

# Psychoneuroimmunology and Oncology

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**SUMMARY:** Psychosocial factors, like stress, have direct effect on tumor progression while their possible effect on tumor development is questionable. Psychoneuroimmunology (PNI) can be applied in oncology by understanding the effect of psychosocial factors on immunosurveillance of tumors. PNI could therefore provide explanation of possible mechanisms by which psychosocial factors can induce tumor growth. Studies have shown that stress can disregulate function of NK-cells as one of the most important parts of immunosurveillance process. There is also explanation for possible mechanisms on direct effect of stress on tumor growth that is not mediated by immune system. Understanding these mechanisms could be beneficiary for understanding of importance of psychosocial support as one of therapeutic methods for cancer patients. Exact mechanisms of stress effect on NK-cells and its possible effect on other immunosurveillance mechanisms such as adaptive and humoral response remain to be elucidated.

**KEYWORDS:** Cancer, Immunosurveillance, NK cells, Psychoneuroimmunology, Stress

Effect of psychological stress as one of the risk factors for development and progression of different types of cancers is considered as fact among general population.<sup>1</sup> Although there really is evidence and there are known mechanisms that directly link psychological stress to cancer progression<sup>2</sup>, science community is still very sceptical about the role of stress in cancer incidence. One of several pathways by which stress could directly induce tumor growth is immune modulation. It is one of the best examples how psychological changes affect immune system and therefore cause suitable environment for tumor development and its progression. With development of psychoneuroimmunology (PNI), as one of relatively new sciences, there is significant number of researches that are trying to find mechanisms of this connection between CNS, immune system and malignant cell alterations. One of the important things to keep in mind is that in the history of studies of these connections a unidirectional approach was present for a longer time period, i.e. researchers have been trying to find mechanisms how psychosocial factors affect immune system and therefore change risks for developing cancer. On the other hand, psychoneuroimmunological connections have bidirectional nature<sup>3</sup>; immune system can affect behavioral and psychological processes. For example, if one knows he is suffering from cancer he will sure enough suffer from certain amount of stress. Understanding this connections and its mechanisms could be beneficiary for determining psychological risk factors (if they even exist) leading to cancer development and its progression, finding new therapeutic methods for and predicting the outcomes of cancer diseases.

Nevertheless, it should be always kept in mind that effect of immune system on cancer also varies between different tumors. Best example for that is that in immunocompromised patients like the ones who suffer from AIDS disease or the ones on immunosuppressive therapy have significantly raised incidence only for some types of cancers while for the other types incidence difference is not so significant<sup>4</sup>. This article, however, does not engage with this topic.

## Tumor surveillance

Several mechanisms that possibly have close connection to prevention of tumorigenesis can be affected from CNS. We can divide them in two groups: immunosurveillance and nonimmune surveillance. CNS can modify cellular apoptosis and DNA-repair processes as mechanisms of nonimmune surveillance. On the other hand, it can modify functioning of immune system and thus modify process of immunosurveillance.

There is several ways how human immune system, in process called immunosurveillance could be defending from malignant diseases. One of first strong evidences for immunosurveillance theory, which has been present for decades, was the one published in year 2001 showing that interferon- $\gamma$  (IFN- $\gamma$ ) together with lymphocytes prevent primary tumor development<sup>5</sup>. Among involved lymphocytes, in great part of literature that is discussing this issue, natural-killer cells (NK-cells) have been highlighted. NK-cells were discovered to play one of the most important roles in destroying tumor cells. Namely, IFN- $\gamma$  together with other cytokines such as interleukin-2 (IL-2) induces activity of NK-cells and thus contribute to destruction of tumor cells<sup>6</sup>. Few researches have shown that stress can cause drop in IFN- $\gamma$  and IL-2 blood levels, modify NK-cells response to these cytokines or can diminish NK-cells cytotoxicity. First one to mention was conducted among medical students in their examination periods. It has shown that their blood level of IFN- $\gamma$  dropped significantly in those periods of examination comparing to other parts of year that hadn't been so stressful<sup>7</sup>. One other research among marriage couples showed that those one who were behaving more negative during discussion about their marriage problems showed noticeable drop in NK-cell activity<sup>8</sup>. Few other researches studied effect of prolonged stress to level of NK-cell and their cytotoxicity. Examples of that stressful situations were caregiving for severely ill (Alzheimer's disease, or cancer) spouse or being bereaved caregiver. Comparing to control,



