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Review Article

# Immune Cells in Adipose Tissue and Obesity

**Karishma Bhatia and Sanjeev K Upadhyay***

*Pharmacology Lab, Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara Gujarat, India*

***Corresponding Author:** Sanjeev K Upadhyay, Pharmacology Lab, Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara Gujarat, India. sanjeev.kumar-biochem@msubaroda.ac.in

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## Abstract

Obesity has emerged as a critical global epidemic, significantly increasing the risk for metabolic conditions such as type 2 diabetes and cardiovascular diseases. Apart from functioning as an energy storage site, adipose tissue operates as an active endocrine organ involved in immune system regulation. During nutrient excess, abnormal expansion of white adipose tissue leads to systemic metabolic dysfunction, lipotoxicity, hypoxia, and a state of chronic, low-grade sterile inflammation known as meta-inflammation. This review examines the cellular shifts within adipose tissue during obesity, characterized by a loss of protective type 2 immune cells (such as M2 macrophages) and an influx of pro-inflammatory subsets including CD8+ T cells, neutrophils, and M1-like macrophages. Adipose tissue macrophages accumulate around dying adipocytes to form crown-like structures, undergoing metabolic activation and driving inflammatory cytokine production. This dynamic crosstalk between macrophages and adipocytes establishes a paracrine feedback loop involving free fatty acids and inflammatory mediators, which disrupts insulin signaling and mitochondrial bioenergetics. Understanding these intricate immunological alterations and macrophage polarization pathways in dysfunctional adipose tissue highlights potential therapeutic targets for mitigating obesity-associated metabolic disorders.

**Keywords:** Obesity; Diabetes Type 2; Immuno-Metabolism; Macrophages; Immune Cells

## Abbreviations

AT: Adipose Tissue; ATM: Adipose Tissue Macrophage; BAT: Brown Adipose Tissue; BMI: Body Mass Index; CLS: Crown-Like Structure; DC: Dendritic Cell; FFA: Free Fatty Acid; HFD: High-Fat Diet; ILC2: Group 2 Innate Lymphoid Cell; IR: Insulin Resistance; LAM: Lipid-Associated Macrophage; MMe: Metabolically Activated Macrophage; NK Cell: Natural Killer Cell; SVF: Stromal Vascular Fraction; Treg: Regulatory T Cell; VAT: Visceral Adipose Tissue; WAT: White Adipose Tissue.

## Introduction

### Obesity: A global health concern

Obesity is indeed a significant global health issue and is often described as an epidemic due to its widespread prevalence and its impact on individuals and societies. The World Health Organization (WHO) defines obesity as the abnormal or excessive accumulation of fat that presents a risk to health. Obesity is a complex and multifaceted condition influenced by a myriad of factors, including dietary patterns, physical activity levels, genetic predispositions,

and environmental influences [1]. Over the past few decades, the prevalence of obesity has risen at an alarming rate, posing significant public health concerns and challenging healthcare infrastructure globally [2].

Due to the widespread distribution of adipose tissue throughout the body, it is not possible to measure obesity directly. Simply assessing body weight fails to provide any understanding of fat accumulation. Instead, range of metrics such as body mass index (BMI), waist circumference, waist-to-hip ratio, skin fold thickness, and bio-impedance are utilized to evaluate obesity and overweight status. The BMI is often used to determine the prevalence of overweight and obesity. BMI is calculated by dividing a person's weight in kilograms by the square of their height in meters ($kg/m^2$). BMI is categorized based on the standards established by the National Institute of Health in the United States and is endorsed by the WHO. Generally, BMI below 18.5 $kg/m^2$ is classified as underweight, whereas a BMI between 18.5 and 24.9 $kg/m^2$ is considered to be within the normal or healthy weight range. A BMI equal to or greater than 25 $kg/m^2$ denotes overweight, while a BMI equal to or greater than 30 $kg/m^2$ signifies obesity. The following table presents the details of the global classification for adult underweight, overweight, and obesity, which is determined by BMI (Table 1).

Several factors that contribute to the obesity epidemic, include:

- **Unhealthy diets**: High consumption of calorie rich foods, often high in fats and sugars.
- **Lack of physical activity**: Sedentary lifestyles and decreased physical activity levels contribute to weight gain. In a study, it is demonstrated that participating in physical exercise, which includes both aerobic and resistance training, plays a crucial role in managing obesity [3].

| Classification | BMI ($kg/m^2$) |
|---|---|
| Underweight | <18.50 |
| Normal Weight | 18.50 -24.99 |
| Over weight | 25.00 -29.99 |
| Obese Class I | 30.00 -34.99 |
| Obese Class II | 35.00 -39.99 |
| Obese Class III | ≥40.00 |

**Table 1:** BMI-based classification of individuals as underweight, overweight or obese.

## Genetic factors

Some individuals are genetically predisposed to obesity. Genome-wide scans have effectively identified more than one hundred loci associated with the common (polygenic) form of obesity. Although genetic factors certainly contribute to an individual's propensity to gain weight, obesity linked Single Nucleotide Polymorphisms (SNPs) identified so far only account for less than 3% of the inherited tendency to develop obesity. The percentage mentioned is significantly lower compared to the heritability estimates of BMI, which vary between 47% and 80%. It is apparent that there are other genomic locations, including alleles with low or rare frequencies, or other genetic changes like copy number variations that probably contribute to making individuals more prone to weight gain. In addition to genetic variables, epigenetic factors such as variations in histone modifications (including methylation, acetylation, phosphorylation), miRNAs and changes in gut flora are also important players in determining susceptibility to obesity [4].

