Biochimica et Biophysica Acta 1842 (2014) 431–439

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

The role of JAK–STAT signaling in adipose tissue function☆,☆☆,★

Allison J. Richard [a], Jacqueline M. Stephens [a,b,*]

[a] Adipocyte Biology Lab, Pennington Biomedical Research Center, USA
[b] Department of Biological Sciences, LSU, Baton Rouge, LA 70808, USA

ARTICLE INFO

Article history:
Received 23 January 2013
Received in revised form 20 May 2013
Accepted 22 May 2013
Available online 2 June 2013

Keywords:
Brown and white adipose
Janus kinase
Immune cell
Cytokine
Tyk2
Obesity

ABSTRACT

Adipocytes play important roles in lipid storage, energy homeostasis and whole body insulin sensitivity. The JAK–STAT (Janus Kinase–Signal Transducer and Activator of Transcription) pathway mediates a variety of physiological processes including development, hematopoiesis, and inflammation. Although the JAK–STAT signaling pathway occurs in all cells, this pathway can mediate cell specific responses. Studies in the last two decades have identified hormones and cytokines that activate the JAK–STAT signaling pathway. These cytokines and hormones have profound effects on adipocytes. The content of this review will introduce the types of adipocytes and immune cells that make up adipose tissue, the impact of obesity on adipose cellular composition and function, and the general constituents of the JAK–STAT pathway and how its activators regulate adipose tissue development and physiology. A summary of the identification of STAT target genes in adipocytes reveals how these transcription factors impact various areas of adipocyte metabolism including insulin action, modulation of lipid stores, and glucose homeostasis. Lastly, we will evaluate exciting new data linking the JAK–STAT pathway and brown adipose tissue and consider the future outlook in this area of investigation. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

1.1. Adipocytes and adipose tissue

Obesity is a condition of excess adipose tissue and is the most common metabolic disorder in the industrialized world. In the US alone, it affects 154.7 million individuals over the age of 20, which is approximately 25% of the adult population. This obesity epidemic has been a prelude to increases in chronic diseases. Obese individuals, particularly those with excess abdominal adipose tissue, have an elevated risk of developing Type 2 diabetes mellitus (T2DM), cardiovascular disease, and hypertension. During obesity, the production of inflammatory cytokines and reactive oxygen species within adipose tissue increases as well as ectopic lipid deposition in liver or skeletal muscle (reviewed in [58]). These consequences reflect potential causative links between adipose tissue dysfunction and insulin resistance. However, the exact nature of this relationship is still poorly understood and the subject of intense investigation. Hence, understanding adipose tissue biology is highly relevant in elucidating the pathogenesis and treatment of metabolic diseases like T2DM.

Adipocytes are highly specialized lipid storage cells that play a key role in modulating energy balance and nutrient flux in vertebrates. They provide a storage reservoir for energy in the form of lipid, which is stored as a single or multiple droplet(s) that give adipocytes their characteristic rounded morphological appearance. Adipocytes also produce and secrete numerous enzymes, hormones, cytokines, and growth factors that modulate appetite, lipid and glucose homeostasis, insulin sensitivity, inflammation, blood vessel formation, and overall energy homeostasis [3]. Several of these secreted factors, such as leptin, prolactin, interleukin-6, and cardiotrophin-1, activate the JAK–STAT pathway and are mentioned in this review. In the context of this review, we also discuss the STAT1-mediated transcriptional regulation of lipoprotein lipase, an enzyme secreted from adipocytes.

The two classical types of fat cells that have been widely studied include white and brown adipocytes. White adipocytes are important in energy storage and have three main functions — they sequester and release lipid, take up glucose in response to insulin, and secrete paracrine and endocrine factors. Brown adipocytes are predominantly classified by their high content of mitochondria containing uncoupling protein-1 (UCP-1) and contribute to energy expenditure. UCP-1 uncouples the electron transport chain from energy production and results in the release of potential energy obtained from food as heat. As a result, brown adipocytes play an important role in adaptive thermogenesis and are

☆☆ This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

★ This work was supported by grant R01DK52968 from the National Institutes of Health to J.M.S.

* Corresponding author at: Louisiana State University, Department of Biological Sciences, 202 Life Sciences Bldg., Baton Rouge, LA 70803, USA. Tel.: +1 225 763 2648; fax: +1 225 578 2597.
E-mail address: jsteph1@lsu.edu (J.M. Stephens).

0925-4439/$ – see front matter
http://dx.doi.org/10.1016/j.bbadis.2013.05.030

essential for non-shivering thermogenesis in response to cold or β3-adrenergic stimulation [23,75]. We will review two recent high impact studies that link the JAK–STAT signaling pathway to brown adipocyte differentiation and adaptive thermogenesis and mark the infancy of our understanding of JAK–STAT signaling in brown adipose tissue (BAT).

Expansion of adipose tissue occurs through both increases in the size and number of the adipocyte population. New, mature adipocytes arise via differentiation of progenitor cells within adipose tissue. Evidence exists suggesting that white and brown adipocytes derive from different types of mesenchymal progenitor cells [78]. However, innovative studies examining the development of brown-like adipocytes within white adipose tissue (WAT) recently have challenged this concept [74]. The signaling factors regulating the transition of mesenchymal progenitor cells to committed preadipocytes are poorly defined. Nonetheless, significant advances towards an understanding of adipose tissue biology have been made by studying the function of transcription factors, which regulate differentiation of committed preadipocytes, and are involved in the modulation of adipocyte gene expression. Fat cell differentiation, known as adipogenesis, proceeds as a highly coordinated and temporally defined series of events that involves the regulated expression of numerous transcription factors (reviewed in [75,104]). Several laboratories have investigated the role of STATs (Signal Transducers and Activators of Transcription) in adipocyte development and function. Additionally, studies show that many STAT activators play a critical role in the regulation of adipocyte gene expression and exhibit differential expression in conditions of obesity and/or insulin resistance [13,75].

