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Review Article

Functional and structural features of adipokine family

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ABSTRACT

In the mid-1990s, the interest in adipose tissue was revived by the discovery of leptin. Since then numerous other hormones have been isolated from white adipose tissue that has no longer considered an inert tissue mainly devoted to energy storage but emerged as an active participant in regulating physiologic and pathologic processes, including immunity and inflammation. Adipose tissue produces and releases a variety of proinflammatory and anti-inflammatory factors, including the adipokines, as well as cytokines and chemokines. Proinflammatory molecules produced by adipose tissue have been implicated as active participants in the development of insulin resistance and the increased risk of cardiovascular disease associated with obesity. In contrast, reduced leptin levels might predispose to increased susceptibility to infection caused by reduced T-cell responses in malnourished individuals. Altered adipokine levels have been observed in a variety of inflammatory conditions, although their pathogenic role has not been completely clarified.

In this paper we want to review: (i) the role of adipose tissue in different biological processes, (ii) the functional and structural description of all the known adipokines subdivided in different subfamilies, (iii) the adipokine involvement in obesity and cancers, and (iv) the adipokine interactome.

1. Role of adipose tissue in different biological processes

The traditional view of adipose tissue as a passive reservoir for energy storage is no longer valid. As early as 1987, adipose tissue was identified as a major site for metabolism of sex steroids and production of adipsin, an endocrine factor that is markedly down-regulated in rodent obesity [1]. The subsequent identification and characterization of leptin in 1994 firmly established adipose tissue as an endocrine organ [2]. Adipose tissue is now known to express and secrete a variety of adipokines, which act at both the local (autocrine/paracrine) and systemic (endocrine) level. In addition to these efferent signals, adipose tissue expresses numerous receptors that allow it to respond to afferent signals from traditional hormone systems. Besides the biological repertoire necessary for storing and releasing energy, adipose tissue contains the metabolic machinery to permit communication with distant organs. Through this interactive network, adipose tissue is integrally involved in coordinating a variety of biological processes including energy metabolism, neuroendocrine function, and immune function [3]. Adipose tissue represents the major source of fatty acids (FFA) in the postprandial fasting state for energy use and heat production [4]. Two types of adipose tissue are present in mammals: white adipose tissue (WAT) and brown adipose tissue (BAT). They have not only different functions, but also a different cellular composition and localization [4]. WAT constitutes the major component of body's adipose tissue, provides most of the total body fat and is the source of FFA, used as energy substrates for the generation through oxidative phosphorylation of adenosine triphosphate (ATP) high-energy bonds [4]. WAT is involved in the control of the metabolism through energy homeostasis, adipocyte differentiation, and insulin sensitivity. Besides, it affects inflammation, through a control mechanism mediated by antiinflammatory molecules and the activation of anti-inflammatory metabolic and immune pathways [5]. Its excessive accumulation determines the development of obesity and the obesity-related diseases. To understand the different WAT distribution and its different link with metabolic and inflammatory complications, several theories have been advanced. Among these, two major theories, not mutually exclusive, have been considered. The first is based on the anatomy of central obesity and its capacity to drain FFA and inflammatory mediators into the portal circulation, where they can act preferentially on the liver to affect metabolism [4]. The second considers cell biology and different properties of WAT cells linked with a major or minor risk to develop metabolic and inflammatory diseases. Several types of cells constitute WAT: mature adipocytes and a variety of other cells (i.e. preadipocytes, fibroblasts, endothelial cells, and macrophages),

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usually grouped and described as the "stromal vascular fraction" [6]. The adipocytes, preadipocytes, and macrophages have metabolic and inflammatory functions, which render WAT able to release several mediators with different biological effects in the WAT itself or other tissues, acting in paracrine or endocrine way. In particular, the macrophages are responsible for the circulating levels of specific inflammatory molecules, determining the "low-grade" chronic obesity-related inflammation [6]. Unlike WAT, BAT provides energy expenditure from nonoxidative phosphorylation in form of heat largely for cold adaptation and also presents a smaller number of fat cells, which have richer vascular supplies with more abundant mitochondrial chromogens, responsible for the brown color [7]. BAT shows a different function respect to WAT and is responsible of the heat for fever, the arousal state from hibernation and cold-induced-thermogenesis [7]. However, the positron emission tomography has clearly shown in adult humans metabolically active BAT depots in cervical, supraclavicular, axillary and paraventral body's regions. Since these depots can be induced in response to cold and SNS activation, it is evident that BAT can be a potential relevant target for both pharmacological and gene expression manipulation to combat human obesity [6].

The important endocrine function of adipose tissue is emphasized by the adverse metabolic consequences of both adipose tissue excess and deficiency. Adipose tissue excess or obesity, particularly in the visceral compartment, is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and prothrombotic and proinflammatory states [3]. The prevalence of obesity and these associated morbidities, known as the metabolic syndrome, has reached epidemic proportions. Interestingly, adipose tissue deficiency or lipodystrophy is also associated with features of the metabolic syndrome in both humans and rodents. Furthermore, the prevalence of lipodystrophy in humans is increasing with the use of highly active antiretroviral therapy for HIV. Thus, both excess and deficiency of adipose tissue have harmful metabolic consequences and represent significant medical and socioeconomic burdens in the world today [3].

