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Epigenetic mechanisms of macrophage activation in type 2 diabetes

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ABSTRACT

The alarming rise of obesity and type 2 diabetes (T2D) has put a tremendous strain on global healthcare systems. Over the past decade extensive research has focused on the role of macrophages as key mediators of inflammation in T2D. The inflammatory environment in the obese adipose tissue and pancreatic β-cell islets creates and perpetuates imbalanced inflammatory macrophage activation. Consequences of this chronic low-grade inflammation include insulin resistance in the adipose tissue and pancreatic β-cell dysfunction. Recently, the emerging field of epigenetics has provided new insights into the pathogenesis of T2D, while also affording potential new opportunities for treatment. In macrophages, epigenetic mechanisms are increasingly being recognized as crucial controllers of their phenotype. Here, we first describe the role of macrophages in T2D. Then we elaborate on epigenetic mechanisms that regulate macrophage activation, thereby focusing on T2D. Next, we highlight how diabetic conditions such as hyperlipidemia and hyperglycemia could induce epigenetic changes that promote an inflammatory macrophage phenotype. In conclusion we discuss possible therapeutic interventions by targeting macrophage epigenetics and speculate on future research directions.

Contents

1. Introduction

Sedentary lifestyles combined with high-energy diets have led to an unprecedented prevalence of obesity and obesity-related disorders. Type 2 diabetes (T2D) is a chronic inflammatory disease induced by obesity (Donath and Shoelson, 2011). Prominent features of T2D include low-grade chronic inflammation, hyperglycemia, hyperlipidemia and pancreatic β-cell dysfunction. Chronic inflammation results in insulin resistance in the primary

Abbreviations: AGE, advanced glycation end product; TLR, toll like receptor; FFA, free fatty acid; ROS, reactive oxygen species; c-JNK, c-Jun N-terminal kinase; HMT, histone methyltransferase; HDM, histone demethylase; DNMT, DNA methyltransferases; TET, ten-eleven translocation; BET, Bromodomain and extra-terminal; PPAR, peroxisome proliferator activated receptor; HAT, histone acetyltransferase; HDAC, histone deacetylases; ChIP, chromatin immunoprecipitation; RAGE, receptor for advanced glycation end products.

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insulin target organs, such as adipose tissue, muscle and liver (Gregor and Hotamisligil, 2011). Macrophages are important mediators of inflammation primarily in the adipose tissue and β-cell islets (Olefsky and Glass, 2010; Odegaard and Chawla, 2008). To a lesser extent does the activation of resident liver macrophages (Kupffer cells) contribute to obesity-induced insulin resistance (Odegaard et al., 2008). Inflammatory cytokines secreted by macrophages in the obese adipose tissue disrupt insulin signaling in adipocytes by inducing inflammatory pathways (Lee, 2013). The resulting insulin resistance causes hyperglycemia and increased formation of glycated proteins or lipids called advanced glycation end products (AGEs)(Ahmed, 2005). Effects of AGEs include vascular stiffness through crosslinking with the extracellular matrix and stimulating reactive oxygen species (ROS) production by macrophages and endothelial cells (Di Marco et al., 2013). Typically, these conditions cause damage to the vasculature with putative complications including atherosclerosis, kidney failure and retinopathy (Ahmed, 2005). Furthermore, sustained inflammatory stimuli significantly reduce wound healing by macrophages (Mirza et al., 2014). As a consequence, foot ulcers are a leading cause for amputations in T2D patients (Brem and Tomic-Canic, 2007).

Macrophages are characterized by a remarkable degree of plasticity and are able to adapt rapidly to a wide range of environmental cues (Lawrence and Natoli, 2011). The classical view presents a highly simplified M1/M2 phenotype classification (Wang et al., 2014). Such an outlook ignores the innumerable variety of phenotypes and has since been replaced with a continuum of macrophage activation states, thus taking into account the diversity of the macrophage population (Mantovani and Locati, 2013).

Eosinophils that migrate into the adipose tissue induce M2-like macrophages in an IL-4/IL-13-dependent manner (Wu et al., 2011). M2-like macrophages help to maintain glucose homeostasis and predominate in lean adipose tissue (Wu et al., 2011; Sun et al., 2011). These macrophages dampen inflammation through IL-10 secretion and participate in wound healing and tissue repair (Wang et al., 2014). In obesity and T2D, these anti-inflammatory macrophages are overruled by pro-inflammatory macrophages(Lumeng et al., 2007; Satoh et al., 2010). Indeed, under diabetic conditions Toll-like receptor (TLR) ligands, such as free fatty acids (FFAs), induce monocyte recruitment and an M1-like inflammatory phenotype characterized by the production of pro-inflammatory cytokines (TNF, IL-6, IL-12) and ROS (Olefsky and Glass, 2010).

