Metabolism Open 15 (2022) 100204

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

A chromatin remodeling checkpoint of diet-induced macrophage activation in adipose tissue

ARTICLE INFO

Keywords
Adipose tissue
BAF60a
Diabetes
Inflammation
Macrophage
Obesity

ABSTRACT

The interplay between the environment and the immune cells is linked to metabolic homeostasis under physiologic and pathophysiologic conditions. Diabetes mellitus type 2 (T2D) is considered an immune-related inflammatory disorder, in which the adipose tissue macrophages (ATMs) are key players orchestrating metabolic chronic meta-inflammation and contributing to the pathogenesis of metabolic disease. However, the molecular regulators that integrate the environmental signals to control ATM activation and adipose inflammation during obesity and T2D remain unclear. Epigenetic mechanisms constitute important parameters in metabolic homeostasis, obesity and T2D via the integration of the environmental factors to the transcriptional regulation of gene programs. In a very recent study published in Diabetes by Kong et al., BAF60a has been identified as a key chromatin remodeling checkpoint factor that associates obesity-associated stress signals with meta-inflammation and systemic homeostasis. Furthermore, this work uncovers Atf3 as an important downstream effector in BAF60a-mediated chromatin remodeling and transcriptional reprogramming of macrophage activation in adipose tissue. The findings of this research may contribute to the development of new therapeutic approaches for obesity-induced metabolic inflammation and associated metabolic disorders.

Adipose tissue has been recently recognized as an active endocrine organ producing several cytokines and biopeptides termed adipokines, which play a critical and dynamic role in fine-tuning metabolism and body homeostasis [1–4]. Obesity represents a chronic subclinical inflammation which is characterized by the increased expression of pro-inflammatory cytokines, adipokines and chemokines, such as Tumor Necrosis Factor-α (TNF-α), interleukin (IL)-1β, IL-6, leptin, resistin, visfatin, chemokine (C–C motif) ligand 5 (Ccl5), and Ccl2, whereby the interplay between adipose tissue macrophages (ATMs) and the microenvironment in adipose tissue plays a crucial role [4–11]. Obesity-associated metabolic dysfunction of the adipose tissue is a significant factor in the pathogenesis of insulin resistance and Type 2 diabetes (T2D). ATMs are dynamically implicated in modulating metabolic homeostasis and the immune milieu in the adipose tissue [9–13].

The interplay between the environment and the immune cells is connected with metabolic homeostasis under pathophysiologic conditions. T2D is considered an immune-related inflammatory disease, in which the ATMs are key players orchestrating metabolic chronic meta-inflammation and contributing to the pathogenesis of metabolic disease [11–13]. M1 polarization (classical activation characterized by the production of pro-inflammatory cytokines and chemokines such as IL-6, IL-12 and TNF-α which may impair insulin action in adipocytes) and M2 polarization (alternative activation characterized by the secretion of anti-inflammatory cytokines protecting adipocytes from inflammation and damage) of ATM present an equilibrium in physiologic conditions. In contrast, during obesity, macrophages that are recruited in the adipose tissue acquire a pro-inflammatory phenotype. Interestingly, there is a distinct metabolically activated phenotype of ATMs, which is different from the M1/M2 activation [11–13]. However, the molecular regulators that integrate the environmental signals to control ATM activation and adipose inflammation during obesity and T2D remain unclear.

A previous study has demonstrated that epigenetic mechanisms are essential for metabolic homeostasis since they serve important roles in the pathogenesis of obesity and diabetes through integrating the environmental factors to the transcriptional regulation of gene programs [11]. In recent years, switch/sucrose-nonfermentable (SWI/SNF) chromatin-remodeling complexes composed of multiple subunits have been shown to play a crucial role in diverse pathophysiologic processes. The BAF60 family members, including BAF60a, BAF60b and BAF60c, can recruit the SWI/SNF complex to target genes to remodel nucleosomes structure and transcription [12]. Recently, a research article published in *Diabetes* titled “BAF60a Deficiency in Macrophage Promotes Diet-Induced Obesity and Metabolic Inflammation” by Kong et al. has identified BAF60a as a pivotal chromatin remodeling checkpoint factor to regulate macrophage pro-inflammatory activation in white adipose tissue upon high fat diet (HFD) feeding [13]. Moreover, the authors also unveiled that BAF60a/Atf3 axis is the key regulator in obesity-associated ATM activation, adipose tissue inflammation and metabolic dysfunction.

