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REVIEW

Common Pathogenesis of Acne Vulgaris and Atherosclerosis

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Abstract— Foam cells are lipid-loaded macrophages and neutrophils that are generated from a massive uptake of oxidized lipid. Foam cells are a pathological hallmark of atherosclerosis, and have also been found in acne lesions. The same pathological changes determine the common pathogenesis. According to the pathological function of foam cells in these lesions, we put forward a viewpoint on the pathogenesis of acne and atherosclerotic plaques.

KEY WORDS: acne; atherosclerosis; foam cells; macrophages; sebum.

Acne vulgaris is the result of the obstruction of sebaceous follicles and the consequent excessive production of sebum by sebaceous glands in the follicle ducts, combined with desquamation of epithelial cells in the follicle walls [1]. Both acne vulgaris and atherosclerosis are inflammatory diseases with three major components [2]. The first component is the buildup of extracellular lipids (sebum and blood lipids), cells (desquamated and apoptotic cells), and debris (Fig. 1) [3, 4]. The second component is the infiltration of neutrophils, macrophages, and CD4+ T lymphocytes (Fig. 1) [5]. The third component is the accumulation of intracellular lipids within macrophages and neutrophils, thereby converting them into foam cells (Fig. 2) [2, 6, 7].

LIPID COMPONENTS IN SEBUM

Sebum contains the same lipid components as blood, including free fatty acids, cholesterol, cholesterol ester, and triglycerides (TG) [8]. The lipid composition of sebum is as follows: wax monoesters 25%, TG 41%, free fatty acids 16%, and squalene (a precursor of cholesterol) 12%. Cholesterol is the least abundant lipid in sebum, which together with its esters, accounts for 4.5% of the total lipids [9, 10]. The increased amount of sebum produced by the associated sebaceous glands contributes to follicular obstruction and the formation of microcomedones, which are believed to be the precursor lesions of acne [11]. Sebum that accumulates in the follicle duct can be modified by oxidation [12, 13] and is a chemoattractant for macrophages and neutrophils. Macrophages and neutrophils phagocytose oxidized lipids continuously until apoptosis, as they need to convert the energy generated from lipid oxidation into adenosine triphosphate (ATP) to ensure normal function and their scavenger receptors are not down regulated by cellular lipid accumulation [2].

FOAM CELLS AS A HALLMARK OF ATHEROSCLEROSIS AND ACNE

Macrophages and neutrophils containing lipid-inclusion bodies and lipid droplets in the atherosclerotic

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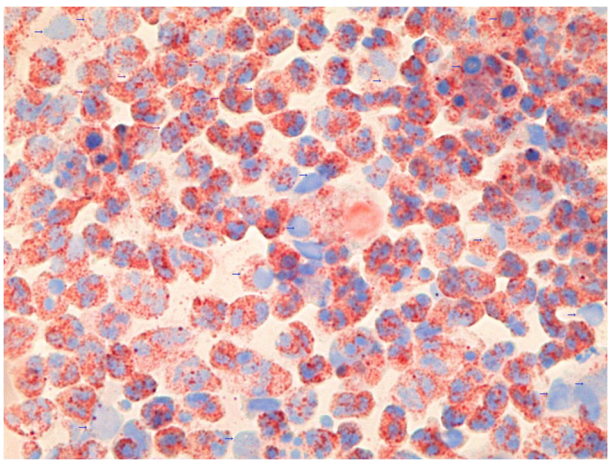

Fig. 1. Foam cells in an acne lesion. Oil red O and hematoxylin staining. Nikon, 40 × 10. Blue arrowhead, monocytes/macrophages; purple arrowhead, neutrophils. The pus from an acne lesion was evenly spread onto slides and stained with hematoxylin and oil red O, and the foam cells were then viewed under the microscope. The lipid droplets in the cytoplasm are stained orange red by oil red O. There are abundant lipid droplets in the cytoplasm of cells, of which contours and nucleus are clearly visible. From morphology and the structure of the nucleus, the cells in the figure are mainly neutrophils with irregular round shape, of which rod-shaped lobular nucleus stained differently and is deformed. The cells with a large size and one big and round nucleus were suspected as foamed macrophages. The nuclear membrane is blurred and gradually dissolved, suggesting that the cell underwent necrosis or apoptosis. The selected suppurative acne lesions are new and present a yellow color. Nine acne patients (six female, three male) with suppurative lesions (pustule, abscess) were recruited. Ethical approval was obtained from the ethics committees of the first affiliated Hospital of Guangxi University of Chinese medicine.

