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Advances in the Study of Resistin and Atherosclerosis Related Factors

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Abstract: Resistin, an important vasoactive substance, is a cysteine-rich secretory protein in plasma.Current research further demonstrates that this factor can directly or indirectly damage the function of vascular endothelial cells and participate in the whole process of inflammation. The resistance is associated with multiple inflammatory markers, related to the lesion of atherosclerosis, and it suggests that the resistance may be of vital importance in atherosclerotic disease.

Keywords: Resistin ; Atherosclerosis

1. Introduction

Resistin is a hormone that STEPPAN [1] has discovered to study the effects of the anti-diabetic drug of Thiazolidinedione in 2001, which is a small protein that is secreted by fat cells, often in the form of a dimmers exist. The resistances are produced by adipocytes, which in the development of rodents liver insulin resistance in rodents, but that have been challenged on the human body [2] .Some of the clinical studies have not been able to get a consistent response to insulin resistance from the body [3], but surprisingly, it has a significant correlation to inflammatory control[4]

2. Molecular Structure, Distribution and Egulation of Resistin

Resistin is a new type of fat cytokines, cysteine-rich secretory proteins, which are an important member of the resistin likemolecules (RELMs) family. It is also called found in inflamma-tory Zone family (FIZZ3), and the other two members are FIZZ1 relm-alpha and FIZZ2 relm-beta. The resistance is made up of 108 amino acid residue, which is about 12.5 kD, and the genetic code section is a fragment of chromosome 19. Resistin is mainly secreted by mononuclear macrophages, and is also expressed in human placental tissue, hypothalamus and pituitary gland.

The resistive genes have a single nucleotide polymorphism (sNPs), which is associated with type 2 diabetes, obesity and insulin resistance as a result of the type of SNP and the different location of it.[5] A study [6]has found that SNPs are not related to type 2 diabetes, and sNP6 is an important factor in the risk of developing A type 2 diabetes. And another study found that 3 'UTR + 62 g a polymorphism was A risk factor for type 2 diabetes [7]

3. Resistin and Insulin Resistance

Resistin has a wide range of functions[8], including the role of insulin target organs , it affect the metabolism of lipid and sugar and participate in the energy regulation of the whole body via which regulate its signal transduction pathway and the transcription of metabolism-related enzymes. Studies [9] have found that human resistin may enhance the proliferation of preadipocytes and the decomposition of triglycerides in adipocytes, leading to the decrease of lipid droplets in cells and the stunted development of cells [10]. Mice with resistin gene knockout showed that a decrease in fasting blood glucose, partly because the activation of adenylate activated protein kinase (AMPK) reduced the expression of glycoisogenic enzymes [11-12]. All these indicated that resistin played a very important role in regulating lipid and carbohydrate metabolism in the liver. Studies have shown that resistin has no effect on glucose transporters (glut-4) membrane translocation and insulin signal transduction in skeletal muscle cells, but its insulin-stimulated glucose uptake is decreased. It is speculated that resistin may play a role by reducing the activity of glut-4 [l3].

4. Correlation Between Resistin and Inflammatory Factors

4.1. Regulation of Inflammatory Factors on Resistin Expression

It was found[14] that four pro-inflammatory cytokines can significantly improve the expression of resistin, while leptin and interferon (ifn-gamma) have no such effect via the treatment of peripheral blood mononuclear cell (PBMC) isolated from human peripheral blood mononuclear cells by interleukin-6 (IL-6), (IL-1β), lipopolysaccharide (LPS) and tumor necrosis factor (TNF-α).

A number of studies have shown that resistance is directly related to inflammatory factors, and inflammation is considered to be a state of high resistin levels of [15]. Serum resistin levels were positively correlated with inflammatory markers in patients with AS, and inflammatory indicators IL-6, TNF-α and c-reactive protein (CRP) in patients with chronic kidney disease were independently correlated with resistin levels[16].

