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Multifaceted Functions of Macrophages in Atherosclerosis

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Macrophages play critical roles in atherogenesis [1,2*]. This commentary summarizes three recent publications that have elucidated effects of mediator subunit 1 (MED1) [3**], Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) [4**] and melanocortin 1 receptor (MC1-R) [5**] in macrophages in the development of atherosclerosis.

MED1, a subunit of mediator, functions as a transcriptional co-activator [6]. MED1 binds peroxisome proliferator-activated receptor (PPAR) γ [7]. Deficiency of MED1 impairs PPAR γ -regulated gene expression [8]. PPAR γ activation drives macrophages toward the M2 phenotype that conveys antiatherogenic properties [9]. Bai et al. [3**] determined effects of MED1 on atherosclerosis and related mechanisms. The authors used two strategies to demonstrate roles of macrophage-derived MED1 in atherosclerosis. One strategy used apolipoprotein E deficient mice with monocyte/macrophage-specific MED1 genetic deficiency. Another was bone marrow transplantation by repopulating bone marrow cells from monocyte/macrophage-specific MED1 deficient mice into lethally irradiated low-density lipoprotein deficient mice. MED1 regulated PPAR γ -induced M2 genes by enhancing the binding of PPAR γ on promoters of M2 marker genes and H3K4me1 and H3K27ac modification. MED1 deficiency in macrophages promoted M1 phenotype switch, augmented inflammatory response in the aorta, and increased atherosclerosis. These findings provide evidence that MED1 shows antiatherosclerotic effects by regulating PPAR γ -mediated macrophage polarization.

CaMKII is a serine-threonine kinase that regulates Ca²⁺-mediated functions [10,11]. Dr. Tabas's group [4**] found that CaMKII γ expression was increased in advanced atherosclerotic lesions. They then determined effects of macrophage CaMKII γ in efferocytosis of advanced atherosclerosis using myeloid-specific CaMKII γ deficient mice in a low-density lipoprotein receptor $-/-$ background. MerTK is a critical efferocytic receptor in macrophages and contributes to efferocytosis in atherosclerosis [12]. Genetic deletion of

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Conflicts of interest

There are no conflicts of interest.

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

CaMKII γ in myeloid cells improved MerTK-mediated efferocytosis and led to decreased necrotic cores and apoptosis in atherosclerotic lesions. Macrophage CaMKII γ inhibited a transcription factor AMP-dependent transcription factor (ATF)6, while ATF6 induced liver X receptor α , a MerTK inducer. These findings link macrophage CaMKII γ with ATF6, liver X receptor α , and MerTK with necrosis during atherosclerotic lesion development.

MC1-R is a G protein-coupled receptor that binds melanocortin peptides. It is abundant in monocytes and macrophages [13]. Rinne et al. [14*] reported previously that MC1-R activation prevented foam cell formation through increasing ABCA1 and ABCG1-mediated reverse cholesterol transport. On the basis of this previous work, the authors [5**] determined whether deficiency in MC1-R signaling would affect atherosclerosis. Whole body deficiency of MC1-R in apolipoprotein E deficient mice increased atherosclerosis, hypercholesterolemia and hepatic lipid accumulation. Deficiency of MC1-R also increased accumulation of Ly6C^{high} monocytes and macrophages in aortas of mice fed a normal rodent laboratory diet. These data highlight the importance of MC1-R in cholesterol metabolism, macrophage infiltration, and atherosclerosis.

Although this commentary only introduces three recent reports, many other studies have also explored extended mechanisms using human tissues, animal models, and culture systems to understand how macrophages or molecules in macrophages contribute to atherosclerosis. It is worth noting that most studies either focus on one sex or have no description of the sex studied in animal models. We expect that more investigators will investigate sex differences in future studies to understand mechanisms of atherosclerosis [15*].

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FURTHER RECOMMENDED READING

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This article reports that deficiency of miR-150 ameliorates atherosclerosis through regulating inflammatory response and macrophages infiltration.

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