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Influence of Stress on the Immune System Associated with Tumor Progression: A Literature Review

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Abstract:- Introduction: Stress has been accompanying human beings since the beginning of their existence, worsening after Industrial Revolution. Due to current circumstances, stress is much discussed, however, it is restricted to psychosocial problems and rarely related to organic diseases such as cancer. According to *Instituto Nacional de Câncer*, by the end of 2022 approximately 2 million new cancer cases will be diagnosed in Brazil. Objective: Understand stress consequences on immune system correlating with tumorigenesis. Methods: Searches on SCIELO, LILACS, PubMed, BIREME and Academic Google databases, using as descriptors "Stress Physiology"; "Stress Influence on immune system"; "Immunovigilance"; "Basic tumor immunology;" "Immune surveillance"; "Tumor microenvironment"; "Immunosuppression by stress"; "Psychoneuroimmunology". Results: Tumorigenesis is defined as malignant mutations accumulation characterized by exacerbated cell multiplication. To prevent this pathological state from materializing the organism has physiological barriers, the first is found in the cell cycle, where at certain points DNA quality is evaluated, when not approved the division is interrupted. If these mechanisms fail, immune system recognizes and destroys the mutant cell. Deficient immune response causes altered cells to develop escape mechanisms. In this context, stress is cited as an important immunosuppressant. Studies show deleterious effects of glucocorticoids on leukocytes, in Th1/Th2 responses imbalances and instability in humoral response. Conclusion: Ineffective immune response is a major contributor to tumorigenesis, which is vulnerable to stress and hormones released in this state.

Keywords:- *Psychological Stress; Neoplasms; Immunologic monitoring; Psychoneuroimmunology.*

I. INTRODUCTION

Tumorigenesis is a complex process of numerous genetic changes that lead to the development of a malignant phenotype with exacerbated cell multiplication. Such changes can be aggravated by external factors such as: smoking, radiation, unhealthy eating habits and infection by different agents, most of them viral in nature [1]. In order to inhibit the progression of genetically altered cells, the organism has physiological monitoring mechanisms. The first is found in the cell cycle where regulatory proteins control the quality of the DNA produced, cell replication is interrupted when gene mutations or the production of oncogenes are identified [2].

If cell cycle monitoring fails and the altered cell develops, the immunosurveillance mechanism must recognize and stop the progression of this abnormality. Tumor cells present specific tumor antigens on their surface which will be recognized by Antigen Presenting Cells (APCs) and later destroyed by Natural Killer (NK) cells and Cytotoxic T Lymphocytes. On the other hand, the weakness of the immune system directly contributes to the ineffective attack of these cells, causing mutated potentially tumor cells to develop mechanisms of evasion of the immune response, contributing to the invasion of healthy tissues and tumor metastasis [3].

Considering the historical perspective on the studies of the harm caused by chronic stress, it must be carefully evaluated. Several studies, such as the one by Celí A., et al. (2005) [4], show a strong correlation between chronic stress and immunosuppression. In this context, the present article brought together notable studies with the aim of understanding the consequences of stress on the immune system and its correlation with tumor development.

II. METHODOLOGY

This is an exploratory research produced through a literature review on the online platforms SCIELO, LILACS, PubMed, BIREME and Google Scholar, in order to understand the consequences of stress on the immune system and its correlation with tumor development.

National and international articles, theses and dissertations were selected, whose texts are fully available in English, Portuguese and Spanish, which presented the following descriptors: "Physiology of stress"; "Influence of stress on the immune system"; "Immuno surveillance"; "Tumor Immunology";"Tumor microenvironment"; "Stress immune suppression"; "Psychoneuroimmunology". As an exclusion criterion, articles published before the year 2000 were disregarded.

III. RESULTS

Stress accompanies humans since the beginning, where life was governed by the cycle of prey and predator, putting humans in a constant state of alert to imminent attacks. After the Industrial Revolution the stress was intensified as it was accompanied by the rural exodus, long working hours and the suspension of holidays [4]. Amid the recent current pandemic scenario by COVID-19, mental health was much discussed and publicized by the media. However, it has rarely been correlated with organic diseases such as cancer. In this context, there is great difficulty in locating recent studies that make a parallel between stress, immune

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suppression and tumor development, highlighting the importance of the present study.

