

DANCE ROUND

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

ADIPOBIOLOGY OF INFLAMMATION

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*Besides its importance for glucose, lipid and energy metabolism, the present paradigm defines adipose tissue as the body's largest endocrine and paracrine organ. Accumulating evidence demonstrates that adipose tissue cells synthesize and release a large number of signaling proteins collectively termed adipokines. Adipokines regulate a broad spectrum of biological processes, with inflammation being a key example. This defines a new field of study: adipobiology of inflammation. Here we shall dance round it, supposing that the pathogenesis of inflammation-related diseases such as atherosclerosis, thyroid-associated ophthalmopathy, inflammatory bowel diseases, and breast cancer may be influenced by competing stimulatory and inhibitory effects mediated by adipokines. This concept may reveal new tools for the development of adipopharmacology of inflammatory disease. **Biomed Rev 2005; 16: 83-88.***

Key words: adipokines, adipose tissue, atherosclerosis, breast cancer, Crohn's disease, ophthalmopathy

INTRODUCTION

In the last decade, the concepts of endocrinology and immunology have been dramatically changed. Previously, endocrine cells have been regarded as the major source of hormones, whereas immune cells – the major source of cytokines and chemokines. However, the adipose tissue may turn out to be at least as important for the secretion of both hormones (1-3) and cytokines (4). The discovery of the adipocyte-secreted cytokine leptin (1) was a trigger for further adipocentric studies on endocrine, paracrine and intracrine functions of adipose tissue. Accumulating basic and clinical studies indicate that adipose tissue cells (adipocytes, matrix cells, stromovascular cells, macrophages, and mast cells) synthesize and release a diverse range of multifunctional

molecules designated adipokines (1-8). Due to recent advance in genomic and proteomic approaches, the secretory proteome of adipose cells (adipokinome) (5) is constantly being enriched with newly identified adipokines (9-16). Further, the whole spectrum of adipose secretory products (secretome) (5) is not limited to adipokines, but also includes non-proteins such as prostaglandins, fatty acids, monobutyrin, and steroid hormones. This intellectual growth process defined a new field of study, adipobiology (16): the study of the molecular and cellular biology of the normal and diseased adipose tissue and related disorders.

Here we present an updated overview of adipobiology of chronic low-grade inflammation in atherosclerotic cardiovascular disease, thyroid-associated (Graves') ophthalmopathy,

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inflammatory bowel disease, and breast cancer. We propose that the pathogenesis of these disorders may be influenced by competing stimulatory and inhibitory effects mediated by adipokines. Adipose-produced inflammation-related non-proteins, such as prostaglandins, steroid hormones and nitric oxide, are out of the scope of present *Dance Round*.

ADIPOSE TISSUE

In humans, particularly well developed is the white adipose tissue. It is partitioned into two large depots (mesenteric and subcutaneous), and many small visceral depots associated with heart, blood vessels, major lymph nodes, ovaries, mammary glands, eyes, and bone marrow. The presence of adipose tissue-associated stem cells throughout life has been revealed; they may differentiate into osteoblasts, chondrocytes, adipocytes, cardiomyocytes, and neural cells (17 and references therein), thus opening novel perspectives for restorative medicine including in diseases herein discussed such as heart failure and fistulising Crohn's disease. Another adipose tissue subtype, brown adipose tissue, is very scarce and probably less functional in adult humans. Through the inner mitochondrial membrane protein uncoupling protein-1, brown adipose tissue is mostly involved in thermogenesis, and less in inflammation.

ADIPOKINES IN INFLAMMATION-RELATED DISEASES

Inflammation is an essential biological response aiming at recovering from injury, wound healing being a paradigm of such a homeostatic phenomenon. However, what begins as a protective response, in excess becomes a damaging process. Hence, the inflammation, and particularly chronic low-grade inflammation, is increasingly recognized as the underlying basis of a significant number of diseases. Recent genomic studies in human white adipose tissue revealed that a panel of pro-inflammatory molecules were upregulated in obese compared to lean subjects (9,10 and references therein). Of note, caloric restriction diet (9) and surgery-induced weight loss (10) improved the inflammatory profile of obese subjects *via* a downregulation of pro-inflammatory and upregulation of anti-inflammatory adipokines. These analyses as well as others (18-23) support the hypothesis that adipose tissue-secreted signaling molecules may be potent modulators of inflammation in various diseases (Table 1). The field of adipobiology of inflammation has thus attracted an increasing attention.

