ADİPOSİTOKİN SİNYAL YOLAĞININ ÖNEMİ

THE IMPORTANCE OF ADIPOCYTOKINE SIGNAL PATHWAYS

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ÖZET

Adipositokinler, beyaz yağ dokusu tarafından üretilen ve hücre regülasyonunu, sinyalizasyonunu, fonksiyonunu, iflamasyonun gibi durumları etkileyen biyoaktif aracılardır. Özellikle immun fonksiyonları ve enflamatuar süreçlerini etkilerler. Leptin, Ghrelin, Adiponectin, Resistin, Visfatin, Omentin, Apelin, Chemerin, Nesfatin adipositokinlerde en çok çalışılanlar arasında yer almaktadir. Ayrıca adipositokinlerin kardiyovasküler hastalıklar, nörolojik hastalıklar ve metabolik hastalıklar gibi birçok hastalıktaki önemli etkileri de gösterilmiştir. Son bilgiler ile artık, inflamasyon veya hastalık durumunda adipositokinlerin nasıl aktive edildiğini, yapılarının moleküler mekanizmaları ve pro- ve anti-inflamatuar sitokinler üzerindeki etkileri, çeşitli adipositokinlerin monositler-makrofaj sistemi üzerindeki etkileri, özellikle bağışıklık sistemi ve bununla bağlantılı hastalıklardaki etkileri ortaya çıkarılmıştır. Ayrıca, adipositokinlerin birçok hastalık için risk faktörü olup olmadığını araştıran birçok çalışma vardır. Bu veriler birlikte ele alındığında, bu sonuçlar, diğer yeni tanımlanan adipositokinlerin etki mekanizmalarının ve hedef dokuların çeşitli hastalıklar üzerindeki etkilerinin gerek moleküler gerek deneysel hatta insan çalışmalarında ayrıntılı olarak araştırılması gerektiğini göstermektedir.

Anahtar Kelimeler : Adipositokinler, inflamasyon, immun sistem

ABSTRACT

Adipocytokines are bioactive mediators produce by white adipose tissue and affecting cell regulation, signaling, function, inflammation, etc. They act mainly immune functions and inflammatory processes. Leptin, Ghrelin, Adiponectin, Resistin, Visfatin, Omentin, Apelin, Chemerin, Nesfatin are among the most widely studied in adipocytokines. Adipocytokines' essential effects in many diseases such as cardiovascular diseases, neurological diseases, and metabolic diseases have been shown. Recent insights have now revealed how adipocytokine is activated during inflammation or diseases, the molecular mechanism for structure and effects on pro-/anti-inflammatory cytokines, and various adipocytokines in the monocytes-macrophage system incredibly immune system and linked diseases. Moreover, many studies are investigating whether adipocytokines are risk factors for many diseases. These results suggest that the mechanisms of action of other newly defined adipocytokines and the effects of target tissues on various diseases should be investigated in detail with molecular and experimental, even human studies.

Keywords: Adipocytokine, inflammation, immune system

INTRODUCTION

In the light of current knowledge, it is known that adipokines are released from white adipose tissue. They have many essential effects and play roles in disorders (Sakurai et al., 2013). Studies have classified adipokines into two groups as anti-inflammatory and inflammatory according to their

impact on obesity and type 2 diabetes. Adiponectin, omentin-1, SFRP5, cardiotrophin-1 are considered anti-inflammatory, whereas FABP-4, ASP, RBP4, lipocalin-2, chemerin, visfatin, leptin, vaspin, resistin, apelin, gremlin-1 have inflammatory effects (Lee et al., 2019). These significant multifunctional effects may impact the development of many different kinds of pathophysiological mechanisms. Recent evidence suggests that adipokines have various autocrine and paracrine interactions (Kalypso and Vidya, 2010).

The alterations in adipose tissue that when the healthy state changed the overnutrition results obesity-associated pathologies. Increased energy intake is followed by adipocyte hypertrophy/death and chemotactic adipokine release and facilitates macrophage infiltration into the tissue. As a result of this, the inflammatory response exacerbates. So normal endothelial function deteriorates (Karastergioua and Mohamed-Ali, 2010).

