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REVIEW

THE ADIPOSE MAST CELL: MASTOKINES AS BINARY MODULATORS OF DISEASE PROCESSES

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Abstract

A paradigm-shifting discovery of the hormone leptin (in the end of 1994) paved the way toward intensive studies on endocrine and paracrine function of the adipose tissue. Onwards, a wide range of signaling proteins collectively termed adipokines were identified as secretory products of adipose cells including mast cells, a "classical" companion of this tissue. The present review addresses the potential translational relevance of adipose paracrine signaling pertinent to various diseases, particularly atherosclerosis, metabolic syndrome, thyroid-associated (Graves') ophthalmopathy, and breast and prostate cancer, with special reference to binary (protective *versus* pathogenic) roles of mastokines, mast cell-derived signaling proteins.

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Keywords: adipose tissue, mast cells, mastokines, adipokines, pathogenesis, inflammation, diseases

Introduction

Adipose tissue has had a long research history, but only in the last three decades the investigations become very intense as related to diseases beyond obesity. Although the birth year of adipoendocrinology may be traced at the identification of adipsin in 1987, the leptin discovery in 1994 (1-3) paved the way toward studies on the adipose tissue endocrine and paracrine function. Adipose tissue, particularly white adipose tissue (WAT), consists of adipocytes, stromal-vascular cells, and associated immune cells including mast cells ("master cells") (4, 5). All these cells contribute to the secretion of a diverse range of signaling proteins termed adipokines (6-12).

In humans, well developed are both the WAT, a major metabolic and secretory organ, and the brown adipose tissue (BAT), a major thermogenic organ. White adipose tissue is partitioned into two large depots (visceral and subcutaneous), and many small depots associated with various organs, including heart,

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blood vessels, major lymph nodes, ovaries, mammary glands, eyes, and bone marrow (Fig. 1).

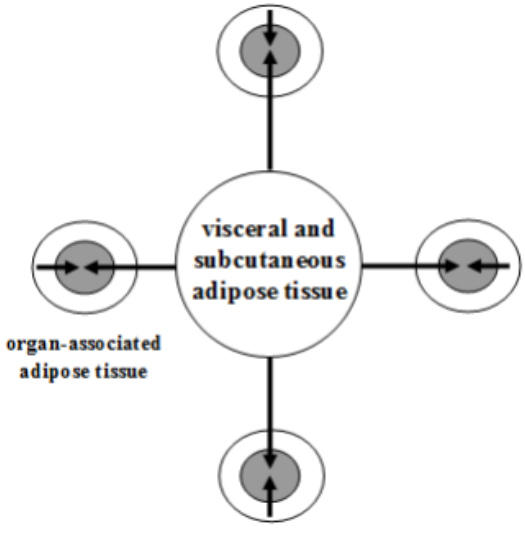

Figure 1. The topography of white adipose tissue. **From:** (6).

Brown adipose tissue can be visualized using ^{18}F-fluorodeoxyglucose, an intravenously administered radioactive glucose analog taken up but not metabolized (by neoplasms and used to delineate metastatic cancers) viewed with positron emission tomography (PET) scans, also localized in BAT by concomitant computed tomography (CT) - PET-CT fusion scans (Table 1).

Table 1. Localization of brown adipose tissue. **From:** (34).

Visceral brown fat
Perivascular: aorta, common carotid artery, brachiocephalic artery, paracardial mediastinal fat, epicardial coronary artery and cardiac veins, internal mammary artery, and intercostal artery and vein
Periviscus: heart, trachea and major bronchi at lung hilum, esophagus, greater omentum, and transverse mesocolon
Around solid organs: thoracic paravertebral, pancreas, kidney, adrenal, liver, and hilum of spleen
Subcutaneous brown fat
Between anterior neck muscles and supraclavicular fossa
Under the clavicles
In the axilla
Anterior abdominal wall
Inguinal fossa

Today, a growing attention has been emerging to the adipobiology of disease, one of the exciting examples being the studies on mast cell-derived signaling proteins collectively designated mastokines (7), multifunctional molecules mediating their effects *via* endocrine and paracrine pathway (8-17).

Herein, we review current data of adipose paracrine signaling in the pathogenesis of "nonclassical" (non-IgE-mediated allergic) mast cell diseases (e.g., atherosclerosis, obesity, metabolic syndrome, thyroid-associated ophthalmopathy, and breast and prostate cancer). Finally, a binary (protective *versus* pathogenic) signature of adipose mastokines in such disease processes is updated (cf. 18).