Epicardial adipose tissue and cardiovascular disease

Recently, the paracrine secretory activity of the small visceral

adipose depots has, at long last, become a focus in the adipobiology of inflammation, including in cardiovascular disease. An example of such depot is epicardial adipose tissue (EAT), which may be involved in possible paracrine transmission of protective and/or pathogenic signals targeted to the heart and associated coronary arteries. Epicardial adipose tissue is a visceral fat depot in the heart, especially in the regions of the right-ventricular free wall and left-ventricular apex. This neglected tissue is now appreciated as a potent producer of various inflammation-related adipokines (24-28). An essential subtype of EAT is the subepicardial adipose tissue surrounding the most atherosclerosis-prone portions of the coronary artery, that is, the most proximal part of its left anterior descending branch. Conceptually, the role of an outside-to-inside signaling pathway (perivascular adipose tissue-adventitia-media-intima signaling), recently dubbed vasocrine signaling (29), became at the focus of several recent studies in cardiovascular research (24-33). Vascular processes that could be controlled by such paracrine signals include (i) artery relaxation (30,31 for adipose-derived relaxing factor, ADRF), (ii) smooth muscle cell growth and migration (32), and also (iii) coronary atherosclerosis (24-28) and other heart diseases (through EAT-myocardium signaling). These topics are reviewed by Montani *et al* (32) and Iacobellis *et al* (33). In perspective, using EAT-depleted mice and ADRF-deficient mice may further our knowledge of EAT and perivascular adipose tissue, respectively.

A major lesson learned from these adipocentric studies is that EAT should no longer be neglected in studies of

Table 1. Low-grade inflammatory diseases as related to adipobiology*

Obesity (4,9,10,18,22,59)
Metabolic syndrome (4,21,24)
Type 2 diabetes (29,63)
Atherosclerosis (6,21-28,32,33)
Thyroid-associated ophthalmopathy (35-37)
Inflammatory bowel diseases (38,39,41,58,61)
Mesenteric panniculitis (61)
Nonalcoholic fatty liver disease (59)
Rheumatoid arthritis (62)
Periodontitis (63,64)
Asthma (65)
Chronic obstructive pulmonary disease (66)
HIV-associated adipose redistribution syndrome (67)
End-stage renal disease (68)
Psoriasis (?), Scleroderma (?)

* References are indicated in parentheses.

cardiovascular disease. Accordingly, echocardiographic assessment of EAT could be a simple and practical tool for cardiovascular risk stratification (33). In coronary artery bypass grafting, where the surgeon has to make a decision how to handle the perivascular adipose tissue of the grafted vessel, it should be considered that tissue is a source of ADRF (30,31), whereas perioperative graft vasospasm remains a concern. Further, the human anterior epicardial fat pad that contains parasympathetic ganglia is often dissected during coronary artery bypass surgery. However, preservation of this tissue may decrease the incidence of postoperative arterial fibrillations (34).

Orbital adipose tissue and thyroid-associated ophthalmopathy

Thyroid-associated ophthalmopathy (TAO) has an autoimmune pathogenesis possibly related to the thyrotropin receptor (35-37). The symptoms of TAO result from inflammation/fibrosis and accumulation of orbital adipose tissue. Immunohistochemical analysis of orbital tissue biopsies from TAO patients demonstrates that the thyrotropin receptor is expressed in fibroblast-like cells, accompanied by mast cell infiltrates (35). Further, transforming growth factor- β inhibits whereas interleukin-6 (IL-6) stimulates thyrotropin receptor expression (36), suggesting that the pathogenesis of TAO may be influenced by competing inhibitory and stimulatory adipokine effects within the orbit.

