Macrophone Polarization and Inflammation at the Interface of Cardiovascular Disease and Metabolism

Zhuxia Shen, PhD;1 Mingxing Lu, BS;1 Shengshu Duan, BS;2 Shengzhong Duan, MD, PhD1*

1Key Laboratory of Nutrition and Metabolism, Institute for Nutritional Sciences; Clinical Research Center of Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China
2Community health center, Datong district office, Lichuan, Enshi Tujia and Miao Autonomous Prefecture, Hubei, China

Classically activated macrophages (M1) and alternatively activated macrophages (M2) are induced by Th1 and Th2 cytokines respectively. These macrophages are phenotypically and functionally different. Polarized macrophages are important players in inflammation because of the pro-inflammatory properties of M1 and the anti-inflammatory properties of M2. Under metabolic stress, interactions between polarized macrophages and adipocytes, hepatocytes, and skeletal myocytes mediate the inflammatory response that ultimately contributes to metabolic diseases. The crosstalk between polarized macrophages and endothelial cells, vascular smooth muscle cells, and possibly cardiomyocytes is important in the progression of cardiovascular diseases (CVDs). Moreover, inflammation and macrophage polarization present as critical links between metabolism and CVDs.


Key Words: inflammation, macrophage polarization, metabolism, cardiovascular diseases

INTRODUCTION

Overweight or obesity, once being considered a symbolic presentation of wealth and possibly health in the old time when food is scarce, has become a characteristic display of metabolic imbalance in the modern world when food is readily available. Obesity has been linked to a host of diseases including type 2 diabetes and cardiovascular diseases (CVDs), both of which are major causes of mortality and morbidity in the modern societies. Moreover, type 2 diabetes and its characteristic insulin resistance exacerbate CVDs in multiple ways. Chronic inflammation originated from metabolic dysregulation is the foundation of insulin resistance and type 2 diabetes as well as a strong connection to CVDs. Macrophone polarization has emerged as a critical control point of inflammation and a link between metabolism and CVDs.

MACROPHAGE POLARIZATION AND INFLAMMATION

Macrophages, an important component of the innate immunity, have multiple functions ranging from host defense, tissue repair, to inflammatory modulation. It has been recognized that a full spectrum of macrophages with different functions exist in a variety of tissue microenvironments. An extreme of such plasticity is macrophage polarization that includes two distinct populations, classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 macrophages with more cytotoxic activity are typically stimulated by lipopolysaccharide (LPS), toll-like receptor (TLR) activation, or T helper (Th)1 cytokines including interferon γ (IFNγ), tumor necrosis factor α (TNFα), and granulocyte monocyte colony stimulating factor (GM-CSF). M2 macrophages, on the other hand, are typically induced by Th2 cytokines interleukin (IL)4, IL13 or IL10. Other anti-inflammatory stimuli such as glucocorticoids and immunocomplexes can also push macrophages toward M2 polarization.

Not only are M1 and M2 induced by different factors but also they demonstrate a variety of differences phenotypically and functionally. M1 macrophages express cell membrane markers TLR2, TLR4, CD80, and CD86. They produce more pro-inflammatory cytokines such as IL12, IL1β, monocyte chemoattractant protein 1 (MCP1) and TNFα, as well as express more Th1 cell–attracting chemokines such as C-X-C motif chemokine (CXCL)9 and CXCL10, both of which are inhibited by IL4 and IL10. These cytokines and chemokines produced by M1 further stimulate and attract Th1 cells to amplify M1 polarization. Functionally, M1 macrophages have enhanced endocytic functions and ability to kill intracellular pathogens, as well as pro-inflammatory response. These functions are mediated by effector molecules such as nitric oxide synthase (iNOS). In contrast, M2 macrophages express cell membrane markers such as scavenger receptors, mannose receptor, and CD163. They produce different sets of cytokines and chemokines, with low level of IL12, high levels of IL10 and IL1 receptor