A population-based study genotyped 12 SNPs linked to obesity and found that the association with BMI was more pronounced in sedentary individuals compared to those who were physically active. Maintaining a physically active lifestyle significantly decreased (up to 40%) the hereditary predisposition towards obesity [5].

## Environmental factors

Obesity rates are significantly associated with variables such as gender, race, ethnicity, and socioeconomic status. The links between each of these traits form complex and varied relationships. The easy accessibility to food options that are high in calories and energy, and are seen as cheaper, combined with reduced physical activity due to changes in job and transportation, might result in a long-term state of having more energy intake than expenditure. Apart from the availability and quality of food, the changes in the type, quantity, and pricing of food are also important factors that contribute to the obesity epidemic. Sedentary lifestyles, reduced physical activity, sleep time, and stress levels are all independently associated with weight growth. Obesity is not just caused by an imbalance between calorie intake and energy expenditure, but is also influenced by environmental, genetic, and psychosocial factors [6]. Obesity increases the chances of developing several comorbid conditions, such as type 2 diabetes, cardiovascular disease, chronic renal disease, site specific malignancies, musculo-skeletal issues, and infections. Weight loss can lead to a substantial decrease in risk for most of these comorbid diseases [7].

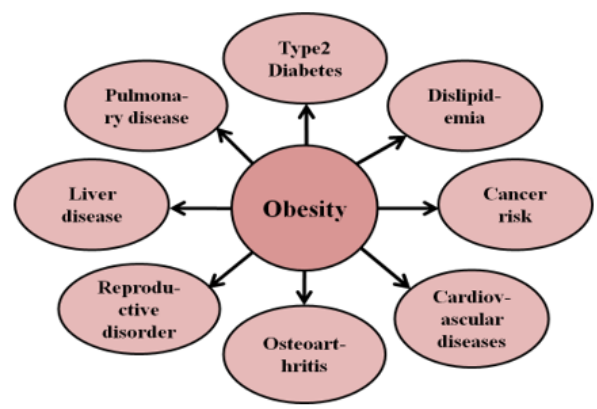


**Figure 1:** Obesity and its associated co-morbidities.

## Obesity in India: A growing health concern

India, once known for its high prevalence of undernutrition, is witnessing a significant shift in its health scenario due to increasing burden of obesity. Rapid urbanization, changing dietary habits, and sedentary lifestyles contribute to the increasing prevalence of obesity across diverse age groups in the country. This shift presents India with a complex health challenge due to the coexistence of undernutrition and obesity, which creates a dual burden of malnutrition.

BMI serves as an indirect measure of body fatness, primarily quantifying excessive weight rather than specifically targeting excess body fat. This approach may not be ideal for assessing body composition in the South Asian Indian population. A considerable portion of the South Asian population may exhibit elevated body fat levels despite falling within the normal range of BMI. This phenomenon is known as normal weight obesity [8]. Besides BMI, alternative indicators for evaluating obesity include waist circumference, waist-hip ratio, neck circumference, waist-height ratio, and body fat estimation (Table 2). In addition to these indicators, more advanced imaging techniques can be utilized to estimate visceral fat. Visceral fat is widely considered the most reliable marker of obesity, offering precise assessment of the underlying cardio-metabolic risk factors.

Several factors were found to increase the risk of both obesity and abdominal obesity, including older age, female gender, higher educational attainment, increased wealth index, marital status, and urban residency. Moreover, North Indian population and their alcohol consumption were associated with an elevated risk of abdominal obesity. While southern India was associated with an increased risk of obesity. A study based on NFHS-5 (9), highlighted that the rate of abdominal obesity in the country is 40% among women and 12% among males. The results indicate that 50-60% of women aged 30-49 are suffering from abdominal obesity. Abdominal obesity in women is more strongly associated with older age groups, urban inhabitants, higher socio-economic status, and junk food diets.

| Markers | Measures in South Asians | | Measures in Western Population | |
|---|---|---|---|---|
| BMI | Females | ≥23 kg/$m^2$ | Females | ≥25 kg/$m^2$ |
| | Males | ≥23 kg/$m^2$ | Males | ≥25 kg/$m^2$ |
| Waist circumference | Females | ≥80 cm | Females | ≥88cm |
| | Males | ≥90 cm | Males | ≥102 cm |
| Waist to Hip ratio | Females | ≥0.8 | Females | ≥0.8 |
| | Males | ≥0.9 | Males | ≥0.9 |
| Body fat percentage | Females | ≥33% | Females | ≥35% |
| | Males | ≥20% | Males | ≥20% |

**Table 2:** Other indicators for evaluating obesity.

The problem of overweight and obesity places a considerable financial strain on the Indian economy. India is ranked third worldwide in terms of estimated economic expenditures linked to overweight and obesity, after China and the USA. Based on a 2017 report from the World Obesity Federation, it is estimated that India will provide a yearly budget of US$13 million by 2025 for the treatment of ailments associated with obesity. In addition to direct medical expenses, which make about 32% of the overall spending on obesity, there are also significant indirect expenditures involved. These indirect costs include expenditures associated with seeking medical treatment, economic losses resulting from early death, absence from work, and the adverse effect on work efficiency. Collectively, indirect expenses account for 68% of the overall cost of obesity, highlighting the complex economic consequences of the obesity crisis in India.

