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DOI: https://doi.org/10.1177/2047487317746249

European Journal of Preventive Cardiology
Editorial

Adipose tissue macrophage polarization in cardiovascular disease

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Keywords: Adipose tissue macrophage, macrophage polarization, subcutaneous adipose tissue, visceral adipose tissue, cardiovascular disease, peripheral artery disease, flow cytometry, phagocytic, pro-inflammatory, anti-inflammatory, transitional macrophages, cardiovascular predictors, sex, age, hypercholesterolemia

Word count: ±1374
References: 21
Figure: 1

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Of adipocytes and macrophages

Although a link between body weight, obesity and cardiovascular risk is generally accepted, the right way to assess and correlate abdominal fat content to cardiovascular risk factors and mortality rates is still being analyzed and debated in the scientific field[1, 2]. Nonetheless, epidemiological studies revealed that abdominal obesity is positively correlated with various cardiovascular risk factors, including systolic blood pressure and triglycerides levels, in adult man and woman as well as in obese children[3-6]. Moreover, recent studies using computed tomography measured radiodensity demonstrated that the density and hence quality of a specific adipose tissue may be more informative and sensitive to predict cardiovascular risk compared to fat volume and quantity[7-9].

In 1993 the group of Bruce Spiegelman published an important study in which they demonstrated that the adipose tissue directly contributes to systemic inflammation by secreting a pro-inflammatory cytokine, thereby linking obesity to insulin resistance and diabetes[10]. Follow up studies demonstrated that the adipose tissue plays important functions in metabolism and inflammation via secretion of various adipokines, including hormones and inflammatory cytokines. In 2003 two different groups showed that a large contribution of the inflammatory state in adipose tissue is attributable to adipose tissue macrophages (ATMs)[11, 12].

Macrophage polarization in adipose tissue

ATMs derive from blood monocytes, and likely infiltrate the adipose tissue as part on an inflammatory response[13]. Depending on the immune response and environment, macrophages can polarize into different subtypes, ranging from pro-inflammatory to anti-inflammatory macrophages[14]. This polarization is dependent on the interaction with other immune cells, such as T helper cells, but also affected by dietary stimuli. An interesting study demonstrated that leptin-deficient mast cells switch ATMs from a pro- to an anti-inflammatory polarization without altering T cell differentiation[15]. Importantly, dietary cholesterol promotes atherosclerosis and ATM accumulation in atherosclerotic mouse models[16, 17]. Bile acids can also affect the function of ATMs, and pharmacological activation of a bile acid receptor reduced the expression of chemokines in ATMs and prevented atherosclerosis[18, 19].

Adipose tissue macrophage polarization and cardiovascular risk

In a new study Ivana Lesna and colleagues analyzed the association between different ATM populations in subcutaneous (SCAT) and visceral (VAT) white adipose tissues and cardiovascular risk factors (reference). VAT was acquired during cleansing of a kidney, either obtained by transplantation from a living kidney donor or during a peripheral arterial tree reconstruction from patients with peripheral arterial disease. SCAT was acquired from similar sites in both groups.

The ATMs were divided into different polarization groups, ranging from pro- to anti-inflammatory states. In the VAT the authors noted a positive correlation between pro-inflammatory ATMs and age, male sex, and hypercholesterolemia. Transitional ATMs, i.e. macrophages expressing both pro- and anti-inflammatory markers, were also increased in hypercholesterolemia, while the content of anti-inflammatory ATMs was reduced. Importantly, statin treatment reversed the enhanced accumulation of pro-inflammatory and transitional ATMs; which is in line with previous studies demonstrating that statins exerts anti-inflammatory functions in macrophages[20-23]. Notably, the authors did not observe any changes in ATM populations in the VAT related to obesity. However, more pro-inflammatory and less anti-inflammatory macrophages were observed in SCAT of obese patients (Figure). This is rather surprising since VAT has a stronger association with metabolic risk factors[24]. However, adipocytes and other immune cells also contribute to the overall effect of adipose tissues on cardiovascular risk.

Future perspective

The clinical relevance of ATMs with regards to cardiovascular disease remains unclear. Most likely these macrophages exert their major cardiovascular effects indirectly via paracrine and endocrine signaling to regulate metabolic and inflammatory processes in other tissues. A recent study demonstrated that ATMs secrete miRNA-containing exosomes, which in turn affect glucose tolerance and insulin sensitivity[25]. It will be very interesting to determine if the miRNAs secreted by these ATMs also exert direct cardiovascular effects.

Funding

We acknowledge support to SS by the Swiss National Science Foundation (PZOOP3_161521), the Novartis Foundation for medical-biological Research (#16B103), and the Olga-Mayenfisch Foundation.

Conflict of interest

None.

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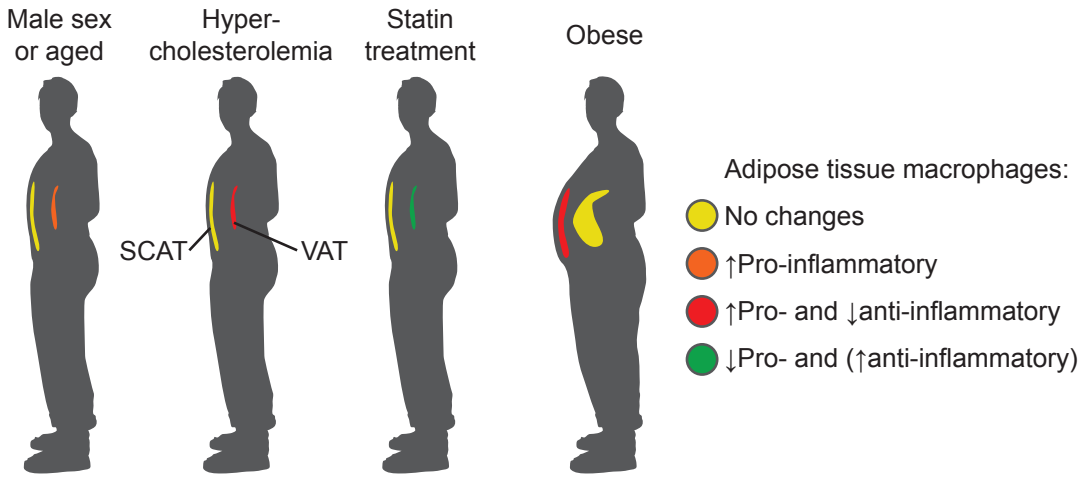

Figure. Scheme illustrating changes in ATM polarization in different patients. SCAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; parenthesis displays a trend; aged, ≥ 51 years.