Based on the studies conducted so far, we can see a wide range of adipokines according to their immune characterization. That is, while those showing cytokine-like molecule activity are leptin, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8, IL-10, migration inhibitory factor (MIF), those showing complement-like factors are Adipsin, ASP, Adiponectin. Visfatin is released from adipose tissue and have growth factor immune characterization. Chemerin also shows chemokine properties (Karastergioua and Mohamed-Ali, 2010).

Various adipocytokines have a risk for various metabolic disorders such as diabetes and heart disease. The concept of adipocytokines balance is vital in terms of the relationship between inflammation and endothelial function. Apelin, TNF-α, IL-6, visfatin, and ghrelin are among the most prominent adipocytokines, especially in endothelial dysfunction. Further, we know that visfatin increases coroner heart disease risk in light of today's data. Similarly, resistin and IL-6 increases in the occurrence of cardiovascular risk (Ravindran et al., 2017).

Adipocytokine signaling pathway was studied in Andrias davidianus. The three leptin signaling pathways have been identified as The Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3) pathway, TNFα receptor signaling by TRAF, 5' adenosine monophosphate-activated protein kinase (AMPK) in this study (Tian et al., 2017). In the JAK2/STAT3 pathway, when the Leptin binding to its receptor, JAK2/STAT3 pathway activates. Researcher suggests that leptin also activates PI3 kinase (PI3K) and Phosphodiesterase 3B (PDE3B), and reduces cyclic adenosine monophosphate (cAMP) levels, so this regulation appears to be essential for STAT3 activation by leptin because PDE3 inhibition reverses this effect of leptin in the hypothalamus. Also, cAMP and STAT3 levels directly affect the nucleus in the hypothalamus (Sahu A, 2011). This action is related to the insulin-like signaling pathway, which is glucose and energy homeostasis and neuroendocrine function. As a result, changes in STAT3 levels in neurons increase Neuropeptide Y (NPY) levels. This, too it causes obesity, hyperphagia, thermal dysregulation (Park and Ahima, 2014). More data on the physiological effects of the leptin inhibits hunger and stimulates satiety, whereas it has many kinds of pathophysiological impacts such as increased cell proliferation, growth, survival, angiogenesis, invasion/migration, inflammation, and dysregulated cytokine signaling (Saygın et al., 2017).

Adiponectin acts AMPK and Peroxisome proliferator-activated receptor-alpha (PPAR-α) pathways, increased ceramidase activity. It has a lot of physiological effects like glucose and lipid homeostasis, insulin sensitivity, besides it has many pathophysiological effects such as hypoadiponectinemia causes insulin resistance and loss of inhibitory effect on cell proliferation, survival, migration, and inflammation (Saygın et al., 2017). Besides the known effects of adiponectin in insulin resistance, obesity, and type 2 diabetes, a new study in adiponectin knockout (AdKO) mice showed that adiponectin is vital in tissue remodeling during regeneration (Mosele et al., 2020). Although the existence of a direct relationship between depression and adiponectin has not yet been demonstrated, adiponectin has been reported to have an anti-depressive effect (Wang et al., 2020).

Current studies have indicated that visfatin affects the cell via the extracellular-signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), and cytokine pathways. It may mediate

several physiological processes such as B cell and vascular smooth muscle maturation, Nicotinamide adenine dinucleotide (NAD) biosynthesis, and pathophysiological effects such as increased cell survival, cytokine production, migration, increased antioxidative enzymes (Saygın et al., 2017). A recent study reviewed that Visfatin is also correlated with glycemic control, and increased levels are correlated positively with HOMA-IR and insulin levels (Ravindran et al., 2017). A study investigating the effects of adipocytokines on febrile convulsions, visfatin, and leptin levels was statistically insignificantly lower in febrile seizures than in the control group (Chen et al., 2020).

Several critical signaling pathways such as PI3K, MAPK, and Nuclear Factor kappa B (NF-kB) have been identified in resistin. Its function is energy homeostasis. Although its physiological function is energy homeostasis, it is now thought that pathophysiological functions as increased inflammation, cell survival, adhesion, migrations, and metastasis (Saygın et al., 2017).

