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VISUALIZING THE INTEREST IN THE PAST FEW DECADES TOWARDS AUTOIMMUNE DISEASES USING AS A MODEL THE SJOGREN'S SYNDROME

Daniela-Georgiana CIOBANU

West University of Timişoara, Faculty of Chemistry, Biology, Geography, Department of Biology-Chemistry
**Corresponding author's e-mail: daniela.ciobanu@e-uvt.ro*
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ABSTRACT
In the past decades the number of patients with autoimmune diseases has increased considerably. Certain autoimmune diseases, such as Sjogren's syndrome, can be used as models to understand the mechanisms underlying autoimmune conflicts. This paper aims to visualize the interest in autoimmune diseases and Sjogren's syndrome respectively, reflected by the number of results found using Google Scholar database.
KEY WORDS: *autoimmune disease, Sjogren`s syndrome, stress, endoplasmatic reticulum stress*

INTRODUCTION

There is an increasing number of patients who are diagnosed with various autoimmune diseases (Dinse et al., 2020). Autoimmune diseases are thought to be plurifactorial. An autoimmune conflict occurs as a result of the interaction of several factors of different origin, such as: genetic factors, environmental factors, immunological factors and hormonal factors (Batalu & Ianovici, 2018). There are cases in which a very clear etiology of autoimmune diseases cannot be established, the autoimmune condition being triggered by "unknown factors". However, it is becoming increasingly clear that most autoimmune diseases have a common substrate: stress. More than 80% of people diagnosed with a particular autoimmune disease have been victims of stress before the outset of the disease (Stojanovich & Marisavljevich, 2008).

The concept behind the relationship between stress and autoimmune diseases can be explained by the relationship between the nervous system and the immune system in terms of the inflammatory response. Stimulation of adrenergic receptors causes the production of essential components in the inflammatory response, termed as cytokines (Szelenyi et al., 2000; Pongratz & Straub, 2014). It has been shown that stress factors are strongly correlated with increased circulating cytokine concentration, especially the cytokines IL6, IL1β, IL10 and TNFα (Marsland et al., 2017).The proinflammatory response is modulated mainly by the cytokines IL-1β, IL-6, and TNF-α, produced foremost by macrophages (Zhang & An, 2009). The inflammatory response focuses to remove the factors that can cause

damage, such as pathogens, and to initiate the healing process. Thus, inflammation is a vital evolutionary mechanism. However, it has been shown that uncontrolled inflammation can lead to profound disruption of the homeostasis (Chen et al., 2017).

The response to stress is modulated primarily by the autonomic nervous system and the hypothalamic-pituitary axis, their key role in the pathogenesis of certain diseases being often correlated with problems in adaptive mechanisms in stressful situations (Agorastos et al., 2019; Chrousos, 2009). The relationship between these two nervous compartments has been repeatedly emphasized, in addition to the fact that there are connections of functional and structural nature, both compartments are subordinated to the prefrontal cortex and the limbic system (Rotenberg & McGrath, 2016).

Certain autoimmune diseases can be used as models in explaining the pathogenesis of autoimmune conflict. Sjogern`s syndrome, for example, has been used as a model to explain how stress in the endoplasmic reticulum can be a trigger for a disease that can eventually become systemic (Skopouli & Katsiougiannis, 2017; Parisis et al., 2020) .

Sjogren`s syndorme sums up symptoms that target mainly salivary and lacrimal epithelia, but which can ultimately become systemic and lead to plurivisceral insufficiency (Malladi et al., 2012). The name "Sjogren's syndrome" was introduced in 1953 by the English physician Morgan who correlated the disease described by Dr. Henrik Sjogren with Mukulicz syndrome and concluded that the two syndromes are similar. Since Mukulicz syndrome has been considered a subset of Sjogren's disease, the name "Sjogren's syndrome" has been retained and the name "Mukulicz syndrome" has been removed (Ghafoor, 2012). Sjogren's syndrome affects, like many other autoimmune diseases, especially women, middle-aged, most often at menopause. The ratio of men to women is 16: 1 (Brandt et al., 2015).

