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Antidepressants Combined with Immunotherapy for Cancer Treatment

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ABSTRACT

As the leading cause of death in people less than 70 years of age, cancer brings not only physical damage to patients, but also great psychological stress. Psychological stress is a well-known risk factor in cancer initiation, progression and metastasis. Studies have reported that chronic psychological stress inhibits anti-tumor immune responses, remodels the tumor microenvironment, disrupts intestinal barrier function and ecological stability, promotes cancer development and metastasis, and reduces the therapeutic effect of cancer. Antidepressants were the most common psychotropic drugs prescribed in patients with depression and had been shown to inhibit the effects of psychological stress on tumors. Fortunately, recent evidence points to a link between antidepressants and cancer immunotherapy based on innate and adaptive immunity. Some of the commonly used antidepressants like monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) etc., have been reported to enhancing antitumor immune response and potential activity against the cancerous cells, acting synergistically in combination with immune checkpoint inhibitors. The purpose of this review is to evaluate current and potential clinical therapies for cancer patients with anxiety and depression.

Keywords: Psychological stress, cancer immunotherapy, antidepressants, tumor immunology

Abbreviations: MAOIs- Monoamine Oxidase Inhibitors; SSRIs- Selective Serotonin Reuptake Inhibitors; TCAs- Tricyclic Antidepressants; HPA- Hypothalamic-Pituitary-Adrenal; SNS- sympathetic nervous system; DCs- Dendritic cells; IFN- I Interferon; NK- Natural killer cells; MDSCs- Myeloid-derived suppressor cells

Introduction

Clinical data presents that patients with cancer experience more severe psychological stress than patients with other diseases [1], 48.2% of cancer patients suffered from depression and 28.2% from anxiety in China [2]. Cancer diagnosis, treatment, and survivor may increase patients' susceptibility to depression and anxiety [3,4]. Cancer is also likely to contribute to the development of depression by modulating the circadian clock-driven inflammatory states[5]. Depression and anxiety were associated with a significantly increased risk of incidence and mortality in cancer patients [6].

Psychological Stress and Cancer Immunotherapy

Cancer immunotherapy is considered to be the most likely therapy to completely cure cancer, inhibiting cancer growth by restarting and maintaining the tumor-immune cycle and restoring the body 's normal anti-tumor immune response [7]. However, psychological stress impairs the efficacy of cancer immunotherapy by suppressing innate and adaptive immune systems. Psychological stress discussed here is defined as chronic psychological stress that can induce changes in the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS) activation, and secretion of other related hormones [8,9].

Impairment of DCs: Dendritic cells (DCs) are professional antigen presenting cells that play a key role in inducing immune responses and immune tolerance. DC-based vaccines proved feasible and safe and may be suitable for all cancer types [10]. Chronic psychological stress elevates plasma corticosterone and upregulates the expression of glucocorticoid-induced factor TSC22D3, blocking the type I Interferon (IFN) response of DCs and the activation of IFN-γ+ T cells, and disrupts immune surveillance and defense [11]. In mouse models of melanoma, chronic stress suppresses the efficacy of cancer vaccines [12] and the immunostimulant CPG-C by impairing DCs and CD8+ T-cell function [13].

Malfunction of NK: Natural killer cells (NK) are innate immune cells that inhibit tumors, and the stress hormones glucocorticoid (GC) rely on Interleukin (IL)-15 and IL-18 to induce programmed death-1 (PD-1) expression and decrease IFN-γ production on NK cells, and IL-12 can eliminate the effect of GC on NK cells [14]. However, chronic psychological stress decreased IL-12, enhanced the level of IL-10, induced the conversion of TH1 response to TH2 response, and promoted GC to inhibit the function of NK cells [15].

Malfunction of CTL: Chronic psychological stress promotes CD8+T cell dysfunction by up-regulating exhaustion phenotypes such as T cell immunoglobulin and mucin domain - 3 (TIM3) and lymphocyte activation gene - 3 (LAG3) expression by CD8+T cells in the tumor microenvironment. PD-1 is an important immunosuppressive molecule, and tumor cells acquire immune escape by expressing programmed death ligand 1 (PD-L1) to bind to PD-1 on T cells, causing T cells to lose their lethality [16]. Stress hormones epinephrine and norepinephrine impair the therapeutic effect of Anti-PD1 through β-adrenergic signaling [17].

