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ROLE OF ADIPOKINES IN THE PATHOGENESIS OF ATHEROSCLEROSIS

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Introduction

Obesity is considered to be one of the modifiable cardiovascular risk factors, while weight loss is generally associated with a beneficial effect on markers of cardiovascular risk. Besides subcutaneous adipose tissue, ectopic fat depots such as epicardial adipose tissue (EAT) or perivascular adipose tissue (PVAT) are of particular interest as several studies point out a strong association between the amount of EAT and PVAT and atherosclerosis. Adipokines, which represent a series of hormones and cytokines secreted by adipose tissue and mediating their effects on endocrine or paracrine way, seem to explain this correlation. Thus, the function of adipose tissue extends far beyond energy storage or mechanical protection, being rather an important endocrine organ.

Keywords

atherosclerosis, adipokine

Purpose

Elucidation of the role of adipokines in the pathogenesis of atherosclerosis.

Material and methods

Literature review of 95 scientific articles, using the Pubmed engine has been performed, the keywords joining the search were the following: adipokine, atherosclerosis, perivascular adipose tissue, adiponectin, leptin.

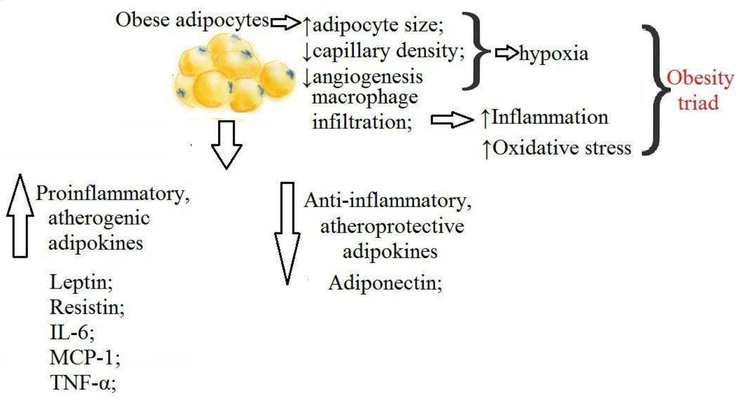
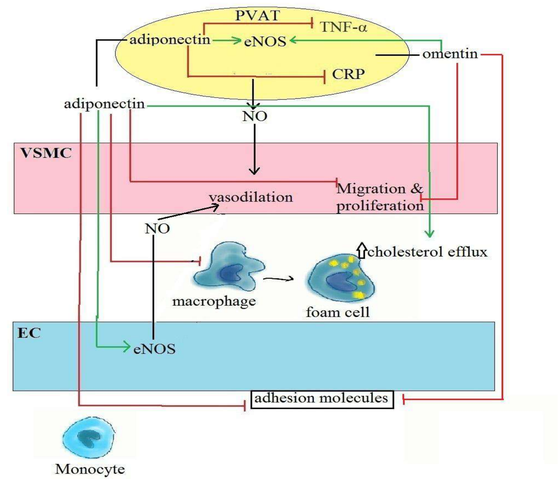
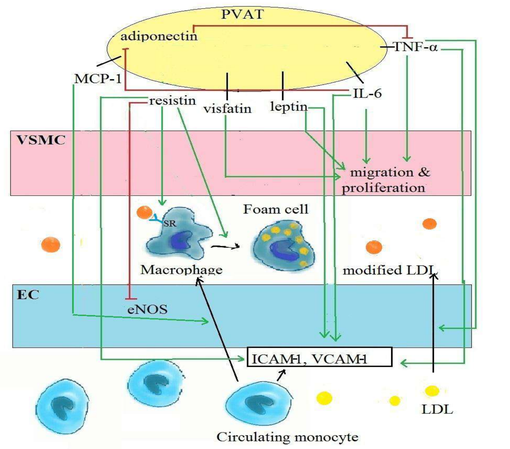


Fig1. Adipokine dysregulation in obesity



PVAT-perivascular adipose tissue
EC-endothelial cells; CRP-C-reactive protein
VSMC-vascular smooth muscle cells;
Green arrows indicate stimulation or upregulation, while red lines indicate inhibition or downregulation

Fig.2 Atheroprotective properties of PVAT- derived factors under physiological conditions.



