ligand-specific manner, activated TLRs recruited the adapter molecules myeloid differentiation primary response differentiation gene 88 (*MYD88*), upregulated *MYD88* activated mTOR signaling pathway by promoting S6K phosphorylation, which induced macrophages metabolic rewiring.[44] Acetyl–coenzyme A (CoA) carboxylase (ACC) enzymes, the central regulators of lipid metabolism, is the downstream of mTOR signaling pathway, ACC deficiency resulted in less redistribution of lipid species and impaired the pro-inflammatory macrophage activation compared to the control group after LPS stimulus.[45] Furthermore, activated *MYD88* spontaneously elevated the expression of downstream mitogen-activated protein kinases (MAPK) signaling pathway.[46] Suppressing the activation of *MYD88* downregulated the phosphorylation of c-Jun N-terminal protein kinase (JNK), extracellular signal-regulated kinase (ERK1/2) and p38, the classical regulators of inflammatory cytokines.[47] Consequently, pro-inflammatory cytokines like IL-6, IL-8 were reduced by suppressing the *MYD88*/MAPK signaling pathways. In addition, excessive expression of MYD88 caused a considerable difference on the activation of NOD-like receptor family pyrin domain containing three inflammasomes, which resulted in exaggeration of inflammation.[48] Recent studies in immunometabolism have shed light on the intricate links between cellular cholesterol metabolism and inflammatory response of macrophage. Accumulating research has displayed that cellular cholesterol metabolism was an essential component of macrophage activation programs, cholesterol metabolism was actively regulated during innate activation of macrophages. Cellular cholesterol levels were temporally changed after TLR activation, accumulated cholesterol was binded to MYD88, which was essential for the activation and self-oligomerization of MYD88. That said, cellular cholesterol metabolism was integral to innate activation of macrophages and closely related to *MYD88*-dependent inflammatory response in macrophage.[49] Meanwhile, macrophages took up the intracellular cholesterol and transformed into foam cells when exceeding the scavenging capacity, the foam cell formation was fundamental in the acne progress.[50]

In the regard of M2 macrophages, they seemed to have a negative effect of lipogenesis and positive effect on lipolysis. Through polarization, IL-12 blunted the lipogenesis progress by inhibiting the activity of lipogenic enzymes, such as fatty acid synthase, and the expression of lipolytic enzymes was confirmed to be increased in the macrophages.[51] Through the lipolysis in lipid droplets, triacylglycerols were disintegrated into diacylglycerols and monoacylglycerols, accompanied by fatty acid release, and significantly increased amounts of three out of four monoacylglycerols were found in M2 macrophages, which indicated the positive effect of lipolysis.[52] What is more, neuropeptide Y prevented 7KC-induced foam cell formation in resting macrophages and shifted macrophages toward the anti-inflammatory M2-like phenotype to exert anti-inflammatory functions.[53]

Mast Cells

Mast cells are well known in allergic inflammatory diseases and are considered to be one of the "first responders" to innate inflammation. Infiltration and degranulation of mast cells were observed in acne lesions.[54] Mast cells are rich in lipid rafts, highly ordered membrane microdomains enriched in cholesterol, glycosphingolipids, and certain proteins, lipid modification is tightly linked to the degranulation, endocytosis of mast cells.[55] Lipid reprogramming exerted a dependent role in mast cell activation. The phosphorylation of immunoreceptor tyrosine-based activation motif activated the mitogen promoter protein (MAK) kinase signaling pathway to decompose membrane phospholipid choline (PC) to produce arachidonic acid, then the arachidonic acid was the essential substance for the synthesis of arachidonic acids such as prostaglandin D2 (PGD2), leukotrienes, and platelet-activating factor, which induced the inflammatory response.[56] Importantly, research reported that supplementing with PC reduced the alteration of lipid profile and attenuated IgE-induced immune responses in mast cells, which suggested the importance of lipid metabolism in mast cells biological activity.[57] Surprisingly, the production of PGD2 was initiated by hydrolysis of membrane phospholipids

by phospholipase A2 (PLA2), an enzyme for cleaving cell membrane phosphodiacylglycerides, loss of PLA2 impaired the maturation of mast cells and failed to facilitate acute anaphylactic response.[58] In addition, palmitoylethanolamide, a pleiotropic endogenous lipid mediator, downmodulated mast cells activation and degranulation by stimulating the activity of diacylglycerol lipase -α and -β.[59]