Received 9/9/2011; Revised 9/22/2011; Accepted 9/24/2011
*Corresponding Author: Key Laboratory ofNutrition and Metabolism, Institute for Nutritional Sciences, Clinical Research Center of Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 320 Yueyang Rd, Building 41, Shanghai, China 200031. (Email: szduan@sibs.ac.cn)
antagonist (IL1ra), as well as different chemokines such as C-C motif ligand (CCL)18, CCL22 and CCL24, which are inhibited by IFNγ.9,10 Further, these cytokines and chemokines attract Th2 or T regulatory cells to amplify M2 polarization.9,10 Functionally, M2 macrophages participate in immunoregulation, parasite clearance, tissue remodeling, as well anti-inflammatory response.12 As a result, M2 macrophages can prevent uncontrolled tissue damage through their ability to phagocytose tissue debris and apoptotic bodies. These functions are mediated by a different set of effector molecules including arginase.11

Similar to other biological processes, macrophage polarization is tightly controlled by multiple factors, among which a series of transcription factors are particularly important. M1 polarization is regulated by nuclear factor (NF)-κB, Activator protein 1 (AP1), interferon regulatory factor (IRF), and mineralocorticoid receptor (MR).13-16 These transcription factors control M1 polarization mostly through their modulation on pro-inflammatory gene expression. M2 polarization is regulated by signal transducer and activator of transcription 6 (STAT6), peroxisome proliferator activated receptors (PPAR) δ and γ, and glucocorticoid receptor (GR).17-21 STAT6 is the most important regulator of M2 polarization. It mediates the effects of IL4/13 and regulates PPARδ and PPARγ to have synergistic end results.

Inflammation has been increasingly recognized as a double-edged sword. Acute inflammation is a net positive in that it is necessary for the body to fight infection and rebuild tissue damage. Chronic inflammation, on the other hand, has been regarded as a driving force for diseases such as type 2 diabetes, obesity, and cardiovascular disease, particularly atherosclerosis.22 The appearance of macrophages is a hallmark of inflammation. As discussed above, M1 macrophages are generally pro-inflammatory and M2 ones are in contrast anti-inflammatory. Therefore, macrophage polarization plays crucial roles in the initiation, progression, and resolution of inflammation.

MACROPHAGE POLARIZATION AND INFLAMMATION IN METABOLISM
Type 2 diabetes has undoubtedly become an epidemic worldwide.23 Type 2 diabetes and obesity, a closely associated public health problem, are major components of metabolic syndrome. Over the past decade or so, inflammation has been widely accepted as the root for obesity and type 2 diabetes.22 Adipose tissue of obese animals can secrete much more TNFα than that of lean counterparts and this classical inflammatory cytokine has been demonstrated to induce insulin resistance.24 Subsequently, a series of inflammatory factors have been described to be involved in insulin resistance, obesity, and type 2 diabetes. Later, macrophage infiltration was identified in adipose tissue and this phenotype was recognized as a major cause of insulin resistance in the setting of obesity.22,25 Therefore, obesity-related insulin resistance was considered as a chronic inflammatory disease.25 More recent studies have discovered the mechanisms how inflammation induces insulin resistance, including alteration in phosphorylation of insulin receptor substrate 1 (IRS1).26 Taken together, these investigations have clearly demonstrated that chronic inflammation is a major cause of obesity and type 2 diabetes.26

It has been well documented that pro-inflammatory M1 macrophages are associated with insulin resistance and that anti-inflammatory M2 macrophages are in connection with improved insulin sensitivity.27 Under different metabolic conditions, differentially polarized macrophages interact with adipocytes, hepatocytes and skeletal myocytes, to affect insulin sensitivity (Figure 1). These interactions are important bridges between inflammation and obesity and type 2 diabetes.

