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Review

The role of cytokines in early foam cells

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Abstract

Atherosclerosis is mainly caused by endothelial cell injury, and the formation of lesions is the result of inflammatory - fibrous hyperplastic reaction to endothelial and endometrial injury. In the process of atherosclerosis, macrophage foam cell formation (FCF) is known to play a key role in the development of atherosclerotic plaques. Due to the long-term risk factors, such as dyslipidemia, LDL-c intrude into the wall lining through the damaged endothelial cells. Then LDL-c can be oxidized and modified into low density lipoprotein cholesterol (oxLDL-c), which causes further damage to the artery intima. Monocytes and lymphocytes change their surface characteristics, and enhance surface adhesion factor expression, leading to adhesion on endothelial cell populations and moving among the endothelial cells. Then they differentiate into macrophages, which can devour ox-LDL with the help of scavenger receptors. At last, macrophages transform into the foam cells, which become the earliest atherosclerotic lesions -- fatty streaks. Macrophages can oxidize LDL-c and form oxides and superoxide ions. Macrophages filled with oxidized lipoprotein can synthesize and secrete growth factors and pro-inflammatory mediators, promote plaque growth, as well as inflammation, eventually atherosclerosis forms. However, how foam cells further promote atherosclerotic plaques, and which cytokines are involved in the formation of atherosclerotic plaques are still unclear. This paper reviews the recent literature on the role of cytokines in early foam cells.

Key words: Atherosclerosis; Foam Cell; Cytokine.

Introduction

The incidence of atherosclerosis increases year by year, which leads to a variety of vascular diseases, including coronary heart disease, hypertension, stroke and so on. Atherosclerosis starts from macrophages and its development is influenced by many factors (1).

1. Atherosclerosis and foam cells

Characterized by involvement of arterial lesions of atherosclerosis, starting from the endometrium, successively in combination with multiple lesions, including local lipid and complex carbohydrate accumulation, fibrous tissue hyperplasia and calcinosis plaque formation, and a middle artery gradually degeneration, hemorrhage secondary lesions with plaque, the plaque rupture and thrombosis. Modern cellular and molecular biology techniques show atherosclerotic lesions have the characteristics of macrophage migration, smooth muscle cell proliferation, the formation of connective tissue matrix, such as collagen fiber, elastic fiber and proteoglycan, as well as the characteristics of lipid accumulation inside and outside the cell.

When lipid is deposited in the endodermis, endothelial cells will secrete chemokines to attract macrophages to swim out, engulf oxldl-c through scavenger receptors, and turn into foam cells, which are a sign of atherosclerosis (2).

2. Influence of srebp-1

Studies have shown that oxLDL can increase the proliferation of monocytes and reduce the survival rate of monocyte-derived macrophage (MDM) in a time and dose-dependent manner. OxLDL (100 micgs/ml) increases the expression of srebp-1 and its downstream proteins (such as fatty acid synthase (FAS) and 3-hydroxyl-3-methylglutenyl coenzyme A reductase (HMGCR) at RNA and protein levels to enhance lipid accumulation in monocytes and MDM. Sterol regulatory element binding protein (srebp-1) was inhibited by synthetic inhibitors to prevent excessive lipid accumulation by down-regulating the expression of downstream proteins. In addition, oxLDL increases the levels of reactive oxygen species (ROS) in both cell types, NLRP3 inflammatory-activating agents, and the release of IL-1β. OxLDL induced NLRP3 may be the reason for the overexpression of srebp-1 and downstream proteins, because the siRNA silencing of NLRP3 reduces the level of serbp-1. It can be seen that srebp-1 may be a key participant in excessive lipid accumulation induced by oxLDL, leading to macrophage derived foam cells through ROS mediated NLRP3 / IL-1β/srebp-1 pathway (1).

3. Interleukin

Macrophages secrete interleukin-1 beta (IL-1β), which is a major driver of the pathogenesis of atherosclerosis (3). It trigger signals that promote the transcription of immature IL-1β, and then endogenous "risk" signals (such as cholesterol crystals) activate innate immune signal complexes called inflammatory bodies (inflammatory body NLRP3) to process the secretion of IL-1β. IL-1β plays a critical role in the development of atherosclerosis and other inflammatory diseases. Due to its low solubility, cholesterol crystalizes in circulation and is taken up by monocyte-derived macrophages (4-5), activating their inflammasomes to release IL-1β and other proinflammatory cytokines (6).