Mesenteric adipose tissue and inflammatory bowel disease

A characteristic feature of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, is mesenteric adipose tissue hypertrophy. Dysregulation of adipokine secretion by this tissue is critically involved in the pathogenesis of IBD. Under healthy conditions, the intestinal mucosa is in a state of "controlled inflammation" regulated by a delicate balance of pro-inflammatory factors, e.g. tumor necrosis factor- α (TNF- α), leptin, interferon- γ , IL-1, IL-6, and IL-12 and anti-inflammatory factors, e.g. adiponectin, IL-4, IL-10, and IL-11 (38; reviewed in 39). The pivotal pathogenic role of TNF- α in IBD is recently targeted in the therapy applying biologicals, for example, infliximab, a monoclonal antibody against TNF- α (38). Further, a recent study demonstrated an enhanced mRNA expression for nerve growth factor (NGF) and its receptor tyrosine kinase A, and an increased NGF-immunoreactivity in intestinal cells in Crohn's disease and ulcerative colitis (40); this calls for similar studies in the inflamed mesenteric adipose tissue in IBD, since NGF is implicated in other inflammatory diseases (5,24). Whether omentin, a recently discovered

adipokine (41), could be embodied in the pathogenesis of IBD remains to be evaluated.

Mammary adipose tissue and breast cancer

It is known that inflammation can promote tumorigenesis. There is compelling evidence indicating that both normal mammary gland development and breast cancer growth depend, in part, on microenvironment of which adipose tissue is a key component (15 and references therein). Recently, Celis *et al* (15) provided the most extensive proteomic analysis of the mammary adipose secretome in high risk breast cancer patients. Adipose fibroblasts are also important cellular component of breast cancer microenvironment. These cells are one of the major extragonadal sources of estrogen secretion in postmenopausal women. The key enzyme in estrogen synthesis is aromatase cytochrome P450 (P450arom) which converts androgens to estrogens. In breast cancer, one of the most aggressive human cancer, intratumoral proliferation of adipose fibroblasts is accompanied by an increased P450arom expression by these cells, leading to proliferation of breast epithelial cells (42). Notably, NGF stimulates breast cancer cell proliferation (43,44), and the antiestrogen drug tamoxifen inhibits NGF-mediated breast cancer cell proliferation through inhibition of NGF TrkA receptor (43). These data suggest a novel, NGF-mediated mechanism in the action of an old drug, tamoxifen, in breast cancer pharmacotherapy. Further, NGF can be produced by both adipocytes (5,15,24) and mast cells (45), and these latter cells commonly associate with breast cancer (46). These findings open possibilities for an adipose NGF-/mast cell-oriented therapy of breast cancer (16), and pressing call for studies on adipopharmacology of this neoplastic disorder.

CONCLUSION

The fattening of humans and the associated emergence of obesity and related diseases are among the major epidemiologic events at present. Their control requires a greater understanding of the pathogenesis of these diseases. Since they are associated with chronic low-grade inflammation affecting adipose tissue, current studies center on the adipobiology of inflammation. Thus adipose tissue is increasingly appreciated as a major source of and target for inflammatory signals. Since the actions of adipokines are complex and diverse, we need to design novel studies to determine how these molecules affect various processes triggered by inflammation. At a mechanistic level, promotion of anti-inflammatory and suppression of pro-inflammatory adipokine-mediated signals may result in an improvement of inflammatory disease therapy (Table 2). *Supposedly*, the present challenge is to cultivate an

Table 2. Adipokines as possible modulators of inflammation*

Anti-inflammatory signals	Pro-inflammatory signals
Adiponectin	Tumor necrosis factor- α
Interleukin-10	Interleukin-1, -6 (?), -18
Interleukin-1 receptor antagonist	Leptin
Transforming growth factor- β	Plasminogen activator inhibitor-1
Nerve growth factor (?)	FIZZ-1**, Resistin (FIZZ-3)
Metallothionein-1,-2	Matrix metalloproteinases
Tissue inhibitor of matrix metalloproteinases	Monocyte chemoattractant protein-1(CCL2) ***
Prohibitin	Interleukin-8 (CXCL8)
Adrenomedullin	Eotaxin (CCL11)
Urocortin	RANTES (CCL5)****
Calcitonin gene-related peptide	

* For references, see the text (2,5,15,16,47-68). Also note that exercise stimulates skeletal muscle endocrine secretion of anti-inflammatory myokines which interact with adipose tissue (56,57), whereas cigarette smoking upregulates pro-inflammatory signals (19). ** FIZZ, found in inflammatory zone, a member of FIZZ family of secreted proteins. *** CCL2, cysteine-cysteine motif chemokine ligand 2. **** RANTES, regulated on activated normal T-cell expressed and secreted.

adipocentric thinking about how we can make adipokines work for the benefit of patients with chronic low-grade inflammatory diseases.

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