

# MicroRNA Regulated Macrophage Activation in Obesity

Srikanth Kanameni<sup>1</sup>, Wei Ying<sup>2</sup>, Fuller W Bazer<sup>2</sup> and Beiyan Zhou<sup>1\*</sup>

<sup>1</sup>Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX 77843, USA

<sup>2</sup>Department of Animal Science, Texas A&M University, College Station, TX 77843, USA

## Abstract

Obesity and many other metabolic disorders, including type 2 diabetes and atherosclerosis, have conventionally been viewed as lipid storage disorders caused by over nutrition. Research has demonstrated that the obesity associated chronic low-grade tissue inflammation and oxidative stress is crucial factors in the initiation, propagation, and development of these metabolic disorders. Disruption in the normal functioning of the immune system and its interaction with host tissue cells makes it difficult to treat these diseases. Macrophages play critical roles in the development of insulin resistance and tissue inflammation, particularly through a unique shift in polarized activation status from an anti-inflammatory M2 function in lean adipose tissues to proinflammatory M1 activation in adipose tissues of obese individuals. Compelling evidence demonstrated the significance of microRNAs as important regulators in the immune system network. Our recent research has demonstrated that microRNA-223 is a crucial regulator of obesity associated insulin resistance through regulation of macrophage polarization in adipose tissue. This review highlights the importance of various microRNAs and their roles played in the polarization of macrophages which could be targeted for development of new therapeutic strategies to treat obesity associated diseases.

**Keywords:** MicroRNA; Obesity; Insulin Resistance; Macrophage; Macrophage Polarization; M1; M2

## Introduction

In the last several decades, lack of balanced diet both in terms of quality and quantity has led to a rapid progression of obesity throughout the world; resulting in a major pandemic situation attracting the attention of many nations. The severity of obesity has been tightly associated with many chronic diseases. Obese patients are prone to conditions like inflammation and insulin resistance which is a causal factor in the pathogenesis of life threatening diseases like Type II Diabetes Mellitus, cardiovascular diseases and many more [1-3]. Recently studies demonstrated that obesity is a disease status characterized with chronic, low-degree tissue inflammations, which can result from elevated infiltration of macrophages into obese tissues, and more importantly, activation status shift from an anti-inflammatory to a proinflammatory status [1,4-9]. Impairment in the immune system makes it more difficult to treat these disease conditions.

Macrophages are key cellular components in the innate immune system. They play an essential role in responding to invading pathogens by triggering elaborate immuno-inflammatory reactions that ultimately results in the elimination of the pathogen and reinstatement of normal conditions. In response to microenvironmental cues like pathogenic and tissue-derived molecules, macrophages undergo profound phenotypic changes and provide appropriate responses by adapting to their microenvironment [4,10,11]. Understanding these 'adaptive' changes will provide pivotal information to open the gate for development of new clinical therapies for in treating chronic diseases within the proper context. Recent studies have shown that microRNAs have a profound influence on immune cell functions, including macrophage activation [12,13]. Results of our previous studies provide new evidence to support an essential role for microRNA in regulating Adipose Tissue Macrophage (ATM) polarization [14]. In this review, we will discuss the importance of macrophage polarization in obesity and related disorders and the newly discovered regulatory network governed by microRNAs.

## Macrophage Polarization and its Diverse Functions

Macrophages play several pivotal roles in innate and adaptive

immune response, tissue repair and remodeling and many more. Of the many key traits of macrophages, a major one is their functional diversity [15,16]. This key feature could be attributed to their capability of responding to diverse stimuli and in turn exhibit diverse phenotypes and functional roles. Macrophages undergo two unique activation programs, classical (M1) and alternate (M2) activation, and a full spectrum of intermediate phenotypes between those two extremes in status [10,15,16]. In response to stimuli provided by bacterial infections like lipopolysaccharide (LPS) and interferon-

$\gamma$  (IFN- $\gamma$ ), or palmitate fatty acid in the context of obesity, macrophages adopt a classical activation strategy and a proinflammatory phenotype and become highly phagocytotic, as well as exerting the bactericidal activity, and secreting proinflammatory cytokines and chemokines to further protect against invading pathogens. On the other hand, signals from interleukins (IL) like IL-4 and IL-13 promote alternative activation of macrophages which have role in parasite elimination, tissue remodeling and repair, and inhibition of tumor progression [6,15,17,18]. The phenomenon of activation of M1 and M2 macrophage polarization has been investigated intensively in recent decades as it could lead into pathways for treatment of many important disease conditions.