4. Clotting factor

Atherosclerosis, recently, has been thought a chronic inflammatory disease factor into the vascular wall. Clotting pathways and immune responses promote the development of disease. However, the role of clotting factor XII in vascular inflammation remains disputable. However, it has been shown that FXII factor into the formation of atherosclerosis, which act as a strong inducer of pro-inflammatory cytokines in antigen-presenting cells. Perhaps, this is a hopeful way to treat the cardiovascular diseases by targeting FXII (7).

5. Tumor necrosis factor α(TNF α) and LDL receptor related protein 1 (LRP1)

Tumor necrosis factor(TNF α) is a cytokine made by macrophages, monocytes and T cells that has been formed to play an important role in shock, cachexia and inflammation. TNFα is a master

regulator of inflammatory responses which accelerates atherosclerosis (8). Anti-atherosclerotic effects of TNFα blockade in patients with systemic inflammatory states has been conclusively demonstrated, which suggests that effects depend on the cause of inflammation. Macrophages LDL receptor related protein 1 (LRP1) is a membrane receptor associated with inflammation, signals, and cell secretion. LRP1 mediated blew a focal adhesion induced decomposition and participate in phagocytosis (9). LRP1 combined with calcium protein network, as recognition receptor mediated apoptosis cells to absorb. Lacking LRP1 damage macrophage phagocytosis and damage to the increase in the number of cells in vivo and in vitro (10). Studies have revealed LRP1, macrophages are specific defects (M Φ LRP1-/-) increased atherosclerosis, hyperlipidemia mice associated with increased disease of grow in quantity of defective cells and inflammation. TNF α blockade plays an anti-atherosclerosis role that depends on the presence of macrophage LRP1 (11).

6. Other factors

Other factors may also affect the development of foam cells, such as HBP that can directly or indirectly injury the vascular endothelial , which lead and accelerate lipid deposition, and IL-10 or TGF-β can alleviate atherosclerosis. However, most may act through the above mentioned factors.

Conclusion

At present, atherosclerosis is the main pathogenesis of cardiovascular diseases. Although our understanding of the mechanism of atherosclerosis has made great progress, it has been not completely clear. Apart from the above factors (Table 1, Figure 1), there are other factors involved in the development of foam cells, each of which may become a new therapeutic target. Therefore, it is very important to actively explore and clarify its pathogenesis. However, the purpose of macrophages to synthesize lipids is not clear, which may be related to the final metabolism of cholesterol. This could also be a way forward for developing anti-atherosclerosis drugs.

Table 1: The Impacting factor and influencing mechanisms to macrophages.

Factor	Mechanism	Effects on macrophage
SREBP-1	The role of NLRP3 / IL-1β/ SREBP-1 by ROS	Promote foam cell formation
Interleukin	Increase the inflammatory response	Further growth of foam cells
FXII	A strong inducer of pro-inflammatory cytokines	Promote foam cell formation
TNF-α	Blocking exerts an anti-atherosclerosis effect dependent on the presence of macrophage LRP1	It weakens the phagocytosis and decomposition ability of macrophages