noncaregiving, group, caregivers had either normal peripheral blood levels of NK-cells with their normal cytotoxicity but NK-cells were significantly less responsive to their stimulators such as recombinant IFN- $\gamma$  (rIFN- $\gamma$ ) and recombinant IL-2 (rIL-2), or either both NK-cell cytotoxicity and their rIFN- $\gamma$  and IL-2 response were lowered. Furthermore, caregivers with lower values for this observed parameters reported significantly less social support for their life situation<sup>9</sup>.

As mentioned earlier few other mechanisms other than immune system response could be also important for preventing tumor development. These belong in group called nonimmune surveillance. Some researches have shown that the CNS has some kind of effect on DNA-repairment process as well as on process of cellular apoptosis. Namely, essence of neoplastic changes are changes in cellular DNA. These changes can disregulate cell function and thus cause its transition from normal to malignant one. DNA-repair process activates when this change occurs and thus prevent tumorigenesis. If DNA-change is too big to repair, process of cellular suicide called apoptosis is activated and the cell dies. There are some evidences that show how CNS can affect listed mechanisms without mediation of immune system. Specimens of peripheral blood leukocytes from non-medicated, newly diagnosed psychiatric patients have been exposed to radiation and after that compared to specimens of healthy controls which had also underwent radiation exposure. Leukocytes from healthy controls after some time showed significantly smaller damages of DNA<sup>10</sup>. Other research assessed DNA repair capacity in 16 healthy medical students during their vacation and examination periods. Results showed that DNA repair capacity was significantly higher during the exam period than after vacation, suggesting a positive association between subject stress levels and DNA repair capacity<sup>11</sup>. Although these two research results may seem contradictory at first glance it is very important to take in consideration many other differences between studies like acute stress in one and chronic stress in the other. Nevertheless both studies prove direct connection between psychological stress and DNA repair capacity.

As mentioned before, stronger relationships have been observed between psycho-social factors and cancer progression than between psycho-social factors and cancer incidence. Reason for that certainly is in fact that there are other known pathways by which tumor cell growth can be stimulated which do not include immune mechanisms. For example, raised level of catecholamines, associated with stress, could induce production of VEGF which can then improve blood supply to tumor cells and therefore provide them with more nutrients

for their growth<sup>2</sup>. Since the topic of this article is primarily PNI, immune mechanisms or mechanisms that are in tight connection with immunity will be elaborated.

