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The Crucial Role of Metabolism in Macrophage Activation

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Abstract

Macrophages are essential to the immunological responses associated with atherosclerosis. Recent research on the role of macrophage autophagy (AP) in the development of atherosclerosis has shown a brand-new mechanism by which these cells contribute to vascular inflammation. The transport of cytoplasmic contents to the lysosomal apparatus during AP is a cellular catabolic process that will ultimately result in destruction and recycling. In the early stages of atherosclerosis, basal levels of macrophage AP are crucial for atheroprotection. However, AP deficiency promotes vascular inflammation, oxidative stress, and plaque necrosis in the latter phases of the pathophysiology when it becomes dysfunctional. In this essay, we'll talk about the involvement of macrophages and AP in atherosclerosis and the growing body of research proving that macrophage AP contributes to vascular disease. We will finally talk on how AP might be targeted for therapeutic utility.

Keywords: Atypical antipsychotic drug; Atherosclerosis; Foam cell; Mitochondria metabolism; chronic lung disease; acute pneumonia.

Introduction

The mononuclear phagocytic system includes monocytes and macrophages, both of which share a number of cell surface markers. In the past, monocytes were thought to be essential for the development of tissue-resident macrophages. The recent identification of embryonically generated macrophage subsets in several tissues, including the brain and heart, has, however, cast doubt on this idea. Independently from the pool of bone marrow-produced monocytes, the pool of embryonically derived macrophages renews itself by self-proliferation. The discovery of monocytes in peripheral tissues outside of the blood vasculature is another observation that contradicted the original theory. Each subset of tissue-resident macrophages has a different transcriptional profile despite having a conserved core signature, according to a genome-wide transcriptional study of macrophages isolated from a large array of tissues. This shows that tissue-resident macrophages are diverse and are influenced by their local environment. Following those findings, transcription factors in control of the growth and destiny of a single population of tissue-resident macrophages were found. For instance, signal-dependent transcription factors refine a core signature in response to tissue-specific signals. This enables macrophages to carry out certain tasks. For instance, heme concentrations control the transcription factor Spi-C, which is required by splenic macrophages. Due to poor erythrocyte clearance, red pulp splenic macrophage deficiency in Spi-C defective mice causes splenic iron build up. Another illustration is the substantial population of peritoneal macrophages, which depends on dietary retinoic acid-induced induction of the transcription factor Gata6 for growth and survival. Large peritoneal macrophage loss of phenotypic and transcriptional core-specific signature when relocated to a different environment or when Gata6 is genetically deleted supports macrophage adaptability with respect to environmental signals. But there are still many gaps in our understanding of the precise relationships between local micro environmental factors and tissue-resident macrophage destiny [1].

The main cause of death worldwide is cardiovascular disease associated to atherosclerosis. Major factors influencing the onset and progression of atherosclerosis include immune-inflammatory reactions in addition to lipid dysfunction and arterial lipid build up. Every stage of the development of a disease involves macrophages in some way. It's interesting to note that current research on macrophage autophagy (AP) has revealed a brand-new mechanism through which these cells

contribute to vascular disease. The contribution of macrophage AP to vascular disease and the involvement of macrophages and AP in atherosclerosis will both be covered in this essay. Finally, we'll talk about how AP might be used therapeutically to treat atherosclerosis.

The major cause of morbidity and mortality in the adult population worldwide is generally identified as cardiovascular disease (CVD), with an estimated forecast of 23.3 million deaths per year owing to these disorders by the year 2030. This global trend is reflected in data from our nation, with CVD accounting for 20.9% of all deaths in Venezuela. Increased prevalence of cardio metabolic risk factors and poor preventive interventions in primary care and public health management have been linked to this rise in cardiovascular morbidity and mortality. The serious socioeconomic and epidemiologic effects of CVD have sparked more research into its pathogenesis, particularly atherosclerosis. Recent research indicates immunologic processes may play important roles in its progression even though other risk variables are involved in this process [2].