4.2. The Regulation of Resistin on the Expression of Inflammatory Factors

Stimulating peripheral blood mononuclear cell (PBMC) with increasing concentration of resistin can improve the secretion of TNF-α, IL-1β, IL-6 and such increase is positively correlated with the concentration of resistin.

There are few studies on the regulation mechanism of resistin on the expression of inflammatory factors. Studies have shown that the resistance has the effect of activating the NF-κB signaling pathway, which allows the synthesis of TNF-a and IL-12 through the NF-κB to produce [17-18]. Nf-kappa B is a transcription factor belonging to Rel family, which is involved in regulating gene transcription related to cell differentiation, inflammation and immunity. Resistin can degrade NFB dimmers and the inhibitory protein kappab by activating two ubiquitination pathways: kappab and NF- kappab, thereby regulating the transcription of il-12 and TNF - a genes. Blocking the NF- KB pathway reduced the expression of TNF-a and il-12 by building Iκ-Ba predominate lack of tryptophan mutation carriers transfection macrophages.

There are interactions among inflammatory factors such as IL-6, TNF-a, IL-1β and resistin, forming a very complex regulatory network to sum up a large number of studies on inflammatory factors. It is responsible for the development of chronic inflammatory disease that increased inflammation of the resistant elements causing the body to be in chronic inflammatory state by induce the secretion of all kinds of inflammatory agents and initiation of inflammatory signaling pathways.

5. Resistin and Vascular Endothelial Cells

Resistin can activate endothelial cells (ECs) and lead to endothelial cell dysfunction, a mechanism that might underlie it: (1) Increase the expression and release of endothelin (ET)-1 mRNA. Et-1 is a potent endodermal vasoconstrictor factor that ACTS on endothelial cells and causes dysfunction. Endothelial cells treated with resistin can increase the expression of Et-1 mRNA and produce a large amount of Et-1, which fully explains the above mechanism of action.(2)Eukaryotic cells transcription factors - KB (NF - KB) is participation. Studies have shown that resistin can induce tnf-kb and il-12 release through NF-kb nuclear transport in human macrophages.(3)Reduce the expression of eNOS. Studies have shown that [19] resistance can cause endothelial cells to be less reactive. The resistances result in dysfunction of endothelial cells and impaired vasodilation and diastolic function through decrease the production and release of endothelial cells NO by inhibiting the activity of the eNOS(4). Oxidative stress (OS) Paolisso et al. [20] found that the ratio of oxidized glutathione/reduced glutathione reflecting OS level in plasma was positively correlated with IR. It indicated that 0S May play a role in the occurrence and development of endothelial dysfunction in patients with metabolic syndrome by antioxidant therapy can reverse the decrease of NO production of endothelial cells under IR and improve the function of endothelial cells. Therefore, it is speculated that it initiating and accelerating the occurrence of atherosclerosis through resistin may decrease PI3K activity and NO production of endothelial cells by increasing 0S products, and lead to impaired endothelial cell-dependent vasodilation function[21-22].

6. Resistin and Vascular Smooth Muscle cells

Resistin induces proliferation of human aortic smooth muscle cells by activating erk1/2 and Akt signaling pathways. Resistin and vascular smooth muscle cells.[23] Specific MEK inhibitors inhibit resistance-induced proliferation of smooth muscle cells by inhibit erk1/2 and Akt pathways. Resistin can improve the mobility of thin smooth muscle and has a dose-effect relationship, while the increased mobility of smooth muscle is closely related to the formation of atherosclerotic plaques.