Adipose tissue has been considered as the initiating point of chronic inflammation that causes insulin resistance and adipose tissue macrophages (ATMs) are one of the most extensively analyzed population.28 The communications between adipocytes and macrophages are bilateral. When metabolism of the body is balanced, adipocytes predominantly send alternative activation signals to promote M2 polarization. For examples, adiponectin and secreted frizzled related protein 5 are both adipokines that have anti-inflammatory properties and that can stimulate M2 polarization.29,30 Moreover, adipocytes have been found to express and secret Th2 cytokines IL4 and IL13.19 Under metabolic stress such as obesity, adipocytes mainly send classical activation signals to propagate pro-inflammatory M1 polarization. Among these signals are pro-inflammatory Th1 cytokines including TNFα, saturated fatty acids, and other factors such as complement protein C3.14,28 Furthermore, chemo-attractants such as MCP1 are secreted by adipocytes to attract more monocytes from blood stream. These newly recruited monocytes would differentiate into M1 macrophages and account for the major numbers of this population. On the other hand, M1 polarized macrophages also secrete chemo-attractants to recruit more inflammatory monocytes. These chemo-attractants from both adipocytes and macrophages set up a feed-forward loop to further increase the number of M1 macrophages in adipose tissue. In addition, M1 macrophages produce more Th1 cytokines such as TNFα and IL6 to induce lipolysis.31,33 As a result, more saturated fatty acids are released to induce inflammation in both adipocytes and macrophages. Thus, another feed-forward loop forms. These two feed-forward loops join force to induce insulin resistance in adipose tissue and contribute to the whole body insulin resistance.14

In the setting of obesity, hepatic insulin resistance is often accompanied by steatosis and elevated expression of inflammatory mediators, indicating the contribution of hepatic inflammation in the development of insulin resistance. Inflammatory activation of hepatic macrophages, also known as Kupffer cells (KCs), is associated with both insulin resistance and fatty liver disease.34,35 Interactions between hepatocytes and KCs play important roles in determination of inflammation and metabolic consequences. Under normal metabolic conditions, hepatocytes, similar to adipocytes, can secrete Th2 cytokine IL4 and IL13 to
stimulate M2 activation of KCs. However, under metabolic stress, M1 activation is predominant because more Th1 cytokines are secreted from liver. On the other hand, alternatively activated KCs are necessary to maintain normal hepatic metabolism.

In obesity induced insulin resistance and type 2 diabetes, accumulation of inflammatory macrophages in skeletal muscle has also been detected. Interactions between macrophage polarization and skeletal myocytes also contribute to inflammation and metabolic consequences. In vitro studies have demonstrated that PPARγ deficiency in macrophages causes M1 polarization, which plays a part in the development of insulin resistance in skeletal myocytes.

These interactions between polarized macrophages and hepatocytes and skeletal myocytes suggest that similar to adipocytes, hepatocytes and skeletal myocytes as well have paracrine and even endocrine functions. Further, macrophages in their specific microenvironments also exert paracrine and even endocrine function to communicate with major insulin target cells and to mediate inflammation and insulin resistance.

MACROPHAGE POLARIZATION AND INFLAMMATION IN CARDIOVASCULAR DISEASES

Chronic inflammation is a risk factor and diagnostic indicator of CVDs. Atherosclerosis is probably the best representative of inflammatory CVDs. Systemic inflammation also precedes any other signs of myocardial infarction. In cardiac hypertrophy caused by angiotensin II or pressure overload such as hypertension, increased amount of macrophage infiltration has also been reported. In fact, recruitment of leukocytes, including monocytes, to injury sites of the cardiovascular system is central to inflammatory response that would later shape the initiation and progression of CVDs. M1 and M2 macrophages, with their differential roles in inflammation, exert different or even opposite functions in the cardiovascular system through their interactions with endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and cardiomyocytes (Figure 1).

ECs, in direct contact with blood monocytes, when activated can secrete adhesion molecules including intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), E-selectin, and P-selectin. These molecules in turn attract monocytes that migrate into vascular wall and differentiate to macrophages. Activated ECs can synthesize pro-inflammatory cytokines, which promotes an M1 polarization. When cultured together with monocytes, ECs secretes GM-CSF, a cytokine that induces M1 activation. On the other hand, M1 macrophages produce
pro-inflammatory cytokines to further activate ECs. These interactions between monocytes/macrophages and ECs set up initiation for cardiovascular diseases such as atherosclerosis and hypertension.