Mast cells

Mast cells were first described in 1878 by Paul Ehrlich (1854-1915) in his doctoral thesis "*Contribution to the Theory and Practice of Histological Staining*". Ehrlich observed that mast cells were commonly located in connective tissue near blood vessels and nerves, as well as in inflammatory and tumor lesions (reviewed in 15, 16). Mast cells are phenotypically and functionally versatile effector cells that have been traditionally associated with the IgE-mediated allergic response. However, recent studies implicate mast cells in the regulation of infammation, fbrosis, angiogenesis, hemostasis, cancerogenesis, neuroimmune interactions, and browning of WAT (13, 14, 25; also see Lakshmi and Sridhar, and Sridhar and Lakshmi in this volume of *Adipobiology*).

Mastokines: binary nature of signals derived from mast cells

Celsus's description (1st century AD) of inflammation signs includes *rubor et tumor cum calor et dolor*. 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, and if could not be resolved, it is increasingly recognized as the underlying basis of a large number of diseases. Recent studies based on a pangenomic microarray approach in human subcutaneous WAT revealed 100 genes linked to inflammatory processes in obesity (reviewed in 6). These sophisticated analyses support the hypothesis that adipokines, including mastokines (6, 7, 18), may be potent modulators of low-grade inflammation-related diseases such as obesity, type 2 diabetes mellitus, metabolic syndrome, atherosclerosis, thyroid-associated (Graves') ophthalmopathy, and breast and prostate cancer. Accordingly, the field of adipobiology of inflammation has attracted great attention, exemplified by a wealth of evidence which demonstrated that the adipose mast cell is indeed a "master" of protein secretion. Hence, adipose mast cell-secreted proteins may potentially contribute to the whole body of mastokinome (Table 2, Fig. 2).

Adipoparacrinology of disease

The possibility that the endocrine activity of the large adipose depots may directly contribute to the altered blood plasma lev-

Table 2. Selected list of adipose mastokines (adipomastokines)

IL-1, TNF-α, LIF, Chymase, MMP, PAI-1, MCP-1 (CCL2), IL-8 (CXCL8), Eotaxin (CCL11), RANTES (CCL5), FGF, TGF-β, NGF, MCSF, VEGF, HGF, SPARC

Abbreviations: Interleukin-1, Tumor Necrosis Factor-α, Leukemia Inhibitory Factor, Matrix Metalloproteinases, Plasminogen Activator Inhibitors-1, Monocyte Chemoattractant Protein-1 (Cystein-Cystein modif Ligand), Regulated on Activated Normal T-cell Expressed and Secreted, Fibroblast Growth Factor, Transforming Growth Factor-β, Nerve Growth Factor, Macrophage Colony-Stimulating Factor, Vascular Endothelium Growth Factor, Hepatocyte Growth Factor, Secretory Protein Acidic and Rich in Cysteine (also known as Osteonectin, a matricellular protein)

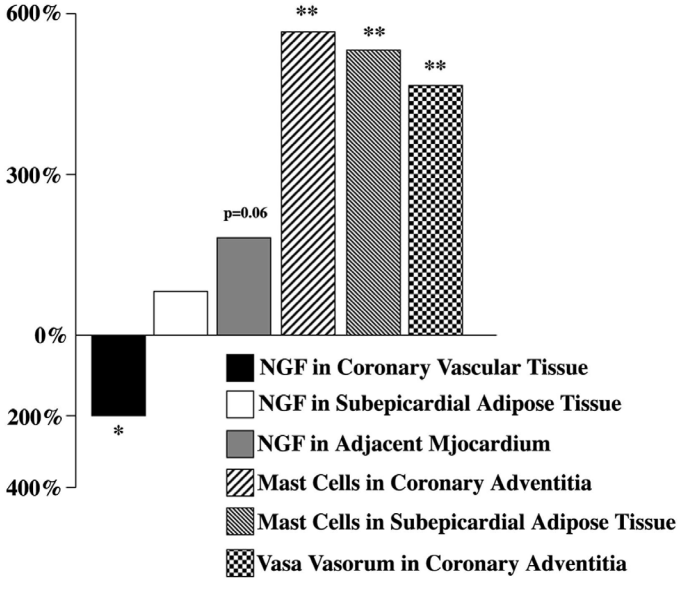

Figure 2. Nerve growth factor, mast cell, and *vasa vasorum* changes in selected human atherosclerotic cardiac tissues expressed as percentage of controls. From: (23).

els of certain adipokines has recently gained considerable attention. Further, the paracrine activity of the small adipose depots has, at long last, become a focus in the adipobiology of disease. Similarly to endocrine products of large adipose depots reaching many organs through the bloodstream, paracrine products of organ-associated adipose depots can affect their neighboring tissues by a variety of adipokines (remind Fig.1). This defines a new field of study: adipoparacrinology (Table 3).