7. Resistin and Mononuclear Macrophages

peripheral blood monocytes/macrophages are an important source of resistin[24]. During the process of monocytes transformation into macrophages, resistin expression and secretion increase in humans. It showed that resistin mRNA level increased 4 times compared with that before differentiation when monocytes differentiated to obtain macrophage phenotype in vitro experiments [25]. Other studies have shown that resistin secreted by macrophages may play a role in the pathogenesis of AS on account of there's a strong case of the resistance, the macrophages have increased and the resistance has increased as the disease progresses in the arterial atheromatous plaque in the human and the mouse. In addition, macrophages ingestion of oxidized low-density lipoprotein (ox-ldl) further forms foam cells, which is a key step in the formation of AS plaques. Ox-ldl is an important regulator of macrophage gene expression, which can regulate the expression of TNF, IL-1β, IL-1α and other inflammatory response genes, and can also be absorbed by macrophages. Studies have found that resistin upregulates the expression of CD36 on the surface of macrophages, promotes the accumulation of lipid in macrophages and the transformation of macrophages into foam

cells, and promotes the formation of AS [26] .The above studies indicated that resistin, on the one hand, is secreted by macrophages in tissues, and on the other hand, it can be found in plasma through the endocrine effect of peripheral blood monocytes. The expression of resistin was significantly increased when monocytes were transformed into macrophages, suggesting that the local effect of resistin may be stronger than the systemic effect.

8. Resistin and Atherosclerosis

Clinical studies have demonstrated the possible role of resistin in atherosclerosis. Reilly et al. [26]found that plasma resistin levels were associated with inflammatory factors and warned of the occurrence and development of coronary atherosclerosis by studying the correlation between plasma resistin levels and inflammatory markers, metabolism and coronary calcification in non-patients with genetic predisposition to coronary atherosclerosis. Therefore, resistin may be an important link between metabolic signals, inflammation and atherosclerosis.

9. Foreground and Prospect

AS mechanism is very complicated. Resistin play a role in the development of the AS through systemic and local inflammation. A large amount of clinical and experimental evidence have proved that resistin plays an important role in the regulation of inflammatory response at present [27-28] ,but the molecular mechanism of this effect is still poorly understood, and many problems remain to be further studied. For example, are there resistin receptors on endothelial cells or smooth muscle cells? If so, how to determine the existence and distribution of resistin receptors in various organs; As well as the specific role of resistin in inflammatory response, the principle of its interaction with various inflammatory factors, and the way of its realization, these questions still need to be further explored. We expect to have laid a foundation reducing the occurrence of cerebrovascular diseases and the mortality and disability rates, revealed the mechanism of resistin causing as through further research.

References

[1] Steppan C.M., Bailley S.T., Bhat S. et a1. The hormone resistin links obesity to diabetes.Nature. 2001, 409, 307-312.

[2] Vozarovade C. B., Degawa Y. M., Considine R.V. et a1.High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima indians. Diabetes. 2004, 53, 1279-1284.

[3] Lee J.H., Chan J.L., Yiannakouris N. et a1. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration l cross-sectional and interventional studies in normal, insulin-resistant. and diabetic subjects. Clin Endocrinol Metab. 2003, 88, 4848-4856.

[4] Steskal D., Adamovska S., Bartek J. et a1.Resistin: concentra - tions in persons with type 2 diabetes mellitus and in individuals with acute inflammatory disease. Biomed Pap Med Fac UnivPalacky Olomouc Czech Repub. 2003, 147, 63-69.

[5] Sentinelli F., Romeo S., Area M. et a1. Human resistin gene, obesity and type 2 diabetes, mutation analysis and population study. Diabetes. 2002, 5, 860-862.

[6] Ma X., Warranl J. H., T schitta V. et a1. Genetic variants atthe resistin locus and risk of type 2 diabetes in Caucasians. J Clin Endocrinol Metab. 2002, 87, 4407-44l0.

[7] Tan M. S., Chang S. Y., Chan g D. M. et a1. Association of resistin gene 3 -untranslated region +62G → A polymorphism with type 2 diabetes and hypertension in a Chinese population. Clin Endocrinol Metab. 2003, 83, l258-l263.

[8] Song H., Shojima N., Sakoda H. et a1. Resistin is regulated by C/EBPs, PPARs, and signaltraned ueing molecules. Biochem Biophys Res Commun. 2002, 299, 291-298.

[9] Seo B. J., Noh M. J., Yoo E. J. et a1. Functional characterization ofthe hunlan resistin promoter th ADD1/SREBPlc and C/EBP alpha. Mol Endocrinol. 2003, 17, 1522-1533.

