

Atherosclerosis: cell biology and lipoproteins

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Abbreviations

KLF Kruppel-like factors
MMP matrix metalloproteinase

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The development of atherosclerotic lesions involves a complex array of cellular events that changes as the disease evolves [1]. Although many cell types have been invoked in the atherogenic process, monocyte-derived macrophages are proposed to have a central role in lesion initiation and progression, in addition to the terminal events that cause acute cardiovascular syndromes. The proposed role of macrophages is largely due to the ubiquitous presence of this cell type throughout lesion development and their absence in normal arteries. Furthermore, monocyte deficiency has a dramatic effect in attenuating development of experimental atherosclerotic lesions [2,3]. The specific functions of macrophages that contribute to lesion formation, however, have not been defined. In addition, it is unclear whether different functions are invoked at different stages of lesion progression.

Much of the previous focus on monocytes in atherogenesis has been on the mechanisms by which this cell type is attracted and tethered to the endothelial layer overlying the region of lesion formation. A recent study by Das *et al.* [4^{••}], however, has focused on the susceptibility of monocytes to express atherogenic proteins. Hematopoietic cells express the transcription factors, Kruppel-like factors (KLF), which have been implicated in growth and differentiation. One member of this group of transcription factors, KLF2, has been previously shown to be expressed by monocytes [5]. Das *et al.* [4^{••}] have studied the role of increased KLF2 expression as a mediator of the anti-inflammatory status of monocytes. In agreement with this tenet, they demonstrated that KLF2 expression is reduced in monocytes isolated from patients with extensive atherosclerosis. Subsequent studies demonstrated that reduced KLF2 is associated with increased inflammatory status. This included the decreased expression of KLF2 as monocytes were differentiated into

macrophages. Adenoviral-induced overexpression of KLF2 had a selective effect on the lipopolysaccharide induction of cytokines and chemokines in monocytes. This included the attenuation of lipopolysaccharide induction of several proteins involved in atherosclerosis, including MCP-1, CD40L, and COX-2 [6–8]. Conversely, knockdown experiments using siRNA enhanced the secretion of atherogenic factors from monocytes such as MCP-1 and COX-2. The overexpression of KLF2 had no effect on monocyte recruitment in an in-vivo assay that assessed influx of cells into the peritoneal cavity in response to a nonspecific irritant. Overexpression of KLF2, however, did impede the phagocytic capacity of monocytes/macrophages. Overall, the role of KLF2 in monocytes appears consistent with a function in atherosclerosis. Confirmation of this role will require studies in which KLF2 is specifically regulated in monocytes/macrophages and its impact on atherosclerotic lesion formation is determined in an animal model of the disease.

A role of macrophages in intravascular lipid metabolism is one of the initially described characteristics in atherogenesis. Despite its long history, the mechanism of lipid entry into lesional macrophages has not been unequivocally defined. While selected members of the scavenger receptor family have been implicated, the literature is replete with contradictions [9]. With the recent recognition of some members of the ABC family being lipid transporters, there has been increased emphasis on the role of lipid efflux mechanisms from macrophages, particularly ABCA1. It has previously been demonstrated that bone marrow transplantation of ABCA1-deficient cells increased lesion formation in low-density lipoprotein receptor-deficient mice [10]. This led to an interest in increasing the expression of macrophage ABCA1 as a therapeutic strategy. As lipid loading greatly increases expression of ABCA1, however, it was unclear whether maximal effective levels are obtained endogenously within lesional macrophages. To test this concept, van Eck *et al.* [11[•]] used bone marrow transplantation with cells isolated from mice that were transgenic for ABCA1 using a bacterial artificial chromosome [12]. Repopulation of irradiated low-density lipoprotein receptor^{-/-} mice with cells overexpressing ABCA1, did not lead to any change in lesion size at early stages of lesion formation. Overexpression of ABCA1, however, attenuated the increased size of lesions that occurred with more prolonged feeding of a saturated fat enriched diet. This is an interesting proof of concept

study, although its implementation as a therapeutic strategy is likely to be challenging.

In addition to aberrant intracellular lipid storage, macrophages have the potential to secrete a myriad of biologically active materials that could influence atherosclerosis. This includes several members of the matrix metalloproteinase (MMP) family of proteolytic enzymes. Whole body manipulations of MMPs have demonstrated that different members of this family can promote or inhibit the development of lesions [13]. MMP-12 has attracted particular interest in atherogenesis due to its relatively restricted expression to macrophages. The study of Liang *et al.* [14^{••}] created transgenic rabbits in which a human MMP-12 cDNA was driven by the human class A scavenger receptor promoter. Macrophage-specific overexpression of MMP-12 had no effect on lesion size or composition in rabbits fed a diet with mild cholesterol enrichment for 16 weeks. This result is consistent with the lack of effect on atherosclerosis in MMP-12 deficiency of lesion-susceptible mice [15]. Macrophage-specific overexpression of MMP12, however, increased lesion size throughout the aorta in rabbits maintained for 28 weeks on a diet with a greater enrichment of cholesterol. In addition to increased size, overexpression of MMP-12 led to enhanced destruction of the medial elastin lamina layers. In some regions, this led to focal outward protrusions. Although MMP-12 may not be involved in the initiation of lesions, these data are consistent with involvement in progression. Even in this model, however, there was an absence of blatant ruptures akin to the appearance of lesions that promote the majority of acute cardiovascular syndromes in humans [16].

The macrophage is probably the most phenotypically diverse cell type in the body. Within atherosclerotic lesions, it is likely that there is a wide range of functional diversity that may vary with stage of lesion progression and by the location of the cell within the lesion. While the macrophage has been a major focus of atherogenesis

studies for decades, we still have much to learn on the specific functions of this cell type that contribute to lesion formation.

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Recommended reading

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- A demonstration that the priming of CD4⁺ cells with oxidized LDL leads to increased atherosclerotic lesion size.