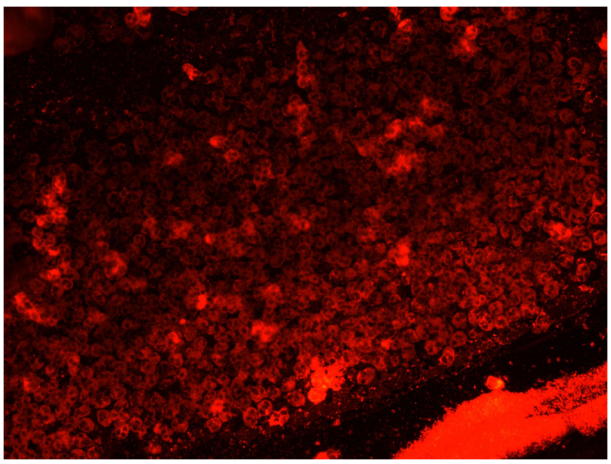

Fig. 2. Foam cell and sebum stained with DiI fluorescent dye. Olympus, BX43, 40 × 10. The concentration of DiI fluorescent probe (provided by Beyotime Institute of Biotechnology) solution is 10 μM. The pyocytes on the slide were covered with DiI solution at room temperature for 20 min and washed carefully with distilled water. Sebum stained by DiI fluorescent dye can be seen in the foam cells.

plaques are called foam cells (also known as lipid-laden cells or lipid-loaded cells), and are a hallmark of both early and late atherosclerotic lesions [14]. The presence of foam cells in acne lesions is significant as it is a concrete evidence connecting atherosclerosis and acne. Foam cells are activated macrophages and neutrophils that retain their metabolic activity [15]. Toll-like receptors are mainly expressed on macrophages and neutrophils [16, 17]. Toll-like receptor-signaling pathways culminate in the activation of transcription factor nuclear factor kappa B, which controls the expression of an array of inflammatory cytokine genes responsible for the production of a variety of cytokines (e.g., interleukin), chemokines (RANTES), adhesion molecules (P-Selectin and E-Selectin), and growth factors in atherosclerosis and acne lesions [18, 19].

High-density lipoprotein (HDL) cholesterol exerts a number of potentially antiatherogenic effects independent of cholesterol efflux and centripetal transport, including antioxidation, impairment of leukocyte adhesion and monocyte activation, and flow-induced vasodilation, preventing endothelial cell damage and death, which may contribute to the ability of HDL cholesterol to protect the blood circulation against damage due to inflammation [20]. Abnormal lipid metabolism and dyslipidemia are believed to be the result of foam cell formation [21, 22]. Acne patients are frequently associated with an abnormal plasma lipid profile. Lipoprotein(a) was found to be significantly higher in male and female patients with mild, moderate, and severe acne than in a healthy control group. Patients with severe acne have significantly lower plasma HDL cholesterol levels [23]. Patients with mild or moderate acne do not have significantly lower plasma HDL cholesterol levels or have a normal lipid profile, but their follicle duct system is full of sebum as acne patients have markedly higher rates of sebum production [24].