PVAT-perivascular adipose tissue;
EC-endothelial cells; SR-scavenger receptor
VSMC-vascular smooth muscle cells;
Green arrows indicate stimulation or upregulation, while red lines indicate inhibition or downregulation

Fig.3 Role of dysfunctional PVAT-derived adipokines in atherosclerosis development.

Results

The main adipokines secreted by the adipose tissue are the proinflammatory cytokines IL-6 and TNF-α, the chemokines IL-8 and monocyte chemotactic protein-1 (MCP-1) and the hormones leptin, resistin, visfatin, and adiponectin. Those factors can target distant organs such as the hypothalamus, liver, skeletal muscle and vessels and regulate a plethora of processes such as appetite, endothelial function, insulin sensitivity, blood pressure and inflammation.

Under physiological conditions PVAT, surrounding large arteries and veins, small and resistance vessels, and skeletal muscle microvessels, through the secretion of factors such as adiponectin, omentin-1, vaspin and NO, has potent atheroprotective properties (Figure 2).

Despite the fact that the former is mainly secreted by the adipocytes, its concentration is inversely correlated with the adipose tissue mass. Adiponectin prevents endothelial cells apoptosis and improves endothelial function by activating eNOS. Through paracrine signaling, adiponectin upregulates NO synthesis in adjacent adipocytes, which would later diffuse towards the endothelium. Moreover, it has antiinflamatory properties thus inhibiting the expression of adhesion molecules on endothelial cells and the transformation of macrophages to foam cells. The concentration of adiponectin is positively correlated with the level of HDL cholesterol, the responsible mechanism being the upregulation of ABCA1 (ATP-binding cassette transporter) receptors which promote cholesterol efflux from foam cells.

Obesity, however, is associated with the so-called “obesity triad” consisting of of hypoxia, inflammation and oxidative stress, further leading to a dysregulated production adipokines –a decrease in the secretion of adiponectin, and an increase in the concentration of the proinflammatory adipokines: leptin, resistin, visfatin, IL-6, TNF-α, thus PVAT looses it’s atheroprotective function.

Leptin is an adipokine mainly secreted by adipocytes. Its concentration is directly proportional with the body mass index, and is associated with high levels of C-reactive protein, independently of other risk factors. Leptin is involved in several stages of atherogenesis by increasing oxidative stress, stimulating vascular smooth muscle cells migration and proliferation, promoting calcification and decreasing arterial distensibility. Moreover it is involved in obesity-associated hypertension -another important risk factor for the development of atherosclerosis.

Besides leptin, other adypokines secreted by dysfunctional PVAT such as TNF-α and IL-6 induce endothelial expression of VCAM-1, ICAM-1 adhesion molecules promoting the adherence of monocytes, whilst MCP-1 promotes their recruitment into the intima. The first two adipokines mentioned above also induce the expression of resistin. This hormone, thought to be involved in insulin resistance, induces endothelial dysfunction by inhibiting eNOS and by promoting oxidative stress, which further decreases NO bioavailability. Resistin, as well promotes the proliferation and migration of vascular smooth muscle cells. It is also involved in foam cell formation due to the fact that it stimulates oxLDL uptake by macrophages through the increase in SR-A (scavenger receptor type A) and CD 36 expression- on one hand, and on the other by reducing cholesterol efflux through ABCA1 . More than that, it induces plaque destabilization, increasing the risk of its rupture and consequently, thrombus formation.

Conclusions

Since the discovery of the first adipokine - leptin in 1994, the mechanisms behind the cardiovascular complications of obesity gained a better understanding. Adipose tissue synthesizes a series of pro- and anti-inflammatory factors. Obesity is associated with the dysregulation of this balance with an increase in the inflammatory tone. Besides the direct impact of PVAT and EAT-derived factors on the vascular wall, subcutaneous adipose tissue promotes a state of low-grade chronic inflammation leading to metabolic dysfunction and thus to a proatherosclerotic milieu. Given the extensive data about the implication of adipokines in cardiometabolic syndrome, they might emerge as useful biomarkers of cardiovascular disease.

References

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