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Review

Immune Regulation of Metabolic Homeostasis in Health and Disease

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Obesity is an increasingly prevalent disease worldwide. While genetic and environmental factors are known to regulate the development of obesity and associated metabolic diseases, emerging studies indicate that innate and adaptive immune cell responses in adipose tissue have critical roles in the regulation of metabolic homeostasis. In the lean state, type 2 cytokine-associated immune cell responses predominate in white adipose tissue and protect against weight gain and insulin resistance through direct effects on adipocytes and elicitation of beige adipose. In obesity, these metabolically beneficial immune pathways become dysregulated, and adipocytes and other factors initiate metabolically deleterious type 1 inflammation that impairs glucose metabolism. This review discusses our current understanding of the functions of different types of adipose tissue and how immune cells regulate adipocyte function and metabolic homeostasis in the context of health and disease. We also highlight the potential of targeting immuno-metabolic pathways as a therapeutic strategy to treat obesity and associated diseases.

Introduction

Obesity is in an increasingly prevalent metabolic disease characterized by excess accumulation of adipose tissue. Obesity increases the risk of developing a wide variety of diseases including but not limited to type 2 diabetes, cardiovascular diseases, and multiple forms of cancer and has been strongly associated with increased mortality (Prospective Studies Collaboration, 2009; Flegal et al., 2013; Oliveros and Villamor, 2008; Pi-Sunyer, 1999; Pontiroli and Morabito, 2011; Reilly and Kelly, 2011; Rodriguez et al., 2001). In the past few decades, the prevalence of obesity has risen dramatically in both industrialized and less industrialized nations across all continents (Kelly et al., 2008; Ng et al., 2014), and this has been associated with high healthcare expenditures (Withrow and Alter, 2011). For example, in the U.S. in 2009–2010, obesity afflicted 36% of adults (Flegal et al., 2012; Ogden et al., 2012, 2014) and accounted for approximately $190 billion in annual healthcare costs, representing nearly 20% of total national healthcare expenditures that year (Cawley and Meyerhoefer, 2012; Finkelstein et al., 2009). More recent statistics indicate that 35% of adults in the U.S. were obese in 2011–2012 but was as high as 48% in some segments of the population (Ogden et al., 2014). Therefore obesity is a critical problem with major health and economic consequences. Increasing our understanding of the pathways involved in the development of obesity will be critical for the development of new intervention strategies to prevent or treat this disease and its associated co-morbidities.

As in many chronic inflammatory diseases, genetic and environmental factors are important for the development of obesity and associated diseases (Bouchard, 2008; Brestoff and Artis, 2013; McCarthy, 2010; Walley et al., 2009). In addition, emerging studies have implicated various cell types of the immune system as critical regulators of metabolic homeostasis (Jin et al., 2013; Lumeng and Saltiel, 2011; Odegaard and Chawla, 2011, 2013b; Osborn and Olefsky, 2012). Seminal studies connecting the immune system to metabolic dysfunction in obesity indicated that tumor necrosis factor-α (TNF-α) production was upregulated in obese mice and that neutralization of TNF-α improved glucose uptake in murine obesity (Hotamisligil et al., 1993). Subsequent studies revealed that mice lacking TNF-α were protected from high-fat-diet-induced insulin resistance (Uysal et al., 1997). Increased TNF-α production was also observed in human obesity, and weight loss in humans was associated with decreased TNF-α levels (Hotamisligil et al., 1995; Kern et al., 1995). Later, it was discovered that pro-inflammatory macrophages accumulate in adipose of obese mice and that these cells were dominant sources of TNF-α to promote insulin resistance (Weisberg et al., 2003; Xu et al., 2003). Collectively, these studies revealed that obesity is associated with chronic low-grade inflammation and suggested that inflammatory responses can have detrimental metabolic consequences. It is now appreciated that in obesity chronic low-grade inflammation occurs in many organs including but not limited to white adipose tissue (WAT), brown adipose tissue (BAT), pancreas, liver, brain, muscle, and intestine (Cildir et al., 2013). Of these, WAT is the most studied organ in terms of immune-metabolic interactions in obesity.

In WAT, which coordinates metabolism at distant tissues such as the brain, liver, pancreas, and muscle, there is a diverse set of immune cells at steady state (Exley et al., 2014; Ibrahim, 2010; McNelis and Olefsky, 2014; Mraz and Haluzik, 2014). This

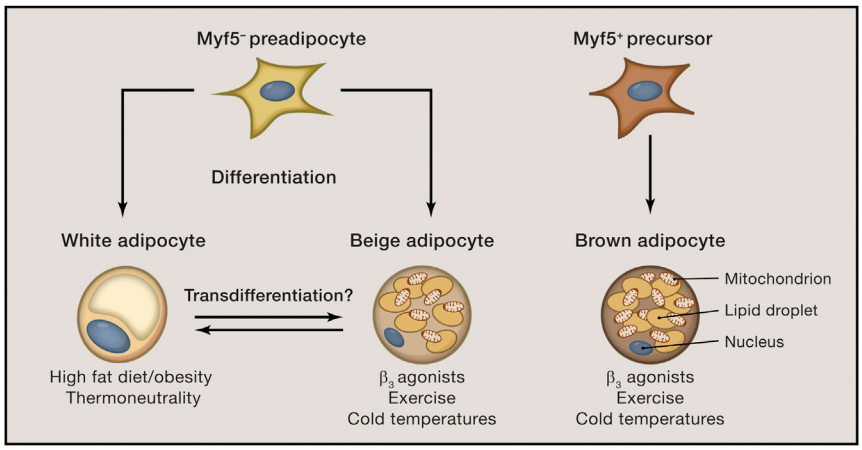

Figure 1. White, Beige, and Brown Adipocytes Are Developmentally and Functionally Distinct Cell Populations