Dendritic Cells

Dendritic cells are the classical antigen-presenting cells to transport the peptide MHC class I complexes to the cell surface. Lipid metabolism has a great impact on the activation and inflammatory response of dendritic cells. When infected, genes related to lipid metabolism, including cholesterol and fatty acid biosynthesis-related genes were uniformly upregulated and resulted in the lipid accumulation in dendritic cells.[60] Meanwhile, the risk of infection was significantly elevated when dendritic cells underwent abnormal lipid peroxidation and greater lipid uptake, which was beneficial for the immune escape. Recent advance highlighted that electrophilic oxidatively truncated lipids covalently binded to heat shock protein 70 impaired the translocation of peptide MHC class I complexes and prevented the cross-presentation.[61] Except electrophilic oxidatively truncated lipids, the fatty acid oxidation was active in dendritic cells in high-fat diet–induced obesity, which indicated that alteration of the lipid reprogram might help improve dendritic cells function in obese individuals.[62]

T Lymphocytes

T lymphocytes, composed of T helper cells (Th cells), regulatory T cells (Tregs), cytotoxic T cells, memory T cells, natural killer cells and gamma delta (γδ) T cells, are essential for the innate immune response as well as adaptive immune response. Acne was characterized by various degrees of T cell infiltration. For instance, a Th1 response instead of Th2 response predominated in acne lesions,[63] and a higher infiltration of Th17 cells in acne lesions was detected relative to nonlesional skin areas of acne patients.[21] Thus, some researches pointed out that acne was immune-mediated chronic inflammatory skin disease, especially characterized by Th1/Th17-mediated immune response, which suggested the pivotal role of Th1/Th17 in acne.[63,64] On the contrary, Tregs were substantially lower, relative to nonlesional sites of acne patients and skin of healthy individuals.[21]

In comparison to the control group, acetylcoenzyme a carboxylase 1 (ACC1), a key enzyme in lipid homeostasis was positively linked with Th1/Th17 cells, Jiang et al recommended the correlation of ACC1 with Th17 and Th1 cells as the potential biomarker of acute ischemic stroke and implied the effect of Th1/Th17 cells in dyslipidemia.[65] The monophosphoryl lipid A had an negative effect on the Th1 cytokines and enhanced the production of the regulatory cytokine IL-10,[66] the pro-resolving lipid mediator lipoxin A4 dampened the activation of Th1/Th17 cells and reduced the inflammatory mediators.[67] In turn, Th1 cells upregulated interferon-gamma response signaling and antigen presentation pathways and downregulated lipid metabolism. While the lipid metabolism appeared to display a mix effect on T cells. Experiments have showed that ACC1-associated de novo fatty acid synthesis mediated the Th17 cell differentiation[68] and long-chain fatty acids enhanced Th1 and Th17 cell differentiation and proliferation via the P38-MAPK pathway, exacerbating the inflammatory disease in vivo.[69] Fatty acid-binding protein (FABP5) is responsible for fatty acid uptake, and it is highly expressed in Treg cells. In vitro studies show that the inhibition of FABP5 in naïve T cells suppresses Treg cell differentiation. The inhibition of *FABP5* activates cyclic GMP-AMP synthase (cGAS) stimulator of interferon gene- (STING-) dependent type I IFN signaling, leading to IL-10 production and Treg cell activation.[70] Sphingomyelin and glycosylphosphatidylinositol, abnormal in acne skin, are components of lipid rafts, which are closely to the activation and differentiation of naïve T cells.[71] Ceramides, one of sphingosine-based lipid molecules, were confirmed to capable of upregulating Tregs and maintaining the Treg function, which ceramides were significantly lower in acne lesions.[72] Moreover, the upregulated lipid synthesis but not fatty acid β-oxidation induced the IFN-γ production accompanying with higher activation of Th1 subsets, while inhibiting fatty acid β-oxidation led to less IL-17 production by pro-inflammatory Th17 cells.[73,74]