The relation of resistin to stress physiology is remarkable in recent studies. Cellular stress increases the unfolded protein load in the endoplasmic reticulum and halts the resistin secretion. So resistin may act as a chaperone-like molecule. Recent reports demonstrated the pleiotropic role of resistin in diseases such as insulin resistance, tumorigenesis, inflammatory pathology, and rheumatic diseases and cardiovascular diseases, atherosclerosis, etc. (Tripathi et al., 2020)

Apelin is also known to have a mechanism of action via G-protein-coupled receptor, PI3K, and ERK pathways effects reach the cells. Besides its physiological functions in blood pressure control and angiogenesis, histamine and insulin release, fluid homeostasis, pathophysiological roles participate in many processes, including increased cell proliferation, migration, survival, lymphangiogenesis, and angiogenesis (Saygın et al., 2017). Apelin/APJ system that is not expressed in most normal tissues but is expressed by tumor tissues or cell lines such as lung cancer, colon cancer, endometrial cancer, gastroesophageal cancer, hepatocellular carcinoma, prostate cancer, oral squamous cell carcinoma, brain tumor, or cancer (Yang et al., 2016). Apelin has been found to affect monocytes/macrophages after myocardial infarction (MI). During acute myocardial infarction at the healing phase, apelin reduces IL-6, IL-8, macrophage inflammatory protein 1α (MIP-1α), macrophage colony-stimulating factor (M-CSF), monocyte chemoattractant protein-1 (MCP-1), and TNF-α. Also, apelin promotes the adhesion of monocytes via vascular cell adhesion molecule-1 (VCAM-1). At the necrotic phase of acute MI, the monocyte/macrophage subset of CD14, CD16 phenotype produces pro-inflammatory cytokines. Later, increasing apelin secretion by endothelial cells inhibits the production of pro-inflammatory cytokines, and CD14, CD16 monocytes/macrophages secrete anti-inflammatory cytokines (Novakova et al., 2016).

In the signaling pathways, the mechanism of action of Chemerin is G-protein-coupled receptor, MAPK/ERK pathways. Chemerin's essential physiological roles of the cell are adipocyte differentiation, chemoattractant. It may also play a role in many pathophysiological processes such as increased inflammation and invasion and recruitment of immune cells (Saygın et al., 2017). It is known that Chemerin is a chemoattractant protein. Circulating chemerin is increased in obesity, and it is closely associated with adiposity-related dyslipidemia, low-grade inflammation, hypertension, and insulin resistance. It has also been suggested that it has tumor-promoting effects in gastric carcinoma. However, Chemerin has immune-mediated tumor-suppressive effects in melanoma and hepatocellular carcinoma (Goralski et al., 2019).

Omentin's mechanism of action mainly relies on the Akt, AMPK/eNOS pathway. Modulation of insulin action increased cell differentiation, and inflammation suppression is the physiological effect of Omentin, whereas Omentin promotes apoptosis is the pathophysiological effect (Saygın et al., 2007). Recent studies have identified that the decrease in serum omentin level is an independent predictor of Coronary Artery Disease (Askın et al., 2020).

Most research indicates that Nesfatin has physiological effects on anorexigenic, glucose metabolism, insulin sensitivity, and also promotes apoptosis in the pathophysiological process. As a molecular mechanism of action of Nesfatin is AMK, Akt pathways (Saygın et al., 2007). Nesfatin is also shown

to plays a crucial role in feeding behavior and gastrointestinal functions such as gastric emptying, gastric motility, acid output (Schalla and Stengel, 2018).

CONCLUSION

In summary, changes in the adipocytokine reserve seem to be necessary for the metabolic and cellular process. It is crucial to identify the yet unknown all function of adipocytokine receptors, receptor-ligand interactions, and the cross-talk with other metabolic signaling pathways. Elucidating the mechanisms underlying the adipocytokines is still unclear now. New studies are required, at least in this context.

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