

An Important Adipokine: Isthmin-1

Önemli Bir Adipokin: İsthmin-1

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ABSTRACT

The presence of isthmin-1 in different body compartments reveals its significance in metabolism, cell proliferation, endothelial permeability, angiogenesis and immunity. Studies have categorized isthmin-1 as an adipokine with insulin-like behavior that uptakes glucose by the adipocytes and inhibits liver steatosis through a not identified tyrosine kinase receptor, that it is distinct from insulin receptor. Additionally, this adipokine demonstrates important functions in regulating organs development and homeostasis. This review aims to summarize the informations of isthmin-1 protein mainly its functions on glucose and lipid metabolisms.

Keywords: Adipokine, Glucose and lipid metabolism, Isthmin-1

ÖZET

İsthmin-1'in farklı vücut bölmelerinde bulunması metabolizma, hücre çoğalması, endotel geçirgenliği, anjiyogenez ve immüitedeki önemini ortaya koymaktadır. Çalışmalar isthmin-1'i, adipositler tarafından glukozu alan ve bilinmeyen bir reseptör aracılığıyla karaciğer yağlanmasını engelleyen insülin benzeri davranışa sahip bir adipokin olarak kategorize etmiştir. Ek olarak, bu adipokin organ gelişimini ve homeostazisini düzenlemede önemli işlevler göstermektedir. Bu derleme, isthmin-1 proteininin esas olarak glukoz ve lipid metabolizmaları üzerindeki işlevleri hakkındaki bilgileri özetlemeyi amaçlamaktadır.

Anahtar Kelimeler: Adipokin, Glukoz ve lipid metabolizması, İsthmin-1

INTRODUCTION

Isthmin-1 gene (*hIsm*) is found on chromosome 20p12.1 in human.¹⁻³ Although it was first discovered in the brain, later studies have shown that it is found in many tissues.^{1,4,5} This 60 kDa protein contains 499 amino acids in human. In mice, the isthmin-1 gene is located on chromosome 2 (2;2F3), has a size of 52 kDa, and contains 454 amino acids.^{3,6} In chickens, this gene is located on chromosome 3 and has an amino acid sequence of 443. In zebrafish, this gene is found on chromosome 13 with an amino acid sequence of 443.³ Isthmin-1 undertakes many important functions through two main receptors: Alpha-v beta-5 (avβ5) receptor and glucose-regulated protein 78 (GRP78) receptor.⁷⁻⁹ The isthmin-1 protein possesses three domains; a N-terminal signal peptide (SP), a thrombospondin type 1 repeat (TSR1) and an adhesion-associated domain in mucin 4 (MUC4) and other proteins in the C-terminal region (AMOP).¹⁰ The TSR1 domain has three important motifs which are “aspartic acid - glutamic acid - glycine” motif, “tryptophan – serine – leucine - tryptophan” motif and “cysteine – serine – valine – threonine - cysteine - glycine”. These motifs display essential biological processes in collagen receptor activation, transforming growth factor β activation and anti-angiogenic activation. On the other hand, the AMOP domain of Isthmin-1 contains two important motifs, which are “arginine – lysine - aspartic acid” motif and “lysine - glycine-aspartic acid” motif; the binding of these motifs to avB5 receptor will initiate cell adhesion, migration, and vascular permeability.¹¹⁻¹⁴ Additionally, this protein has crucial posttranslational modification sites, such as N-glycosylation and C-mannosylation sites, which they play an important role in the export of isthmin-1 from the endoplasmic reticulum to the golgi, protein folding and secretion.^{3,15}

Functions of isthmin-1 in metabolism

The term adipokine indicates a set of cytokines and hormones secreted from adipose tissues.¹⁶ To date, approximately 600 adipokines with different functions have been discovered.¹⁷ Adipokines regulate the circulatory and immune systems, affecting many organs such as the brain, liver, muscle, and heart. These proteins regulate glucose and lipid metabolism, endothelial functions, apoptosis, angiogenesis, inflammation, hemostasis, etc.¹⁸

A study by Jiang *et al.* (2021) suggested isthmin-1 is an adipokine that manifests endocrine functions and performs important functions in adipose tissues,

regulating growth, metabolism, and development of distant organs.¹⁹ Additionally, a study by Liao *et al.* (2023) has stated that the adipokine isthmin-1 significantly regulates insulin sensitivity, glucose tolerance, and inflammation.²⁰ Isthmin-1 increases glucose uptake by the phosphorylation of phosphoinositide 3-kinase/protein kinase pathway and represses de novo lipogenesis and liver steatosis through interfering with the inductions of sterol regulated element binding protein-1c, acetyl-CoA carboxylase, low density lipoprotein receptor, peroxisome proliferator-activated receptor γ coactivator 1β and carbohydrate response element binding protein. Additionally, it enhances protein synthesis in the liver through the protein kinase-mammalian target of rapamycin kinase 1- ribosomal protein S6 pathway.^{3,21,22} Thus, excision of isthmin-1 can result in reduction in the muscles fiber size and intensity.²³ However, the above-mentioned metabolic processes are achieved by still not-identified receptor tyrosine kinase.¹⁷