B Lymphocytes

In acne, B lymphocytes were responsible for the long-standing scar, B-cell infiltrations, which were not found in early papules of acne, were involved in 23% of all acne scar specimen.[75,76] Despite secreting antibodies is the hallmark of B cells, it is increasingly appreciated that B cells dysfunction contribute to the inflammatory cytokines production. DHA, a n-3 LCPUFAs, was incorporated into the B cell membrane to alter lipid microdomain clustering and enhanced the level of IgA.[77] In vivo, inhibiting B-cell-activating factor signaling, which caused a difference in promoting differentiation of the B-cell population, led to lipid reprogramming in liver. Lipid content was notably enriched in BAFF-R$^{-/-}$ group, genes related to lipid metabolism such as fatty acid-binding protein, ACC, FAS were significantly upregulated in BAFF-R$^{-/-}$ group.[78] Lipid G-protein coupled receptor *GPR55*, expressed by splenic plasma cells, was involved in plasma cells maturation. Lack of *GPR55* hyperactivated B cells, disturbed PC maturation and supported a possible relevance for complications in human atherosclerosis pathophysiology.[79] In conclusion, lipid metabolism interacts with B cells function.

Conclusion

Acne has proven challenging to treat due to its chronicity, a tendency to relapse, and inherent recalcitrance. To date, topical antibiotics, retinoids, hormonal therapy are still the first line and mainstay for the treatment of acne. Retinoids are the first approach used worldwide for the treatment of acne.[80] All the lines and recommendations of dermatologists and skin experts support the use of these substances, especially for acne vulgaris. Furthermore, lasers and light-based modalities like intense pulsed light, photodynamic therapy, and picosecond lasers are used in the treatment of refractory acne.[81] However, research has shown that the effect of topical therapy, possibly leading to the damage of skin barrier, rebound postinflammatory hyperpigmentation and recurrence, is not obvious, which limits the widespread application.[82–84] Considering the long duration of acne treatment, the visibility of the lesions, and the struggle with various side effects, researchers have paid more attention to TCM for fewer side effects and definite anti-inflammatory effect.[85] Infiltration of immunocytes and inflammatory response are the hallmark of acne, moreover, lipid levels, as well as abnormal metabolism of immunocytes also contribute to acne development and occurrence. Immunocytes, such as neutrophils, macrophages, T cells, B cells, and dendritic cells regulate their own phenotypes or functions via metabolic changes due to metabolite accumulation. When lipid accumulates, macrophages can be transformed from pro-inflammatory M1 to anti-inflammatory M2. In addition, pro-inflammatory cytokines were produced in the neutrophils when abnormal lipid peroxidation and greater lipid uptake happened. Thus, lipid metabolism reprogramming of immunocytes appears to contribute to the acne development and aggravate the inflammatory response. Furthermore, the immune response rate can be improved by regulating immune cell metabolism and improving the microenvironmental immune status. Inhibiting the lipid metabolism reprogramming can effectively decreasing the secretion of pro-inflammatory cytokines and improve the progress of acne. Therefore, further study on the cometabolic targets of acne and immune cells is of great importance for achieving satisfactory treatment outcomes that shorten the duration of acne treatment.

Data Sharing Statement

Data openly available in a public repository.

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Disclosure

The authors report no competing interests in this work.

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