PATHOLOGICAL CHANGES IN FOAM CELLS (FIG. 3)

Macrophages and neutrophils phagocytose microorganisms and substances such as bacteria, viruses, sebum, and oxidized low-density lipoproteins. Macrophages and neutrophilic lysosomes contain lipoxygenase, myeloperoxidase, inducible nitric oxide synthase, and nicotinamide-adenine dinucleotide phosphate oxidases [25–27]. They use these oxidases to generate antimicrobial

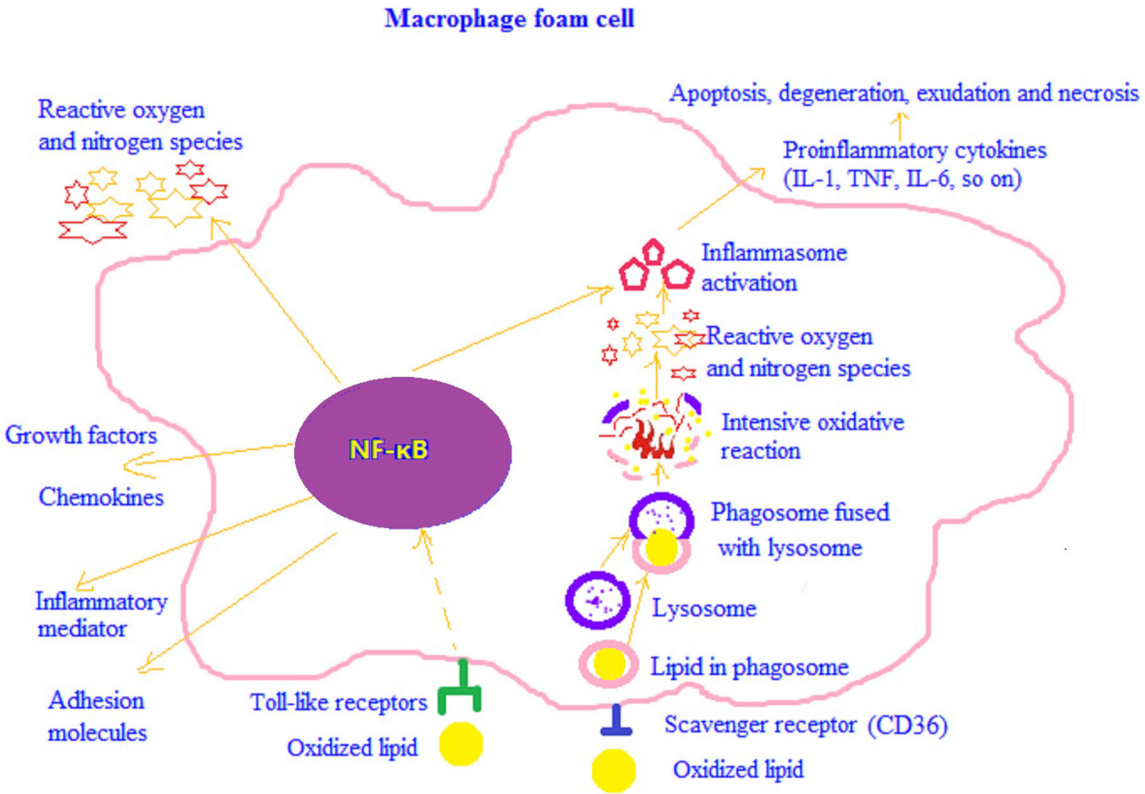

Fig. 3. Signaling pathway in foam cells. Macrophages and neutrophils express toll-like receptors and scavenger receptors that bind oxidized lipids, which activate inflammation via the same signaling pathway.

reactive oxygen species (ROS) and reactive nitrogen species (RNS) essential for native immunity. Macrophages and neutrophils play an important role in lipid metabolism and may be required to initiate lipid oxidation to generate energy (ATP) to maintain physiological functions [28]. Myeloperoxidase catalyzes the production of hypochlorous acid from hydrogen peroxide and chloride anions (or the equivalent from a non-chlorine halide). The liquid in lysosomes is strongly corrosive due to the content of hypochlorous acid, which is 50 times more potent in microbial killing than hydrogen peroxide [29]. Extracellular lipids are ingested by macrophages and neutrophils, trapped in phagosomes, and fused with the lysosome, which is similar to a "micro incinerator" in which the engulfed lipids are oxidized by the strongly corrosive liquid. However, the "incinerator" is damaged by the strongly corrosive lipid flowing out of the lysosome, as lipid oxidation in lysosomes is similar to fuel combustion in that the lysosomal membrane breaks down under such an intensive oxidative reaction. The lipids engulfed by macrophages and neutrophils are not oxidized to generate ATP, but to generate large amounts of ROS and RNS. Excessive ROS and RNS production in a very short time not only destroys the incinerator and other foam cell organelles, but it also damages normal tissue cells and induces inflammation. Crater-like ulcers with a significant amount of necrotic tissue (colliquative necrosis) [30] can be found in both atherosclerotic plaques and acne lesions.