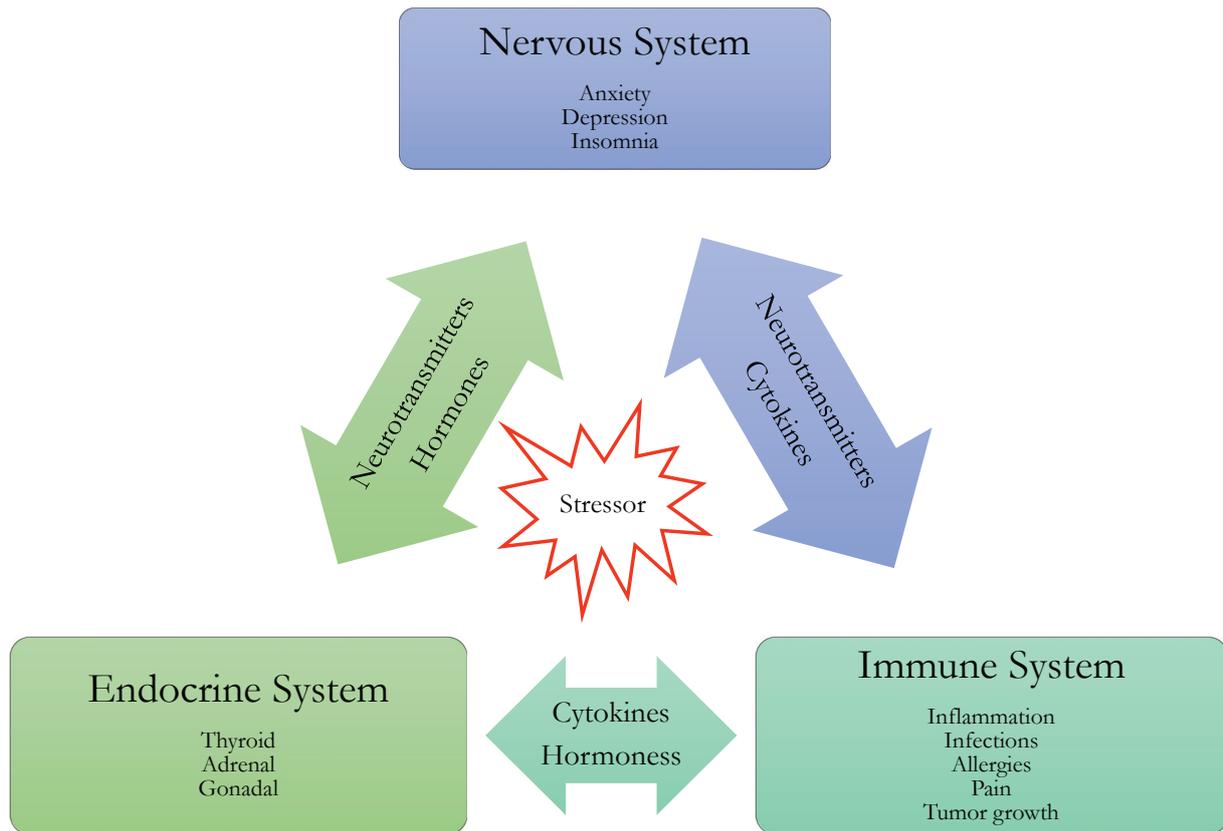
### CNS Affects surveillance mechanisms

Now, after we discussed which are the most important components of immune system in process of surveillance over possible malignant cell alterations and tumor growth and which of these components are sometimes changed under psychological influence. However, there is another important question to consider. It is important to answer how exactly can CNS affect tumor relevant immune components. Hormones play a key role in this process i.e. catecholamines and glucocorticoids. Both of these groups could be released from suprarenal gland but there are also adrenergic nerves terminating in the lymphoid organs<sup>12</sup>.

Glucocorticoids haven't only been discovered as immunomodulators, but they have already been used for considerable amount of time as drugs in different kinds of immune diseases. Glucocorticoids can alter different components of the immune system such as lymphocyte proliferation, cytotoxic and phagocytic activity, antibody and cytokine production, and redistribution of immune cells among the different lymphoid organs. Therefore their ability to suppress cellular immune functions, including the cytotoxic activity of natural killer cells is not questionable. Unfortunately the exact molecular mechanism how glucocorticoids suppress cellular cytotoxicity mediated by NK-cells, which has been highlighted in tumor suppression, is not yet understood. One research suggests that cortisol is able to regulate NK function by disabling granzyme A synthesis<sup>13</sup>. Granzyme A belongs to group of serine proteases and is released from NK-cells to induce the process of apoptosis in target cells. Therefore, lack of this enzyme disables NK-cells to perform their cytotoxic function.

Adrenergic receptors have been discovered in different types of immune cells. Therefore catecholamines certainly have an effect on immune system. Most of researches, however, have been concentrating on their effect to inflammatory response. Therefore their importance for immunosurveillance remains to be elucidated. On the other hand catecholamines can induce tumor growth by direct effect on adrenergic receptors on tumor cells<sup>14</sup>, but as mentioned before, topic of this article is brain-immune system-cancer connection so this direct effect will not be discussed.





