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REVIEW

Translating the biology of adipokines in atherosclerosis and cardiovascular diseases: Gaps and open questions

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Abstract *Aim:* Critically discuss the available data, to identify the current gaps and to provide key concepts that will help clinicians in translating the biology of adipokines in the context of atherosclerosis and cardio-metabolic diseases.
Data synthesis: Adipose tissue is nowadays recognized as an active endocrine organ, a function related to the ability to secrete adipokines (such as leptin and adiponectin) and pro-inflammatory cytokines (tumor necrosis factor alpha and resistin). Studies *in vitro* and in animal models have observed that obesity status presents a chronic low-grade inflammation as the consequence of the immune cells infiltrating the adipose tissue as well as adipocytes. This inflammatory signature is often related to the presence of cardiovascular diseases, including atherosclerosis and thrombosis. These links are less clear in humans, where the role of adipokines as prognostic marker and/or player in cardiovascular diseases is not as clear as that observed in experimental models. Moreover, plasma adipokine levels might reflect a condition of adipokine-resistance in which adipokine redundancy occurs. The investigation of the cardio-metabolic phenotype of carriers of single nucleotide polymorphisms affecting the levels or function of a specific adipokine might help determine their relevance in humans. Thus, the aim of the present review is to critically discuss the available data, identify the current gaps and provide key concepts that will help clinicians translate the biology of adipokines in the context of atherosclerosis and cardio-metabolic diseases.

Introduction

In the last 30 years, our understanding of the function of adipose tissue has changed dramatically. The landmark discovery and characterization of leptin in the '90s changed the traditional view of adipose tissue from being a simple depot organ for energy storage to an active endocrine organ. Indeed, not only adipose tissue synthetizes several bioactive compounds but also undergoes dynamic changes in response to circulating and local signals [1].

Immune cells, including macrophages and lymphocytes, infiltrate the adipose tissue where they alter adipocyte responses to metabolic signals, including insulin, as well as adipokine secretion, thus favouring adipose

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tissue expansion and activation [2–4]. Visceral fat depots and hypertrophic adipocytes drive the secretion of pro-inflammatory cytokines (*i.e.* interleukine-6 (IL-6), tumor necrosis factor-alpha (TNF-α) [5], macrophage chemo-attractant protein-1 (MCP-1) and adipokines (*i.e.*, leptin and adiponectin). Many of these cytokines determine a pathophysiological status having a detrimental effect on insulin signalling and beta-cells functionality [6], as well as on cardiovascular pathology, including atherogenesis, plaque progression and thrombosis [7].

Although clustered as adipokines, these molecules exert different effects, which could improve or impair the metabolic responses. Hence, in a condition of adipocyte hypertrophy, it has been shown that adipokines play an important role in cardiovascular diseases and atherosclerosis by influencing glucose and lipid metabolism, and their impact on the disease but also by affecting vascular function [8]. Moreover, adipokines secretion may contribute to impaired regulation of appetite and satiety, fat distribution, energy expenditure and blood pressure [9]. Although the role of adipokines on atherosclerosis has been investigated extensively in *in vitro* and *in vivo* experimental models, the translation of these findings in human has been limited, with contradictory evidence reported [10].

Hence, the aim of this review is to critically discuss the available data, identify the current gaps and provide key concepts that will help clinicians translate available information on the biology of adipokines and of cytokines in the context of atherosclerosis.

Biology of adipose tissue derived cytokines and adipokines

The pivotal role of the adipose tissue in the homeostasis of energy stores in response to excessive nutritional intake and to the demand for energy expenditure rose attention with the discovery of leptin [11] and leptin receptor [12].

Physiologically, there is a complex interplay between brain, adipose tissue and other organs which includes long-term afferent signals from fat (leptin) and pancreatic cells (insulin) and short-term, meal-related afferent signals from the gut, such as the stimulator of feeding (ghrelin) [13].

Adipokines are molecules produced and secreted by the adipose tissue and act as paracrine or endocrine hormones [14]. They regulate appetite and satiety, fat distribution, inflammation, blood pressure and endothelial dysfunction. Therefore, adipokines secretion may play a role in several obesity-related metabolic abnormalities, such as hypertension, type 2 diabetes mellitus (T2DM), fatty liver and vascular disease [15].

Of note, adipokines and adipose tissue derived cytokines form a complex network and share common physiopathological pathways that support the transition from the obese state to an inflamed and dysmetabolic state. Inflammation is known also to have a role in atherogenesis and atherothrombosis [16]. Therefore, understanding the biology of adipokines represents the first step to delineate their role in humans.

Leptin

Leptin (Greek, leptos), meaning “thin”, is a cytokine-like hormone secreted by adipose tissue (mainly by white adipose tissue) which plays an important regulatory role in energy metabolism by inducing satiety and increasing energy expenditure [17]. Human leptin, a 16 kDa protein of 146 amino acids, circulates in the blood in two forms: the monomeric one (free leptin) and the higher molecular weight form which is bound to the soluble leptin receptor [18]. In humans, free leptin mediates satiety effects [19,20], whereas bound leptin seems to modulate sympathetic activity and energy expenditure [21,22]. Variations in adipose fat mass are also associated to a specific partitioning of leptin into free and bound form [23,24], with the latter being prevalent in lean subjects, whereas, free leptin is the major plasma fraction in obese subjects [19,24]. Circulating leptin levels are also affected by gender [25,26] with women presenting increased levels, a finding associated to presence of larger adipose tissue mass and a higher production rate per unit mass of adipose tissue [27].

Leptin belongs to the so called ‘long chain’ cytokine family sharing a unique aspect of class-I cytokines, which consists of four alpha-helices arranged in a ‘up-up-down-down’ fashion [28]. Leptin exerts its effects through specific transmembrane receptors, produced in several alternatively spliced forms [29]. Six leptin receptors (LepRa-f), most of which are ubiquitously expressed, have been identified and categorized into short (LepRa, LepRc, LepRd and LepRf) and long (LepRb) isoforms depending on their intracellular domain size and the presence of JAK/STAT binding sites [30]. LepRd and LepRf isoforms are present only in mouse [31] and rat [32], respectively. LepRe, which is the smallest isoform, is a secreted isoform containing only the extracellular domain [33]. LepRa/b and LepRb/c can exist as heteromers, which are further stabilized by leptin binding [34] (Fig. 1).

The engagement of leptin receptors results in the activation of different signal transduction pathways, including those of (i) the Janus kinases (JAKs), (ii) the signal transducers and activators of transcription (STATs), (iii) the suppressor of cytokine-signalling-3 (SOCS3) representing the intracellular negative-feedback loop inhibiting JAK activity and thereby switching off cytokine signal transduction, (iv) the mitogen-activated protein kinase (MAPK) and the (v) AKT [35] (Fig. 1).

Leptin plays a key role also in linking obesity to immunity [4]. Indeed, specialized lymphocyte T cell subsets such as regulatory T cells (Treg), which are present in adipose tissue [36], constitutively express high amounts of leptin and of LepR [37]. Leptin, was initially described to constrain the proliferation of human naturally occurring $Foxp3^{+}CD4^{+}CD25^{+}$ Treg cells [38]; later on, the same group described the mammalian target of rapamycin (mTOR) pathway as the key driver of the effects of leptin on Treg cells proliferation [39]. More in details, a dynamic and oscillatory mechanism takes place, which is characterized by early downregulation of the leptin-mTOR pathway, later followed by an increase in mTOR