Obesity and resistin: What is the link?

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It is apparent that obesity can no longer be regarded simply as a social disease. The major elements that lead to obesity as a chronic medical condition are heredity and environmental, the latter impact greatly on underlying heredity tendencies. This is certainly the case with type 2 Diabetes Mellitus, and the Insulin Resistance Syndrome. The high incidence of obesity among people with type 2 diabetes suggests a connection between the two conditions. Scientists have sought a link by studying insulin resistance, the trademark symptom of type 2, or adult-onset, diabetes. But they still don't know why cells in people with insulin resistance ignore insulin's signals to process blood glucose for use by muscles and other tissues. Researchers working with mice have discovered four years ago a hormone, called resistin, that is secreted by fat cells and appears to play a direct role in type 2 diabetes by causing increase insulin resistance and glucose level. It is suggested to link obesity to type 2 diabetes by modulating steps in insulin-signaling pathway and inducing insulin resistance [1].

Structure and Biochemistry of resistin:
The hormone resistin is one amongst a novel family of three proteins , known as resistin-like molecules (RELMs). They are cysteine-rich secreted proteins associated with pulmonary inflammation (also known as FIZZ3, found in inflammatory zone). It has 11 cysteine-residues synthesized as a propeptide of 108 amino acids and secreted as a dimmer, build by a disulfide bridge of cysteine residues. Beside this intermolecular disulfide bridge, 5 additional intramolecular ones exist.

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Source of resistin :
mRNA expression for resistin is demonstrated in white adipose tissue, pituitary and pancreatic islet of mice and also in brown adipose tissue of rats. In humans, resistin expression in adiposite can be detected at a low level. it is higher in abdominal fat stores than in thigh adipose tissue, this suggest a potential role in linking central obesity to type 2 diabetes and/or cardiovascular disease[2]. Human resistin is expressed mainly in pancreatic islet, preadiposites, macrophages and bone marrow. So resistin is of relevance for inflammation processes as well as for lipid metabolism. In mice a correlation between adiposity, insulin resistance and resistin expression was found empirically. In humans respective studies are not clear. Several show an association of resistin serum concentration and adiposity or insulin resistance.

Resistin in human

Most clinically oriented studies of resistin have focused on:

a. Genetic polymorphisms,
b. Different patterns of tissue expression of resistin,
c. Correlation analyses between serum levels of resistin and body fat mass or biochemical markers of glycemic control.

The human resistin gene has been mapped onto chromosome 19, and various single nucleotide polymorphisms have been identified in northern Europeans [3] . Italians [4, 5, 6] Canadians [7] Chinese [8] and Japanese [9]. The largest of these case-control studies compared 1102 Chinese patients with type 2 diabetes and 743 control subjects. The authors showed that a resisting en variant in the unsaturated region (3'UTR+62A) is associated with a reduced risk of type 2 diabetes and hypertension associated with insulin resistance[8]]. None of the other studies have been able to confirm such a direct link between resistin genotype and metabolic outcome.

There is continued uncertainty about possible relationships between serum concentrations of resistin and markers of insulin resistance. Although some studies have shown positive correlations with body fat mass[10, 11] and indeed insulin resistance[12] others have found no

relationship between resistin gene expression and body weight or insulin sensitivity[13] [In a large study of patients with and without diabetes, including those with a wide range of body mass index (BMI) values, there was no relationship between plasma resistin concentration and BMI or diabetes status[14] . More recently, amongst 65 patients with essential hypertension (including 13 withtype 2 diabetes and 26 with impaired glucose tolerance), fasting serum resistin levels were significantly higher amongst patients with diabetes compared with those with impared glucose tolerance, and there was a correlation between resistin and AUC glucose following an oral glucose challenge. This correlation was still significant even after adjustment for age, BMI and gender[15] .

Resistin putative role(s):

Relevance of resistin in physiological processes other than energy metabolism was investigated. Experiments with endothelial cells gave interesting results, in which resistin shown to be potentially able to influence endothelial inflammation and thereby atherosclerosis[16]. Resistin shares some qualities with another protein secreted by fat cells and associated with obesity, the hormone leptin. This hormone, discovered in 1995, seems to regulate food intake. Establishing that fat cells secrete resistin together with adiponectin and leptin confirms that these cells are more than just "oily stuff in the body,". Fat in the body "is an endocrine gland, a hormone-producing substance involved in a dialogue with the brain, liver, and muscle in a complex [process] of nutrient metabolism,"[17] Like resistin, adiponectin is also thought to mediate inflammation, possibly inhibiting obesity-induced atherogenesis[18] There is still much to learn about resistin. But with each new piece fitted into the diabetes puzzle, new possibilities arise. There are two putative roles of resitin:

a. To directly cause insulin resistance (as proposed by Lazar et al.)[19]
b. To block adipocyte differentiation as proposed by Sul et al. [20] . The latter might lead to ectopic fat storage (increased amounts of fat in skeletal muscle and liver. [21]

In a recent study it was roved that resistin was positively and independently correlated with insulin resistance and hepatic fat as measured by liver X-ray attenuation. [22] These data potential implicate resistin in the pathophysiology of the human insulin resistance syndrome, an effect mediated by the -180C>G promoter single nucleotide polymorphism (SNP) and , possibly cellular oxidative stress.

Future work....

The Pennsylvania researchers [23] have already devised an antibody to resistin, which they used in the mouse tests to inhibit the newfound substance's effects. However, they still haven't found the molecular receptor that allows resistin binding to cells. Identifying this molecule could give drug makers a target by which to chemically block the effects of resistin. Future research in this area aims to establish the role of resistin in human disease. Measurement of resistin in a simple blood test might then be useful in detecting insulin resistance and prediabetic conditions. Looking forward, counteracting resistin's affects on the body might be a new approach to preventing and treating diabetes.

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