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# 慢性应激与肿瘤的发生与演进*

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**【摘要】** 慢性应激是指激活经典的下丘脑-垂体-肾上腺轴神经内分泌系统和交感神经系统而引发的机体持续非特异性适应性反应。现已证实，慢性应激可诱发肿瘤发生并促进肿瘤演进，特别是对机体的免疫功能和肿瘤微环境的重塑具有重要影响。然而，由于慢性应激自身机制复杂，个体耐受差异较大，导致其在肿瘤发生与演进中的研究证据尚不确切。因此，本文就慢性应激与肿瘤发生、演进的相关性研究进行综述，重点解析慢性应激促进肿瘤发生发展的分子机制，抑制机体免疫反应、重塑肿瘤免疫微环境的作用及机制，探讨健康人群与肿瘤患者的应激管理方案，以期为靶向慢性应激逆转肿瘤的新策略研究提供新的线索与方向。我们认为，靶向环磷酸腺苷/蛋白激酶A/环磷腺苷效应元件结合蛋白（cAMP/PKA/CREB）信号通路逆转肿瘤发生的治疗策略，应激、炎症与免疫以及肿瘤之间的关系，β受体拮抗剂的“抑癌”活性及其机制以及与不同联合治疗方案的选择，仍需进一步探索。健康的生活方式、积极的生活态度与专业的应激管理指导对肿瘤的防治来说至关重要。

**【关键词】** 慢性应激 肿瘤演进 免疫功能 免疫微环境 应激管理

**A Review of Chronic Stress and the Initiation and Evolution of Cancer**

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**【Abstract】** Chronic stress activates the typical neuroendocrine system, hypothalamus pituitary adrenal axis and sympathetic nervous system, and leads to a sustained non-specific adaptive response. It has been proved that chronic stress can promote tumor initiation and induce tumor evolution, especially in immune function and remodeling of tumor microenvironment. However, due to the complex mechanism of chronic stress and the great difference in individual tolerance, the research evidence of chronic stress in tumor genesis and progression is still unclear. Therefore, in this paper, we review the research on the relationship between chronic stress and tumor initiation and evolution, focusing on the molecular mechanism of chronic stress promoting tumor occurrence and development, inhibiting immune response and remodeling tumor immune microenvironment, and exploring the stress management program of healthy people and cancer patients, so as to provide clues for exploring new strategies of cancer prevention and treatment. In our opinion, targeting the cAMP/PKA/CREB signaling pathway to reverse tumor treatment strategy, the relationship between the tumor and stress, inflammation, immunity, the suppressor activity of β receptor antagonist and its mechanism as well as associated with different treatment options, still need to be further explored. A healthy lifestyle, positive life attitudes and professional stress management guidance are essential for the prevention and treatment of cancer.

**【Key words】** Chronic stress Tumor initiation Immune function Immune microenvironment Stress management

慢性应激（chronic stress）已被证实可以削弱心理或生理健康，促使疾病恶化，特别是对恶性肿瘤的演进和肿瘤微环境的重塑具有严重不良影响[1-2]。近年来的研究证据表明，慢性应激诱发肿瘤发生并促进肿瘤的演进[3]。本文就慢性应激与肿瘤发生演进的相关性研究进行综述，重点介绍慢性应激促进肿瘤发生与演进的分子机制，抑制机体免疫反应、重塑肿瘤免疫微环境的作用及机制，探讨健康人群与肿瘤患者的应激管理策略。

## 1 应激反应的生理机制

人类应激反应系一系列动态的连续过程，机制较为复杂，经典的全身适应综合征学说（general adaptation syndrome，GAS）将其分为包括警觉期、抵抗期以及衰竭期在内的三个阶段（表1）。经典的应激通路包括下丘脑-