Cancer is among the main causes of premature death in the world, keeping its incidence increasing mainly due to aggravating environmental factors. Studies carried out in recent decades show that industrialized countries have a higher prevalence of cancer in relation to countries with low industrial potential. In addition, tobacco, poor eating habits and exposure to carcinogenic agents contribute to this increased incidence of cancer [5]. According to the *Ministério da Saúde*, it is estimated that in Brazil there will be 625 thousand new cases per year between the years 2020 and 2022, totaling approximately 2 million new cases by the end of the year 2022. Non-melanoma skin cancer will be the most frequent, followed by breast cancer and prostate cancer [6].

Conceptually, cancer can be defined as the progressive accumulation of malignant genetic mutations, which induce the exacerbated growth of cells [7]. Hardly a single gene mutation will cause any significant abnormality in the cell, however, a single altered cell is capable of developing a tumor. From a molecular point of view, the initial genes that characterize a tumor cell can be subdivided into two classes. The first will result in a gain of functions favorable to tumor growth (proto-oncogenes and oncogenes) and the second in the functional loss of tumor suppressor genes, both of which assiduously contribute to the progression of cancer (Fig. 1).

During a lifetime, the human organism will perform approximately 1016 cell divisions and about 1010 of these divisions will have some kind of random mutation [2]. Therefore, when evaluating this proportion, tumor development can be considered a relatively rare event. The fact that every mutation does not progress to cancer is due to the physiological barriers established by the organism, the first barrier happens in the cell cycle: In the G1 phase environmental factors are important to define the quality of the genetic material, mitosis will be interrupted under unfavorable conditions. When starting the G2 phase, the replicated material will be evaluated and divided equally among the daughter cells in the mitotic phase. However, mitosis can be aborted at any time if there are chromosomal changes [5].

Tumor cells have some fundamental characteristics: disrespect of the limits of cell division, great capacity for invasion and colonization of other tissues, mechanisms of escape from apoptosis and ease in the development of angiogenesis. In this way, they undermine homeostasis and start to control the entire metabolism of the environment where they are inserted, configuring cellular stress [7].

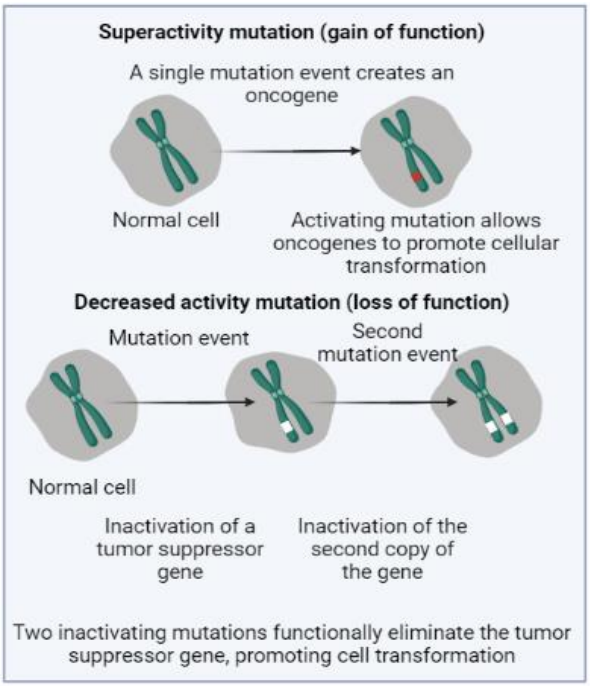

Fig. 1: Cells en route to cancer: Demonstration of the two categories of gene mutations that contribute to tumor development [2]

The main difference between malignant and benign tumors is in the invasiveness, malignant tumors do not recognize the basal lamina barrier and cross into other tissues (Fig. 2).

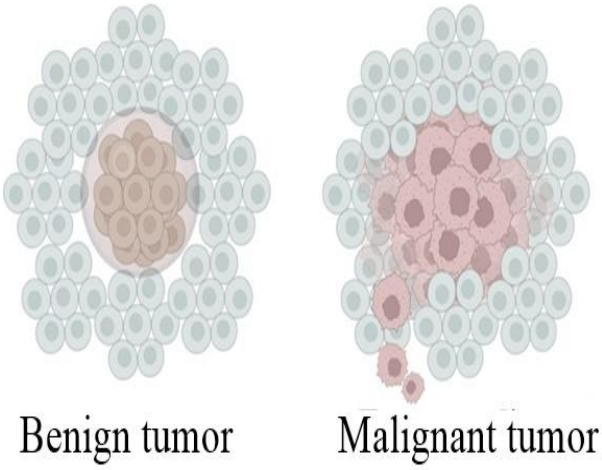

Fig. 2: Difference between benign and malignant tumors, showing the invasiveness of malignant cells [2]

Once significant genetic mutations are transferred from the parent cell to the daughter cell, the process of tumorigenesis is initiated. Simultaneously, the aberrant cell can communicate with healthy cells and transfer somatic mutations to them. These events are commonly triggered after exposure to chemical carcinogens, which can facilitate the occurrence of alteration in the nucleotide sequence. Radiation is also an event that predisposes the individual to genetic damage, as it results in chromosomal breaks, translocations and changes in DNA bases [2].