Infiltration of MDSC: Myeloid-derived suppressor cells (MDSCs) are heterogeneous immature immune cell populations that inhibit T cell proliferation and activity and are involved in the development, invasion, metastasis, as well as drug resistance of a variety of cancers. Chronic psychological stress promotes regulatory T cell infiltration in peripheral blood and tumor tissues, upregulates CXC chemokine motif ligand (CXCL) 5 in tumor tissues, enhances the expression of CXC chemokine receptor (CXCR) 2 and pERK1/2 expressed by MDSCs in bone marrow, and recruits MDSCs to infiltrate into tumoral and distant tissues [18].

Antidepressants Enhancing Anti-Tumor Immune Response

Timely and effective intervention for anxiety and depression helps to improve the quality of life in cancer patients, and reduce cancer incidence and mortality [6,19]. Antidepressants refer to a group of psychotropic drugs mainly used to treat mental illness with emotional depression as a prominent symptom. There are various studies which show that antidepressants approved for clinical depression have shown promising anti-cancer activities and enhancing anti-tumor immune response [20].

TCAs: TCAs blocked the reuptake of NA and 5-HT by noradrenergic and serotonergic nerve terminals and increased the concentration of monoamine transmitters in the synaptic cleft, which clinically showed improvement in depressive symptoms. Amitriptyline blocks autophagy by inhibiting autophagosome-lysosome fusion and enhances the expression of death receptors (DR) 4 and 5 necessary for apoptosis, sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) -resistant A549 lung cancer cells, and promotes TRAIL-induced apoptosis [21]. Imipramine, a tricyclic antidepressant, combined with the mitochondrial uncoupling agent niclosamide ethanolamine (NEN) can induce cancer cell death by activating a comprehensive stress response pathway and catabolizing the CLEAR network [22].

SSRIs: The main mechanism of action of SSRIs is antidepressant effects in the central nervous system by selectively inhibiting 5-HT reuptake. Fluoxetine (FLX) induced cell cycle arrest and autophagy restraining cancer cells' growth via triggered the ATF4-AKT-mTOR signaling pathway in non-small cell lung cancer [23]. Indoleamine-2,3-Dioxygenase (IDO) exerts immunosuppressive effects by oxidize tryptophan to kynurenine and is upregulated in a variety of cancers. IDO inhibitors combined with immune checkpoint inhibitors are considered effective strategies for tumor control [24]. FLX administration reversed chronic stress induced high IDO1 and

IDO2 expression suppressing kynurenine pathway and enhancing cellular immunity [25]. In lung cancer models, FLX increased CD4+ Th and CD8+ Tc cells, and reduced Tregs (CD25+ FOXP3+). FLX increased IL-2 and IFN-γ by promoting the differentiation of Th into Th1 cells, while decreased the concentrations of IL-4, IL-6, IL-10, and IL-17A by inhibiting the differentiation of Th into Th2 and Th17 cells [25]. IL-6 was shown to be involved in immune-related adverse effects (IRAE) induced by immune checkpoint inhibitor (ICB) therapy, and the combination of IL6 blockade and ICB enhanced antitumor immune responses and reduced symptoms of IRAE [26]. Therefore, the combination of FLX with ICBs may reduce symptoms of IRAE by decreasing IL-6.

Recent studies have reported that FLX reduces 5-HT levels in the peripheral circulation, enhances the infiltration of CD8 + T cells in tumors, and slows the growth of pancreatic and colon cancer in mice, and shows a synergistic effect in combination with Anti-PD1, which can completely cure large tumors in 20% of mice [27]. Sertraline (STL) significantly inhibited the growth and angiogenesis of prostate cancer stem cells by inducing oxidative stress and promoting cell death via dual activation of apoptosis and autophagy process [28]. STL inhibits autophagic flux by up-regulating death receptors and reduces TRAIL resistance in lung cancer [29]. FLX or STL treatment suppresses the effects of chronic psychological stress on tumors by restoring antitumor immune responses [30].

MAOI: Monoamine oxidase (MAO), including MAO-A and MAO-B, is an enzyme that catalyzes oxidative deamination of neurotransmitters and thereby influences mood and behavior. MAO-A has been shown to be elevated in a variety of cancers [31]. MAOIs have been developed and increase the content of 5-HT between synapses in the brain by inhibiting MAO activity and are commonly used in the treatment of depression in clinical practice. Recent reports indicated that MAO-A expression in tumor is associated with T-cell dysfunction and reduced survival in cancer patients, restrains antitumor T cell immunity through controlling T cell in tumor autocrine serotonin signaling. MAOI treatment significantly suppressed tumor growth in a T cell-dependent manner and synergized with anti-PD-1 combination therapy [32]. In addition, MAO-A was shown to be involved in polarization of TAM and influences TAM-associated T-cell antitumor reactivity. MAO-A promotes macrophage polarization to M2 via ROS upregulation. Phenelzine, a non-selective irreversible MAOI, treatment regulates TAM polarization via inhibiting MAO-A and thereby inhibiting tumor growth [33].

