


**Opinion**

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# From Psychoneuroimmunology to Immunometabolism: a New Reading for Oral Emerging Pathologies



**Flora Ippoliti\***

*Sapienza University, Rome Italy*

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**\*Corresponding author:** Flora Ippoliti, Department of Experimental Medicine, Associate Professor, Sapienza University, Rome Italy, Email: flora.ippoliti@uniroma1.it

## Opinion

Gingivitis and periodontitis are the two most common forms of oral emerging pathologies and recently the attention of researchers has focused on the relationship between above-mentioned local pathologies and systemic chronic diseases. Especially several case-control and cohort studies have reported the contribution of obesity and type 2 diabetes due to their alarming spread in our western societies [1]. This evidence suggest that destructive periodontal disease is linked to obesity and metabolic syndrome, as an example of interorgan crosstalk under inflammatory conditions [2,3].

Psychoneuroimmunology deals with the wide relationship between organism and the environment through the study about stress, the immune system and particularly psychosocial stress [4] often associated with a lifestyle (night work, inadequate nutrition, forced sedentary, etc.) induces, in the long term, activation of the immune system with secretion of inflammatory substances, cytokines and neuropeptides, leading to health consequences [5]. Such molecules are indispensable and useful in connecting the “periphery” to the Central Nervous System. In this way, activation of the immune response is defined as “acute neurogenic inflammation”, which must have its resolution within 28-30 days. This does not happen if the stress stimulus persists and activates a chronic inflammatory response that is the source of the onset of the above-mentioned systemic pathologies [5].

Communication between the immune system and the brain is vital for controlling inflammation by the inflammatory reflex in which afferent Vagus nerve signaling, activated by cytokines is functionally associated with efferent vagus nerve-mediated output (cholinergic anti-inflammatory pathways). Vagus nerve signaling has an important role in the regulation of feeding behaviour and metabolic homeostasis. This regulation retains energy balance and prevents fluctuations in body weight and metabolism [6,7]. The organs with high density receptors for

neuropeptides, such as the lung and the intestine, are much more susceptible to stress and neurogenic inflammation. The latter is closely associated with non-myelinated fibers of sensory nerves called fibers C also present in the dental pulp. Its neuropeptides involved in the nociceptive process are the substance P (SP), neurokinins A and B, somatostatin [8]. SP increases in the brain in response to numerous and different types of stress-induced psycho-social stimuli and especially in times of anxiety. Well then, all this contributes to the risk of periodontal disease for which once again inflammation is the main and common pathogenetic cause [9].

During psychological stress the brain demands extra energy from the body and a persistent cerebral energy crisis contributes to systemic malfunction. These neuroenergetic alterations promote visceral fat accumulation, subcutaneous fat loss, with subsequent dysmetabolic events [10]. More and more evidence indicates that stress induces an alteration in the energy balance of our organism. In fact, some structures of the limbic system, responsible for the perception of our emotions, are connected through specific nerve pathways to the hypothalamic centers of hunger and satiety that control the daily metabolic activity, influencing its function. For the same reason, individuals suffering for stress seek pleasure from comfort food and they consume high amounts of cariogenic foods [11]. In fact they are eating too much and badly, prefer high-fat and high-carbohydrate meals that stimulate and trigger a vicious cycle leading to fat accumulation, especially visceral fat and several lines of evidence indicate that vagus nerve activity could be impaired in obesity and especially in stressed patients where the balance of the vagus / sympathetic system is completely impaired [5,6,12].

Adipose tissue should be considered as an endocrine organ with high metabolic activity. Its cells, adipocytes, produce and secrete many proteins, adipokines, acting by real hormones responsible for energy regulation, and their production depends

on the typology of adipose tissue: subcutaneous or visceral fat. Indeed, in healthy individuals the synthesis of anti-inflammatory adipokines, such as adiponectin prevails, while in stressed individuals with alterations in lean mass and fat mass, pro-inflammatory adipokines such as Leptin, IL-1 $\beta$  or TNF- $\alpha$  are prevalent [12]. TNF- $\alpha$  is one of the key periodontal pathogens-induced early inflammatory cytokines in destructive periodontal disease [3,13]. In this regard, we recall that hypernutrition states alter the cross-talk between immune system and metabolism regulation with increased serum levels of pro-inflammatory cytokines, adipokines and other inflammatory markers.

The excess of these molecules contributes to determining that state of *low chronic inflammation*, which is the common denominator not only of obesity and type 2 diabetes, but also of periodontal diseases characterized by dysmetabolic processes involving the alveolar bone by stimulating the formation of bone-resorbing cells (osteoclasts) with degradation of the connective tissue surrounding by the metalloproteinases of the extracellular matrix which becomes an additional energy source for the activated immune system [14]. Effector T-cells and inflammatory M1 macrophages undergo active glycolysis, to quickly supply energy to carry out immune activities and proliferate; on the contrary the metabolic profile of anti-inflammatory M2 macrophages is defined by oxidative phosphorylation with lower energy consumption and higher production of ATP [15]. Since chronic activation of the immune system during stress requires metabolic energy more than physiological balance, this is consumed to the detriment of other organs and apparatus. This could explain why they become insulin resistant [5]. Indeed it is indispensable to remember that the immune system follows a rigid circadian rhythm: it activates at night when the brain and other organs are at the minimum of energy demand [16]. Studies on metabolism of immune cells have shown that metabolic processes determine immune function [17]. Therefore, so far Psychoneuroimmunology has allowed us to know the close relationship between mind and body and therefore between stressful events and illnesses, the most recent study of the chronobiology of the immune system and its metabolism, known as *Immunometabolism*, could help us to understand the pathogenetic association between apparently different systemic diseases and increasingly emerging oral pathologies [17].

In dendritic cells and macrophages, the switch from oxidative phosphorylation to aerobic glycolysis, triggered by immune ligands like LPS and stress metabolites as free fatty acids [5,12], leads to profound immune activity changes especially release of proinflammatory cytokines [18-20].

Summing up the prolonged activation of the immune system (inflammation), due to unresolved stressful events, draws energy to the whole organism with consequent functional alterations of organs and apparatus that cause dysmetabolic systemic diseases such as obesity and type 2 diabetes, which are also associated with oral pathologies [6,21,22]. Based on this knowledge, in my opinion, specialists in dentistry and dental hygienists should

consider not only pathogenic microbes but also and especially psychosocial stress among the causes of oral disease.

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