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As the tumor progresses, the diversification of the original cells occurs in order to guarantee them advantages over other cells, an example is the ability to evade apoptosis. This phenomenon happens again under the influence of mutations and epigenetic changes. All these events show the genetic instability of these cells, demonstrating the inability to correct the damaged DNA [2].

Another important mechanism of cancer cells is metastasis. On this occasion, the malignant cell detaches itself from the tumor of origin and travels through the bloodstream until it finds a tissue with favorable conditions for its installation [2]. Briefly, tumorigenesis depends on the imbalance between apoptosis and cell division, as shown in Fig. 3.

Stress is defined as the organism's physiological and behavioral response to an event or stimulus. Stress can be classified according to the organism's response, for example, when it causes a feeling of euphoria it is called “eustress”; however, if its response harms the health or functioning of the organism it is called “distress”, distress is associated with immunosuppression and tumor development [4].

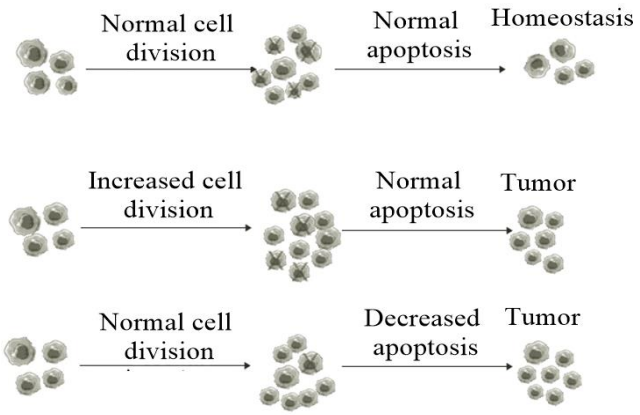

Fig. 3: Demonstration of the importance of apoptosis for the control of tissue homeostasis [2]

In 1963 Salye described the General Adaptation Syndrome, which subdivides into three stages the physiological reactions caused by distress. The first phase is the Alarm Phase and consists of the immediate exaltation of the organism through the stressful stimulus, which at first is a healthy reaction. However, the individual will progress to the Resistance Phase (Second phase) if the stimulus is continuous, when there is an increase in adrenocortical hormones. At this stage psychological disorders can be expressed. In the third phase, or Exhaustion Phase, the organism is exhausted due to hyperactivity and high energy expenditure, and then it will present secondary effects which correspond to the development of chronic diseases [8].

Physiologically, the autonomic nervous system sends stimuli to the hypothalamic-pituitary-adrenal axis (HPA) which respectively release Corticotropin Releasing Factor Hormone (CRH), Adrenocorticotropic Hormone (ACTH) and Cortisol. In parallel, the sympathetic nervous system stimulates the adrenal medulla to release the catecholamines Noradrenaline and Adrenaline (Fig. 4).

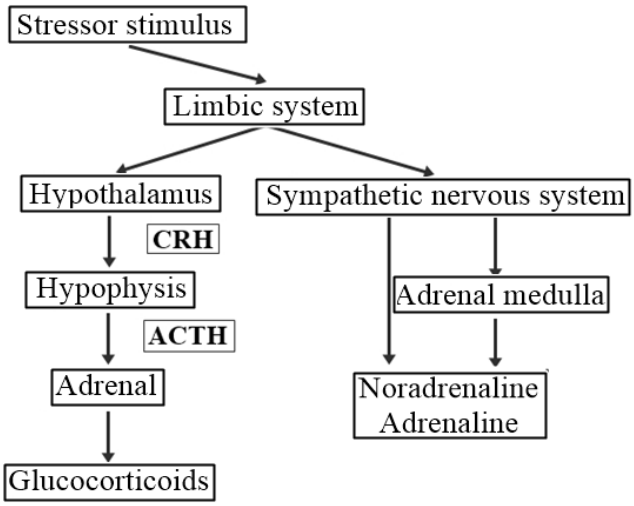

Fig. 4: Activation sequence after the stressful stimulus [11]

Catecholamines are stored in cells located in the adrenal medulla and upon stimulation are released immediately, triggering an increase in heart rate and blood pressure, vasodilation and availability of glucose in the blood. These effects are intended to prepare the individual for the “fight and flight” mechanism [8].

