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Perspective

Macrophage Polarization Dynamics in Atherosclerotic Plaque Development and Plaque Instability

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DESCRIPTION

Atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by lipid accumulation, immune cell infiltration, and progressive structural changes that may lead to cardiovascular events such as myocardial infarction and stroke. Macrophages are central cellular components within atherosclerotic lesions and exhibit remarkable functional plasticity. Depending on environmental cues, macrophages can adopt distinct activation states that influence lipid handling, inflammatory signaling, and tissue remodeling. This article examines macrophage polarization dynamics in atherosclerotic plaque development and explores their contribution to plaque stability and rupture risk.

The arterial wall is a dynamic structure composed of endothelial cells, smooth muscle cells, extracellular matrix, and immune components. Under normal physiological conditions, the endothelium regulates vascular tone, maintains barrier function, and prevents excessive leukocyte adhesion. However, exposure to risk factors such as hyperlipidemia, hypertension, smoking, and metabolic dysfunction leads to endothelial activation and dysfunction. Endothelial dysfunction is an early event in atherogenesis. It is characterized by increased permeability, expression of adhesion molecules, and enhanced recruitment of circulating monocytes into the subendothelial space. Once monocytes migrate into the intima, they differentiate into macrophages under the influence of local growth factors and cytokines. Macrophages in atherosclerotic lesions display functional diversity depending on environmental signals. These cells are broadly categorized into pro-inflammatory and anti-inflammatory activation states, although in reality they exist along a continuum of phenotypes. Pro-inflammatory macrophages contribute to lesion progression by producing cytokines, reactive oxygen species, and proteolytic enzymes. Anti-inflammatory macrophages are involved in tissue repair, lipid clearance, and resolution of inflammation.

Lipid uptake is a defining feature of macrophage involvement in atherosclerosis. Modified low-density lipoproteins accumulate in the arterial wall and are internalized by macrophages through scavenger receptors. Excessive lipid uptake leads to formation of foam cells, which are lipid-laden macrophages that contribute to plaque growth and structural instability. Foam cell formation represents a critical step in lesion development. These cells secrete inflammatory mediators that amplify local immune responses and recruit additional immune cells. Over time, accumulation of foam cells contributes to the formation of fatty streaks, which are early visible lesions in atherosclerosis. Cytokine signaling plays an important role in regulating macrophage behavior within plaques. Pro-inflammatory cytokines promote activation of macrophages that enhance tissue inflammation and degradation of extracellular matrix components. Anti-inflammatory signals promote resolution pathways and support cholesterol efflux mechanisms. Cholesterol handling within macrophages is tightly regulated by transport proteins that facilitate efflux of excess lipids. When these mechanisms are overwhelmed, intracellular lipid accumulation leads to cellular dysfunction and death. Dead macrophages contribute to formation of necrotic cores within advanced plaques.

Necrotic core formation is a hallmark of unstable atherosclerotic lesions. These regions contain cellular debris, lipids, and extracellular matrix fragments that weaken plaque structure. Expansion of necrotic cores increases risk of plaque rupture and subsequent thrombotic events. Matrix degradation is another key factor influencing plaque stability. Macrophages produce enzymes that degrade collagen and elastin within the fibrous cap. Thinning of the fibrous cap reduces mechanical stability and increases susceptibility to rupture under hemodynamic stress. Oxidative stress is elevated within atherosclerotic lesions. Reactive oxygen species produced by macrophages and other cells contribute to lipid oxidation and further endothelial dysfunction. Oxidized lipids are particularly potent stimulators of macrophage activation and foam cell formation. Macrophage polarization is influenced by metabolic conditions within the plaque microenvironment. Glycolytic metabolism is associated with pro-inflammatory activation, while oxidative metabolism supports tissue repair functions. Metabolic reprogramming of macrophages therefore plays a role in determining plaque progression. Hypoxic conditions develop within growing plaques

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due to inadequate oxygen diffusion. Hypoxia induces expression of genes that promote angiogenesis and inflammatory signaling. Newly formed microvessels within plaques are often fragile and prone to leakage, contributing to intraplaque hemorrhage. Intraplaque hemorrhage introduces additional red blood cell-derived lipids and iron, further accelerating inflammatory processes. Iron accumulation promotes oxidative stress and enhances macrophage activation, contributing to lesion instability.

Cell death pathways such as apoptosis and necrosis are important determinants of plaque composition. Efficient clearance of apoptotic cells by macrophages helps maintain tissue stability. However, when clearance mechanisms are impaired, secondary necrosis occurs, contributing to necrotic core expansion. Macrophages also interact with smooth muscle cells within the arterial wall. Smooth muscle cells contribute to formation of the fibrous cap by producing extracellular matrix proteins. Crosstalk between macrophages and smooth muscle cells influences cap thickness and mechanical integrity. Single-cell sequencing studies have revealed multiple macrophage subsets within atherosclerotic plaques. These subsets exhibit distinct gene expression profiles and functional properties. Some subsets are associated with inflammation and lipid accumulation, while others are linked to tissue repair and plaque stabilization.

CONCLUSION

Macrophage polarization plays a central role in the development, progression, and destabilization of atherosclerotic plaques. The balance between pro-inflammatory and anti-inflammatory macrophage states influences lipid accumulation, inflammatory activity, and plaque stability. Continued investigation of macrophage biology may support improved strategies for preventing cardiovascular events associated with atherosclerosis.