



# THE MAST CELL: ANOTHER MASTER IN ADIPOIMMUNOLOGY

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## Abstract

Recently, a large number of studies focus on (i) adipose tissue endocrine and paracrine function, and (ii) adipose-immune interactions herein referred to as adipoimmunology. In effect, a wide range of signaling proteins, dubbed adipokines, was identified as endocrine and paracrine secretory products of adipocytes and associated stromal vascular cells, including macrophages, lymphocytes and mast cells, the latter being less evaluated as compare to the formers. During obesity immune cells migrate into adipose tissue and inflame it by the secretion of a large amount of adipokines and thus trigger the development of so-called low grade inflammation-related diseases. Based on Steve Galli's concept of mast cell as *master cells* in many biological and pathological processes (*New Engl J Meet* 1993; 328:257-265), here we highlight recent studies on the significance of adipose mast cells in the pathogenesis and therapy of cardiometabolic diseases (atherosclerosis, obesity, type 2 diabetes mellitus, metabolic syndrome) and breast cancer. Knowledge of the master work of these cells may provide a background for mast cell-targeted pharmacology for low grade inflammation-related diseases.

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**Key words:** adipose tissue, adipokines, atherosclerosis, breast cancer, inflammation, mast cells, obesity

## Introduction

In the last 20 years there is an increasing attention to the adipobiology of various diseases, one of the most exciting examples being the rapidly growing interest in understanding the adipose tissue secretion of multifunctional signaling proteins collectively designated adipokines (1-3). These molecules, *via* endocrine and paracrine way, are potent modulators of many biological processes including metabolism, inflammation, immunity, vascular contractility, and cell proliferation (4-17).

Here we review current data of adipose tissue paracrine signaling in the pathogenesis of low grade inflammation-related diseases, with special reference to the possible involvement of adipose mast cell's secretion of mastokines (mast cell-derived adipokines). This may provide basis of mast cell-targeted adipopharmacology (18-22).

## Adipose tissue

Adipose tissue is a cellular and extracellular matrix assembly composed of adipocytes, fibroblasts, immune cells and matrix components, also rich in sympathetic nerve fibers, blood vessels, and

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stem cells. In humans, particularly well developed is the white adipose tissue (WAT), a major metabolic and secretory organ. Human WAT is partitioned into two large depots (visceral and subcutaneous), and many small depots associated with various organs, including heart, blood vessels, major lymph nodes, pancreas, ovaries, bone marrow, eyes, prostate, and mammary glands. White adipose tissue may grow and shrink dramatically to meet the energetic needs of an organism. However, severe metabolic and inflammatory consequences can result from excessive WAT accumulation, featuring cardiometabolic diseases (CMD). Adipoimmunology of brown adipose tissue is out of the scope of present review.

Lean adipose tissue is populated with resident immune cells, which maintain tissue homeostasis through the secretion of adipokines that polarize adipose tissue macrophages (M) in an anti-inflammatory phenotype, M2 state. Diet-induced obesity is associated with the loss of tissue homeostasis and development of type 1 inflammatory responses in WAT expressed by pro-inflammatory M1 phenotype (5, 9, 12-15).

### Adipokines: new players in inflammation and immunity

Celsus's description (1<sup>st</sup> century AD) of inflammation feature 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, hence the inflammation is increasingly recognized as the underlying basis of a significant number of diseases. Recent genomic studies in human WAT revealed that a panel of inflammatory molecules was upregulated in obese compared to lean subjects (2, 3). These molecules are secretory products of adipocytes and associated stromal vascular cells, including macrophages, lymphocytes and mast cells. Of note, calorie restriction diet improved the anti-inflammatory profile of obese subjects *via* increase of anti-inflammatory and decrease of pro-inflammatory molecules. Further, weight loss resulted in decrease of adipose-associated immune cells and increased production of anti-inflammatory adipokines (7, 9-17). Such a sophisticated biology supports the hypothesis that adipokines may indeed be potent modulators of low grade inflammation associated with atherosclerosis, obesity, type 2 diabetes, metabolic syndrome, inflammatory bowel diseases, thyroid-associated (Graves') ophthalmopathy, breast cancer, and non-alcoholic fatty liver disease, to list some of many examples (1, 7, 9-18). Accordingly, the field of adipoimmunology of disease has attracted great attention, exemplified by the rapidly growing interest in understanding the adipose tissue protein secretion (4, 5, 7, 22, 24-26).