Acute stress can increase the number of NK cells and granulocytes, mainly in the skin, being reasonably favorable to the immune system. Researchers suggest that this feat occurs as a protective instinct, since at the moment of “fight and flight” the individual may end up injured [9]. On the other hand, chronic stress can cause important immunosuppression [10]. Lymphocytes may travel to the bone marrow in order to protect themselves from the harmful effects of glucocorticoids. There may also be a change in the humoral response, compromising the production of immunoglobulins and, consequently, the action of the Complement System [9].

Immuno surveillance is the term used to name the mechanism of recognition and destruction of tumor cells. Immunosurveillance counts on the participation of innate and adaptive immunity. Tumor cells present specific tumor antigens on their surface which will be recognized by APCs, mainly Macrophages and Dendritic Cells. APCs with Major Histocompatibility Complex (MHC) class II present to the TCR receptor of TCD4+ lymphocytes, and those with MHC class I will be recognized by TCD8+ lymphocytes. After recognition, CD4+ T lymphocytes start producing cytokines with the aim of intensifying the action of NK cells, CD8+ T lymphocytes and the production of immunoglobulins by B lymphocytes, which will contribute to the Complement System [3]. However, the ineffective action of the immune system to attack tumor cells can make these cells develop mechanisms to evade the immune response. The first stage of tumor evasion consists of all the processes of immunosurveillance itself. In the second phase, there is an equilibrium between the immune system and tumor cells, however, the remaining cells of this process generate mutant clones of low immunogenicity that will proliferate in a tumor microenvironment in the third phase (Fig. 5). After evasion the tumor is able to reproduce inflammatory conditions

similar to normal tissues in order to use the immune system in its favor, producing growth and angiogenic factors [12].

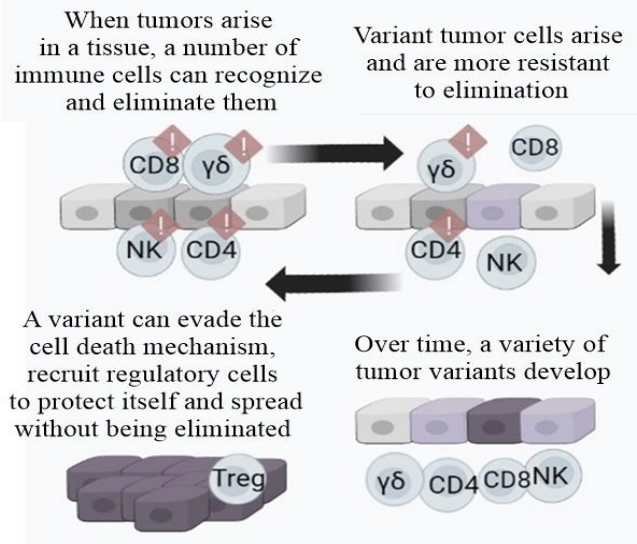

Fig. 5: Immunosurveillance process [12]

Evidences demonstrate that the disposition of catecholamines and glucocorticoids in the blood are contrary to the functional activities of monocytes and lymphocytes. These hormones released during stress are important contributors to the destabilization of Th1 and Th2 cell responses, favoring the overlap of Th1 cells by Th2, compromising the tumor immune response, which is mediated by Th1 cells [13]. Stress can also be related to the elevation of IL-1 and TNF-α, decline of IL-2 and IFN-y, functional decrease of NK and mainly the decrease of MHC class II expression, making recognition of abnormal cells difficult by the CD4+ T lymphocytes [14].

A study carried out with 6,284 Jews who lost their children between 1970 and 1977, revealed an increased incidence of lymphatic, hematological and skin tumors in this group. In addition, other research showed that there was a significant increase in the incidence of cancer in parents who lost their children in an accident or in war [14]. In this context, other studies reinforce the correlation between stress, immunosuppression and tumor development, such as the work conducted by Alves and Neto (2007) [17], which induced physical and psychological stress in mice, demonstrating that submissive animals presented greater anxiety when compared to the dominant ones. For this reason, the submissive animals showed behavioral, neurochemical and immunological changes, contributing to the superior development of experimental murine melanoma metastasis and decreased effectiveness of NK cells [2].