Genomic and transcriptional studies and other phenotypic analyses of M1 and M2 macrophages provided immense knowledge on several distinct characteristics extending from traits inherent in their chemokine to metabolome [19]. For example, M1 macrophages express the Th1-attracting chemokines such as CXCL9 and CXCL10,

**\*Corresponding author:** Dr. Beiyan Zhou, Department of Physiology and Pharmacology, CVM, Texas A&M University, College Station, TX 77843-4466, USA, Tel: 979-845-7175; Fax: 979-862-4929; E-mail: [bzhou@cvm.tamu.edu](mailto:bzhou@cvm.tamu.edu)

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whereas M2 macrophages express the chemokines CCL17, CCL22 and CCL24 [10,19-24]. In the same fashion, M1 and M2 macrophages display different functional phenotypes in response to glucose, amino acid, lipid and iron metabolism [10,15,16]. Even though the macrophage polarization was originally studied and defined *in vitro* using conventional methods, numerous studies have shown such polarization states *in vivo*, under physiological and pathological conditions. Of note, macrophages stimulated in response to parasite infections, allergy and in many tumor types resemble to a large extent an M2-or M2-like phenotype [25,26]. But it is to be considered that, *in vivo* conditions are often complex to interpret as other cues involved both M1 and M2 macrophages which may show a mixture of multiple functional phenotypes [4,18,27]. Further, many studies that cues which induce polarization *in vivo* are due to interactions among various immune and non-immune cell types like lymphocytes, dendritic cells, fibroblasts, and mesenchymal stem cells [7,10,18,28] and several other factors including non-coding RNA [14,29,30]. These factors make the study on macrophage polarization in relation to these diverse cell types important.

As mentioned, macrophages show functional diversity ranging from inflammation, phagocytosis, immunoregulation, tissue remodeling and even metabolism. The contribution of macrophages to inflammation is one of its most well-documented functions. In contrast to its proinflammatory functions, macrophages also contribute to the dampening of inflammation through their immunoregulatory properties [16,31,32]. Phagocytosis is a defining feature of macrophages. Macrophages not only play roles in killing pathogens but also in elimination of dead cells and remnants of cells which is important for resolution of inflammation. In fact, it is known that phagocytosis of apoptotic cells polarize these cells into an anti-inflammatory mode that supports their immunoregulatory functions [33].

### Adipose Tissue Macrophages are Major Contributor to Obesity Associated Inflammation

The central feature of obesity which aggravates the progression of insulin resistance is chronic low-grade inflammation due to the infiltration of adipose tissue by macrophages [1,4-9]. The dysfunction of adipose tissue with respect to maintaining energy homeostasis is associated with obesity, inflammation and metabolic complications [34]. In addition, in the case of obese persons, weight loss is linked to improved insulin sensitivity and their risk of cardiovascular diseases is decreased. The inflammatory condition in obese patients is different from inflammation caused by classical activated macrophages which are stimulated by pathogens. In response to nutrient excess and is relatively chronic in nature, adipose tissue in obese individuals has an enhanced production of proinflammatory cytokines, infiltration by immune related cells, especially ATMs and the formation of crown like structures where apoptotic or soon to be apoptotic adipocytes and their remnants accumulate and cluster around phagocytic macrophages [5,35,36]. In lean mice, the ATMs are mainly the alternatively activated M2 macrophages and when these mice were subjected to high fat diet there is seen a phenotypic switch in macrophage polarization towards a proinflammatory type in mouse adipose tissue [28]. Polarized macrophages play an important role in lipid metabolism and homeostasis. Studies showed ATMs from tissues of lean subjects and ATMs during weight loss to resemble M2 macrophage and found to express high levels of the anti-inflammatory cytokine IL-10 [20,37,38]. It is believed that these ATMs maintain adipose tissue homeostasis by protecting from inflammation in response to high fat concentrations [39].

As explained, obesity is associated with increased accumulation of macrophages as well as with enhanced switching in polarization of ATMs from an anti-inflammatory (M2) to a proinflammatory (M1) state [6]. This change in polarization could be related to pathogen interference and could be specified by the targeted grouping of M1 macrophages around adipocytes which are apoptotic and having necrotic like structures [40]. Interestingly, some studies suggested that in people who are experiencing weight loss, there is a reduction in the infiltration of inflammatory macrophages into the adipose tissue and an improvement in the inflammatory response and oxidant profile of adipocytes as well as the circulating monocytes [30].

### MicroRNAs are Important for Adipose Tissue Function

Compelling evidence suggest critical roles of microRNAs in regulating adipose tissue function in the context of obesity [41]. The discovery of microRNAs, a class of 21-23-nucleotide non-coding RNAs revealed a new layer of gene regulation in almost every aspect of biological processes, including those of the immune systems [12,13]. MicroRNAs are short non-coding RNAs that are approximately 22-nucleotide in length and bind to target mRNAs and regulate gene expression. The microRNA pairs to its target mRNAs typically result in their degradation and/or repression of translation [42].