Conclusion

In summary, psychological stress reduces the therapeutic effect of cancer immunotherapy by damaging the innate and adaptive immune systems and inhibiting anti-tumor immune responses. Relieving psychological stress in clinical oncology patients may be a strategy to improve the efficacy of existing cancer immunotherapy. The development of new drugs for the treatment of tumors is a very long and expensive process. Many oncology drugs have been rejected in clinical trials because they are ineffective against tumors or adverse effects on healthy cells. Therefore, exploring the new therapeutic benefits of anticancer effects of existing clinical antidepressants may lead to a therapeutic approach to prevent toxicities occurring during clinical trials. Antidepressants not only inhibit the negative impact of chronic psychological stress on cancer development and treatment, but also show good anti-tumor immune effects and enhance the therapeutic effects of immune checkpoint inhibitors on tumors. Antidepressants combined with immunotherapy may be a new potentially effective combination immunotherapy for the treatment of cancer patients with depression or anxiety, however there is a lack of clinical trials demonstrating its effectiveness in cancer treatment. Moreover, the sensitivity of particular cancer types or groups of patients for this combination immunotherapy should be evaluated.

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References

1. Yang W, Xiao L, Yuan Z, Huan H, Yilei X, et al. (2021) Anxiety and Depression in Patients with Physical Diseases and Associated Factors: A Large-Scale Field Survey in General Hospitals in China. Front Psychiatry 12: 689787.
2. Yan R, Xia J, Yang R, Binghui LV, Peng Wu, et al. (2019) Association between anxiety, depression, and comorbid chronic diseases among cancer survivors. Psycho-oncology 28(6): 1269-1277.
3. Gil F, Costa G, Hilker I, llucia B (2012) First anxiety, afterwards depression: Psychological distress in cancer patients at diagnosis and after medical treatment. Stress Health 28(5): 362-367.
4. Linden W, Vodermaier A, Mackenzie R, Greig D (2012) Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. Journal of Affective Disorders 141(2-3): 343-351.
5. Su K, Din ZU, Cui B, Fei P, Zhou Y, et al. (2022) A broken circadian clock: The emerging neuro-immune link connecting depression to cancer. Brain Behav Immun Health 26: 100533.
6. Wang YH, Li JQ, Ssi JF, Jian YQ, Liq JJ, et al. (2020) Depression and anxiety in relation to cancer incidence and mortality: A systematic review and meta-analysis of cohort studies. Molecular Psychiatry 25(7): 1487-1499.
7. Pan C, Liu H, Robins E, Wenru S, Delong L, et al. (2020) Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. Journal of Hematology & Oncology 13(1): 29.

8. Houslay TM, Earley RL, White SJ, Wiebke L, Andrew JG, et al. (2022) Genetic integration of behavioural and endocrine components of the stress response. Elife 11: e67126

9. Calvani M, Bruno G, Dal Monte M, Romina N, Fontani F, et al. (2019) β -Adrenoceptor as a potential immuno-suppressor agent in melanoma. Br J Pharmacol 176(14): 2509-2524.

10. Bol KF, Schreibelt G, Gerritsen WR, Jolanda MV, Carl GF, et al. (2016) Dendritic Cell-Based Immunotherapy: State of the Art and Beyond. Clin Cancer Res 22(8): 1897-1906.

11. Yang H, Xia L, Chen J, Zhang S, Vincent M, et al. (2019) Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. Nat Med 25(9): 1428-1441.

12. Sommershof A, Scheuermann L, Koerner J, Marchus G, et al. (2017) Chronic stress suppresses anti-tumor T responses and tumor regression following cancer immunotherapy in a mouse model of melanoma. Brain Behav Immun 65: 140-149.

13. Levi B, Matzner P, Goldfarb Y, Sorski L, Shaashua L, et al. (2016) Stress impairs the efficacy of immune stimulation by CpG-C: Potential neuroendocrine mediating mechanisms and significance to tumor metastasis and the perioperative period. Brain Behav Immun 56: 209-220.

14. Quatrini L, Wieduwild E, Escaliere B, Jessica F, Lionel C, et al. (2018) Endogenous glucocorticoids control host resistance to viral infection through the tissue-specific regulation of PD-1 expression on NK cells. Nat Immunol 19(9): 954-962.

15. Sarjan HN, Yajurvedi HN (2018) Chronic stress induced duration dependent alterations in immune system and their reversibility in rats. Immunol Lett 197: 31-43.