In order to establish a plausible path to clarify the pathogenesis of Sjogren's syndrome, Skopouli and Katsiougiannis (2017) propose the following scenario: starting from a background involving genetic factors, sex and other antecedents, stressful events can lead to the disruption of stress adaptation mechanisms and thus, the installation of chronic stress. Once chronic, stress leads to disorders of the nervous mechanisms that control stress management, so, via the hypothalamic-pituitary axis, the autonomic nervous system exerts deep sympathetic activity and weaker parasympathetic activity (Tsigos et al., 2020). The targets of the nervous system, in this case, are the cells in the salivary epithelium. Sympathetic stimulation of beta-adrenergic receptors causes the production of a large amount of protein that will induce a state of stress in the endoplasmic reticulum. The endoplasmic reticulum is the center of "packing" of the proteins,

hence any disturbance at this level will cause an unfolded protein response (UPR) as a result of the imbalance at this level (Adams et al., 2019). An UPR-type response will further cause phosphorylation of interferon regulatory factors (IFRs) and eventually the production of type I interferon (Smith, 2018). Following the activation of UPR, IL-6 is also synthesized as a proinflammatory interleukin which, in large quantities, determines the appearance of chronic inflammation and autoimmune conflicts (Tanaka et al., 2014). In parallel, there is a weak, insufficient stimulation of cholinergic receptors that results in a deficiency of IP3R, an inositol triphosphate that intervenes in IP3-type signaling coupled with calcium, being a vital mechanism. Calcium deficiency further disrupts calcium metabolism (Decrock et al., 2013). IP3 deficiency may also be related to the interaction with the GRP78 protein, also produced during UPR signaling (Higo et al., 2010). GRP78 is a thermal shock chaperone protein that "compel" unpacked proteins to reach their conformational structure, suitable for performing their function or stimulates the degradation of unpacked or improperly packed proteins, through cellular degradation mechanisms (Ibrahim et al., 2019). Due to the acumullation of stress at the cellular level, a very large amount of energy is required to restore homeostasis, at this time the phenomenon of autophagy occurs. Autophagy is a self-degrading process with the utmost importance in balancing energy sources at critical times. Autophagy occurs mainly through the degradation of improperly packed or aggregated proteins. Thus autophagy becomes a survival mechanism (Glick et al., 2010). Autophagy also intervenes in the process of antigen presentation through major histocompatibility complexes, class II (Munz, 2016). If the intensity of the stressors increases or if an additional stressor occurs, apoptosis sets in. Both apoptosis and autophagy are key molecular processes for maintaining cellular and systemic homeostasis. Autophagy and apoptosis can be stimulated by the same stressors, between the two processes there are cross-talk relationships. Unlike autophagy, which "recycles" cellular material, apoptosis removes cellular material that is considered improper, discharging apoptotic fragments into circulation, such as apoptotic bodies or apoptotic vesicles (Fan & Zong, 2013; Elmore, 2007). In this case, the apoptotic vesicles contain autoimmune structures that determine the autoimmune conflict. The autoimmune antigens present in Sjogren's syndrome are Ro/SSA and La/SSb, respectively, polypeptides also found in the case of lupus erythematosus (Tong et al., 2017).

In this scenario stress at the level of the endoplasmic reticulum is highlighted as the key point in the pathogenesis of Sjogren's syndrome. In addition to this syndrome, stress in the endoplasmic reticulum, involving UPR signaling, has been noted in other conflicts of an autoimmune nature also, such as: rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, inflammatory bowel disease (Liu et al., 2020). This study aims to visualize the

interest in certain key concepts related to autoimmune diseases to highlight the directions of research in recent decades on the connection between stress and autoimmune diseases. Interest in a subject is considered to be directly proportional to the number of results found with reference to that subject.