## Adipose tissue dysfunction in obesity

Obesity arises as a result of an imbalance between energy intake and expenditure. Adipose tissues (AT) are reservoirs of en-

ergy, which is stored in the form of triglycerides. AT has a crucial role in maintaining energy balance. There are two forms of adipose tissue, Brown Adipose Tissue (BAT) and White Adipose Tissue (WAT). BAT is involved in non- shivering thermogenesis, while WAT is responsible for maintaining metabolic homeostasis. Additionally, inducible BAT, also known as beige adipocytes, has gained attention for its thermogenic properties in response to external stimuli such as cold, exercise, prolonged exposure to PPARγ agonists, β3-adrenergic receptor activation, and tissue injury [10]. AT expansion in a non-neoplastic manner is an important feature of obesity.AT formed at distinct areas as specific depots, commonly classified as subcutaneous and visceral fat. The visceral fat is well linked with metabolic disorders [11].

Furthermore, adipose tissue also serves as a vital endocrine organ, secreting a variety of adipokines. Apart from adipocytes, immune cells and endothelial cells residing within AT are also significant sources of adipokine production [12]. Obesity results in increase in both the number of adipocytes, known as hyperplasia and their volume, known as hypertrophy, consequently leading to an augmentation of adipose mass [13].

The abnormal expansion of the AT induces alterations in the composition of immune cells withintheAT.Thisabnormalexpansionofadipocytesalsoleadstofunctionalimpairment due to lipotoxicity, endoplasmic reticulum (ER) stress, hypoxia, and metabolic inflammation in AT. These processes are implicated in the development of insulin resistance (IR) [14]. Metabolic stress and dysfunction in AT establish a close connection between obesity and inflammation. Inflammation originating from within the adipose tissue is recognized as a significant contributing factor to systemic inflammation, further compromising the insulin signaling pathway [15,16].

## Inflammation

As mentioned, obesity is marked by the low grade sterile inflammation, known as meta-inflammation. Inflammation in obesity is a complex process involving dysregulation of the immune system and chronic low-grade inflammation throughout the body. Adipose tissue, once thought to be just a storage site for excess energy, is also an endocrine organ that secretes various pro-inflammatory molecules. Several adipokines, including adiponectin, leptin, resistin, visfatin, chemerin, TNFα, IL1β, IL6, IL8, IL10, plasminogen activator inhibitor 1, monocyte chemoattractant protein-1 (MCP1), and retinol binding protein-4, have a role in regulating insulin resistance (IR).

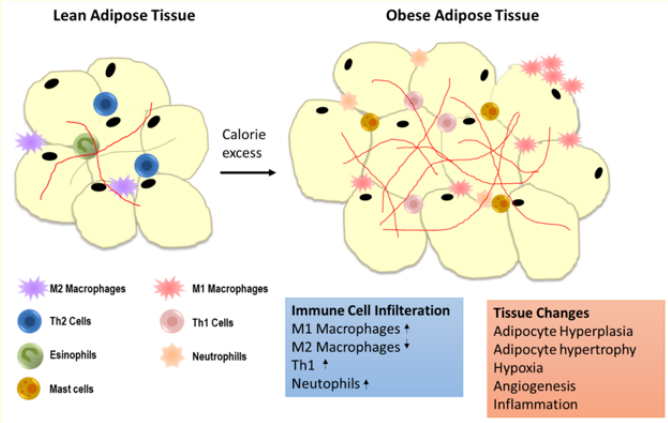


**Figure 2:** AT Remodeling during obesity.

In obesity, adipose tissue undergoes significant changes, including an increase in adipocyte size (hypertrophy) and an influx of immune cells such as macrophages, T cells and neutrophils. These immune cells, along with adipocytes, produce pro-inflammatory cytokines. This chronic low-grade inflammation can disrupt normal metabolic processes and contribute to the development of insulin resistance, type 2 diabetes, cardiovascular diseases, and other metabolic disorders. Furthermore, obesity-associated inflammation can also affect other tissues and organs in the body, such as the liver, skeletal muscle and brain, contributing to systemic metabolic dysfunction. Major cytokines which are important in development of diabetes are TNFα, IL6, IL1 family (includes IL1α, IL1β, IL18, IL33), IL1β, IL10, TGFβ, IL13 and IL4 are well documented. Apart from these secreted by immune cells there are some secreted by adipocytes which also has major contribution in obesity. Three of them are very well studied, Adiponectin, Leptin and Resistin. Adiponectin is secreted in proportion to the total adipose tissue mass and is an indicator of fat mass in the body. Leptin controls hunger and also energy expenditure by the body. Resistin is primarily linked with fatty acid breakdown and works through PPARγ modulation. It also activates immune cells within adipose. Together these three adipokines are major players in insulin resistance. While higher levels of adiponectin and leptin are protective, resistin increases insulin resistance.

## Cellular alterations in AT

The AT contains innate immune cells, including macrophages, dendritic cells, neutrophils, natural killer cells, eosinophils, and innate lymphoid cells (ILCs), as well as adaptive immune cells like B and T cells. During the lean state, immune cells associated with type 2 immunity, such as alternatively activated M2-like macrophages, eosinophils, and ILCs, play a significant role in preserving metabolic homeostasis in AT and promoting insulin sensitivity by secreting cytokines such as IL4, IL13, IL5, and IL33. Conversely, with obesity, the immune cell makeup and behavior of the adipose tissue undergoes a shift towards a more pro-inflammatory state, mostly dominated by M1 type macrophages, mast cells, $CD8^+$ T cells, and neutrophils. Pro-inflammatory mediators released by adipocytes, such as MCP1, IL6, TNFα, leptin, chemerin, and resistin promote the activation and recruitment of immune cells. This shift contributes to metabolic dysfunction and insulin resistance in AT [17].

