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M1 AND M2 MACROPHAGES ARE PREDICTORS OF ADVERSE OUTCOMES IN HUMAN ATHEROSCLEROSIS

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Abstract: Macrophages play a central role in the development of atherosclerotic cardiovascular diseases (ACCDS), which include coronary heart disease, peripheral artery disease, cerebrovascular disease, and aortic atherosclerosis. In each vascular bed, macrophages help maintain a local inflammatory response, promote plaque development, and promote thrombosis. This central role, combined with their plasticity, makes macrophages attractive therapeutic targets for stopping the development and stabilizing existing atherosclerosis. In the context of ACCSS, classically activated M1 macrophages1 initiate and maintain inflammation, and alternatively activated M2 macrophages resolve inflammation. Atherosclerotic cardiovascular diseases (ACCDS) are the leading cause of morbidity and mortality worldwide [1]. Vascular inflammation, even after a significant reduction in cholesterol levels, is considered an important risk factor for recurrent atherothrombotic events, and macrophages are a likely contributor to the risk of residual inflammation.

Key words: Ischemic heart disease, inflammation, atherosclerosis, macrophages.

The defining feature of macrophages is their plasticity, which allows them to give an individual response to stimuli of the local microenvironment. During inflammation, macrophages can either promote inflammation or resolve it during wound and tissue healing [5]. The classical macrophage activation model defines both pre-and anti-inflammatory macrophages with different physiological roles and activators. At the broadest level, macrophages are classified as classically activatedM1 or alternatively activated M2 [6]. In In vitro, M1 macrophages are polarized in response to toll-like receptor ligands, interferons, pathogen-associated molecular complexes and lipoproteins[7]. Macrophages M1, fed mainly by glycolysis, promote tissue destruction and secrete pro-inflammatory factors, including high levels of IL (interleukin) - 1β, IL-6, and TNF-α (tumor necrosis factor-α)[8]. According to their inflammatory phenotype, they express pro-inflammatory transcription factors, including nuclear factor kB and STAT (signal transduction and transcription activator)-1. M2 macrophages2 are at the other end of the spectrum with a phenotype dependent on fatty acid oxidation and anti-inflammatory properties[9]. M2 macrophages2 are polarized in response to the cytokines IL-4 and IL-13 and secrete anti-inflammatory factors such as IL-1 receptor agonist, IL-10, and collagen. M2 macrophages are characterized by the expression of CD163, mannose receptor 1, resistin-likeo-β, and high levels of arginase-1. As for plaques, macrophages adhering to both classically activated and alternatively activated subsets are present in human and mouse lesions, with M1 being the predominant subtype [10]. In human lesions, macrophages expressing proinflammatory markers are found in rupture-prone, unstable areas, while M2-like macrophages are found insterile areas and adventitia [3]. However, recent evidence suggests that macrophages exist on an activation continuum and that the M1/M2 classification system is an over simplification of macrophage heterogeneity and their diverse functions. As described above, there are various ways to activate macrophages. Taken together, they demonstrate that macrophages in plaques can only partially resemble the phenotypesof macrophages M1 and M2 [4]. Further research is needed to

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identify the gene expression profiles and transcription pathways that underlie macrophage identity and diversity in ASSD. In addition, the question of whether the results obtained in mice can be transferred to human plaques that have distinct phenotypic differences (for example, bleeding and rupture) is important to determine the development of treatments that reduce the risk of residual inflammation associated with macrophages. Macrophages are the hallmarks of ACCS, contributing to plaque formation, local inflammation, and the development of thrombosis. This central role, combined with their plasticity, makes macrophages attractive therapeutic targets for stopping plaque progression and stabilizing existing atherosclerosis. Studies conducted in primates and pigs in the 1970s made it possible for the first time to detect the contribution of macrophages to the regression of atherosclerosis [11].These seminal studies used atherogenic diets high in fat and cholesterol to induce the progression of atherosclerosis and subsequent diets low in fat and cholesterol to reduce hypercholesterolemia. In both models, feeding a regression diet for 4-6 months reduced the foam cells of macrophages of the aortic lesion, reduced the area of necrotic plaques, and increased the thickness and density of fibrous capsules. A review of ASCVD regression conducted in 1985 stated: "It is obvious that the role of macrophages in regression can be very complex, and its comprehensive study cannot be achieved with a single experiment conducted by one or a small group of researchers"[12]. Since then, the creation of hyperlipidemic mouse models, widely used to model human ASCVD that allow rapid, reproducible plaque development, has further expanded the understanding of regulators of plaque progression in this area. In 2001, in response to the need for further development of a mouse model of atherosclerosis, basic research on the mechanisms that control the regression or stabilization of ASCVD was stimulated by the creation of an approach to aorta transplantation [13]. Human clinical trials have shown that significantly lowering cholesterol levels prevents serious adverse cardiovascular events. Imaging studies using intravascular ultrasound and optical coherence tomography show that dramatic reductions in LDL (low-density lipoproteins) (i.e. statins, inhibition of PCSK9 [subtilisin/kexin type 9 proprotein convertase]) prevent plaque progression and may even cause plaque regression [14]. The development of treatments that lower LDL cholesterol (LDL cholesterol), which contribute to an unprecedented reduction in LDL cholesterol compared to traditional statins, is likely to provide further understanding of the role of residual inflammatory risk, as well as plaque progression and regression [15]. Advances in imaging techniques provide insight into compositional changes in plaque remodeling[16].Optical coherence tomography allows detailed visualization of plaques and provides information about the composition of plaques (for example, lipids and calcification) and the thickness of the fibrous capsule, a classic marker of inflammation and vulnerability of plaques. Given that plaque lipid concentrations are positively associated with macrophage accumulation, this relationship is indirect evidence for a decrease in the number of macrophages in plaques during human ACCD regression[16]. Evidence for monocyte and macrophage phenotypes associated with plaque vulnerability was obtained from plaques taken from patients with various stages of atherosclerosis [17]. However, translating mouse macrophage studies to human ASCVD regression requires the caveat that the responses of monocyte-derived macrophages in mice and humans still need to be compared ɪin parallel. Further advances in imaging suggest that monitoring the content and phenotype of plaque macrophages may one day be possible in humans, as in mice [17]. These findings are likely to improve our understanding of human and mouse lesions during ASCVD regression. Current mouse models of ASCVD regression, well-described macrophage contributions, and preclinical efforts to develop macrophage-targeted drugs to inhibit plaque growth and inflammation are discussed below macrophage retention in plaques is determined by monocyte recruitment and macrophage proliferation, their emigration and death

