EDITORIAL

OBESITY, INFLAMMATION AND NEUROLOGICAL ALTERATIONS

E. SPINAS[1], A. SAGGINI[2], S.K. KRITAS[3], G. CERULLI[4], A. CARAFFA[5], P. ANTINOLFI[5], A. PANTALONE[6], A. FRYDAS[7], M. TEI[4], A. SPEZIALI[4], R. SAGGINI[8] and P. CONTI[9]

[1] Department of Surgery and Odontostomatological Sciences, University of Cagliari, Italy; [2]Department of Dermatology, University of Rome Tor Vergata, Rome, Italy; [3]Department of Microbiology and Infectious Diseases, School of Veterinary Medicine, Aristotle University of Thessaloniki, Macedonia, Greece; [4]Nicola's Foundation, Onlus, Arezzo, Italy; [5]Orthopedic Division, University of Perugia, Perugia, Italy; [6]Orthopedic Division, University of Chieti-Pescara, Chieti, Italy; [7]Aristotelian University, Thessaloniki, Greece; [8]Department of Neurosciences and Imaging, Faculty of Medicine and Surgery, G. d'Annunzio University Chieti-Pescara, Chieti, Italy; [9]Immunology Division, Medical School, University of Chieti-Pescara, Chieti, Italy.

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Inflammation, neurodegeneration, imbalance of neurotransmitter systems, oxidative stress and depression are all risk factors for obesity. There is evidence regarding the cross-talk between adipose tissue and the immune system and obese patients may show an alteration of immune functions with major depression, including immune suppression with reduced T-cell and macrophage activity. Obesity is mediated by inflammatory cells such as lymphocytes, macrophages and mast cells which release pro-inflammatory cytokines and chemokines. Obesity-induced leukocyte infiltrations in adipose tissue cause cytokine/chemokine release and inflammation. Here, we report the relationship between obesity, neurological alterations and inflammation.

Considerable research and clinical evidence exists regarding the cross-talk between adipose tissue and the immune system (1). LDL cholesterol and cholesteryl ester are associated with obesity, atherosclerosis and cardiovascular diseases which present narrowing of the artery, predisposition to thrombosis, calcifications, weakening of the muscle and inflammation. Inflammation, neurodegeneration, imbalance of neurotransmitter systems, oxidative stress and depression are all risk factors for obesity (2). Depressed patients may show an alteration of immune functions with major depression including immune suppression with reduced T-cell and macrophage activity, inflammatory activity and obesity. Therefore, prolonged exposure to stressful events, which result in chronic elevation of glucocorticoids and corticotropin-releasing hormone (CRH) release, have been associated with depression and obesity (3). CRH is generated by mast cells and released by the hypothalamus, stimulates the anterior pituitary gland and adrenocorticotropic hormone (ACTH). Therefore, the glucocorticoids upregulated by ACTH, are opposed to the stress and regulate neuronal transmission and synaptic plasticity (4). An excessive increase of glucocorticoid levels are associated with the risk of depressive disorders. It is well known that depression and anxiety are co-morbidities of obesity and a functional defect of

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Mailing address: Prof. Enrico Spinas,
Department of Surgery and Odontostomatological Sciences,
University of Cagliari,
Cso Vittorio Emanuele 340,
09123 Cagliari, Italy
Tel.: +39 330412295
e-mail: enricospinas@tiscali.it

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the central nervous system (CNS) which is linked to obesity that in turn impacts mental and physical health (5). On the other hand, obesity is linked to an increased risk of developing depression. In experimental animal model, injection of inflammatory interleukin (IL)-1 shows an augmentation of CRH in hypothalamic neurons which may mediate depression (6). It is well known that depression is related to obesity where pro-inflammatory cytokines such as IL-1, TNF and IL-6 are involved and play an important role (7). Thus, obesity is characterized by increased levels of circulating pro-inflammatory cytokines such as IL-1 beta (an immunoregulatory cytokine which requires cleavage with caspase-1 to become active), TNF, and IL-6, accumulation of leukocytes within the adipose tissue, activation of macrophages in the fat, and activation of pro-inflammatory signaling pathways (8). Lymphocytes, and macrophages, as well as endothelial cells, secrete cytokines and growth factors that promote the migration and proliferation of smooth muscle cells.

The transcription and translation of pro- and anti-inflammatory mediators are influenced by various factors such as rheumatic diseases, myocardial infarction, angina, aging, and obesity.