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表 1 全身适应综合征

Table 1 General adaptation syndrome (GAS)

| Stage | Time of occurrence | Characteristics | Significance |
|---|---|---|---|
| Alarm | Appear after stress immediately | Activating the sympathetic- adrenal medulla system;Increasing adrenal corticosteroids | Defense mechanism;Last for a short time |
| Resistance | Appear after the warning response | High level secretion of adrenal corticosteroids | Increase the metabolic rate; Weaken inflammation and immune response |
| Exhaustion | Appears after stimulation of continuous and intensive stressors | Continuous increase in levels of adrenal corticosteroids; Decrease in the number and affinity of glucocorticoid receptors | The negative effects of the stress response start to appear, such as the related diseases, declined of organ function, even shock or death may occur |

It is not necessarily to occur in the same order, most of stressors only induce the appearance of alarm stage or resistance stage.

垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)和交感神经系统(sympathetic nervous system, SNS)激活为主的两种方式,几乎动员了所有的器官组织。常见的应激源分为躯体性应激源(各种物理、化学和生物学刺激物)、心理性应激源(冲突、挫折、憎恨、恐惧等)以及社会性应激源(职业竞争、工作负担等)。慢性应激状态之下,HPA与SNS的持续激活可使机体长期暴露于高浓度的应激激素环境之下,打破机体的平衡和负荷能力,产生不利的影响[4](图1A)。

## 2 慢性应激与肿瘤的发生与演进

### 2.1 慢性应激与肿瘤的流行病学证据

越来越多的证据表明,慢性应激会增加女性的肿瘤患病风险[5-6]。在一项排除年龄、人乳头状瘤病毒(HPV)感染以及性伴侣数量等干扰因素后的研究结果显示,婚姻不和谐引发的暴力事件等与宫颈癌前病变的显著增加有关[7]。此外,Kirsi 团队通过对双胞胎队列的随访研究也发现离婚/分居、配偶死亡以及亲属/朋友的死亡等个人重大生活事件会增加女性乳腺癌的患病风险[8]。对男性而言,工作压力也被证明与前列腺癌的患病风险相关[9]。综上,不论性别如何,慢性应激均在肿瘤的发生与演进中发挥重要作用[10]。

### 2.2 慢性应激促肿瘤发生与演进的机制

**2.2.1** 慢性应激诱导肿瘤发生 慢性应激相关的环磷酸腺苷/蛋白激酶A/环磷腺苷效应元件结合蛋白(cAMP/PKA/CREB)信号通路的激活可能促进肿瘤的发生[11](图1B)。XIA等[12]在小细胞肺癌中研究发现,CREB可上调肿瘤细胞的增殖活性、维持其神经内分泌特征。在前