It is now clear that adipose tissue is a complex and highly active metabolic and endocrine organ [8]. Although adipocytes express and secrete several endocrine hormones such as leptin and adiponectin, many secreted proteins are derived from the non-adipocyte fraction of adipose tissue [4]. Regardless, these components function as an integrated unit, making adipose tissue a true endocrine organ [8]. Here we present an overview of all the known adipokines and its involvement in type 2 diabetes, obesity and cancers (Table 1).

Table 1
Overview of all the known adipokines. For each protein we report the synonyms commonly used, and Uniprot and PDB codes.

Adipokines	Synonyms	Uniprot code	PDB code
Adiponectin	ADIPOQ	Q15848	n.d.
Adipsin	CFD	P00746	1DSU, 1BIO
Angiotensin II	AGT	P01019	1N9U, 1N9 V
Apelin	APLN	Q9ULZ1	n.d.
Appetite-regulating hormone	GHRL	Q9UBU3	n.d.
C1QTNF1	Complement C1q tumor necrosis factor-related protein 1	Q9BXJ1	n.d.
Chemerin	Retinoic acid receptor responder protein 2 (RARRES2)	Q99969	n.d.
IL-6	Interleukin-6	P05231	1ALU, 1IL6, 2IL6
IL-8	Interleukin-8, CXCL8	P10145	1ICW
Leptin	LEP	P41159, O15158, Q56A88	1AX8
Lipocalin 2	NGAL, LCN2	P80188	1DFV, 1QQS
MCP-1	Monocyte chemoattractant protein 1, CCL2	P13500	1DOK, 1DOL
Omentin	ITLN1, intelectin-1	Q8WWA0	n.d.
PAI-1	Plasminogen activator inhibitor 1, SERPINE1	P05121	1DVM, 1DVN
Resistin	RETN	Q9HD89	n.d.
Retinol Protein Binding 4	RBP4, POLR2D	P02753	1JYD, 1JYJ, 1QAB
SFRP-5	Secreted frizzled-related protein 5	Q5T4F7	n.d.
TNF-α	Tumor Necrosis Factor – alpha	P01375	1TNF
Vaspin		Q8IW75	n.d.
Visfatin	Pre-B-cell colony-enhancing factor 1 (PBEF1), Nicotinamide phosphoribosyltransferase (NAmPRTase or Nampt)	P43490	2GVG, 2GVJ

n.d. = not available in PDB.

2. Structural and functional description of all the known adipokines

2.1. Adiponectin

Human adiponectin (ADIPOQ) (UniProt code: Q15848) is a 30-kDa protein abundantly produced by adipose tissue where, like leptin, its expression is restricted to mature fat cells in man. It is present in the blood stream in three main forms: trimer, hexamer and high molecular weight (HMW) [9]. In contrast to most other adipokines, circulating adiponectin is negatively correlated with the BMI (body mass index) and decreased in obese subjects, in patients with type 2 diabetes or cardiovascular disease (CVD) [10]. The mechanisms underlying downregulated ADIPOQ production may involve the abnormal hormonal milieu, together with the enhanced oxidative stress and the pro-inflammatory state that prevail in obesity and the metabolic syndrome (MS) [11].

AdipoR1 and AdipoR2 serve as major receptors for ADIPOQ in vivo and belong to a new family of receptors predicted to contain seven transmembrane domains but to be structurally and functionally distinct from G-protein coupled receptors. AdipoR1 is abundantly expressed in muscle, whereas AdipoR2 is also expressed in liver. AdipoR1 is more tightly linked to the activation of AMPK pathways that regulate the inhibition of gluconeogenesis together with increased fatty acid oxidation, while AdipoR2 is more involved in the activation of the PPAR-α pathways, which stimulate energy dissipation by increasing fatty acid oxidation and inhibit oxidative stress and inflammation [12]. After binding, ADIPOQ exhibits insulin-sensitizing and fat-burning effects reminiscent of those of leptin, but possesses anti-atherogenic, anti-inflammatory and anti-oxidant properties.

Furthermore, reduced plasma levels of adiponectin have been implicated in the pathogenesis of obesity and type 2 diabetes mellitus. Mice lacking adiponectin have been found to display insulin resistance in some conditions [13].

Structurally ADIPOQ consists of four regions: (i) a short signal sequence, (ii) a short region that varies between species, (iii) a 65-amino acid region similar to collagenous proteins, and (iv) a globular domain. In PDB there are not experimental structures for this human protein but only for that in mouse (PDB code: 1C28, 1C3H) [14]. However recently Miele et al. [15] modelled the human adiponectin trimer by computational methods. In particular, the three-dimensional models of the three human adiponectin chains (region 108–244) were performed by a