

# Macrophages Switch: The Fate of Adipose Tissue in Obesity

## Abstract

The development of Insulin resistance in obesity is associated with infiltration of immune cells in white adipose tissue (WAT). Especially macrophage infiltration in WAT is known to produce several proinflammatory cytokines which induces the state of inflammation and impairs the insulin signaling and related pathways. Several animal and human studies have been conducted to unravel the mystery of metabolic dysregulation in adipose tissue because of chronic inflammation. A new and promising explanation is the switching of macrophages within WAT between M1 and M2 phenotype. In this short review, we addressed the recent advances in macrophage switch concept to explain the dysregulation of adipose tissue.

**Keywords:** Macrophages; Adipose tissue; Inflammation; Obesity; Metabolic Syndrome

## Review Article

Volume 3 Issue 6 - 2016

**Manish Kumar Saraf<sup>1,2</sup>, Michael Shen<sup>3</sup> and Umesh D Wankhade<sup>1,2\*</sup>**

<sup>1</sup>Arkansas Children's Nutrition Center, USA

<sup>2</sup>Departments of Pediatrics, University of Arkansas for Medical Sciences, USA

<sup>3</sup>Duke University, USA

**\*Corresponding author:** Umesh D Wankhade, Arkansas Children's Nutrition Center, Departments of Pediatrics, University of Arkansas for Medical Sciences, 15 Children's Way, Slot 512-20B, Little Rock, AR, USA 72202, Tel: 501-364-2847; Fax: 501-364-3161; E-mail: [udvets@vt.edu](mailto:udvets@vt.edu)

**Received:** July 28, 2016 | **Published:** August 29, 2016

**Abbreviations:** WAT: White Adipose Tissue; CLS: Crown-Like Structures; ATMs: Adipose Tissue Macrophages; sWAT: Subcutaneous Adipose Tissue

## Introduction

Chronic low-grade inflammation has been tightly correlated with obesity and its several complications [1-4]. In a pioneering study, Weisberg et al. [4] showed that the macrophage content of adipose tissue correlated positively with BMI and adiposity. Macrophages can be classified into two major categories: classically activated M1 macrophages and alternatively activated M2 macrophages. With regards to adipose tissue in humans, the obese phenotype is primarily characterized by the presence of M1 macrophages, whereas the lean phenotype is characterized by M2 macrophages. M2 macrophages produce anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, promote remodeling, efferocytosis, and improve systemic insulin sensitivity [2]. On the other hand, M1 macrophages are known to secrete proinflammatory cytokines such as IL-6, TNF $\alpha$  and MCP1, which can lead to inflammation and impaired insulin signaling [2]. Macrophages will notably generate necrosis in obese adipose tissue, resulting in the formation of bodies of aggregated macrophages around dead adipocytes that have been termed crown-like structures (CLS) [3].

Adipose tissue, though traditionally regarded as a depot for energy storage, has been increasingly acknowledged as an endocrine organ due to its secretion of cytokines and adipokines and the modulatory role it possesses in metabolism. Macrophages play a significant role in regulating adipose tissue function in both normal and pathological settings. In addition to conventional functions such as clearing apoptotic cellular debris and participating in tissue immune function, adipose tissue macrophages (ATMs) serve an important function in lipid buffering. Obesity-induced inflammation, characterized by an elevated number of proinflammatory macrophages in adipose

tissue, has been suggested to contribute to systemic insulin resistance and other obesity comorbidities [3]. The otherwise physiologically healthy role of macrophages is transformed into a pathological and dysfunctional phenotype which contributes to and exacerbates the inflammatory state during obesity. Immunohistochemical analysis of adipose tissue has demonstrated a high percentage of cells expressing the macrophage marker F4/80, and this was furthermore positively correlated with both adipocyte size and body mass [4].

Although it has been more than a decade since the seminal study by Weisberg et al. [4] describing the infiltration of macrophages in adipose tissue, there are still many questions which remain to be answered [4]. For instance, elucidation of the origin of ATMs in lean and obese conditions could benefit present understanding of the root cause of macrophage induced pathogenesis in adipose tissue. Are the pathological macrophages ordinarily resident in adipose tissue, or recruited by certain external cues? A plethora of animal and human studies have been performed in the last decade to unravel the mystery of metabolic dysregulation in adipose tissue. A new and promising explanation is the switching of macrophages within adipose tissue.

The phenomenon of macrophage switching is regulated by various endogenous molecules such as RBP4 proteins and exogenous dietary components. For example, Omega-3 PUFA drives the cellular phenotype towards M2 ATMs [5,6]. Resolvin 1 (DHA derived lipid mediators) reduces ATM accumulation, and induces a shift towards M2 polarization in obese mice [6,7]. Macrophage recruitment and switching are also influenced by other immune cells. T-regulatory cells promote M2 polarization by secreting anti-inflammatory mediators [8,9] CD8+ T cells contribute in recruitment and differentiation of ATMs [10].

Eosinophils contributes to M2 polarization [11-13], while neutrophils and mast cells in obese conditions are associated with inflammation possibly ATM recruitment [6]. Macrophage infiltration increase lipolysis in WAT and impairs the liver's carbohydrate and lipid metabolism in several ways [14]. A recent cohort study with 65 subjects demonstrated that non-classical monocytes are positively associated with ATM lipid content [15].