### 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" (4, 23 and references therein). Ehrlich observed that mast cells were commonly located in connective tissue near blood vessels and nerves, as well as in inflammatory and tumor lesions. Mast cells are phenotypically and functionally versatile effector cells that have been traditionally associated with the immunoglobulin E-mediated allergic response. However, recent studies implicate these cells in the regulation of inflammation, fibrosis, angiogenesis, hemostasis, cancerogenesis, and neuroimmune interactions (4, 7, 8, 18, 23-28), which could associate with various low grade inflammatory diseases.

### Adipose mast cells

Accumulating evidence demonstrates that the adipose mast cells could also be Galli's *master cells* (also see 8) in the secretion of multifunctional biomolecules herein referred to as mastokines (mast cells-derived cytokines/adipokines; Table 1). Their Yin-Yang (4, 7), dual (8) regulatory activity should also be considered in adipoimmunology. At present, the study on adipo-biology of mast cells is, however, limited as compared to that on other types of immune cells. PubMed search using the key words "adipose tissue and mast cells" up-regulates 162 articles in period between 1963 – December 2015, while "adipose tissue and macrophages" – 2539 articles, "adipose and lymphocytes" – 1171 articles.

**Table 1.** Selected list of adipose-derived mastokines

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Leptin, IL-1, IL-4, TNF- $\alpha$ , LIF, MCP-1 (CCL2), IL-8 (CXCL8),  
Eotaxin (CCL11)  
RANTES (CCL5), FGF, TGF- $\beta$ , NGF, CNTF, MCSF, VEGF, HGF  
Chymase, Tryptase, MMP, PAI-1, NO, VIP, Heparin, Histamine

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Abbreviations: IL, interleukin; TNF-alpha, Tumor Necrosis Factor- $\alpha$ ;  
LIF, Leukemia Inhibitory Factor; MCP, Monocyte Chemoattractant  
Protein-1 (Cystein-Cystein modif Ligand); RANTES, Regulated on  
Activated Normal T-cell Expressed and Secreted; FGF, Fibroblast  
Growth Factor; TGF- $\beta$ , Transforming Growth Factor-beta;  
NGF, Nerve Growth Factor; CNTF, Ciliary Neurotrophic Factor;  
MCSF, Macrophage Colony-Stimulating Factor; VEGF, Vascular  
Endothelium Growth Factor; HGF, Hepatocyte Growth Factor; MMP,  
Matrix Metalloproteinase; PAI, plasminogen activator inhibitor; NO,  
nitric oxide; VIP, vasointestinal peptide

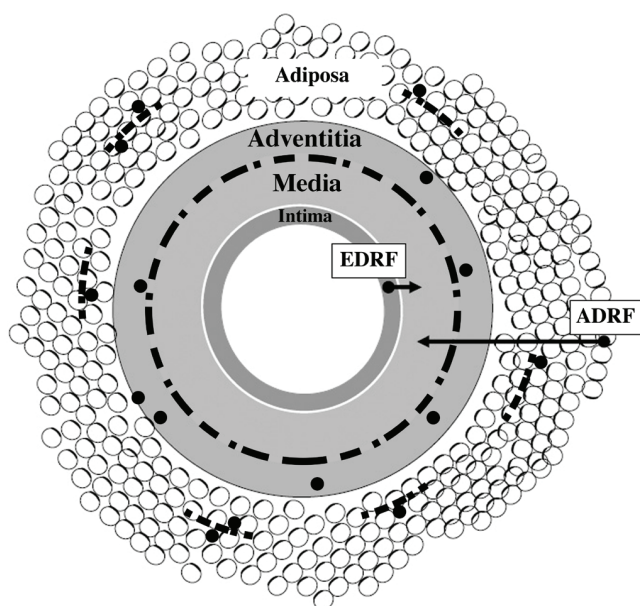
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## Adipoimmunology of cardiometabolic disease