## T Cells

Alterations in the T-lymphocyte numbers in AT have been observed during obesity and are associated with inflammation and hypoxia [18]. Increased infiltration of $CD8^+$ effector cells in the AT of obese mice promotes macrophage accumulation and thus contributes to local inflammation. On the other hand, $CD4^+$ T cell and regulatory T cell ($T_{reg}$) numbers are low. $CD8^+$T cell depletion mitigates inflammation and macrophage infiltration while improving glucose homeostasis and insulin sensitivity [19]. The diminished number of $CD4^+FOX3^+T_{reg}$ cells in obese mice drives the secretion of several chemokines including IFNγ and metabolic dysfunction. Reduced expression of FOX3P is linked to BMI in humans [20]. Further, other studies also demonstrated that $T_H2$ $CD4^+$ cells are replaced by those of $T_H1$ sub- lineage in the VAT of obese mice. VAT in lean mice had a high proportion of $CD4^+$ $FOX3^+$ T cells, while VAT in obese mice consisted of IFNγ-secreting $T_H1$ cells [21,22]. Similarly, BMI in humans correlates with the$T_H1$ to FOX3+ ratio. T cells orchestrate the invasion of $CD11c^+$ ATMs. $T_H2$-primed $CD4^+$ $FOX3^+$ T cells limit inflammation by secreting IL10. This maintains the macrophages in the M2 state, thus preserving insulin sensitivity. On the other hand, $T_H1$ T cells contribute to inflammation and glucose intolerance [22]. Thus, T-cell phenotype alterations in AT have significant metabolic influences.

## B cells

B cells are lymphocytes involved in humoral immunity. B cells provoke inflammation, adipocyte hypertrophy, glucose intolerance, and IR [23]. HFD in mice led to an increase in class-switched $IgG^+$ B cells in VAT. B-cell null mice exhibited a reduced number of $CD8^+$ cells and Th1 $CD4^+$ T cells in VAT [24]. B cells promote T cell mediated inflammation and IR in both mice and humans [23,24]. Distinct IgG profiles were characterized in IR humans, suggesting IgG mediates IR [24]. However, Nishimura., *et al*. demonstrated that $B_{reg}$ cells maintain metabolic homeostasis in AT, which predominates during a lean state. These cells produce IL-10, suppress inflammation, and maintain glucose homeostasis. B cell-specific IL10 deletion in obese mice also triggers the activation of $CD8^+$ T cells. Similarly, B-cell markers were inversely correlated to BMI and IL10 in humans subcutaneous AT [25]. These studies demonstrated the importance of adaptive immune responses in IR.

Therefore, immunological dysregulation in individuals with obesity leads to a persistent, mild inflammation. Furthermore, the variation in the distribution of immune cells in adipose tissue is a significant factor to consider in order to have a deeper understanding of their impact on metabolic dysfunction [26,27].

## Neutrophils

Similar to the classical immune response, where neutrophils are the first cells recruited to the site of acute inflammation. These also infiltrate adipose tissues early on, before macrophages. In mice, this infiltration starts early in response to a high-fat diet, peaks between 3-7 days in duration, and then starts to recede [28]. The functions of neutrophils undergo alterations during obesity. Peripheral blood neutrophils from obese patients exhibit increased levels of superoxide emission and chemotactic activity. The correlation between basal superoxide generation and BMI, suggests that obesity is linked to low grade inflammation and oxidative stress. Nevertheless, the adhesion and phagocytic activity of neutrophils remain unaffected [29]. Increased secretion of elastase by neutrophils, while decreased serum levels of the Neutrophil elastase (NE) inhibitor, α1 antitrypsin (A1AT, SerpinA1) which are involved in sterile inflammation, have been reported in both mice and humans [30]. Genetic ablation of neutrophil-specific elastase in mice led to resistance to obesity caused by a high-fat diet. It also resulted in reduced inflammation, improved glucose tolerance and insulin sensitivity, increased fatty acid oxidation in the liver, and decreased

infiltration of macrophages [30,31]. Similarly, Wang Q., *et al*. have demonstrated elevated levels and heightened activity of myeloperoxidase (MPO), released from recruited neutrophils, in the adipose tissue of obese mice. HFD fed MPO deficient mice demonstrated reduced body weight and IR while increasing expressions of UCP1 in BAT [32]. Therefore, the recruitment of neutrophils to the AT during the initial phase of obesity plays a crucial role in the development of adipose tissue inflammation and IR.

### Eosinophils

Eosinophils are mainly involved in allergic reactions, helminth immunity and maintaining anti-inflammatory responses. The decreased proportions of eosinophils in adipose tissue is associated with obesity in mice. These cells secrete IL4 and IL13 and this aids macrophages towards maintaining the M2 phenotype [33], thereby providing protection against obesity and IR. The absence of eosinophils in HFD mice led to increased adiposity and impaired glucose tolerance. While infecting mice with helminth resulted in eosinophilia and improved insulin sensitivity [33]. Weight loss can reinstate eosinophil numbers and thus rehabilitating cellular homeostasis in AT [34]. In contrast, a study has demonstrated that there is an elevated localization of eosinophils in AT during obesity to counteract metabolic dysfunction in AT. Lack of eosinophils in mice resulted in reduced adiposity, impaired adipocyte maturation, and glucose intolerance. However, they had higher numbers of macrophages, B cells, and CD4+T cells [35].