16. Fritz JM, Lenardo MJ (2019) Development of immune checkpoint therapy for cancer. J Exp Med 216(6): 1244-1254.

17. Bucsek MJ, Qiao G, Macdonald CR, Giridharan T, Evans L, et al. (2017) β-Adrenergic Signaling in Mice Housed at Standard Temperatures Suppresses an Effector Phenotype in CD8 T Cells and Undermines Checkpoint Inhibitor Therapy. Cancer Res 77(20): 5639-5651.

18. Cao M, Huang W, Chen Y, Gaoxiang Li, Nasi L, et al. (2021) Chronic restraint stress promotes the mobilization and recruitment of myeloid-derived suppressor cells through β-adrenergic-activated CXCL5-CXCR2-Erk signaling cascades. Int J Cancer 149(2): 460-472.

19. Breidenbach C, Heidkamp P, Hiltrop K, Holger H, Anna E, et al. (2022) Prevalence and determinants of anxiety and depression in long-term breast cancer survivors. BMC Psychiatry 22(1): 101.

20. Di Rosso ME, Palumbo ML, Genaro AM (2016) Immunomodulatory effects of fluoxetine: A new potential pharmacological action for a classic antidepressant drug?. Pharmacol Res 109: 101-107.

21. Zinnah KMA, Park SY (2021) Sensitizing TRAIL-resistant A549 lung cancer cells and enhancing TRAIL-induced apoptosis with the antidepressant amitriptyline. Oncol Rep 46(1): 144.

22. Hartleben G, Schorpp K, Kwon Y, Barbara B, Tsokanos FF, et al. (2021) Combination therapies induce cancer cell death through the integrated stress response and disturbed pyrimidine metabolism. EMBO Mol Med 13(4): e12461.

23. Shao S, Zhuang X, Zhang L, Qiao T (2022) Antidepressants Fluoxetine Mediates Endoplasmic Reticulum Stress and Autophagy of Non-Small Cell Lung Cancer Cells Through the ATF4-AKT-mTOR Signaling Pathway. Front Pharmacol 13: 904701.

24. Yentz S, Smith D (2018) Indoleamine 2,3-Dioxygenase (IDO) Inhibition as a Strategy to Augment Cancer Immunotherapy. BioDrugs 32(4): 311-317.

25. Yang Z, Li Z, Guo Z, Yu Ren, Ting Z, et al. (2021) Antitumor Effect of Fluoxetine on Chronic Stress-Promoted Lung Cancer Growth via Suppressing Kynurenine Pathway and Enhancing Cellular Immunity. Front Pharmacol 12: 685898.

26. Hailemichael Y, Johnson DH, Abdel Wahab N, Wai Chin F, Salah EB, et al. (2022) Interleukin-6 blockade abrogates immunotherapy toxicity and promotes tumor immunity. Cancer Cell 40(5): 509-523.

27. Schneider MA, Heeb L, Beffinger MM, Stanislav P, Michael L, et al. (2021) Attenuation of peripheral serotonin inhibits tumor growth and enhances immune checkpoint blockade therapy in murine tumor models. Sci Transl Med 13(611): eabc8188.

28. Chinnapaka S, Bakthavachalam V, Munirathinam G (2020) Repurposing antidepressant sertraline as a pharmacological drug to target prostate cancer stem cells: Dual activation of apoptosis and autophagy signaling by deregulating redox balance. Am J Cancer Res 10(7): 2043-2065.

29. Zinnah KMA, Seol JW, Park SY (2020) Inhibition of autophagy flux by sertraline attenuates TRAIL resistance in lung cancer via death receptor 5 upregulation. Int J Mol Med 46(2): 795-805.

30. Di Rosso ME, Sterle HA, Cremaschi GA, Ana Maria G (2018) Beneficial Effect of Fluoxetine and Sertraline on Chronic Stress-Induced Tumor Growth and Cell Dissemination in a Mouse Model of Lymphoma: Crucial Role of Antitumor Immunity. Frontiers In Immunology 9: 1341.

31. Zarmouh NO, Messeha SS, Mateeva N, Madhavi G, Kacy F, et al. (2020) The Antiproliferative Effects of Flavonoid MAO Inhibitors on Prostate Cancer Cells. Molecules 25(9): 2257.

32. Wang X, Li B, Kim YJ, Wang YC, Zhe li, et al. (2021) Targeting monoamine oxidase A for T cell-based cancer immunotherapy. Sci Immunol 6(59): eabh23832383

33. Wang YC, Wang X, Yu J, Feiyang Ma, Zhe li, et al. (2021) Targeting monoamine oxidase A-regulated tumor-associated macrophage polarization for cancer immunotherapy. Nature Communications 12(1): 3530.

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