In addition, stressed individuals usually practice habits that predispose them to immunological and endocrine imbalance, such as the use of alcohol, cigarettes, sleep disturbances, etc. Although stress is a major contributor to the deficit of the tumor immune response, there is still a lack of studies on the subject. Mental health is much more commonly related to the psychosocial scope, and there are few studies that are willing to relate immunology and psychology, and even fewer are those that are predisposed to explain the mechanisms that involve both scopes.

IV. DISCUSSION

During the entire research, we did not come across articles that discredited the relationship between stress and the immune system at any point and its consequent tendency to neoplasms. Many studies correlate the themes through statistical and observational findings, while others emphasize chemical and cellular variations through results with more practical and technical methodologies, such as correlating dosages of interleukins and hormones [14]. However, although the relationship is evident and there are markers to measure such discrepancies, many of the mechanisms involved are not yet mastered, especially in relation to chemotaxis of leukocytes during stress [9].

Understanding the chemical cascade that involves such events can be the door to the development of drugs that aim to remodel some immunological tendencies of the chronically mentally ill in a more specific way.

V. CONCLUSION

Through this study it is possible to evidence the strong correlation between stress, immunosuppression and tumor development, demonstrating the bidirectional interaction between the nervous system and the immune system. However, psychoneuroimmunology still lacks clear technical results. As it is still a new science, many of its bases are built on statistical evidence, often observational, which does not discredit the facts, but only emphasizes the need for scientific approaches that describe its mechanisms.

REFERENCES

[1.] Carlos V, Eid C. Oncologia Básica. 1st ed., Brazil: Lemar&Goi, 2015.
[2.] Bruce A, Alexander J, Julian L, David M, Martin R, Keith R, et al. Biologia Molecular da Célula. 6th ed., Brazil: Artmed, 2017.
[3.] Paolo R. E. Imunovigilância e mecanismos de evasão tumoral. Rev UNILUS. 2020. São Paulo, Mar;(17):240-250.
[4.] Celí A, Neide A, Iouri K. Aspectos Fisiológicos e Psicológicos do Estresse. PUnC. 2005; 2(2):84-92.
[5.] Laura W. Entendendo o Processo Molecular da Tumorigênese. ArqBrasEndocrinolMetab. 2002 Aug; 46 (4): 351-358.
[6.] Instituto Nacional do Câncer. Estimativa 2020: Incidência de Câncer no Brasil. Rio de Janeiro (RJ): 2019. 120p.
[7.] Ana O, Roger C. Câncer e o microambiente tumoral. Rev Med. 2010; 89(1): 21-31.
[8.] Natália N, Sthefany F, Alessandro Ri, Gutemberg C, Nazaré H. Estresse, conceitos, manifestações e avaliação em saúde: revisão de literatura. Rev SDH. 2014; 2(1):62-70.
[9.] Moisés B. Estresse: como ele abala as defesas do corpo?.CiênciaHoje. 2002; 30(179):22-25.
[10.] Ana P, José S, Estresse: revisão sobre seus efeitos no sistema imunológico. Rev Biosaúde. 2009; 11(1):57-90.

[11.] Ana T, Fernanda M. Estresse, ciclo reprodutivo e sensibilidade cardíaca às catecolaminas. Rev BCF. 2002; 38(3).
[12.] Kenneth M, Denise M, Gaby R, Lucien G. Imunobiologia de Janeway. 8ª edição. Brasil: Artmed, 2014.
[13.] Maria S, Hélderes S, Nicole G. Resposta ao estresse: I. Homeostase e teoria da alostase. Estud. psicol. 2015;20(1):2-11.
[14.] Edna R, Sandra N, Helena M. Disfunções no Sistema Imune Induzidas pelo Estresse e Depressão: Implicações no Desenvolvimento e Progressão do Câncer. Rev Bras OncologiaClínica. 2005;1(5):19-28.
[15.] Yirmiya R, Pollak Y, Morag M, et al. Illness, Cytokines, and Depression. Neuro: PerspThe New Millennium. 2006;917(1)478-487.
[16.] Andrea M, Esther S. Psiconeuroimunologia: a relação entre o sistema nervoso central e o sistema imunológico.
[17.] Glaucie A, João P. Neuroimunomodulação: sobre o diálogo entre os sistemas nervoso e imune. Braz. J. Psychiatry. 2007;29(4).