White and beige adipocytes arise from a Myf5⁻ precursor cell population that is bipotent. These pre-adipocytes give rise to white or beige adipocytes depending on the stimulus and physiologic setting. White adipocytes are promoted by high-fat-diet feeding or obesity and by thermoneutrality (30°C in mice). Beige adipocytes are elicited by β_3 adrenergic receptor agonists such as norepinephrine or epinephrine, and are recruited within WAT in the settings of chronic exercise or exposure to cold temperatures. Although white and beige adipocytes emerge from pre-adipocytes via cell differentiation, mature white and beige adipocytes might undergo a process called transdifferentiation, in which one cell type acquires phenotypic characteristics of the other. There is uncertainty about whether transdifferentiation occurs. In contrast, brown adipocytes arise from a Myf5⁺ precursor cell population and are present in discrete brown adipose tissue depots. Despite being developmentally distinct cell populations, beige and brown adipocytes are activated by similar physiologic stimuli, including exercise- and cold temperature-induced hormones and metabolites.

network of immune cells appears to be poised to recognize, integrate, and respond to environmental signals including bacterial products, endogenous lipid species and hormones in order to regulate metabolism (Odegaard and Chawla, 2013a). Changes in immune cell composition and function in WAT have been closely associated with obesity and the regulation of metabolic homeostasis, and disruption of this network of immune cells can have either detrimental or beneficial effects on mammalian health (Exley et al., 2014; Lumeng and Saltiel, 2011; Mraz and Haluzik, 2014; Odegaard and Chawla, 2013b; Osborn and Olefsky, 2012). In addition, recent work has demonstrated that immune-system-associated transcription factors including but not limited to nuclear factor-κ B (NK-κB), c-Jun kinase (JNK), and interferon regulatory factor 4 (IRF4) are key regulators of metabolic homeostasis (Lumeng and Saltiel, 2011; Osborn and Olefsky, 2012). Conversely, metabolite-sensing receptors such as peroxisome proliferator-activated receptor (PPAR)-γ, farnesoid X receptor (FXR), liver X receptor (LXR), G protein coupled receptor 120 (GPR120), and carbohydrate-responsive element binding protein (ChREBP) among others have been shown to regulate immune responses (Brestoff and Artis, 2013; Glass and Saijo, 2010; Hotamisligil and Erbay, 2008; Shoelson et al., 2007; Zelcer and Tontonoz, 2006). Therefore dissecting the complex interactions between immune and metabolic systems will provide important insights into the biology underlying obesity and have implications for understanding how current and future therapeutics might influence metabolism.

The purpose of this review is to describe our current understanding of how immune cells in adipose tissue regulate metabolism. First, we will summarize recent advances in understanding the roles of white, beige, and brown adipose tissues in the regulation of weight gain. Second, we will describe the immune cell composition of adipose tissue at steady state and discuss how these immune cell pathways interact and contribute to the maintenance of metabolic homeostasis. Third, we will discuss immunologic changes that occur in adipose in the setting of obesity and highlight how these changes contribute to metabolic dysfunction. Finally, we will discuss potential therapeutic implications of targeting the immune system to treat obesity and its associated diseases.

Roles of Adipose Tissues in the Regulation of Obesity

Mammals possess multiple types of adipose tissues including white, brown, and beige adipose. These tissues are found in distinct anatomic locations and are comprised of different adipocyte cell types—white, beige, and/or brown—that have unique developmental and functional properties that are critical for host metabolism (Figure 1) (Bartelt and Heeren, 2014; Cannon and Nedergaard, 2004; Harms and Seale, 2013; Ibrahim, 2010; Peirce et al., 2014; Pfeifer and Hoffmann, 2015; Wu et al., 2013). This section describes white, brown, and beige adipocyte cell types and summarizes their roles in regulating weight gain.

White Adipocytes

WAT is distributed throughout the mammalian body in subcutaneous depots and in association with organs, where it has important roles in insulation and physical protection of the viscera, and is comprised predominantly of white adipocytes (Peirce et al., 2014; Pfeifer and Hoffmann, 2015). These specialized cell types arise from a Myf5⁻ pre-adipocyte lineage and store large amounts of triglycerides in a single large lipid droplet (Pfeifer and Hoffmann, 2015; Sanchez-Gurmaches and Guertin, 2014). In addition to their ability to store triglycerides, white adipocytes respond to hormonal signals to induce lipolysis and release free fatty acids (FFA) into the circulation for oxidation or storage by other cell types (Arner et al., 2011; Bartness et al., 2010). Therefore white adipocytes are critical for regulating both fat storage and release. Beyond this function, white adipocytes produce various adipocyte-specific hormones (also known as adipokines) including but not limited to leptin, resistin, retinol binding protein 4 (RBP4), fibroblast grown factor 21 (FGF21), and adiponectin that regulate metabolic homeostasis by acting on distant organs such as the brain, kidney, liver, pancreas, and skeletal muscle (Allison and Myers, 2014; Itoh, 2014; Kadowaki et al., 2006; Kershaw and Flier, 2004; Kotnik et al., 2011; Lazar, 2007; Ouchi et al., 2011).