1.2. Other AT cell types

In addition to adipocytes, immune cells significantly contribute to the cellular composition of adipose tissue. Their presence within adipose tissue is regulated by obesity and metabolic dysfunction. The purpose of these immune cells and their relationship to metabolic dysfunction within obese adipose tissue is the subject of intense investigation and debate. Whether their presence is a cause or consequence with regard to insulin resistance is unknown, and both hypotheses have been proposed. Some types of immune cells, such as macrophages, increase in obese adipose tissue, and are associated with inflammation and metabolic disease. Yet the levels of eosinophils, which are anti-inflammatory and associated with healthy adipose tissue, decrease during obesity and insulin resistance (reviewed in [77]). Many studies suggest that adipose tissue macrophages (ATMs) are associated with insulin resistance in a manner that is dependent upon their activation status. Yet, more recent studies suggest that ATMs may have housekeeping functions in adipose tissue and may serve physiological roles in modulating lipid flux in adipocytes [47]. Interestingly, the JAK–STAT pathway was first identified and characterized as the result of immunological studies focused on understanding the signal transduction pathway utilized by interferon gamma (IFNγ) (reviewed in [84]).

Interest in adipose tissue immune cells has prompted recent studies examining the role of JAK–STAT activators and signaling in adipose tissue immune cells. Several cytokines that are activators of the JAK–STAT pathway are produced from immune cells, preadipocytes, and adipocytes within adipose tissue and have paracrine and endocrine effects on other cells with important functions in regulating metabolism and energy balance. Little is known regarding the complex interplay of JAK–STAT signaling between adipose tissue cells, but activators of this pathway have been shown to regulate development and function of both immune cells and adipocytes.

1.3. JAK–STAT signaling pathway

The STAT family of mammalian transcription factors is comprised of seven members (STATs 1–4, 5A, 5B, and 6) that have cell and tissue-specific distribution that influences their specificity and function [76]. STATs 5A and 5B, although highly homologous, are transcribed from different genes. While the expression level of STAT5A relative to STAT5B is tissue specific, the STAT5 proteins typically share similar patterns of tissue-dependent gene expression. Intriguingly, they have been shown to exhibit both redundant and non-redundant functions [94]. STATs are predominantly activated by phosphorylation of one tyrosine residue near the C-terminus that is catalyzed by a Janus Kinase (JAK). Members of the JAK family include JAKs 1–3 and Tyk2. The JAK–STAT pathway is present in all cells, mediates the action of numerous cytokines, growth factors, and hormones, and regulates diverse biological functions, including immune responses, energy expenditure, and cellular differentiation. Under basal conditions, STATs are largely inactive and localized to the cytoplasm. Upon ligand binding to a membrane-bound receptor, the receptor-associated JAKs become activated and phosphorylate tyrosine residues within the receptor, which then direct recruitment of specific STATs. STATs bind the activated receptor via their SH2 domains and become JAK substrates. Tyrosine phosphorylation of STATs results in the formation of homo- or hetero-dimers that translocate to the nucleus where they regulate transcription of specific target genes.

This review provides in depth coverage of the literature that relates to the role of JAK–STAT signaling in adipogenesis. We also address the ability of STATs to modulate fat cell function via transcriptional regulation of adipocyte-specific gene targets in response to activator stimulation. Additionally, we explore knockout studies of JAK–STAT activators in mice. These studies suggest that JAK–STAT signaling in adipose tissue plays an important role in paracrine communication between adipocytes and AT immune cells that might influence the pathogenesis of obesity. Lastly, we highlight novel studies regarding JAK–STAT signaling in brown adipose tissue.

2. Regulation of adipogenesis by STAT proteins

The first studies on the modulation of STATs during adipocyte development were performed over fifteen years ago and demonstrated that protein levels of STATs 1, 3, 5A and 5B increased during 3T3–L1 fat cell differentiation, providing the first suggestion that these STAT proteins may play a role in the transcriptional control of adipogenesis [86]. Five years later, studies in subcutaneous human primary adipocytes confirmed the up regulation of STATs 3 and 5 during differentiation [32]. However, the pattern of STAT1 protein expression during human [32] and murine [86] adipogenesis differed, suggesting species-specific regulation. Decreased STAT1 expression during adipogenesis of human adipocytes indicates that it does not promote human fat cell differentiation. There are few studies that examine the role of STATs 1 and 3 in the transcriptional control of adipogenesis. However, substantial *in vitro* and *in vivo* evidence from over a dozen independent laboratories supports the hypothesis that STAT5 promotes fat cell differentiation in mouse and man.

2.1. The role of STAT5 proteins in adipocyte development

Studies of transgenic mice containing knockouts or deletions of the STAT proteins have been critical in obtaining an understanding of the function of these proteins *in vivo*. Deletion of STAT5A, STAT5B, or both STAT5 proteins in genetically modified mice results in impaired adipose tissue development with the double knockout mice having fat pads only 20% of the normal size [94]. Since these are non-inducible whole-body deletions of STAT5, it is unclear if the reduced adipose tissue is related to developmental deficiencies. However, a recent study provides evidence that STAT5 proteins can promote adipocyte development *in vivo* in a mature animal. Fibroblasts were genetically engineered to express STAT5A and injected into athymic mice. STAT5A-expressing fibroblasts conferred the formation of ectopic fat pads and demonstrated that STAT5A is physiologically