Severe damage to all cellular components induced by oxidative stress causes rapid consumption and depletion of nuclear nicotinamide-adenine dinucleotide (NAD) pools, cellular energy (ATP), thiols, and the local antioxidant enzyme system [31]. NAD from capillary blood is insufficient to compensate for NAD consumption in acne lesions. In such cases, even if circulating NAD concentration is normal and the capillaries are dilating, NAD deficiency in an acne lesion is a serious condition in which the abnormal energy of free radicals is converted into various signals passing through the tissue cells. These cascade-amplified signals constitute a variety of complex-signaling pathways that result in pathological and pathophysiological changes in the follicle ducts, including such untoward events as

capillary expansion, edema, apoptosis, necrosis, keratinization, inflammatory cell infiltration, fibrosis, and DNA damage [32]. The anomalous function of foam cells and inflammation amplification in acne lesions and atherosclerotic plaques is driven by the energy derived from the abnormal oxidation of lipids (sebum). The signal source is the lipid and sebum abnormally oxidized in foam cells.

INFECTION

Propionibacterium acnes (*P. acnes*), as a secondary factor, has not been shown to be present in early acne lesions [33]. The membrane of a bacteria is composed of a lipid (phospholipid) bilayer. The presence of foam cells in acne lesions suggests that lipid metabolism is disordered. Macrophages and neutrophils are unable to effectively deal with the engulfed lipid bilayer of bacteria even though the bacteria have been killed by antibiotics and antibodies. Bacterial infection impairs and aggravates acne lesions, and antibiotic therapy is essential in severe cases. However, when antibiotic therapy is ineffective, we assume that severe inflammation exists not only because of bacterial resistance but also due to dyslipidemia and possible dysfunction of HDL cholesterol. Niacin improves HDL cholesterol function [34], and the most likely reason for dyslipidemia and HDL cholesterol dysfunction is niacin deficiency.

PHYSICAL EXAMINATION AND TREATMENT RECOMMENDATIONS

The serum lipid profile and homocysteine level were found to be significantly higher in acne patients compared with healthy controls [23, 35]. Serum lipoprotien(a) level in acne patients can be several times higher than the normal range. Reduced serum lipids suggest that acne patients have malnutrition. Malnourished acne patients may also have abnormal liver function tests, such as low serum albumin, globulin, and total proteins. Determination of the serum lipid profile, homocysteine concentration, and liver function tests are necessary in acne patients.

According to the common pathogenesis of acne vulgaris and atherosclerosis, the therapeutic principle of acne vulgaris is similar to that of atherosclerosis: high doses of niacin (2000–3000 mg/day, 30–50 mg/kg/day) to improve plasma levels of HDL cholesterol or HDL cholesterol function, antioxidation, and inhibit inflammation [36]. A pilot study showed that high-dose niacin can significantly improve moderate and severe acne vulgaris [37]. We propose that a larger, multicenter clinical trial of niacin treatment in patients with acne should be carried out. The efficacy, safety, and dosage of niacin in the treatment of pregnant women and children of different ages with acne require careful evaluation in future clinical trials.

SUMMARY

Acne occurs in pregnant women, lactating women, neonatal, infants, children, and adolescents who required plenty of nutrition to promote the normal growth and development. Reduced hyperlipidemia may be not suitable for all acne patients. The pathogenesis and treatment of acne and atherosclerosis need further study. Even so, it is important not only to be aware of the common pathogenesis of acne and atherosclerosis, but also to be able to identify therapeutics and preventive strategies which may have curative and preventive effects for both diseases.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest. The authors declare that they have no conflict of interest.