### ILC2

Similar to eosinophils, innate lymphoid cells type 2 (ILC2s) also contribute to type 2 immunity and significantly influence adipose tissue function and metabolic homeostasis. Both humans and mice exhibit dysregulated numbers of ILC2s in WAT during obesity. IL33 mediates the maintenance of ILC2s in WAT. ILC2s can also activate beige adipogenesis in WAT by promoting UCP1 expression [36]. ILC2s residing in visceral AT secrete IL5 and IL13, which promote eosinophil accumulation and thereby sustain the M2 phenotype of macrophages. Further, helminth infection or IL33 administration promotes ILC2 activation [37]. Thus, the ILC2- eosinophil-M2 axis is important in lean physiology.

### NK cells

Natural Killer (NK) cells are effector cells that provide defense against pathogens and tumors. HFD in mice led to an increase in the number and activation of NK cells in AT. NK cells also regulate macrophage activation. Genetic elimination of NK cells in obese mice resulted in a reduced inflammation, decreased proportion of macrophages, and improved systemic insulin resistance [38]. Similarly, NK cell accumulation in the VAT of obese humans contributes to low grade inflammation and IR. NK cells in VAT were associated with BMI, circulating levels of TNFα, the M1/M2 ratio and whole body glucose disposal [39]. NK cells exhibit altered metabolism during obesity, resulting in reduced glycolytic capacity and OXPHOS, while increased lipid uptake occurs via PPARα/δ that leads to functional impairment. The lipid overload or lipotoxic obese environment impairs the cytotoxic and anti-tumor responses of NK cells [40].

### Mast cells

Mast cells are important in immune response against infection and in allergic hypersensitivity. WAT from obese humans and mice displays a higher number of mast cells compared to WAT from subjects who are not obese [41]. Although there was no significant difference in the number of mast cells in subcutaneous WAT between obese and lean mice, the number of mast cells in visceral WAT increased considerably in obese mice compared to lean mice. Additionally, obese visceral WAT exhibited a higher prevalence of mast cell containing crown-like structures [42]. Diabetes patients with obesity showed an accumulation of mast cells in their adipose tissue. Mast cell number was linked to fibrosis, macrophages, and clinical parameters like fasting glucose and HbA1c. In addition to their increased density, a significant proportion was activated, releasing their granular enzymes tryptase and chymase [43]. Mast cells also release preformed TNFα upon degranulation [42]. The number of mast cells in the adipose tissue of American adults with metabolic syndrome is positively associated with waist circumference, glucose levels, HOMA-IR, leptin, inflammation markers (IL6, IL1β), and circulating macrophages [44]. Genetic deletion or pharmacological stabilization of mast cells resulted in reduced obesity and inflammation in the WAT and serum of obese mice [41]. The secretion of 15-deoxy-δPGJ2 (a prostaglandin) from mast cells cultivated in high glucose stimulates adipocyte development by activating PPARγ [45]. Additionally, treating these cells with a high concentration of leptin leads to a reduced responsiveness of mast cells to leptin [46]. Leptin-deficient mast cells predominate in lean human and mouse adipose tissues and are involved in facilitating the polarization of M2 macrophages, thereby attenuating weight

gain and diabetes [47]. Thus, mast cells are a potential contributor to adipose homeostasis.

## Dendritic cells

Dendritic cells (DCs) are specialized antigen-presenting cells and play a crucial role in AT inflammation. Stefanovic-Racic., *et al*. showed that the abundance of $CD11c^+$ DCs significantly increases in the liver and AT of obese mice, and their numbers correlate with crown like structures. The mice lacking DC displayed reduced macrophage trafficking, weight gain, IR, and liver steatosis [48]. Simultaneously, in a study by Bertola., *et al*. (2012), DCs in mice and humans were characterized as $CD11c^{high}$ $F4/80^{Low}$ and $CD11c^+CD1c^+$, respectively as inflammatory and associated with BMI and insulin resistance. HOMA-IR showed a strong relationship with the expression of $CD1c^+$ cells [49]. Since F4/80 is also a marker for ATMs in mice, Cho., *et al*. described $CD11c^+CD64^-$ as ATDC, distinguishing it from ATMs, which are identified as $CD45^+$ $CD64^+$ in both mice and humans. This study also clarified that DCs, residing in AT independently contribute to inflammation during obesity. CCR7 regulates the recruitment of DCs while ATM accumulation is dependent on CCR2 [50]. AT-derived chemerin, a chemoattractant chemokine believed to stimulate DC recruitment to the VAT in obesity, induces Type I IFN response, resulting in meta-inflammation [51]. In addition, $CD11c^+$ dendritic cells also produce IL17, IL6, TGFβ, and IL23, and stimulate $TH_{17}$ response [49,52]. Therefore, DCs are important regulators of AT inflammation and are involved in linking innate immune responses to adaptive responses during obesity.