MicroRNAs are expressed in a tissue- and cell-type specific manner and play important roles in many molecular and biological processes, including proliferation, apoptosis, development, and differentiation [12,42-44]. During adipogenesis, microRNAs are modulating the formation and function of adipose tissue from various aspects. MicroRNA-33a and microRNA-33b target genes are related to metabolism [45,46] and microRNA-103 and microRNA-107 regulate insulin sensitivity and glucose homeostasis by modulating the abundance of caveolin-1 in adipocytes [47,48]. Furthermore, microRNAs have been associated with inflammation, oxidative stress, impaired adipogenesis and insulin signaling, and apoptosis and angiogenesis in relation to obesity. All of these processes contribute to the development of type 2 diabetes, atherosclerosis, and associated cardiovascular disorders [30,41,49-51]. However, their association with these processes does not necessarily imply a causal role. Each microRNA can have different roles under various conditions. For instance, microRNA-17-92 cluster, microRNA-21, microRNA-103, miR-143, microRNA-371, and miR-378/378\* have shown to increase adipogenesis [47,48,52-57]. This is evidenced by increased concentrations of triglycerides in the circulation and enhanced expression of adipogenic markers [33,52,54,56,57]. The microRNA-17-92 cluster induces and accelerates adipocyte differentiation by suppressing expression of the pivotal cell cycle regulator Rb2/p130 [52]. In addition, let-7, microRNA-27, microRNA-130, microRNA-138, microRNA-369-5p, and microRNA-448 inhibit adipogenesis which results in a decrease in triglycerides and down-regulation of adipogenic factors [53,58-60]. Similarly, microRNA-21 stalls adipogenesis by inhibiting the TGF- $\beta$  signaling pathway and microRNA-143 acts in the similar fashion through down-regulating ERK-5 function [54]. The let-7 microRNA inhibits adipogenesis by targeting high-mobility group AT-hook 2 (HMGA-2) [53], whereas microRNA-27 and microRNA-130 function through suppressing peroxisome proliferator activated receptor  $\gamma$  directly [61,62].

### Significance of MicroRNAs in Regulating Adipose Tissue Macrophage Activation

MicroRNAs are now accepted as important posttranscriptional

regulators of gene expression in immune cells like monocytes and macrophages [12,13]. Variety of inflammatory signals stimulate microRNA expression induction like LPS, TNF $\alpha$  or IL-1 $\beta$  and these tune down TLR4/IL-1R signaling pathways in macrophages/monocytes [12,13]. A decrease in microRNA-17, microRNA-92a and microRNA-155 is associated with an increase in monocyte/macrophage proliferation and enhanced TLR-4 activation [63-65]. Similarly, microRNA-424 expression in endothelial cells is increased by hypoxia and switches on a pathway to regulate monocyte/macrophage differentiation [66,67]. For example, different studies have shown that microRNA-146, microRNA-125b, microRNA-155 and microRNA-9 are induced by LPS and subsequently inhibiting TLR4/IL-1R signaling pathway by posttranscriptional regulation of the pathway components' levels [68-71]. In a similar fashion, some studies suggested microRNAs can directly regulate production of type 2 cytokine productions during macrophage activation, for example, microRNA-98 and microRNA-21 can control the expression of IL-10 in macrophages and monocytes that in turn inhibit induction of expression of inflammatory genes [60,72]. Recent study found that let-7c regulates bactericidal and phagocytic activities of macrophages, two functional phenotypes implicated in macrophage polarization [29].

Based on these evidences, it may be hypothesized that, in the context of obesity, the switching of inflammatory macrophages to an anti-inflammatory phenotype could be promoted by microRNAs. A study by Zhuang et.al identified that microRNA-223 acts as an important regulator of ATMs polarization and further demonstrated that it plays a significant role in modulating obesity associated insulin resistance [14]. MicroRNA-223 is differentially expressed during macrophage polarization, and microRNA-223-deficient macrophages were hypersensitive to LPS stimulation and exhibited delayed responses to IL-4 compared with controls. Furthermore, there is increase in M1 and decreases in M2 polarization biomarkers in microRNA-223 deficient macrophages indicated a suppressive effects on activation of pro-inflammatory macrophages and stimulatory effect on anti-inflammatory activation. MicroRNA-223-deficient mice displayed enhanced adipose tissue inflammatory responses and decreased adipose tissue insulin signaling accompanied by inappropriate adipokine expression, which are indicators for adipose tissue dysfunction. These results support the hypothesis that microRNA-223-regulated macrophage polarization, likely acting through suppressing a proinflammatory gene Pknox1, is important for adipose tissue function. These studies provided profound knowledge in the complex interaction in the macrophage-mediated adipose tissue inflammatory response and metabolic regulation as well as indicating the possibility of targeting microRNAs for treatment of metabolic disorders and disease resulting from insulin resistance.

## Conclusion

Thus this review collectively signifies the importance of microRNAs in diverse roles of macrophage polarization with specific focus on the dysfunction of adipose tissue and its disorders. Impairment in the normal functioning of adipocytes leads to an inflammatory phenotype, with enhanced expression of proinflammatory adipocytokines and down regulation of expression of anti-inflammatory adipocytokines. The roles played by polarized macrophages are immense and the significant contribution by microRNAs could not be ignored as well. Future research a profound understanding of the complex network of interactions among different factors involved in state of polarization of macrophages in health and disease.

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