MATERIAL AND METHODS

The time interval 1950-2020 was chosen, which was divided into 7 decades, respectively 1950-1960, 1960-1970, 1970-1980, 1980-1990, 1990-2000, 2000-2010, 2010-2020. The following keywords were entered in the Google Scholar database search field: "autoimmune disease", "autoimmune disease stress", "autoimmune disease endoplasmic reticulum stress", "Sjogren`s syndrome", "Sjogren`s syndrome stress ", " Sjogren`s endoplasmic reticulum stress syndrome", for each decade. The number of results on Sjogren's syndrome was also considered to be of interest, considering the primary and secondary sources, respectively. For a more accessible view, the data has been transposed into graphs.

RESULTS AND DISCUSSIONS

The following graphs were obtained, corresponding to each search:

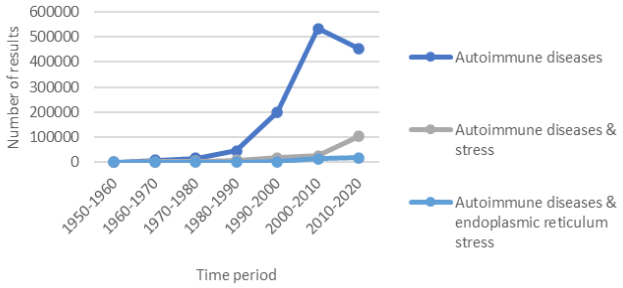

FIG. 1.The variation of the number of results regarding autoimmune diseases in general

In the case of the results regarding autoimmune diseases (fig. 1.) an increasing interest can be observed in the last four decades. Regarding the introduction of the concept of "stress" in general or at the level endoplasmic reticulum, there has been an increase in the last two decades. In relation to the results regarding the Sjogren syndrome (fig. 2.) there is a massive increase in the number of results starting with the years 2000-2010, both in general and in the association of this syndrome with stress.

Considering the number of research-type articles and review-type articles on Sjogren's syndrome (fig. 3.), it is possible to emphasize a close dependence between them, but of course a higher increase in the case of primary articles has been highlighted.

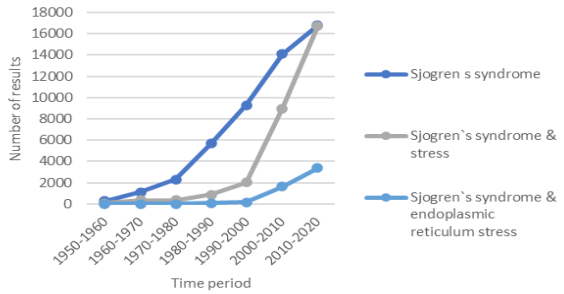

FIG. 2.The variation of the number of results regarding Sjogren`s syndrome

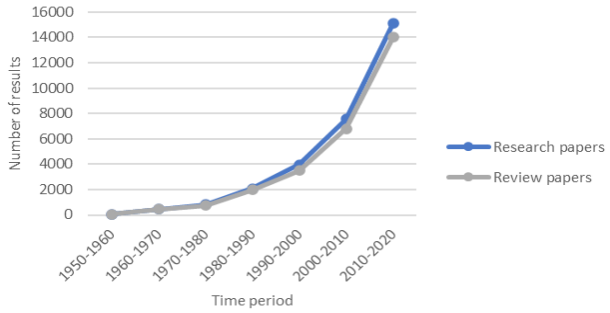

FIG. 3. The variation of the number of results regarding Sjogren`s syndrome considering research papers and review papers

CONCLUSION

It can be concluded that the last four decades have opened new horizons regarding autoimmune diseases. This event can be probably correlated with a refinement of the techniques used in research, especially in immunology. Regarding Sjogren's syndrome, the growing interest, observable in the last two decades, raises the certainty that the coming years will bring a better understanding of the mechanisms undelying the pathogenesis of the disease and the development of a suitable therapy that will improve the lives of patients with Sjogren's syndrome.

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