## Macrophages

Macrophages represent most prevalent cell population of immune cells within adipose tissue, and their numbers expand during obesity. This increase occurs due to recruitment, proliferation, and retention. During obesity, macrophages accumulate in AT via both monocyte recruitment and in situ proliferation, driven by factors like monocyte chemoattractant protein1 (MCP1) [53]. Their proportion increases from 10% of the stromal vascular fraction (SVF) in normal physiological conditions to 40-50% of the SVF in cases of obesity [54]. ATMs undergo a phenotypic transition from the M2, alternatively activated phenotype in the normal state to the pro-inflammatory M1 classically activated phenotype in obese adipose tissue. Macrophages with M1-like characteristics in the adipose tissue of obese individuals release pro- inflammatory cytokines, including TNFα and IL1β [55]. These cytokines directly affect adipocytes and hinder insulin signaling in these cells [56]. Despite displaying pro-inflammatory characteristics, macrophages found in obese adipose tissue exhibit clear distinctions from M1 macrophages, which typically arise during acute inflammation. Instead, ATMs become metabolically activated during obesity [57]. Similarly, lipid-associated macrophages (LAMs) expressing a unique lipid receptor, Trem2, identified from obese mice and humans AT localized in CLS. $Trem2^+$ LAMs demonstrate increased transcription of genes associated with phagocytosis and endocytosis, lysosome function, PPARγ signaling, and oxidative phosphorylation [58]. Thus, ATMs display heterogeneity and engage in a variety of functions, such as lipid scavenging, phagocytosis, and cytokine synthesis.

## Macrophage polarization

Macrophages are important cells of the immune system that are formed in response to an infection or accumulating damaged or dead cells. Based on the inflammatory state, macrophages are classified as classically activated, M1, known to be pro-inflammatory or alternatively activated, M2 that are anti-inflammatory (Figure 3).

## M1 macrophages

M1 macrophages are typically activated in response to microbial products (e.g., lipopolysaccharide, LPS) or pro-inflammatory cytokines (e.g., IFNγ) and produce proinflammatory cytokines including IL1β, TNFα, IL12, IL18 and IL23. These cells also secrete chemokines like CXCL9 and CXCL10 [59]. This facilitates the antigen specific Th1 and Th17 response mediated inflammation by upregulating IRF5 [60]. M1 macrophages express major histocompatibility complex class II (MHC II), CD68 and CD86 [59]. LPS and TLR4 interaction activates STAT1 and upregulates intracellular protein suppressor of cytokine signaling 3 (SOCS3) which further induces NFκB pathway to promote inflammation [61]. Additionally, activation of iNOS (NOS2) is also an important characteristic of M1 in supporting inflammation. iNOS is an enzyme that produces NO from L-arginine. NO is an important pro-inflammatory mediator [62]. M1 macrophages show higher glycolysis facilitating rapid energy production to support their robust pro-inflammatory functions. These cells also have higher level of lipid synthesis to meet the need of increased prostaglandin synthesis as inflammatory mediators. Thus, M1 are implicated in initiation and amplification of inflammatory responses [63].

## M2 macrophages

M2 macrophages are activated in response to anti-inflammatory cytokines IL4; IL13 or signals associated with tissue repair and remodeling. M2 activation is also induced by apoptotic cells, fungal and helminth infection. These signals provoke secretion of anti-inflammatory cytokines IL4, IL10, while suppresses IL12, IL23, IL1β and IL2. These cells express mannose receptor (CD206) and scavenger receptors (CD163). Unlike M1, M2 utilizes arginine to produce ornithine and polyamine, which promotes growth [59].

Based on the stimuli, phenotype and functional characters, M2 are further categorized as M2a, M2b, M2c and M2d. M2a are stimulated by IL4 or IL13 and produce IL10, IL1Ra, CXCL9 and CXC10. M2b are elicited by immune complexes and LPS which promote Th2 response and secretion of IL10, IL1β, TNFα and CCL1. M2c are activated by IL10 (or glucocorticoids). These cells control the deactivation of inflammation and promote tissue remodeling by secreting TGFβ [64]. M2d are induced by IL6 and adenosine, release VEGF and promote angiogenesis and tumor progression. Overall, M2 macrophages play a role in resolving inflammation, tissue repair, and remodeling. They contribute to the clearance of apoptotic cells, the resolution of inflammation, and the promotion of tissue healing and regeneration [59,65].

| | M2a | M2b | M2c | M2d |
|---|---|---|---|---|
| Stimulations | IL4, IL13, Fungal/Helminth Infection | ICs | IL10, TGFβ, GCs | IL6, Adenosine |
| Markers | CD163, CD209, IL1R | CD86, MHC-II | CD163, CD206, TLR8 | IL10R, IL12R |
| Cytokines/Chemokines | IL10, IL1R, CCL17, CCL22 | IL10, TNFα, IL1β, CCL1 | IL10, TGFβ, CCL16, CCL18 | IL10, TGFβ, VEGF |

**Table 3:** Types of M2 macrophages based on stimulations and their phenotype.

## Macrophage phenotype and metabolism

Metabolism and macrophage polarization are intricately intertwined processes, and different macrophage subtypes exhibit their distinct metabolic characteristics (Figure 3). In a study, LPS stimulation was found to shift metabolism towards glycolysis, increasing mitochondrial membrane potential and ROS through succinate dehydrogenase [66]. The glycolytic pathway enables quick ATP generation, crucial for the production of pro-inflammatory cytokines and ROS during immune responses. Studies have shown that the metabolic reprogramming towards glycolysis in M1 macrophages is orchestrated by specific signaling pathways, including the activation of AMPK and HIF-1α [63]. Treatment with 2-deoxy-D- glucose (2DG) affected the production of IL1β and IL10.

Metabolically, M2 macrophages rely more on oxidative phosphorylation and fatty acid oxidation. IL4 induced activation of STAT6 and PGC1β is crucial for promoting FAO in M2 macrophages [67]. This metabolic preference aligns with their roles in tissue repair, immune-regulation and resolution of inflammation. Multiple studies have also highlighted the critical role of glycolysis in M2 macrophage activation, [68] while FAO is redundant for M2 polarization [69].