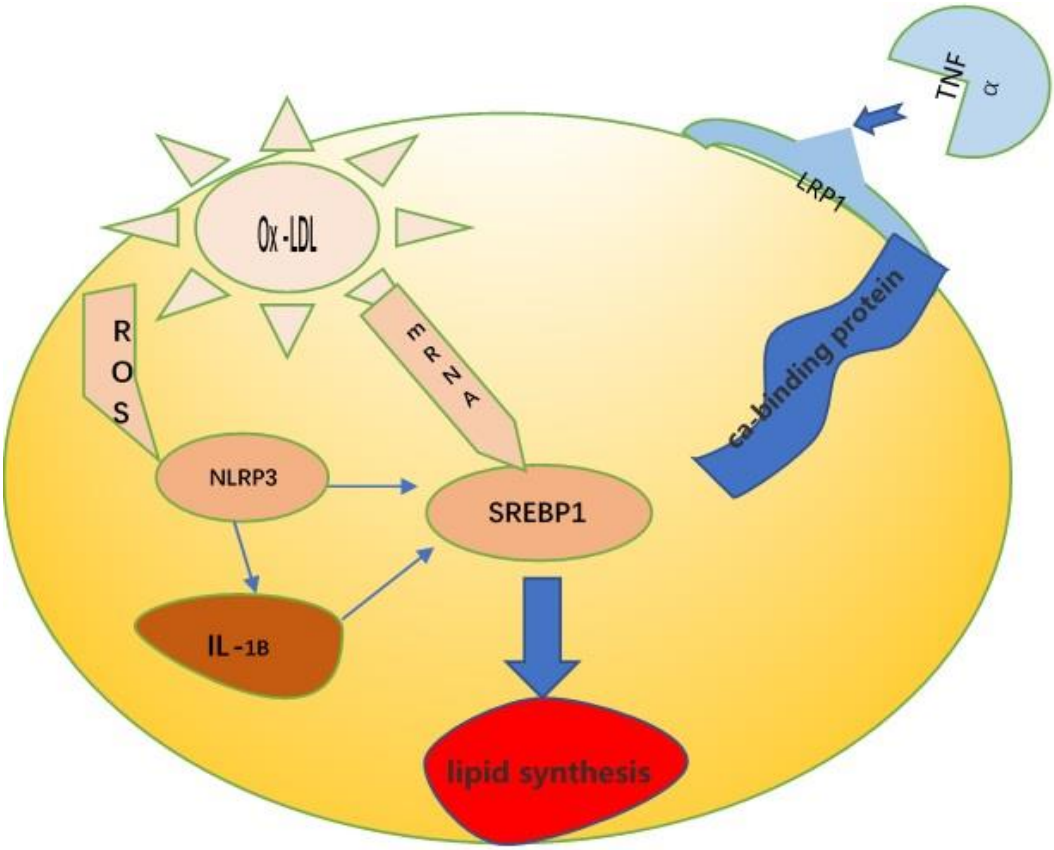

Figure 1: Ox-LDL, SREBP-1, and FXII promote plaque formation mainly by increasing the lipid synthesis. TNF promotes atherosclerosis mainly by binding and activating LRP1.

Declarations

1) ***Consent to publication***
We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement, and followed publication ethics.
2) ***Ethical approval and consent to participants***
Not applicable.
3) ***Disclosure of conflict of interests***
We declare that no conflict of interest exists.
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None
5) ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article.
6) ***Authors' Contributions***
Authors contributed to this paper with the design (PZX), literature search (PZX), drafting (PZX), revision (PZX), editing (PZX) and final approval (PZX).
7) ***Acknowledgement***
None
8) ***Authors' biography***
None

References

1. Varghese, J.F., R. Patel, and U.C.S. Yadav, *Sterol regulatory element binding protein (SREBP) -1 mediates oxidized low-density lipoprotein (oxLDL) induced macrophage foam cell formation through NLRP3 inflammasome activation.* Cell Signal, 2019. **53**: p. 316-326.
2. Xu, W., et al., *Global Metabolomics Reveals the Metabolic Dysfunction in Ox-LDL Induced Macrophage-Derived Foam Cells.* Front Pharmacol, 2017. **8**: p. 586.
3. Warnatsch, A., et al., *Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis.* Science, 2015. **349**(6245): p. 316-20.
4. Landsman, L., et al., *CX3CR1 is required for monocyte homeostasis and atherogenesis by*

promoting cell survival. Blood, 2009. **113**(4): p. 963-72.
5. Lessner, S.M., et al., *Atherosclerotic lesions grow through recruitment and proliferation of circulating monocytes in a murine model.* Am J Pathol, 2002. **160**(6): p. 2145-55.
6. Duewell, P., et al., *NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals.* Nature, 2010. **464**(7293): p. 1357-61.
7. Vorlova, S., et al., *Coagulation factor XII induces pro-inflammatory cytokine responses in macrophages and promotes atherosclerosis in mice.* Thromb Haemost, 2017. **117**(1): p. 176-187.
8. Cerami, A., *Tumor necrosis factor as a mediator of shock, cachexia and inflammation.* Blood Purif, 1993. **11**(2): p. 108-17.
9. Lillis, A.P., et al., *LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies.* Physiol Rev, 2008. **88**(3): p. 887-918.
10. Yancey, P.G., et al., *Macrophage LRP-1 controls plaque cellularity by regulating efferocytosis and Akt activation.* Arterioscler Thromb Vasc Biol, 2010. **30**(4): p. 787-95.
11. Zhu, L., et al., *Loss of Macrophage Low-Density Lipoprotein Receptor-Related Protein 1 Confers Resistance to the Antiatherogenic Effects of Tumor Necrosis Factor-α Inhibition.* Arterioscler Thromb Vasc Biol, 2016. **36**(8): p. 1483-95.