An increasing number of studies demonstrate the importance of epigenetics in the regulation of macrophage activation (Gosselin and Glass, 2014; Van den Bossche et al., 2014a; Kittan et al., 2013). The emerging field of epigenetics studies the mechanisms by which chromatin modifications regulate gene expression (Gosselin and Glass, 2014). Importantly, diabetic conditions elicit epigenetic changes in a variety of cell types, including monocytes and macrophages (Hanson and Godfrey, 2015; Miao et al., 2007; Reddy et al., 2014). Understanding the precise mechanisms by which epigenetics governs macrophage activation in T2D could help to better understand disease pathology and progression and provide new possibilities for treatment. This review will discuss recent findings regarding macrophage epigenetics in T2D and will address tentative therapeutics targeting the macrophage's epigenetic machinery.

2. Macrophages contribute to chronic inflammation in T2D

Overnutrition causes cellular stress in hypertrophic adipocytes, resulting in the release of pro-inflammatory cytokines, FFAs and the monocyte-attracting chemokine MCP-1 (CCL2) (Lee, 2013; Suganami and Ogawa, 2010) (Fig. 1). Circulating Ly6C$^+$ inflammatory monocytes continuously infiltrate the obese adipose tissue in a MCP-1/CCR2-dependent manner and differentiate into adipose tissue macrophages (ATMs) (Kraakman et al., 2014; Oh et al., 2012). Under the influence of inflammatory cytokines and FFAs, the recruited monocytes differentiate into pro-inflammatory ATMs. As such, a vicious cycle of inflammation is established in which adipocytes release FFAs and inflammatory mediators that elicit the production of even more inflammatory cytokines (TNF, IL-6, IL-1β) by the ATMs (Suganami et al., 2005). Hypoxia in the obese adipose tissue further promotes the inflammatory phenotype (Fujisaka et al., 2013). *In vitro*, hypoxia significantly increases TNF and IL-6 expression in macrophages (Ye et al., 2007). Within the adipocytes, TNF activates serine kinases, such as c-Jun N-terminal kinases (c-JNKs), and impairs insulin signaling (Kanety et al., 1995; Zeyda and Stulnig, 2009). In contrast to the adipose tissue, the liver does not experience macrophage infiltration during obesity (Gregor and Hotamisligil, 2011), but resident Kupffer cells adopt a pro-inflammatory phenotype without increasing in numbers (Tateya et al., 2013). Remarkably, overexpression of CCL2 in adipocytes promotes development of hepatic steatosis (Kanda et al., 2006). In another study, inhibition of CCL2 enhanced M2 macrophage polarization and improved insulin sensitivity (Nio et al., 2012). Likewise, CCR2 inhibition ameliorates insulin resistance and hepatic steatosis (Tamura et al., 2008). Possibly, adipocyte-derived CCL2 reaches the liver where it recruits macrophages and thus induces steatosis. Similarly, macrophages direct inflammation in the pancreas, characterized by loss of β-islets cells and decreased insulin production (Morris, 2015). Through ligation of TLR4 by saturated FFAs, β-cells produce inflammatory cytokines that attract inflammatory monocytes (Eguchi et al., 2012). Hyperglycemia-induced overproduction of IL-1β by β-cells triggers IL-1β secretion by islet macrophages resulting in β-cell cytotoxicity and dysfunction (Morris, 2015; Maedler et al., 2002). During this chronic inflammatory state, insulin secretion by β-cells is depressed, exacerbating hyperglycemia and its harmful effects.

3. Epigenetic regulation of macrophage activation

Epigenetic regulation of macrophages is mediated by epigenetic enzymes, which by the addition or removal of acetyl or methyl groups can alter gene expression (Fig. 2) (Van den Bossche et al., 2014b). These enzymes primarily target lysine (K) residues in tails of various histones (H). Firstly, acetylation and deacetylation is facilitated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively (Fig. 2A). Histone acetylation is linked to transcriptional activity whereas histone deacetylation is associated with transcriptional repression (Sterner and Berger, 2000). Bromodomain and extra-terminal (BET) proteins recognize histone acetylation marks and initiate the assembly of the transcriptional machinery (Filippakopoulos and Knapp, 2014). Similarly, methylation and demethylation of histones is achieved by histone methyltransferases (HMTs) and histone demethylases (HDMs), respectively (Fig. 2B) (Van den Bossche et al., 2014b; Cedar and Bergman, 2009). Histone methylation can induce both transcriptional activation and repression, depending on the number and location of the methyl groups. An active transcriptional state is characterized by positive marks such as di- or trimethylation (me2/me3) at H3K4, H3K36, H3K79. A repressed transcriptional state manifests itself by increased markings at H3K9me2/me3 and H3K27me3 (Ivashkiv, 2013). Lastly, direct methylation of DNA at CpG nucleotides is regulated by DNA methyltransferases (DNMTs) resulting in gene-silencing (Fig. 2C). DNA demethylation is associated with active chromatin and is catalyzed by ten-eleven translocation (TET) family of proteins (Schubeler, 2015).