However, interfering with metabolic pathways in ATMs from obese mice has been shown to impact cytokine release. This study suggested that etomoxir, an inhibitor of CPT1α did not significantly impact cytokine expression. In contrast, 2DG reduced the expression of cytokines and concurrently increased the production of lactate [70].

## Adipose tissue macrophages

ATMs are a critical contributing factor in the development of AT inflammation and metabolic dysfunction associated with obesity. Macrophage infiltration is an important event for these functional and phenotypic changes in AT. Macrophages accumulate around the dead adipocytes in obese mice and humans, forming a “crown

like structure" (CLS). Macrophage recruitment to AT is facilitated by dead and dying adipocytes. The frequency of adipocyte death increases in obesity and is associated with WAT inflammation in both mice and humans. Macrophages forming syncytia or CLS around the dead adipocytes scavenge the lipids from residual adipocytes and result in chronic inflammation. This induces PLIN2 expression in macrophages [71]. FFAs, such as palmitic acid, are reported to cause IKK activation and IκB phosphorylation through the activation of TLR4 and subsequent inflammatory signaling [72]. FFAs have been identified as crucial adipocyte-derived paracrine molecules triggering inflammation in macrophages *in vitro* [73].

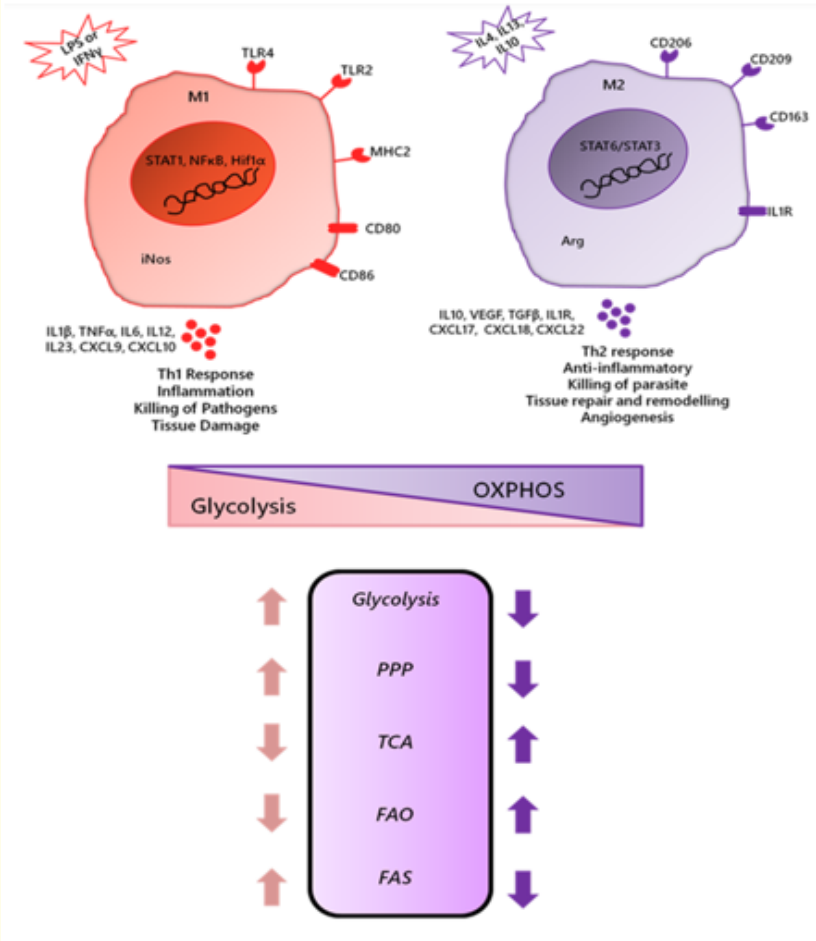


**Figure 3:** Phenotypic and metabolic characters of M1 and M2 macrophages.

Lumeng., *et al*. suggested that macrophages recruited to AT upon HFD in mice showed upregulated expressions of genes associated with inflammation and migration that included IL6, iNOS and CCR2. These macrophages had increased lipid content and overexpression of genes associated with lipid metabolism, including PPARγ, PLIN2 and Srebp4 [74]. Further, the same group demonstrated that resident macrophages possess M2a phenotype and remain localized to interstitial spaces between adipocytes while in diet induced obesity (DIO), AT recruits macrophages to form clusters around dead adipocytes and switch their phenotype towards M1 activation [55]. This creates an inflammatory environment in AT by recruiting macrophages from circulation but not by converting resident M2 macrophages [53,55]. At the same time, Zeyda., *et al*. proposed that ATMs from human WAT exhibit expressions of CD206 and CD163 on their surface and possess endocytic capacity

which are characteristic features of M2 macrophages but also have a capability to produce high amount of inflammatory cytokines [75].

Bourlier., *et al*. suggested that most of the ATMs in humans are $CD14^+$ $CD206^+$ $CD16^-$ and their numbers are correlated with BMI. These ATMs affect markers of both M1 (TNFα, IL6, IL23, MCP-1, IL8) and M2 (TGFβ, IL10, CCL18, COX1). ATMs from obese AT affect adipogenesis while promoting the migration of endothelial cells in humans [76].