Perivascular adipose tissue and cardiovascular disease

Recently, it was emphasized the importance of investigating the molecular composition of the artery-associated adipose tissue

Table 3. Examples of adipoparacrinology of diseases*

(i)	Epicardial adipose tissue and cardiometabolic diseases
(ii)	Periadventitial adipose tissue (tunica adiposa) and peripheral atherosclerosis
(iii)	Orbital adipose tissue and thyroid-associated (Graves') ophthalmopathy
(iv)	Mammary gland-associated adipose tissue and breast cancer
(v)	Periprostatic and anterior perirectal adipose tissue and prostate cancer
(vi)	Lymph node-associated (perinodal) adipose tissue and Crohn's disease and HIV-associated adipose redistribution syndrome (HARS)
(vii)	Infrapatellar fat pad (Hoffa's fat pad) and osteoarthritis
(viii)	Parasellar region (cavernous sinus)-associated adipose body and brain disorders
(ix)	Peripancreatic adipose tissue and type 2 diabetes mellitus
(x)	Periovarian adipose tissue and ovary gland disorders
(xi)	Epididymal adipose tissue and sexual disorders (?)
(xii)	Retromalleolar adipose tissue and Achilles tendon disorders
(xiii)	Epidural adipose tissue and spinal cord disorders
(xiv)	Subcutaneous adipose tissue and skin diseases

*From: (10). For references (6, 9-54)

as it may yield clues to a possible paracrine transmission of protective and/or pathogenic signals derived from the perivascular adipose tissue (PVAT, *tunica adiposa*) towards the adjacent artery wall (6, 9-12, 19-25). Such an outside-to-inside signaling could lead to obesity-related insulin resistance and various vascular disorders. Phenotypically, healthy PVAT is composed of the thermogenic brown and beige adipocytes. However, recent data suggest a loss of PVAT thermogenic phenotype during the metabolic syndrome in a process called "PVAT whitening" that is a pathogenic event (54).

An intriguing example of PVAT is the epicardial adipose tissue (EAT) that is conjunctioned to the adventitia of the most atherosclerosis-prone portions of the coronary artery, that is, the most proximal part of its left anterior descending (LAD) branch. Specifically, recent findings demonstrate: (i) the portion of the LAD coronary artery running in the EAT develops atherosclerotic lesions, while the portion running in the myocardium is free of atherosclerotic lesions, (*ii*) the "atherosclerotic" EAT exhibits reduced levels of adiponectin, an anti-inflammatory and anti-atherosclerotic adipokine, whereas elevated levels of MCP-1/CCL2, IL-1β, IL-6, TNF-α, and NGF, and *(iii)* the presence of inflammatory cell infiltrates, including mast cells, lymphocyte, and macrophages (reviewed in 19-25, 34-38).

Whatever changes occur in EAT, little is known of whether

they can be causally associated with atherogenesis or whether they are a paracrine reaction to the injury developing within the artery wall, particularly in the adventitia.

Orbital adipose tissue and thyroid-associated (Graves') ophthalmopathy

Thyroid-associated ophthalmopathy (TAO) has an autoimmune pathogenesis possibly related to the thyrotropin receptor. The symptoms of TAO result from inflammation and fibrosis and accumulation of orbital adipose tissues. Immunohistochemical analysis of orbital tissue biopsies from patients with TAO demonstrates that the thyrotropin receptor is expressed in fibroblast-like cells, accompanied by mast cell infiltrates. Further, TGF-β inhibits whereas IL-6 stimulates thyrotropin receptor expression, suggesting that the pathogenesis of TAO may be influenced by the binary effects of mastokines within the orbital adipose tissue. One study examined 2,686 genes, of which 25 known genes were upregulated in TAO orbital tissues, whereas 11 genes were downregulated. Upregulated genes included secreted frizzled-related protein-1 (sFRP-1) and several adipocyte-related genes, including peroxisome proliferator activated receptor-gamma (PPAR-γ) and adiponectin. Treatment of TAO orbital preadipocytes *in vitro* with recombinant sFRP-1 significantly increased their adiponectin and leptin secretion. These results support the hypothesis that orbital adipogenesis is enhanced in TAO and suggest that elevated local expression of sFRP-1, adiponectin and/or PPAR-γ may contribute to its pathology (18, 43-45 and Refs therein).

