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Review

Macrophage phenotypic plasticity in atherosclerosis: The associated features and the peculiarities of the expression of inflammatory genes

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ABSTRACT

Macrophages are essential players in induction and progression of atherosclerotic inflammation. The complexity of macrophage phenotypes was observed in human plaques and atherosclerotic lesions in mouse models of atherosclerosis. Plaque macrophages were shown to exhibit a phenotypic range that is intermediate between two extremes, M1 (pro-inflammatory) and M2 (anti-inflammatory). Indeed, in atherosclerosis, macrophages demonstrate phenotypic plasticity to rapidly adjust to changing microenvironmental conditions. In the plaque, serum lipids, serum lipoproteins and various pro- or anti-inflammatory stimuli such as cytokines, chemokines and small bioactive molecules could greatly influence the macrophage phenotype inducing switch towards more pro-inflammatory or anti-inflammatory properties. Dynamic plasticity of macrophages is achieved by up-regulation and down-regulation of an overlapping set of transcription factors that drive macrophage polarization. Understanding of mechanisms of macrophage plasticity and resolving functional characteristics of distinct macrophage phenotypes should help in the development of new strategies for treatment of chronic inflammation in atherosclerosis and other cardiovascular diseases.

1. Introduction

It is widely accepted that atherosclerosis is a chronic inflammatory vascular disease [1–3]. Macrophages play a pivotal role in the initial stages and further progression of atherogenesis [1,4,5]. In early atherosclerotic stages, blood-derived monocytes migrate from the lumen to the subendothelial space of the arterial wall where they accumulate and differentiate to macrophages (Fig. 1) [6–8]. Experiments utilizing macrophages in *in vitro* experiments demonstrated that modified low density lipoproteins (LDL) are captured by macrophages followed by association of vacuoles containing LDL with lysosomes (Fig. 2A) [10,11]. The molecular mechanisms of interaction of modified LDL with macrophages have been detailed in a large number of reviews [12–16]. Despite the fact that the principal pathways of interaction of modified LDL are generally well understood [11–16], morphological data suggest that differently modified LDL might have yet-unknown specific fates in the cytoplasm of macrophages (Fig. 2B). The functional insufficiency of lysosomes is thought to lead to excessive accumulation of lipids ("lipid droplets") in the cytoplasm of macrophages (Fig. 3A, B) [10,18,19]. Eventually, macrophages engulfing modified LDL become overloaded with lipids, and this transforms them into foam cells (Fig. 3C), an event representing the most striking morphological feature of the formation of atherosclerotic lesions [1,4,11]. Foam cells are not able to leave the initial plaque and contribute to the failure of inflammation resolution and further establishment of a complicated atherosclerotic plaque [15]. Macrophages could be commonly identified in the lesion shoulder and calcified plaque regions [5,11]. Dying macrophages extensively contribute to the formation of the necrotic core and aggravation of the proatherosclerotic inflammatory response [16,20]. Even though there are reports suggesting that macrophages can transdifferentiate into dendritic cells [21–23], it is commonly thought that plaque macrophages represent a population of terminally differentiated cells of monocyte origin; nevertheless, macrophages are influenced by multiple microenvironmental stimuli that could drive macrophage polarization towards more proinflammatory or less proinflammatory phenotype

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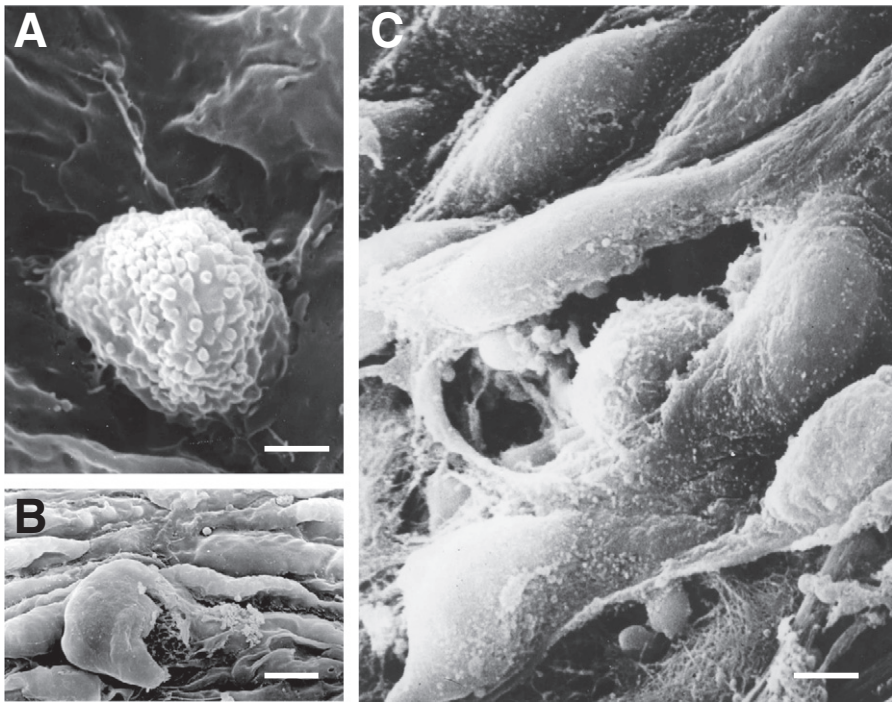

