Cellular Immunology 315 (2017) 18–26

Contents lists available at ScienceDirect

Cellular Immunology

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

Review article

Role of immune cells in obesity induced low grade inflammation and insulin resistance

Ambreen Asghar, Nadeem Sheikh *

Cell and Molecular Biology Lab, Department of Zoology, University of the Punjab, Q-A Campus, Lahore 54590, Pakistan

ARTICLE INFO

Article history:
Received 29 March 2016
Revised 9 February 2017
Accepted 5 March 2017
Available online 7 March 2017

Keywords:
Adipose tissues
Immune cells
Inflammation
Insulin resistance
Obesity

ABSTRACT

The frequency of obesity is enormously growing worldwide. Obesity results when energy intake exceeds, energy expenditure. Excess adiposity is a major risk factor in the progress of various metabolic disorders accounting insulin resistance, hypertension, Type 2 diabetes, nonalcoholic fatty liver disease, polycystic ovarian disease and several types of cancers. Obesity is characterized by pro-inflammatory condition in which hypertrophied adipose tissue along with immune cells contribute to increase the level of pro-inflammatory cytokines. Immune cells are the key players in inducing low grade chronic inflammation in obesity and are main factor responsible for pathogenesis of insulin resistance resulting Type 2 diabetes. The current review is aimed to investigate the mechanism of pro-inflammatory responses and insulin resistance involving immune cells and their products in obesity.

Contents

Abbreviations: AT, Adipose tissue; ATM, adipose tissue macrophages; AMPK, AMP activated protein kinases; APCs, Antigen presenting cells; CCR2, CC chemokine receptor 2; CD, Cluster of differentiation; DCs, Dendritic cells; ER, Endoplasmic reticulum; FGF-β, Fibroblast growth factor beta; GLUT-4, Glucose transporter-4; Ig, Immunoglobulin; IK-κB, Inhibitor of kappa B; IRS-1, Insulin receptor substrate-1; IR, Insulin resistance; IFN-ϒ, Interferon gamma; IL, Interleukin; JNK, Jun NH2-terminal kinase; LPs, Lipopolysaccharides; M1, Macrophage 1; M2, Macrophage 2; MIP-1α, Macrophage inflammatory protein-1 alpha; MHC, Major histocompatibility complex; MCP-1, Monocyte chemoattractant protein; NKT cells, Natural killer T cells; NEFA, Non-essential fatty acids; NF-κB, Nuclear factor kappa B; foxP3, Fork head box P3; PI3K, Phosphatidylinositol-3 kinase; PAI-1, Plasminogen activator inhibitor-1; Pref-1, Pre-adipocyte factor-1; PKC, Protein kinase C; Ras, Renin angiotensin system; STAT-6, Signal transducer and activator of transcription-6; SOCS, Suppressor of cytokine signaling; T regulatory, T reg; T helper, Th; TDZ, Thioridazone; TLRs, Toll like receptors; TGF-β, Tumor growth factor beta; TNF-α, Tumor necrosis factor alpha.

* Corresponding author.
E-mail addresses: muhammadafaqaziz@yahoo.com (A. Asghar), s_nadeem77@yahoo.com (N. Sheikh).

http://dx.doi.org/10.1016/j.cellimm.2017.03.001
0008-8749/

1. Introduction

Obesity is an emerging nutritional problem globally and is characterized by an imbalance of energy that results in adipocyte hypertrophy and then hyperplasia leading to low grade chronic inflammation of the adipose tissues which in turn is the regulator of various chronic disorders, due to increased production of cytokines secreted by macrophages and pre-adipocytes [1,2]. Obesity has a significant part in development of many metabolic disorders such as insulin resistance, hypertension, asthma, hypertriglyceridemia, cardiovascular diseases, arthritis, Type 2 diabetes hypercholesterolemia and different types of cancer [2–4]. In obesity, free fatty acids and many active metabolites such as ceramides, diacylglycerol and acetyl-CoA work to stimulate the protein kinases like Jun kinase (JNK), Protein kinase C (PKC) and inhibitor of nuclear factor kappa B (NFκB) kinase (IKK). Insulin receptor substrate (IRS) facilitates insulin receptor signaling. The above mentioned kinases impair its function by raising the inhibitory phosphorylation [5]. As excess fat is the major player of all these problems so adipose tissue acts as a key player in obesity linked disorders. To understand the mechanism of metabolic disorders associated with obesity it is necessary to know about the biology of adipose tissue [6]. Adipose tissue is not only a storage site it also has secretory functions because it secretes various substances that are required for the specific biological functions [7]. These secretions include various types of hormones like leptin, adiponectin, resistin and cytokines for example interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Obesity results in an increased production of these substances by adipocytes and non-adipocytes thus effects produced in the body due to these substances are changed, resulting in metabolic disturbances. Adipose tissues consist of adipocytes and non-adipocytes including immune cells [8].