Lei *et al.* (2024) found that serum isthmin-1 levels were higher in patients with fatty liver and type 2 diabetes when compared to healthy controls; in those with metabolic syndrome when compared to those without metabolic syndrome; in obese people when compared to lean people; in those with low levels of high density lipoprotein cholesterol compared to those with high levels of high density lipoprotein cholesterol; and in men when compared to women.²⁴ Ruiz-Ojeda *et al.* (2023) found high isthmin-1 and leptin levels in obese children, but they didn't find any significant correlation between them.²⁵ They also determined that isthmin-1 levels were directly proportional to body mass index, alanine aminotransferase and total cholesterol levels, and inversely proportional to high density lipoprotein cholesterol levels.^{24,26} Supportingly, a study expressed that isthmin-1 blood levels have been found to be higher in men than in women and showed positive correlation with waist circumference and β-cell function.²⁷ Notably, direct correlations were detected between serum isthmin-1 concentration and the values of maternal waist circumference, oral glucose tolerance test 2nd-hour blood glucose, glycated haemoglobin, homeostasis model assessment insulin resistance, and epigastric subcutaneous and periumbilical adipose tissue density. However, another study determined that no major association was found between maternal serum isthmin-1 concentration and maternal age and fasting blood glucose level.²⁸

Interestingly, isthmin-1 is positively correlated with type 2 diabetes, and acts as a protective factor for diabetes. Serum isthmin-1 levels were higher in slim females compared to obese females with type 2 diabetic mellitus. However, no significant alterations in isthmin-1 levels were observed in obese males with type 2 diabetic mellitus. The same study pointed out that there is no relationship between serum isthmin-1 levels and the occurrence of diabetic sensorimotor peripheral neuropathy.²⁰ A study by Menghuan *et al.* (2023) stated that serum isthmin-1 concentration is elevated in individuals with macroalbuminuria, which is a key feature of diabetic nephropathy. This indicates that isthmin-1 increases the risk of developing type 2 diabetes mellitus.²²

Studies have confirmed that the aging heart depends mainly on energy sources from glycolysis instead of

glucose oxidation and lipid catabolism. A study conducted by Hu *et al.* (2024) found that isthmin-1 plays a prominent role in promoting glycolysis, the hexosamine biosynthetic pathway, glucose transporter-4 (GLUT4) transportation to the cell surface, and activation of sirtuin 1 deacetylase in aging mice; thus, isthmin-1 significantly inhibits cardiac dysfunction and inflammation and improves the quality of life in aging mice.²⁹

As a result, it can be said that although isthmin-1 has similar action to insulin in the aspect of glucose and protein metabolism, it shows different effect on lipid metabolism (lipogenesis) in liver.

Other functions of isthmin-1

Isthmin-1 has a lot of functions in addition to its anti-adipogenic functions, and so in metabolism. These functions are summarized in table-1.

Table 1. A brief overview about the functions of isthmin-1

Functions	Explanations	References
Anti-angiogenesis	The AMOP domain of isthmin-1 binds to avB5 integrin, inhibits vascular endothelial growth factor and restrains the development of new blood vessels.	3,5,30
Anti-cancer	It controls the proliferation of hepatocellular cancer, gastric cancer, breast cancer and melanoma.	3,31-33
Anti-inflammation	It suppresses NF-κB activation and inflammatory cytokine and chemokine production.	18,34
Apoptosis	Mobilized isthmin-1 acts on avB5 integrin in extracellular endothelial cells to initiate an activation series of caspase-3 and caspase-8, leading to apoptosis. Immobilized isthmin-1 binds to avB5 receptor and activates focal adhesion kinase, resulting in cell division, migration, and proliferation. Soluble isthmin-1 binds to the GRP78 receptor on the surface of endothelial cells. Then isthmin-GRP78 complex penetrates the cell through endocytosis, which is then transferred to the inner mitochondrial membrane, which can interact with AAC and block the transportation of ATP from mitochondria to the cytosol, resulting in apoptosis.	6,22,30
Endothelial permeability	Isthmin-1 boosts endothelial permeability by binding to GRP78 and avβ5 receptors.	35
Hematopoiesis	Isthmin-1 ameliorates the production of mesenchymal progenitors, endothelial progenitor cells, hematopoietic stem and progenitor cells, neutrophils, macrophages, and erythrocytes.	36,37
Kidney development	Isthmin-1 is shown to be expressed in metanephric mesenchyme and ureteric epithelium and takes a part in kidney development through three essential receptors, which are α8β1, ephrin-β1, and plexin-β2.	38
Lung homeostasis	Isthmin-1 efficiently preserves lung homeostasis in several diseases, such as asthma and chronic obstructive pulmonary disease, by preventing emphysema, bronchial hyperresponsiveness, and severe lung inflammation. This protein binds to GRP78 receptor, thereby causes the stimulation of adiponectin secretion from alveolar cells and ultimately alleviates allergic asthma.	39,40

Abbreviations: Alpha-v beta-5 (avβ5), Adenine nucleotide translocase (AAC), adhesion-associated domain in mucin 4 (MUC4) and other proteins (AMOP), adenosine triphosphate (ATP), Glucose regulated protein 78 (GRP78), nuclear factor kappa B (NF-κB).

CONCLUSION and RECOMMENDATIONS

Isthmin-1 is a recently expressed adipokine protein that exhibits multiple functions in different body organs. So far, few studies have been done on isthmin-1. However, the research on isthmin-1 has been going rapidly in the last few years. There is still a need to determine isthmin-1 in different aspects, such as the mechanism of interaction of isthmin-1 with its receptor in metabolism. In addition, more detailed studies are required to identify the physiological and pathological functions of isthmin-1. The relationships between isthmin-1 and various diseases such as cardiovascular, neurological, skin and joint disorders are also suggested to be investigated. We think that the significance of isthmin-1 in many biological areas will make it an attractive topic in the future.

Authorship contribution statement

Concept and design: KAMSA, BK.

Drafting of the manuscript: KAMSA, SK.

Critical revision of the manuscript for important intellectual content: KAMSA, BK, SK.

Declaration of competing interest

No conflicts of interest to be disclosed.

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