Fig. 1. Intrusion of monocytes through the endothelial barrier into the arterial intima in atherosclerosis (A–C). (A): Monocyte penetrating the endothelial barrier; note that the endothelial barrier did not show structural damage. (B, C): Area of the endothelium with structural damage (B) and a penetrating monocyte seen in an area of damaged endothelium (C). Scanning electron microscopy (SEM). Scale bars = 3 μm (A), 6 μm (B), 3 μm (C).

[24]. Several macrophage phenotypes could be observed in the plaque [25]. Indeed, macrophage phenotype is reversible and could be changed in response to different microenvironmental signals.

In this review, we discuss phenotypic plasticity of macrophages in response to different stimuli and heterogeneity of macrophage subsets in the atherosclerotic plaque that play either proatherogenic or atheroprotective roles.

2. Physiological phenotypic plasticity of macrophages

In hematopoiesis, monocyte differentiation is driven by two growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) that leads to the formation of macrophages that are phenotypically similar to M1 and M2 subsets of macrophages [26]. The classic M1 phenotype of activated macrophages is induced by inflammatory cytokines including tumor necrosis factor (TNF)-α and interferon (IFN)-γ and by stimulation with bacterial constituents such as lipopolysaccharides (LPS) and flagellin or in response to an intracellular parasite infection [27,28]. M1 macrophages are characterized by the expression of a broad spectrum of proinflammory cytokines (TNF-α, interleukin (IL)-1β, IL-12, and IL-23) and chemokines (C-X-C motif chemokine (CXCL9, CXCL10, and CXCL11)) [19] (Table 1). These macrophages also release high levels of reactive oxygen species (ROS) and nitric oxygen (NO) and are involved in the cascade of immune response mediated by Th1 cells. The anti-inflammatory M2 macrophage phenotype is induced by Th2-type

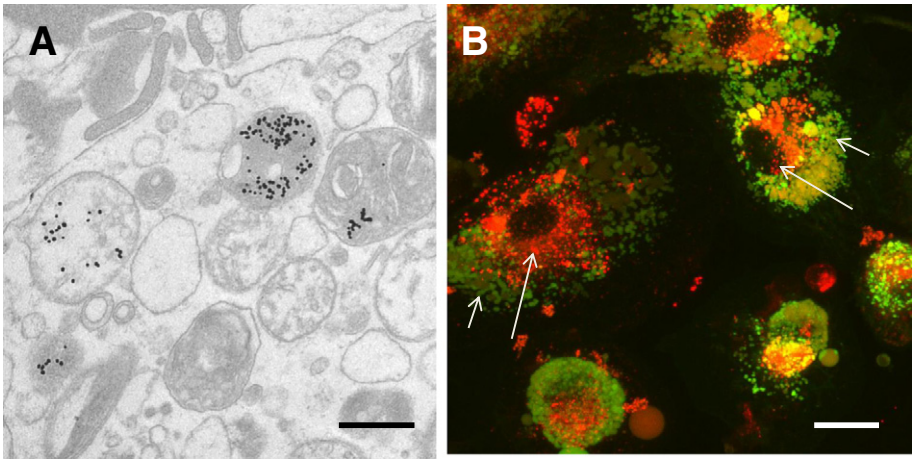

Fig. 2. Visualization of modified lipoproteins of low density (LDL)* in macrophages in *in vitro* experiment (A, B). (A): Visualization of oxidized LDL (non-aggregated, labeled with gold particles) in the cytoplasm of a macrophage; 8 h after the addition of oxLDL to cell culture. Electron micrograph. *Possible modifications of LDL are detailed elsewhere [9]. (B): Distribution of aggregated LDL (red color; large arrows) and oxidized LDL (non-aggregated) (green color; small arrows) in macrophages *in vitro*; 8 h after addition of both LDL modifications to cell culture. Immunofluorescent microscopy; immunofluorescent procedures were carried as detailed elsewhere [17]. Scale bars = 400 nm (A), 6 μm (B).