Breast cancer

Studies on breast cancer have revealed a significant correlation between increased angiogenesis and metastasis. Among cellular and molecular regulators of these processes, mast cells, nerve growth factor (NGF) (27, 28) and vascular endothelial growth factor (VEGF) are correlated with tumor progression and prognosis in breast cancer (reviewed in 6, 18, 31-33). Accordingly, the binary role of mast cells, in terms of both pro- or anti-cancer activity, should be considered.

Further, 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. Interestingly, the mammary gland microenvironment during postlactational involution shares similarities with inflammation, which is promotional for tumor cell dissemination during involution, thus providing a plausible mechanism to explain the high rate of metastases that occur with pregnancy-associated breast cancer.

Adipose fibroblasts are another important cellular component of breast cancer microenvironment. These cells, being *bona fide* steroidogenic cells, are one of the major extragonadal sources of estrogen secretion. Estrogen synthesis is mediated by the enzyme aromatase cytochrome P450 (P450arom) which converts androgens to estrogens. In breast cancer, one of the most aggressive human cancer, intratumoral proliferation of breast adipose fibroblasts is accompanied by an increased P450arom expression by these cells, leading to proliferation of breast epithelial cells. Further, breast cancer commonly associates with a comprised immune, especially mast cell, response. Notably, both adipocytes and mast cells produce various adipokines and mastokines known to upregulate aromatase expression. Noteworthy, the mast cell-derived protease tryptase is a potent stimulator of fibroblast proliferation as well as a potent angiogenic factor. A novel piece to the puzzle of breast cancer is that NGF stimulates breast cancer cell proliferation in a manner comparable to that of other breast cancer-associated growth factor, such as epidermal growth factor. Importantly, the antiestrogen drug tamoxifen inhibits NGF-mediated breast cancer cell proliferation through inhibition of TrkA receptor. These data suggest a novel, NGF-mediated mechanism in the action of an old drug, tamoxifen, in breast (and prostate?) cancer pharmacotherapy as discussed previously (6, 46). Notably, NGF can be produced by both mast cells (27, 28) and adipocytes (10, 23, 24, 46). Together these findings open possibilities for an adipose NGF-mast cell-oriented therapy of breast and prostate cancer, and pressingly call for specific studies on adipopharmacology of these neoplastic disorders (31-33, 46, 47, 51).

Conclusion

Adipose tissue is a major source of and target for inflammatory signals, mast cells being its essential component. However, to fill the gaps in our knowledge of adipobiology of mast cells, further studies aimed at pursuing mast cell secretory pathways should be scheduled. Notably, recent study shows that activated human mast cells synthesize and release large amount of functionally active plasminogen activator inhibitor type 1 through nonconventional secretory pathway, using endosome-mediated secretion (55). Further, comparing the biological responses of wild-type mice with those of genetically engineered knock-out mice may provide new insights into adipose mast cells in health and disease.

Mechanistically, promotion of anti-inflammatory and pro-resolving and/or suppression of pro-inflammatory mastokine-derived signals (Table 3) may result in an improvement of inflammatory disease therapy.

The present challenge is thus to cultivate an adipocentric

Table 3. Examples of mastokines as possible binary modulators of inflammation

Anti-inflammatory	Pro-inflammatory
Adiponectin	Tumor necrosis factor-α
Inteleukin-10	Interleukin-1, -6, -18
Nerve growth factor	Leptin
Transforming growth factor-β	Plasminogen activator inhibitor-1
Interleukin-1 receptor antagonist	Matrix metalloproteinases
Tissue inhibitor of matrix metalloproteinases	Resistin
Prohibitin	Monocyte chemoattractant
Ciliary neurotrophic factor	Interleukin-8 (CXCL8)
Adrenomedullin	RANTES (CCL5)
Metallothionein-1,-2	Eotaxin (CCL11)
Pro-resolving lipid mediators*	
Resolvins	

* Specialized pro-resolving lipid mediators are part of a large family of resolvins (RvE1-RvE3 and RvD1-RvD6) and related molecules, such as arachidonic acid-derived lipoxins (LXA4 and LXB4), protectins, and maresins (56).

thinking about how we can make mastokines work for the therapy of patients. It is our belief that we should stay much in collaboration to effectively achieve that goal.

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Conflict of interest statement

The authors declare that no conflicts of interest exists.

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