[10] Ort T., Arjoan A. A., MacDougall J. R. et a1. Recombinant human F1ZE3/resistin stimulates lipo lysis in cultured human adipocytes. mouse adipose explants and in normal mice. Endocrinology. 2005, 146, 2200-2209.

[11] Sato H., Nguyen M.T., Miles P.D. et a1. Adenovirus-mediated chronic"hy-perresistinemia",leads to in vivo insulin resistance in normal rats.C1inInvest. 2004, 114, 224-231.

[12] Rangwala S. M., Rich A.S., Rhoades B. et a1. Abnormal ghic homeostasis due to chronic hvoerresistinemia. Diabetes. 2004, 53, 1937-1941.

[13] Banerjee R.R., Rangwala S.M., Shapiro J.S. et a1. Regulation offasted blood-ucese by resistin. Science. 2004, 303, l195-l198

[14] Kaser S., Kaser A., Sandhofer A. et a1. Resistin messenger-RNA expression is increased by proinflammatory cytokines/nvitro. Biochem Biophys Res Commun. 2003, 309, 286-290.

[15] Lehrke M., Reilly M.P., Millington S.C. et a1. An inflammatory cascade leading to hyperresistinemia in humans. PloSMed. 2004, 1, E45.

[16] Axelsson J., Bergsten A., Qureshi A.R. et a1. Elevated resis-tin levels in chronic kidney disease are associated with de-creased glomerular filtration rate and inflam mation, but not with insulin resistance. Kidney Int. 2006, 69, 596-604.

[17] Bokarewa M., Nagaev I., Dahlberg I. et a1. Resistin, an adipo kine with potent proinflammatory properties. The Journal of Immunology. 2005, 18, 5789-5795.

[18] Silswal N., Singh A.K.., Aruna B. et a1. Human resistin stimulates the proinflammatory cytokines TNF-alpha and IL-12 in macrophages by NFkappaB-dependent pathway. Biochem Biophys Res Commun. 2005, 334, 1092-1101.

[19] Kougias P., Chai H., Lin P.H. et a1. Adipocyte-derived eytokine resistin causes endothelial dysfunction of porcine cornary arteries Vase Surg. 2005, 41, 691-698.

[20] Paolisso G., Di Maro G., Pizza G. et a1. Plasma GSH/GSSG affects glucose homeostasis in healthy subjects and noninsu independent diabetics. Am J Physiol. 1992, 263, 435-440.

[21] Verma S., Li S.H., Wang C. H. et a1. Resistin promotes endo the lial cell activation, further evidence of adipokine endo the lial interaction. Circulation. 2003, 108, 736-740.

[22] Rothwell S.E., Richards A.M., Pemberton C.J. et a1. Resistin worsens cardiac ischaemia-reperfusion injury. Biochem Biophys Res Commun. 2006, 349, 400-407.

[23] Calabro P., Samudio I., Willerson J.T. et a1. Resistin promotes smooth muscle cell proliferation through activation of

extracellular signal regulated kinase 1/2 and phosphatidyli nositol 3-kinase pathways Circulation. 2004, 110, 3335-3340.

[24] Jung H.S., Park K.H., Cho Y.M. et a1. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res. 2006, 69, 76-85.

[25] Patel L., Buckels A. C., Kinghorn I. J. et a1. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun. 2003, 300, 472-476.

[26] Reilly M. P., Lehrke M., Wolfe M. L. et a1. Resistin is an inflammatory marker of atherosclerosisin humans. Circulation. 2005, 111, 932-939.

[27] Burnett M.S., Lee C.W. , Kinnaird T.D. et a1. The potential role of resistin in atherogenesis Atheroselerosis. 2005, 182, 241-248.

[28] Hu W.L., Qiao S.B., Hou Q. et a1. Plasma resistin is increased in patients with unstable angina. Chin Med J . 2007, 120, 871-875.