Interactions between VSMCs and macrophages are particularly important in the progression of atherosclerosis. Oxidized LDL can stimulate VSMCs secret more Th1 cytokines including TNFα and MCP1 to induce M1 macrophage polarization and monocyte recruitment respectively.46,47 In addition, these activated VSMCs produce more VCMA1 to increase monocyte recruitment and amplify the inflammatory response. The impact of polarized macrophages on VSMCs and atherosclerosis is controversial in vitro vs. in vivo. In vitro data indicate that M1 polarization may be beneficial and that M2 polarization detrimental. Conditioned media from M1 macrophages increase apoptosis and decrease proliferation of VSMCs and those from M2 macrophages increase the proliferation.48,49 However, in vivo data suggest the opposite. Blockade of M1 polarization in general reduces atherosclerosis.50 Conversely, M2 polarization has been reported to reduce atherosclerosis while blockade of M2 in general increases it.51-52 These obvious contradictions may be because of the nature of the VSMCs in culture dishes is distinctly different from that in the body. Another possibility is that the oversimplification of the definition of macrophage polarization hits its limitation and renders the inability to distinguish the subtle differences of macrophages in the complex setting of atherosclerosis. Indeed, a distinct population of macrophages named Mox, strikingly different from M1 and M2, has been identified in atherosclerotic lesions recently.53

Monocytes infiltrate into cardiac tissue in response to myocardial injury or stress.54 Recent studies have suggested that macrophage polarization plays important roles in myocardial infarction and cardiac hypertrophy. Class A scavenger receptor (SR-A) deletion causes M1 polarization and exacerbates myocardial infarction.55,56 MR deficiency in macrophages induces M2 polarization and protect cardiac hypertrophy caused by N (G)-nitro-L-arginine methyl ester (L-NAME) in combination with angiotensin II (Ang II).16 Further delineation of how these polarized macrophages interact with cardiomyocytes will provide more exciting input for the field.

MACROPHAGE POLARIZATION AND INFLAMMATION LINK METABOLISM AND CARDIOVASCULAR DISEASES

Inflammation induced by obesity is a chronic and low-grade inflammatory response involving multiple organs.57 This inflammation links metabolism and cardiovascular diseases via the endocrine function of adipose tissue and possibly liver and skeletal muscle.

Adipose tissue has been accepted as an endocrine organ and a mediator of inflammation and innate immunity. In the state of metabolic stress, adipocytes, interacting with M1 macrophages, secrete multiple pro-inflammatory cytokines and release increased amount of free fatty acids into the blood stream. M1 polarized ATMs also secrete pro-inflammatory cytokines to join the force. These factors then initiate or exacerbate injuries in the cardiovascular system, as well as potentiate the interactions between cardiovascular cells and polarized macrophages (Figure 1).

Inflammation and macrophage polarization may also connect metabolism to cardiovascular system through perivascular adipose tissue in a paracrine fashion.58 Perivascular adipose tissue exists at coronary vessels, aorta, microvascular beds of the mesentery, muscle, kidney, and adipose tissue itself. On these sites, adipocytes, ATMs, ECs, and VSMCs are all conveniently located nearby. Inflamed adipocytes and M1 polarized ATMs can release pro-inflammatory factors to have direct impact on ECs and VSMCs.

CONCLUSIONS

Research in the past two decades has clearly demonstrated the importance of inflammation in metabolic disease and CVDs and recognized inflammation as a strong association between these diseases. Polarized macrophages crossstalk with different cells in particular microenvironments to modulate inflammation, affect metabolic diseases and CVDs, and tie metabolic imbalance to CVDs. Taken together, inflammation and macrophage polarization are vital links between metabolism and CVDs. These advances in the field have provided numerous new therapeutic opportunities targeting inflammation or macrophage polarization in searching for more effective treatment for these deadly diseases.
Rγδ controls alternative activation and improves hepatic insulin sensitivity. Current Opinion in Inflammatory. 2007;27(9):3350.