2. Adipocytes

Obesity is characterized by increase in number and size of adipocytes and this renders them their flexibility. Due to this property of adipocytes they have a significant role in shaping metabolic health [9]. Hypertrophy and hyperplasia of adipose tissue is followed by change in cytokine secretions, oxygen depletion, necrosis, increased recruitment of immune cells and dysregulated fat metabolism [10]. Cytokines secreted by the mature adipocytes include IL-6, TNF-α, Monocyte chemoattractant protein (MCP-1), adiponectin and leptin that function as endocrine, autocrine or paracrine regulators of glucose and lipid metabolism. Adiponectin is involved in insulin sensitivity, decreased fatty acids flux, decreased hepatic glucose output and increased fatty acid oxidation in liver [11]. Increased fatty acid oxidation and glucose uptake by muscles is stimulated by adiponectin as it triggers AMP-activated protein kinases (AMPK) [12–14]. Low adiponectin level has been observed in obesity and adiponectin treatment has been seen to improve insulin insensitivity [15–17]. In liver AMPK and gluconeogenic enzymes are also affected by resistin that triggers insulin insensitivity during obesity. Furthermore, it also induces expression of suppressor of cytokine signaling-3 (SOCS-3) that negatively regulates the insulin signaling [18]. Leptin and insulin have a significant role in peripheral glucose metabolism as these triggers the feeding behavior control centers in brain promoting metabolism and homeostasis [19]. In response to high levels of MCP-1, there is increased recruitment of monocytes to adipose tissues where these are differentiated into adipose tissue macrophages (ATM) [20]. These macrophages are responsible for further increase in production of cytokines and chemokines that result in pro-inflammatory environment [10].

3. Pre-Adipocyte

There are two different types of adipocytes seen in human visceral fat [21]. Adipocytes are found to be accompanied by small, nucleated cells containing lower amount of lipid, called pre adipocytes. With obesity there is increase in number of these pre-adipocytes and it is estimated that this increase is linked with insulin resistance [22]. Pre-adipocytes represent intermediary stage during development of mature adipocytes from mesenchymal stem cells [23,24].

Function of the pre adipocytes is altered due to differential level of cytokines expression. These include TNF α, IL-1β, IL-6 and interferon gamma (IFN-ϒ) that impair adipogenesis [25,26]. IL-6 reduces the secretion of resistin, adiponectin, glucose transporter-4 (GLUT-4) and insulin receptor substrate-1 (IRS-1) expression; whereas TNF-α causes an elevated secretion of MCP-1 and IL-6 from pre-adipocytes [27]. These immature cells also secrete marked up levels of pro-inflammatory regulators like MCP-1 and IL-6 than adipocytes [28,29]. Pre-adipocytes also secrete basic fibroblast growth factor beta (FGF-β/FGF-2) that work only in presence of IFN-ϒ and TNF-α. FGF-β cause vascular endothelial cell growth and in obesity FGF-β level is increased. This increased level results in infiltration of monocytes and neutrophils [30–32].

Another transmembrane protein known as Pre-adipocyte factor-1 (Pref-1) is involved in impairment of adipogenesis [27,33].

4. Immune cells of adipose tissues

Formerly liver and bone marrow were considered to be involved in immunity but recently it has been observed that adipose tissues also contribute in immunity [34]. Immune cells in adipose tissues include myeloid and lymphoid cells (see Fig. 1).

4.1. Macrophages

Macrophages were the first studied immune cells in adipose tissues. These cells constitute 5% of immune cells of adipose tissues (AT) in normal rodents and this number exceeds to 50% in obese rodents. In case of humans macrophages are 4% of the total AT immune cells and it increases up to 12% when a person is becoming obese [36]. Macrophages are involved in defense mechanisms of body and also engulf or degrade infected cells [8]. Apart from their phagocytic activities they produce different kinds of cytokines to induce chronic inflammation and triggering the mobilization of other immune cells into the local inflammatory site and produce inflammatory cytokines [37].

Studies show that number of macrophages increase with increasing adiposity [10,38]. Macrophage infiltration can be