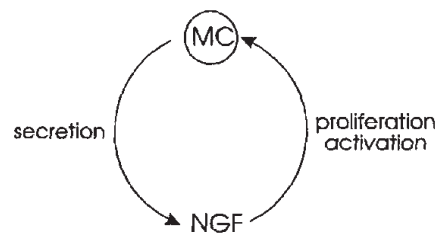
The possibility that the endocrine secretory activity of large adipose depots may directly contribute to the altered blood levels of certain adipokines has recently gained considerable attention in studying obesity, type 2 diabetes and metabolic syndrome, examples of CMD (1, 7, 18, 24, 25, 29-31). Further, the paracrine secretory activity of periadventitial adipose tissue has also become a focus in the pathobiology of another part of CMD – atherosclerosis and hypertension (18, 26-28).

A long standing paradigm holds that the vascular wall is composed of three concentric tissue coats (*tunicae*): intima, media, and adventitia. However, large- and medium-sized arteries, where usually atherosclerotic lesions develop, are consistently surrounded by periadventitial adipose tissue, which was recently designated *tunica adiposa* (in brief, adiposa like intima, media, and adventitia) (26 and references therein).

Neuro-immune-adipose interactions are illustrated in Figure 1 (also see Fig. 2 for neuro-immune link).



**Figure 1.** Schematic presentation of vascular wall composed of four tissue coats (*tunicae*): intima, media, adventitia, and adiposa. Arrows show that *tunica media* is a target for at least two vasorelaxing factors, endothelium-derived relaxing factor (EDRF) and adipocyte-derived relaxing factor (ADRF) respectively. Discontinuous black line positioned at the adventitia-media border illustrates perivascular nerves. Small-sized discontinuous black lines located in *tunica adiposa* indicate adipose nerves. Black granules (except those linked to arrows) illustrate immune cells - their association with nerves and adipocytes is also depicted. From (26).



**Figure 2.** Mast cells (MC) are source of and target for nerve growth factor (NGF). From (4; also see 24, 25, 38).

## Adipoimmunology of 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. Adipose fibroblasts are thus 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 (CYP19) 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 CYP19 expression by these cells, leading to proliferation of breast epithelial cells (7, 18 and references therein). Further, breast cancer commonly associates with a prominent immune, especially mast cell, response. Notably, both adipocytes and mast cells produce various adipokines known to upregulate aromatase expression. And, adipose- and mast cell-derived tryptase is a potent stimulator of fibroblast proliferation (4) as well as a potent angiogenic factor (see 7, 18).

A novel piece to the puzzle of breast cancer is that nerve growth factor (NGF), a neurotrophin known to be produced by mast cells (24, 25) as well as adipocytes (32), stimulates breast cancer cell proliferation (see 7, 18). Importantly, the antiestrogen drug tamoxifen inhibits NGF-mediated breast cancer cell proliferation through inhibition of the Trk-A receptor (see 7, 18). These data suggest a novel, NGF/mast cell-mediated mechanism in the action of an old drug, tamoxifen, in breast cancer pharmacotherapy. Together these findings open possibilities for an adipose NGF/mast cell-oriented therapy of breast cancer, and pressing call for specific studies on both adipoimmunology and adipopharmacology of this neoplastic disorder. Noteworthy, an elegant study by Julio Celis and colleagues (33) provided the most extensive proteomic analysis of the mammary adipose secretome in high risk breast cancer patients.

## Coda

Adipose tissue is a major source of and target for inflammatory and fibroproliferative signals, mast cells being their master producer. It is worth concluding that adipocytes and mast cells both share several biological features in common: (i) they are *bona fide* secretory cell types, (ii) they secrete a wide range of same signaling molecules, and (iii) they are implicated in the pathobiology of various low grade inflammatory diseases. Further investigations aimed at pursuing cell-to-cell communications *via* adipose mast cell-derived extracellular vesicles (exosomes and ectosomes) (34-36) may bring a novel insight in adipoimmunology. And may prove whether adipose mast cells stand indeed as a master in this research field (8, 23-26, 37, 38).

## Conflict of interest

The authors declare no conflict of interest.

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