Resistin as a marker of severe sepsis

Thesis

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Introduction

A new hormone has been identified that links obesity to type 2 diabetes. It has been called resistin (for "resistance to insulin"). Resistin is expressed in white adipose tissue and is induced during adipogenesis. It is one amongst a family of three proteins, known as resistin-like molecules (RELMs), which have a conserved pattern of 11 cysteine residues at the C-terminal end of the structure ***(Steppan et al., 2001).***

Resistin gene expression is induced during adipocyte differentiation, and the resistin polypeptide is specifically expressed and secreted by adipocytes. Resistin expression is greater in white adipose tissue than in brown adipose tissue, where resistin mRNA is barely detectable. Resistin mRNA levels varied as a function of white adipose depot and gender, with the highest level of expression in female gonadal fat. Immunohistochemistry of epididymal white adipose tissue showed that the resistin protein is abundant in adipocyte cytoplasm ***(Steppan et al. 2001).***

Resistin mRNA expression was similar in both subcutaneous abdominal and omental fat depots. However, the abdominal depots showed a 418% increase in resistin mRNA expression compared with the thigh. The authors suggested that increased resistin expression in abdominal fat could explain the increased risk of type II diabetes associated with central obesity ***(McTernan et al. 2002)***.

The structure of resistin revealed an unusual multimeric structure. Each protomer comprises a carboxy-terminal disulfide-rich beta-sandwich 'head' domain and an amino-terminal alpha-helical 'tail' segment. The alpha-helical segments associate to form 3-stranded coiled-coils, and surface-exposed interchain disulfide linkages mediate the formation of tail-to-tail hexamers. Analysis of serum samples showed that resistin circulates in 2 distinct assembly states, likely corresponding to hexamers and trimers. Infusion of a resistin mutant, lacking the intertrimer disulfide bonds, in pancreatic insulin clamp studies revealed substantially more potent effects on hepatic insulin sensitivity than those observed with wild type resistin ***(Patel et al., 2004)***.

Sepsis is one of the most frequent complications in the surgical patient and one of the leading causes of mortality in intensive care units ***(Sands et al., 1997).***

Sepsis can be caused by infection with Gram-negative bacteria, Gram-positive bacteria, and fungi (particularly *Candida*), or viruses. Sepsis may also occur in the absence of detectable bacterial invasion, and in these cases, microbial toxins, particularly Gram-negative bacterial endotoxin (lipopolysaccharide, LPS), and endogenous cytokine production have been implicated as initiators and mediators ***(Hardaway*, 2000).**

Septic shock is the syndrome characterized by a persistent arterial hypotension in a septic patient. Hypotension is defined by a systolic arterial pressure <90 mmHg (in children <2 SD below normal for their age), a MAP <60, or a reduction in systolic blood pressure of >40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension ***(Adelais et al., 2005).***

The mortality of severe sepsis (infection-induced organ dysfunction or hypoperfusion abnormalities) and septic shock (hypotension not reversed with fluid resuscitation and associated with organ dysfunction or hypoperfusion abnormalities) in most centers remains unacceptably high (***Dellinger, 2003).***