The identification of the abnormal expression and orchestration of several cytokines and inflammatory mediators that are associated with rheumatic diseases like rheumatoid arthritis (RA), systemic lupus erythematous (SLE), and systemic vasculitis represents a significant advancement in our understanding of the pathogenesis of these illnesses. New research suggests that several of these chemicals serve important roles in cell activation and contribute to disease development. The histological hallmark of RA, for instance, is the development of the inflammatory pannus, which may be brought on by an excess of synoviocytes and infiltration by inflammatory and immune cells, and which is followed by tissue death. Numerous mediators, such as adhesion molecules and inflammatory cytokines, have been linked to this process. It is also well known that the coordination of

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intricate cytokine networks plays a crucial role in the development of synovitis. Among the cytokines implicated is macrophage migration inhibitory factor (MIF), which after being secreted by T lymphocytes, macrophages, endothelial cells (ECs), and other inflammatory cells, appears to be a key modulator of inflammatory reactions. The function and expressional regulation of MIF in various rheumatic diseases and associated disorders will be the main topics of this essay [3].

Materials and Methods

Smooth muscle cells (SMCs) and leukocytes in atherosclerotic plaques exhibit elevated inflammatory responses and apoptotic signals as a result of macrophages' function in promoting plaque formation by dilution of the fibrous cap and necrotic core components. Additionally, macrophages over secrete matrix metalloproteinase, which causes them to decrease the number of SMCs that resemble intimal fibroblasts and destroy collagen (MMP). Macrophage apoptosis and phagocytic clearance of apoptotic cells increased the necrotic core and lowered plaque stability at the site of vascular damage [4]. The necrotic core of the plaque, which is connected to the diluent fibre cap, is nearly always close to the rupture site of plaque. In order to assess the possible risk of plaque rupture, the stability of the plaque can be determined by the strength of the fibre cap. Mhem, a no foam protecting macrophage, stabilised plaque at the advanced stage of AS by suppressing foam cell development and promoting tissue regeneration and anti-inflammation. Mox, a macrophage produced in response to phospholipid oxide, may also be employed to provide protection from AS. Because of the rapid atherogenesis that comes from myeloid Nrf2 loss, Mox macrophages, which are abundant in advanced mouse lesions, serve an atheroprotective role. Additionally, some inflammatory genes had elevated expression in Mox macrophages, consistent with the way that wild-type mice's macrophages respond to oxidised phospholipids by up regulating the expression of inflammatory genes [5].

Drug loading into macrophages occur mostly either in vitro incubation or in vivo direct injection in the macrophage drug carrier. The in vitro incubation method entails properly incubating macrophages with medications in vitro and then reinjection the cargo-loaded macrophage carrier into the body for therapy. The term "in vivo direct injection method" refers to a direct injection into the body employing modified particular ligands or drug delivery systems with the right particle size to harvest the phagocytic macrophages as a medicinal agent. The development of macrophage targeting can improve the targeted delivery of therapeutic cargo (anti-inflammatory medicines and diagnostic imaging) to atherosclerotic lesions. showed that rhodamine-labeled lipid films that had been rehydrated with macrophage proteins were capable of locating active endothelia via CD11a and CD18, both of which bind to ICAM-1. The platform may be loaded with therapies with a variety of physical properties because of the extended circulation duration and homing capabilities, which makes it promising for use in magnetic resonance imaging applications [6]. However, there are some preparational shortcomings with the earlier approach of directly loading pharmaceuticals into macrophages, including limited loading efficiency, early drug release, and unfavourable drug inactivation. In order to further coat the drug carrier on its surface, the macrophage membrane was used to create the macrophage membrane-camouflaged drug carrier. The macrophage membrane carrier inherits the distinctive biological properties of the parent cells, including extended circulation and AS-relevant homing, as a result of the macrophage membrane's surface modification. This design strategy establishes the framework for the creation of cutting-edge cell membrane-based Nano therapies for AS. In order

to target medication delivery in AS lesions, Cheng and Li created a biomimetic "core-shell" shaped nanoparticle with PLGA as the "core" and macrophage membrane as the "shell" based on the strong affinity between 41 integrin and VCAM-1 in the macrophage membrane. The findings showed that the target receptor VCAM-1 had a strong affinity for the macrophage membrane-coated PLGA nanoparticle, which could successfully identify the target cells and target tissues in vivo [7].