**Therapy applications**

Ideal treatment for cancer has to remove every cancer cell while sparing normal, healthy cells. Even the best radiation therapy, surgery, or chemotherapy is unable to complete that task. The only hope for achieving this goal is by using the immune system<sup>15</sup>. It could be achieved by interventions that would augment immune responses to cancer. Understanding that psychosocial factors can reduce this response could help in development of new therapies that will be aimed to psychosocial status of cancer patients.

From previous paragraphs it is understandable that stress could be one of the cancer development risk factors and certainly is a cancer progression risk factor. From objective reasons it is very hard to discuss how could stress-reduction in everyday life be beneficial for cancer prevention but it is very possible to discuss how stress-reduction could and can be beneficial for cancer patients.

There is a significant amount of researches that show how psychosocial intervention, besides conventional therapy (chemotherapy, radiation, surgery), in cancer affected patients has effect on cancer survival rates and its outcomes. Improvements in psychological status among those patients have been connected to an improved physiological profile during and after treatment, which may increase the odds for disease-free survival in some cancers. Although this therapy method is imaginable without participation of PNI, PNI can certainly help in

better understanding of this therapy mechanism. One study conducted among stage I and II melanoma patients, which had not been receiving any therapy after surgical excision of their tumor, showed positive effect of psychosocial intervention on their immune status. Namely, patient who had learned stress management techniques and had received psychosocial support showed significant increases in the percentage of NK cells, as well as an increase in NK cell cytotoxic activity, lesser tumor recurrence and smaller mortality rates compared with controls<sup>16</sup>. The other study in group of healthy older adults showed that those adults which were involved in stress relaxation training or social support showed significant enhancement in NK cell activity while the others who served as controls showed no NK cell activity change<sup>17</sup>.

Problem with these kind of researches is that they have been inconsistent. In several occasions replication of latter studies showed different results. For example in patients with breast cancer psychosocial support had no effect on survival rate<sup>18</sup>. This inconsistency can be result of multiple reasons like therapy compliance and general health behavior. As mentioned before results can also depend on role of immune system in specific tumors.

Most of the recent studies of this topic have been focused on mechanisms that are part of an innate immunity (NK cells). Further studies should, however, aim on adaptive immune responses including humoral antibody response and tumor-specific T-cell response.

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## Psihoneuroimunologija i onkologija

**SAŽETAK:** Dokazano je da psihosocijalni čimbenici, kao što je stres, imaju izravan utjecaj na napredovanje tumora prisutnog u organizmu, ali mogućnost da oni potaknu sam nastanak tumora i dalje je upitna. Razumijevanje mehanizama kojim psihosocijalni čimbenici utječu na nadzor imunosnog sustava nad tumorima predstavlja primjenu psihoneuroimunologije u onkologiji. Psihoneuroimunologija stoga možda može objasniti kako psihosocijalni čimbenici mogu potaknuti nastanak tumora. Istraživanja su pokazala da stres može poremetiti funkciju NK stanica koje su jedan od najvažnijih medijatora imunosnog nadzora nad tumorima. Također postoje objašnjenja kako stres izravno utječe na napredovanje tumora. Razumijevanje ovih mehanizama moglo bi koristiti za razumijevanje i primjenu novih terapijskih metoda kod pacijenata oboljelih od tumora kao što je psihosocijalna pomoć. Ostaje i dalje za razjasniti koji je točan mehanizam djelovanja stresa na NK stanice kao i na druge dijelove imunosnog sustava kao što su stečeni i humoralni koji bi također mogli biti važni u nastanku tumora.

**KIJUČNE RIJEČI:** imunosni nadzor nad tumorima, NK stanice, psihoneuroimunologija, stres, zloćudni tumor