In line with these studies, Xu., *et al*. demonstrated that ATMs in HFD mice are proinflammatory but accumulate lipids and activate lysosomal biogenesis to reduce lipid load. These properties distinguish ATMs from classically activated M1 macrophages [77]. Similarly, lipid filled macrophages similar to foam cells have been reported from SC and Omental (Om) AT. The lipid content in these cells from Om fat was associated with BMI and fasting insulin. These cells surrounded the dead adipocytes to form CLS [78].

### MMe Macrophages

Kratz., *et al*. suggested that ATMs from humans and mice do not express M1 markers like CD38, CD274 and CD319. They demonstrated that "metabolic activation" of blood derived monocytes using palmitate, glucose and insulin closely mirrors the characters of obese ATMs *in vivo*, beyond the M1/M2 dichotomy. They called these macrophages as "Metabolically Activated Macrophages" or "MMe", unlike M1 macrophages, MMe and ATMs express CD36, PLIN2 and ABCA1 on their surface. CD36 and ABCA1 expression in ATMs were correlated with BMI [57]. MMe are able to produce inflammatory cytokines. These macrophages accumulate around the dead adipocytes and clear apoptotic adipocytes via lysosomal exocytosis, thus aiding in restoring adipose tissue health. PPARγ and p62 also limit the inflammation due to metabolic activation, thus lowering its intensity [57,79]. Thus, these possess both damaging and protective characteristics within the context of obesity, depending on the duration of HFD in mice [79].

### Macrophage Adipocyte interaction

Over nutrition results in adipocyte hypertrophy with increased cellular stress. Further it leads to adipocyte death. Necrotic- like adipocyte is characteristic of obesity and its frequency is correlated with adipocyte size in mice and humans. Adipocyte death further encourages macrophage accumulation at the site of death characterized in obese mice and human, forming crown like structure. This promotes adipose and systemic inflammation. Free lipid droplets of dead adipocyte act as site for macrophage fusion and lipid uptake [71]. Macrophage does efferocytosis, i.e. it forms hydrolytic extracellular compartments at the contact site for degrading adipocyte fragments. This leads to macrophage foam cell formation which alters metabolic characters of macrophages [80]. Similarly, *in vitro* co-culture of macrophages and differentiated adipocytes (using primary preadipocytes or SGBS cell line) has revealed that macrophage phagocytosed differentiated adipocytes which resulted in IL6 secretion via NFκB pathway [81].

Adipocytes from obese mice release lipid filled vesicles and AdExos, that transport neutral lipids, taken up by macrophages and this modulates macrophage polarization. This leads to lipid accumulation, increases lysosomal biogenesis and upregulates genes associated with lipid metabolism in macrophages [82]. Further miR34a released from adipocytes also alters macrophage polarization and interferes with insulin sensitivity. miR34a expression from obese VAT have been associated with HOMA-IR and cytokines [83]. Further, adipocyte conditioned media modulates macrophages phenotype in AT of obese human by secreting soluble factors. Lipid mediators (palmitic acid being the most abundant) are the major players in immunomodulatory effects and also display relative concentrations along the BMI [84].

*In vitro* co-culture of differentiated 3T3-L1 and Raw264 has resulted in upregulation of MCP-1, IL6 and TNFα while decreased expression of adiponectin along with increase in the release of FFAs. Conditioned media from Raw264 cells promote MCP1, IL6 and TNFα and similarly conditioned media from 3T3-L1 induces IL6 and TNFα in Raw264 cells. Thus, FFAs released from adipocyte induces TNFα in macrophages and TNFα from macrophages increases the release of FFAs from 3T3-L1, thereby making a paracrine loop in AT mediating inflammation during obesity [73]. Further, 3T3-L1 co-cultured with macrophages also demonstrated decreased expression of GLUT4. This alters the macrophage phenotype. TNFα, IL1β and IL6 block the Akt phosphorylation and impact adipocyte differentiation and therefore decrease in lipid accumulation [85]. Macrophage secreted factors block insulin action by repressing GLUT4 and IRS1 expression thereby repressing Akt phosphorylation in mouse and human [86]. Neutralizing TNFα partially reversed the IR caused by exposure to conditioned media of LPS stimulated macrophages [74]. In addition, IL1β downregulates

GLUT4, GSK3β, PPARα and PPARγ expressions while inducing expressions of inflammatory genes that include IL6, CCL5 and NFκB. IL1β also alters adipocyte metabolism causing reduction in glucose consumption while enhancing lipolysis [86].

Cytokines released from macrophages affect mitochondrial biogenesis. IL6 and IL1β also affect the maximal respiratory capacity of 3T3-L1. Similarly, TNFα increases proton leak and decreases membrane potential [87]. Activated macrophages modifies complex I and complex III activity in adipocyte mitochondria. Treating adipocytes with conditioned media of IL10/TGFβ activated macrophages decreased the expression of UQCRC2 (component of complex III) and NDUFB8 (component of complex I), thus shifting adipocytes bioenergetics towards glycolysis from OXPHOS while LPS/IFNγ activated macrophages increased OXPHOS in human adipocytes [88].

Thus, the crosstalk between macrophage and adipocytes in AT is crucial in maintaining energy homeostasis. Their interaction in AT microenvironment influences local and systemic inflammation, macrophage recruitment and polarization, adipocyte differentiation and energy metabolism and ultimately insulin sensitivity.

## Conclusion

The Role of immune cells in obesity is extremely important and cannot be ignored while looking for potential therapies. Macrophages emerge as the most important player in pathophysiology of obesity and must be explored for therapeutic avenues.

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## Conflict of Interest

Authors declare no conflict of interest.

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