Discussion

An excessive inflammatory response and hyper secretion of cytokines like interferon gamma (IFN), tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-6, IL-10, IL-12, IL-18, and macrophage colony-stimulating factor result from the proliferation and activation of T cells and macrophages, which causes MAS. Clinical symptoms of MAS include an on-going high fever, widespread lymphadenopathy, hepatosplenomegaly, and a range of central nervous system involvements, from mild disorientation to severe convulsions to outright coma [8]. In more severe cases, patients experience skin rashes, bleeding from the respiratory and gastrointestinal tracts, and hemorrhagic characteristics resembling disseminated intravascular coagulopathy (DIC). Pancytopenia elevated liver enzymes in the serum, and an aberrant coagulation profile with hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia are frequently present. In most situations, as in our two cases, the presence of many, well-differentiated macrophages actively phagocytosing hematopoietic cells during bone marrow examination validates the diagnosis of MAS. That is not always achievable, though, because of sampling problems, macrophage infiltration in other tissues (such as the liver, lymph nodes, skin, and lungs), or just because the test Despite the International Histiocyte Society's validation of HLH's diagnostic criteria, MAS diagnosis is frequently difficult, particularly when it affects SLE patients who frequently have cytopenia that cannot be separated from that of MAS [9].

Finding diagnostic guidelines for MAS in SLE patients became more important as a result. Found that, with the exception of white blood cell count and bilirubin, laboratory results are often poorer in MAS patients compared to those with SLE, and their study highlighted the rise in CRP in MAS patients. They also observed that, with the exception of fever, practically all MAS symptoms have high specificity and low sensitivity in the diagnosis of MAS. Hyperferritinemia, elevated lactate dehydrogenase levels, hypertriglyceridemia, and hypofibrinogenemia were the lab abnormalities with the highest sensitivity and specificity. In light of this, the researchers proposed criteria for MAS diagnosis in patients with juvenile SLE, and bone marrow aspiration was not thought to be required unless in dubious situations. With five clinical criteria and four laboratory criteria for case one and three clinical criteria and four laboratory criteria for case two, respectively, our two instances met the specified criteria. These parameters do have some restrictions, though. First, the study had a retrospective design and a small patient population, and the lab data came from just one location. Second, these criteria were put forth to separate MAS from active rheumatic disorders because those conditions make it challenging to tell MAS apart from some sequelae, like infection [10].

Conclusion

Key macrophage processes including phagocytosis and efferocytosis are controlled by metabolism, helping to maintain the homeostasis of healthy tissues and protect them from infection and inflammation. Through cell-intrinsic metabolic rewiring and/or cell-extrinsic ambient metabolite modification, macrophage responses and functions can be

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varied. This resulted in the creation of an overly simplistic but effective classification of macrophages into M1 and M2 subsets, respectively. However, this pattern is seen in tissue-resident macrophages at a steady state and is most likely an indication of their metabolism, which is controlled by the microenvironment of each individual organ. A change in macrophage markers toward a proinflammatory phenotype coincides with tissue structure remodelling and metabolite availability in the immediate environment during tissue inflammation, as seen in the case of obese adipose tissue [11].

Therefore, it is important to manage macrophage metabolic requirements and preserve their function in tissue homeostasis by obstructing metabolites that result in a proinflammatory phenotype. This calls for a deeper knowledge of tissue macrophage populations, their characterisation, and the presence or absence of common metabolic pathways in both embryonically generated macrophages and macrophages formed from monocytes. This objective appears more and more achievable, and it indicates that new metabolic targets utilised to reduce inflammation associated to macrophages may soon be proven [12].

Acknowledgments

Conflicts of Interest

None

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