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[18].Historically, research on atherosclerosis has focused heavily on understanding the mechanisms of recruiting monocytes into the vascular wall and developing strategies to block their influx into plaques[2]. However, recent studies show that there are also factors that determine macrophage retention in plaques, and it is assumed that if these processes are favorably modulated, the macrophage content in plaques can be reduced and ASCVD regression can be achieved. Broad changes in the transcriptome of plaque macrophages are characteristic of ASCVD regression, which is most often characterized by the enrichmentof M2-associated transcripts[19]. Dynamic changes in the plaque macrophage phenotype increase the likelihood that inducing macrophage polarization potential in in vivo will be a viable therapeutic option for regression of ASCVD and suppression of residual inflammatory risk. Known factors that modulate the content and phenotype of plaque macrophages in the context of ASCVD regression are described in detail below.

A recent study showed that after hypercholesterolemia is relieved , recruitment of Ly6C hi monocytes and their STAT6-dependent conversion to M2 macrophages is important for reducing macrophage content in plaques and suppressing ACSVD inflammation during regression[20]. To date, the factors that regulate STAT6 signaling to mediate this change are unknown, but given that IL-4 and IL-13 facilitate M2 polarization via the STAT6-dependent pathway, it is assumed that local production of these cytokines (e.g., basophils, eosinophils) during regression may mediate this process. However, it is important to note the results of an alternative model of plaque regression, which showed that suppression of monocyte recruitment is important for the regression of macrophage plaques [20]. This is consistent with studies in diabetic mice showing impaired regression after lowering lipid levels due to increased monocyte recruitment [21]. These results from various mouse regression models show that many different pathways positively affect the regression of formed plaques. They also emphasize that despite a significant decrease липопротеина in apoB lipoprotein, plaques did not regress completely, suggesting that there are additional unidentified mechanisms that contribute to residual inflammatory risk during regression. A certain function of macrophages is their efferocytosis ability, an important process of resolving inflammation and stabilizing plaques by reducing the area of the necrotic nucleus[22]. Macrophage efferocytosis, which means their ability to purify apoptotic cells and debris, is mediated through receptors including MERTK (tyrosine protein kinase MER), LRP-1, and CD47, and is considered as a protective anti-inflammatory function of M2 macrophages [23]. Thus, enriching macrophages with M2 or enhancing the efferocytosis capacity of macrophages (for example, by activating PPAR-γ) may be a viable strategy that promotes ASCVD regression and plaque stabilization.

Our research shows that the inflammatory responses of macrophages and their metabolism are interdependent. Classically activated M1 macrophages1 switch to anabolic metabolism by enhancing glycolysis or the pentose phosphate pathway, while M2 macrophages feed through oxidative phosphorylation and fatty acid oxidation. In the context of ACCSS, environmental signals, including hyperlipidemia, hypoxia, and hyperglycemia, distort macrophage polarization toward the glycolytic inflammatory M1-like phenotype, the macrophage phenotype of both unstable murine and human plaques[24]. How metabolic shifts in macrophages contribute to the progression and stability of the lesion, as well as the changes that occur after lowering LDL cholesterol, is currently unknown. However, preclinical studies provide insight into how reprogramming macrophages to the anti-inflammatory M2-like phenotype suppresses plaque progression.

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