A variety of environmental, chemical, and biological factors play a role in determining the extent and impact of macrophage infiltration within adipose tissue. In a randomized open labeled study on 13 women, it was suggested that Phosphatidylcholine and deoxycholate injection increases the presence of crown like structures and degree of macrophage infiltration in subcutaneous abdominal fat, and thereby reduces abdominal fat volume and thickness by inducing adipocyte necrosis [16]. A randomized, double-blind, placebo-controlled parallel-group study on 38 subjects demonstrated that valsartan, a renin-angiotensin system inhibitor, decreases adipocyte size and is associated with reduced degree of macrophage infiltration [17]. Injection of lipostabil, a phosphatidylcholine containing substance, results in a distinct inflammatory reaction as demonstrated by the formation of macrophages and foam cells in the affected fat tissue [18].

Subcutaneous adipose tissue (sWAT) from burn victims exhibits CD68 positive macrophages, multiple fat droplets, and a greater abundance of mitochondria. Moreover tissue cytokines IL-6, IL-8, IL-13, IL-1 $\alpha$ , IL-1 $\beta$ , MCP-1, and TNF- $\alpha$  were all significantly greater in the sWAT of burned vs healthy subjects, providing an ostensible link between morphological/functional changes in sWAT and tissue inflammation [19]. Arachidonic acid is elevated in sWAT, and correlate strongly with macrophage presence in obese women with type 2 diabetes mellitus [20]. Infusion of glucose-dependent insulinotropic peptide, a gut hormone, triggers a crosstalk between adipocytes and macrophages involving MCP-1, initiating a state of low grade of adipose tissue inflammation [21].

Despite being a primary focus of recent obesity research, the role of adipose tissue derived circulating metabolites, stressors during the pathological state, and the ultimate origin of diseased ATMs are still not completely understood. In the future, characterization of the adipose resident population of macrophages and its subsets using specific cellular markers will help to distinguish metabolically functional and dysfunctional ATMs. Each adipose tissue depot has a distinct and heterogenous cell population, which implies that physiological roles and inflammatory responses may vary. A promising avenue of work may be to characterize these differences in ATMs across multiple adipose tissue depots. Finally, the abundance of animal studies which have been performed must be corroborated with work in humans in order to establish findings which are clinically relevant.

## Disclaimer

We apologize to authors whose contribution to this field of research have not been cited or have been cited only indirectly due to space limitations.

## References

- Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N (2014) Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* 105(2): 141-150.
- Hotamisligil GS (2006) Inflammation and metabolic disorders. *Nature* 444(7121): 860-867.
- Eagle TF, Gurm R, Goldberg CS, DuRussel-Weston J, Kline-Rogers E, et al. (2010) Health status and behavior among middle-school children in a mid west community: what are the underpinnings of childhood obesity? *Am Heart J* 160(6): 1185-1189.
- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, et al. (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 112(12): 1796-1808.
- Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, et al. (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 142(5): 687-698.
- Masoodi M, Kuda O, Rossmeisl M, Flachs P, Kopecky J (2015) Lipid signaling in adipose tissue: Connecting inflammation & metabolism. *Biochim Biophys Acta* 1851(4): 503-518.
- Hellmann J, Tang Y, Kosuri M, Bhatnagar A, Spite M (2011) Resolvin D1 decreases adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice. *FASEB J* 25(7): 2399-2407.
- Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, et al. (2009) Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat med* 15(8): 930-939.
- Winer S, Chan Y, Paltser G, Truong D, Tsui H, et al. (2009) Normalization of obesity-associated insulin resistance through immunotherapy. *Nat med* 15(8): 921-929.
- Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, et al. (2009) CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat med* 15(8): 914-920.
- Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, et al. (2011) Eosinophils sustains adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 332(6026): 243-247.
- Rao RR, Long JZ, White JP, Svensson KJ, Lou J, et al. (2014) Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell* 157(6): 1279-1291.
- Qiu Y, Nguyen KD, Odegaard JI, Cui X, Tian X, et al. (2014) Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. *Cell* 157(6): 1292-1308.
- Samuel VT, Shulman GI (2016) The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J Clin Invest* 126(1): 12-22.
- Pecht T, Haim Y, Bashan N, Shapiro H, Harman-Boehm I, et al. (2016) Circulating Blood Monocyte Subclasses and Lipid-Laden Adipose Tissue Macrophages in Human Obesity. *PLoS one* 11(7): e0159350.
- Reeds DN, Mohammed BS, Klein S, Boswell CB, Young VL (2013) Metabolic and structural effects of phosphatidylcholine and deoxycholate injections on subcutaneous fat: a randomized, controlled trial. *Aesthet Surg J* 33(3): 400-408.
- Goossens GH, Moors CC, van der Zijl NJ, Venticlef N, Alili R, et al. (2012) Valsartan improves adipose tissue function in humans with impaired glucose metabolism: a randomized placebo-controlled double-blind trial. *PLoS one* 7(6): e39930.
- Bechara FG, Sand M, Hoffmann K, Sand D, Altmeyer P, et al. (2007) Fat tissue after lipolysis of lipomas: a histopathological and immunohistochemical study. *J Cutan Pathol* 34(7): 552-557.
- Saraf MK, Herndon DN, Porter C, Toliver-Kinsky T, Radhakrishnan R, et al. (2016) Morphological Changes in Subcutaneous White Adipose Tissue after Severe Burn Injury. *J Burn Care Res* 37(2): e96-e103.

20. Heemskerk MM, Giera M, Bouazzaoui FE, Lips MA, Pijl H, et al. (2015) Increased PUFA Content and 5-Lipoxygenase Pathway Expression Are Associated with Subcutaneous Adipose Tissue Inflammation in Obese Women with Type 2 Diabetes. *Nutrients* 7(9): 7676-7690.
21. Gögebakan Ö, Osterhoff MA, Schüler R, Pivovarova O, Kruse M, et al. (2015) GIP increases adipose tissue expression and blood levels of MCP-1 in humans and links high energy diets to inflammation: a randomised trial. *Diabetologia* 58(8): 1759-1768.