It has been previously reported that BAF60a is enriched in liver and adipose tissue, and is mainly involved in regulating fatty acid oxidation, cholesterol homeostasis, circadian regulation of hepatic energy metabolism, and adipose tissue thermogenesis [14–17]. BAF60c is highly expressed in skeletal muscle, especially in white muscle with more glycolysis, and plays a key role in glucose sensing, utilization, and regulation of glucose homeostasis [18–21]. BAF60b is highly expressed

https://doi.org/10.1016/j.metop.2022.100204
Received 23 July 2022; Accepted 23 July 2022
Available online 31 July 2022

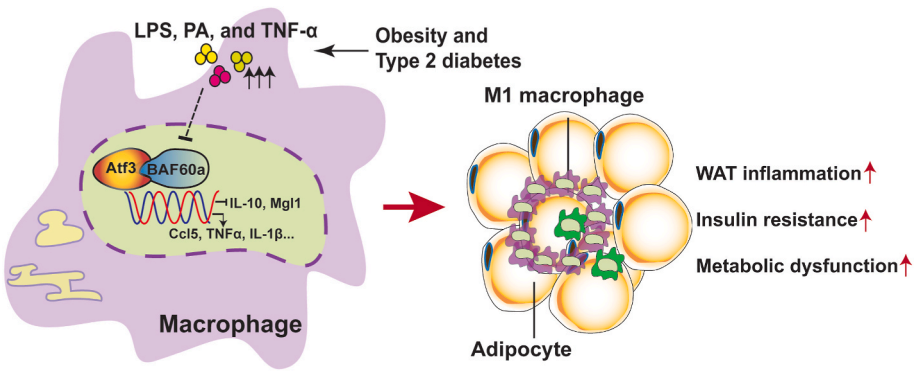

Fig. 1. legend. Model depicting the pivotal role of BAF60a in macrophage activation. BAF60a interacts with Atf3 to regulate pro-inflammatory gene expression program in adipose macrophages, thereby regulating obesity-induced inflammation and metabolic dysfunction. Abbreviations: IL: interleukin; LPS: Lipopolysaccharide; PA: Palmitic acid; TNF-α: Tumor Necrosis factor-α

in immune cells with an identity of the important regulator in mediating granulocyte development [22]. However, the role of BAF60 proteins in obesity-induced macrophage activation and chronic inflammation in adipose tissue remains unclear.

In this new study [13], the authors first observed that expression of BAF60a, but not BAF60b and BAF60c, is significantly reduced in stromal vascular fraction (SVF) of white adipose tissue (WAT) in diabetic mice compared to those from control mice. Further studies have shown that the lower expression of BAF60a in SVFs is mainly due to the down-regulation of BAF60a expression in macrophages in response to palmitic acid and TNF-α, or lipopolysaccharide (LPS) treatments, suggesting that the decreased BAF60a expression in macrophages, downstream of lipid-toxicity, inflammatory signaling, and metabolic endotoxemia, may be involved in the pro-inflammatory activation of ATM in adipose tissue during obesity and type 2 diabetes pathogenesis. To this end, Kong et al. generated myeloid-specific BAF60a ablation (BaMKO) mice and observed that BaMKO mice significantly aggravated HFD-induced obesity, insulin resistance and impaired glucose tolerance in mice, accompanied by a large number of macrophage infiltration in white adipose tissue, forming a typical crown-like structure. Moreover, the authors found ATM pro-inflammatory activation in BaMKO while myeloid-specific overexpression of BAF60a in mice attenuates macrophage pro-inflammatory activation. To explore the upstream factors that modulate macrophage activation, the authors performed transcriptome combined with motif analysis of ATAC-Seq and CUT&Tag-Seq overlapping peaks, and identified the transcription factor Atf3 that physically interacts with BAF60a to suppress the pro-inflammatory gene expression, thereby controlling ATM activation and metabolic inflammation in obesity. Consistently, myeloid-specific Atf3 deficiency also promotes the pro-inflammatory activation of macrophage.

Collectively, this study has identified BAF60a as a key chromatin remodeling checkpoint factor that associates obesity-associated stress signals with meta-inflammation and systemic homeostasis (Fig. 1). In addition, this work uncovers Atf3 as an important downstream effector in BAF60a-mediated chromatin remodeling and transcriptional reprogramming of macrophage activation in adipose tissue. The findings of this research may contribute to the development of new therapeutic approaches for obesity-induced metabolic inflammation and associated metabolic disorders.

Conflict of interest

None.

Funding information

None.

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