TNF is a powerful inflammatory cytokine that causes lipolysis in adipose tissue. These pro-inflammatory cytokines induce activation of intracellular signaling molecules including Janus Kinases (JAK), c-Jun N-terminal Kinase (JNK), p38, ERK, Signal Transducer and Activator of Transcription (STAT), and nuclear factor-κB (NFkB) (9). In several diseases, such as autoimmunity and cancer, the patient presents depression most probably mediated by elevated inflammatory cytokines, confirming that inflammation is one of the major risk factors for depression and obesity. Proinflammatory cytokines released by several immune cells can access the brain and induce the activation of neuroinflammatory processes. Chronic inflammation may represent a triggering factor in the origin of the metabolic syndrome: stimuli such as over-nutrition, physical inactivity, and aging would result in cytokine hypersecretion. In addition, adipocytes of all differentiation stages spontaneously secrete IL-18, supporting the concept that these cells participate in innate immunity and that IL-18 mediates a fraction of the complications of obesity such as atherosclerosis, cardiovascular and inflammatory diseases (10).

Selectins, integrins and chemokines mediate and favor the action of the inflammatory cells such as adherent leukocytes, diapedesis, migration and chemotactic stimulus (11).

In the brain, proinflammatory cytokines damage neuroendocrine activity, and neurotransmitter function, involving notably the hippocampus, the hypothalamus, and the basal ganglia (12). These brain alterations lead ultimately to the development of behavioral and neuropsychiatric symptoms. The majority of patients undergoing therapeutic treatments with cytokines have fever and depression (13). Therefore, the use of antidepressant, anti-cancer and flavonoids which are a potential drugs for improvement of neural processes, can give relief. Research has reported that flavonoids such as luteolin and quercetin have neuroprotective effects against cell death, contribute to maintaining cell viability and regulation of synaptic function and antagonize anti-inflammatory cytokines (14). Th1 cytokines are directly involved in inflammation, while those Th2 may have an anti-inflammatory action since they produce IL-10, IL-4 and IL-13. In addition, administration of cytokine antagonists, such as IL-1 receptor antagonist (IL-1ra), or anti-inflammatory cytokines such as IL-4 or IL-10, can block the behavioral effects of treatment with pro-inflammatory compounds in experimental animal model (14), even though cytokine-mediated depressive-like behaviors remain a controversial issue and the mechanisms by which inflammatory cytokines are increased during obesity is still unclear (15). As mentioned above, in adipose tissue there is an accumulation of immune cells such as TH2 cells, macrophages, T_{reg} cells, eosinophils, mast cells and rare neutrophils. The role of macrophages in adipose tissue inflammation has been clearly demonstrated (16). Macrophages which participate in the innate immunity during host defense, play a physiological and pathological state in adipose tissue. Most resident macrophages are M2 macrophages that contribute to inflammation but also may have anti-inflammatory properties since they generate IL-10 (17); while M1 macrophages mediate inflammation by generating pro-inflammatory cytokines such as IL-1, TNF, and

IL-6 (18). Th2 cells and eosinophils, sustain the M2 activation of macrophages through secreting IL-4 and IL-13.

Obesity-induced macrophage infiltration into adipose tissue causes cytokine/chemokine release and inflammation. CCL2 (MCP-1) a representative CC chemokine is increased in adipose tissue and participates in the recruitment and infiltration of macrophages which mediate inflammatory processes (19).

Mast cells can be activated to release potent mediators of inflammation by antibody-dependent mechanisms, and they have been known to amplify inflammatory responses to antigen challenge (20). Mast cell mediators are either contained within secretory granules or can be synthesized de novo and can be released upon activation by either a massive degranulation, or by a selective release of specific molecules (21). Mast cells can be also activated by bacterial or viral antigens, cytokines, growth factors, and hormones, leading to differential release of distinct mediators without degranulation (22-23). They are also involved in obesity-induced adipose tissue inflammation by generating their biological mediators such as IL-6 and IFNγ (19).

It has been reported in experimental animal model that lack of mast cells gives resistance to diet-induced obesity and show reduced inflammatory responses (24).

A number of treatments have been used to decrease adipose tissue inflammation, one of which is with statins (25). Statin therapy is associated with absolute reduction in LDL cholesterol and in the risk of myocardial infarction or death from cardiovascular causes, but still a number of individuals treated with these drugs suffer from cardiovascular and circulatory diseases (26). Omega-3 polyunsaturated fatty acids (ω-3 PUFA) from fish oil have also anti-inflammatory properties and therapeutic effects in inflammatory states including obesity (27). One of its actions is to inhibit the generation of MCP-1 which has a potent chemotactic effect on both mast cells and macrophages (28) and regulate leukocyte trafficking to tissue sites of inflammation.

However, these studies demonstrate once again a clear cross-talk between the immune system and adipose cells but the true role of immune cells in the metabolism and generation of adipose tissue has yet to be determined.

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