REFERENCES

1. Leyden, J.J. 1997. Therapy for acne vulgaris. *The New England Journal of Medicine* 336 (16): 1156–1162.
2. Crowther, M.A. 2005. Pathogenesis of atherosclerosis. *Hematology. American Society of Hematology. Education Program*: 436–441.
3. Zouboulis, C.C., E. Jourdan, and M. Picardo. 2013. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. *Journal of the European Academy of Dermatology & Venereology* 28 (5): 527–532.
4. Sang, W.Y. 2010. The role of facial sebum secretion in acne pathogenesis: Facts and controversies. *Clinics in Dermatology* 28 (1): 8–11.
5. Jeremy, A.H., D.B. Holland, S.G. Roberts, K.F. Thomson, and W.J. Cunliffe. 2003. Inflammatory events are involved in acne lesion initiation. *Journal of Investigative Dermatology* 121 (1): 20–27.
6. Hansson, G.K., and A. Hermansson. 2011. The immune system in atherosclerosis. *Nature Immunology* 12 (3): 204–212.
7. Yuan, Y., P. Li, and J. Ye. 2012. Lipid homeostasis and the formation of macrophage-derived foam cells in atherosclerosis. *Protein & Cell* 3 (3): 173–181.
8. Pappas, A., S. Johnsen, J.C. Liu, and M. Eisinger. 2009. Sebum analysis of individuals with and without acne. *Dermatoendocrinology* 1 (3): 157–161.
9. Cheng, J.B., and D.W. Russell. 2004. Mammalian wax biosynthesis. II. Expression cloning of wax synthase cDNAs encoding a member

of the acyltransferase enzyme family. *The Journal of Biological Chemistry* 279 (36): 37798–37807.
10. Picardo, Mauro, Monica Ottaviani, Emanuela Camera, and Arianna Mastrofrancesco. 2009. Sebaceous gland lipids. *Dermatoendocrinology* 1 (2): 68–71.
11. Kurokawa, I., F.W. Danby, Q. Ju, X. Wang, L.F. Xiang, L. Xia, W. Chen, I. Nagy, M. Picardo, D.H. Suh, R. Ganceviciene, S. Schagen, F. Tsatsou, and C.C. Zouboulis. 2009. New developments in our understanding of acne pathogenesis and treatment. *Experimental Dermatology* 18 (10): 821–832.
12. Tochio, T., H. Tanaka, S. Nakata, and H. Ikeno. 2009. Accumulation of lipid peroxide in the content of comedones may be involved in the progression of comedogenesis and inflammatory changes in comedones. *Journal of Cosmetic Dermatology* 8 (2): 152–158.
13. Abulnaja, K.O. 2009. Oxidant/antioxidant status in obese adolescent females with acne vulgaris. *Indian Journal of Dermatology* 54 (1): 36–40.
14. Falk, Erling. 2006. Pathogenesis of atherosclerosis. *Journal of the American College of Cardiology* 47 (8 Suppl): C7–C12.
15. Soehnlein, O. 2012. Multiple roles for neutrophils in atherosclerosis. *Circulation Research* 110 (6): 875–888.
16. Hayashi, F., T.K. Means, and A.D. Luster. 2003. Toll-like receptors stimulate human neutrophil function. *Blood* 102 (7): 2660–2669.
17. Sanjuan, M.A., C.P. Dillon, S.W. Tait, S. Moshiach, F. Dorsey, S. Connell, M. Komatsu, K. Tanaka, J.L. Cleveland, S. Withoff, and D.R. Green. 2007. Toll-like receptor signalling in macrophages links the autophagy pathway to phagocytosis. *Nature* 450 (7173): 1253–1257.
18. Monaco, C. 2012. The tolls and dangers of atherosclerotic disease. *Current Pharmaceutical Biotechnology* 13 (1): 77–87.
19. Bakry, O.A., R.M. Samaka, H. Sebika, and I. Seleit. 2014. Toll-like receptor 2 and *P. acnes*: do they trigger initial acne vulgaris lesions? *Analytical and Quantitative Cytology and Histology* 36 (2): 100–110.
20. Säemann, M.D., M. Poglitsch, C. Kopecky, M. Haidinger, W.H. Hörl, and T. Weichhart. 2010. The versatility of HDL: a crucial anti-inflammatory regulator. *European Journal of Clinical Investigation* 40 (12): 1131–1143.
21. Lewis, G.F., and D.J. Rader. 2005. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circulation Research* 96 (12): 1221–1232.
22. Oyewole, A.O., and M.A. Birch-Machin. 2015. Sebum, inflammasomes and the skin: current concepts and future perspective. *Experimental Dermatology* 24 (9): 651–654.
23. Jiang, H., C.Y. Li, L. Zhou, B. Lu, Y. Lin, X. Huang, B. Wei, Q. Wang, L. Wang, and J. Lu. 2015. Acne patients frequently associated with abnormal plasma lipid profile. *The Journal of Dermatology* 42 (3): 296–299.
24. Okoro, E.O., N.G. Bulus, and C.C. Zouboulis. 2015. Study of facial sebum levels and follicular red fluorescence in patients with acne vulgaris in Nigeria. *Dermatology* 232 (2).
25. Li, A.C., and C.K. Glass. 2002. The macrophage foam cell as a target for therapeutic intervention. *Nature Medicine* 8 (11): 1235–1242.
26. Röhm, Marc, Melissa J. Grimm, Anthony C. D'Auria, Nikolaos G. Almyroudis, Brahm H. Segal, and Constantin F. Urban. 2014. NADPH oxidase promotes neutrophil extracellular trap formation in pulmonary aspergillosis. *Infection & Immunity* 82 (5): 1766–1777.
27. Nauseef, W.M. 2014. Myeloperoxidase in human neutrophil host defense. *Cellular Microbiology* 16 (8): 1146–1155.
28. Fernandez-Ruiz, I., P. Puchalska, C.A. Narasimhulu, B. Sengupta, and S. Parthasarathy. 2016. Differential lipid metabolism in monocytes and macrophages-influence of cholesterol loading. *Journal of Lipid Research* 57 (4): 574–586.
29. Saran, M., I. Beck-Speier, B. Fellerhoff, and G. Bauer. 1999. Phagocytic killing of microorganisms by radical processes: consequences of the reaction of hydroxyl radicals with chloride yielding chlorine atoms. *Free Radical Biology & Medicine* 26 (3–4): 482–490.
30. Boer, J., and G.B. Jemec. 2016. Mechanical stress and the development of pseudo-comedones and tunnels in hidradenitis suppurativa/acne inversa. *Experimental Dermatology* 25 (5): 396–397.
31. Yang, J., and J.D. Adams Jr. 2004. Structure activity relationships for nicotinamide in the treatment of stroke. *Letters in Drug Design & Discovery* 1: 58–65.
32. Thompson, B.C., D. Surjana, G.M. Halliday, and D.L. Damian. 2014. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in primary melanocytes. *Experimental Dermatology* 23 (7): 509–511.
33. Brüggemann, H., A. Henne, F. Hoster, H. Liesegang, A. Wiezer, A. Strittmatter, S. Hujer, P. Dürre, and G. Gottschalk. 2004. The complete genome sequence of *Propionibacterium acnes*, a commensal of human skin. *Science* 305 (5684): 671–673.
34. McKenney, J. 2004. New perspectives on the use of niacin in the treatment of lipid disorders. *Archives of Internal Medicine* 164 (7): 697–705.
35. Jiang, H., C. Li, B. Wei, Q. Wang, J. Zhong, and J. Lu. 2017. Serum homocysteine levels in acne patients. *Journal of Cosmetic Dermatology.*
36. Duffy, D., and D.J. Rader. 2009. Update on strategies to increase HDL quantity and function. *Nature Reviews. Cardiology* 6 (7): 455–463.
37. Hao, Jiang, and Li Changyi. 2016. High dose niacin in the treatment of acne vulgaris: a pilot study. *Chinese Journal of Aesthetic Medicine.* 25 (12): 54–59.