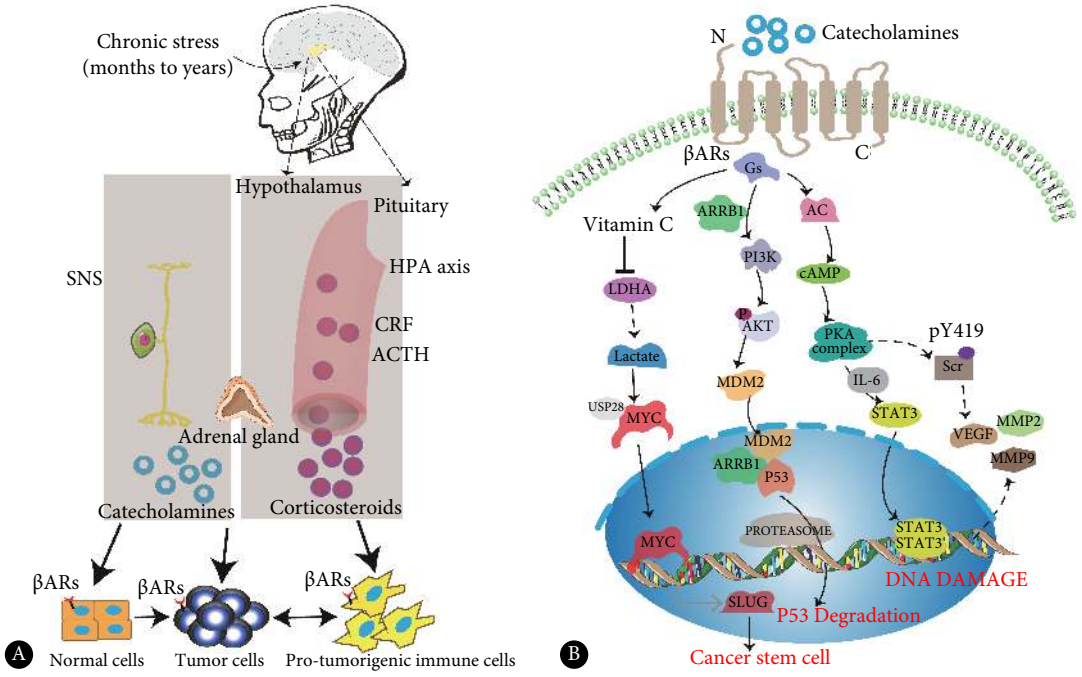


图 1 慢性应激参与肿瘤发生和发展的机制

Fig 1 The mechanism of chronic stress involved in tumor initiation and evolution

A: Chronic stress promotes the occurrence and initiation of tumors by activating two classical stress pathways, hypothalamic-pituitary-adrenal axis (HPA axis) and sympathetic nervous system (SNS); B: Catecholamine promotes tumorigenesis through the cAMP/PKA/CREB signaling pathway. CRF: Corticotropin releasing factor; ACTH: Adrenocorticotropic hormone; βARs: β Adrenergic receptors; VEGF: Vascular endothelial growth factor; MMPs: Matrix metalloproteinases; PKA: Proteinkinase A.

列腺小鼠模型中，慢性应激可以激活肾上腺素/B淋巴细胞瘤-2基因相关启动子（BAD）的抗凋亡信号通路，降低治疗敏感性[13]。尽管如此，仍有部分研究显示cAMP/PKA/CREB信号通路的肿瘤抑制作用[14]，例如，该信号通路可激活ATM蛋白激酶进而促进放射治疗诱导的肺癌细胞凋亡[15]。由于cAMP/PKA/CREB信号通路自身的进化保守性以及其在多种生理及病理过程中的不同作用机制，现有的大部分研究数据均来源于体外实验，动物模型等体内实验证据相对匮乏，而有关慢性应激及肿瘤的临床研究更加少见，因此，笔者认为，靶向cAMP/PKA/CREB信号通路逆转肿瘤发生的治疗策略仍需进一步探索。

肿瘤干细胞（cancer stem cells，CSCs）具有自我更新和多向分化潜能，并能启动和重建肿瘤恶性表型[16-17]，对肿瘤的发生、演进以及临床结局具有重要作用。研究表明，慢性应激可通过促进癌细胞的干细胞样特性增强其致癌潜能[18]。研究发现慢性应激导致的肾上腺素水平异常升高，可通过增强乳酸脱氢酶（LDHA）的表达提升乳腺癌的糖酵解水平，从而引起肿瘤酸性微环境的改变，进而增强乳腺癌的干性特征导致乳腺癌发生发展的新机制，同时证明靶向LDHA的潜在治疗药物维生素C能够显著逆转高肾上腺素水平对乳腺癌的致癌作用，为肿瘤患者的临床治疗提供了崭新的思路[19]。

**2.2.2**　*慢性应激促进肿瘤的转移*　慢性应激可加速肿瘤转移从而促进肿瘤演进[20-21]。毋庸置疑，肿瘤异质性作为恶性肿瘤的特征之一，是引起转移的重要原因之一。糖皮质激素受体（GRs）的过表达与过度活化与糖皮质激素（GCs）分泌增加有关，可促进小鼠乳腺癌细胞的异质性[22]。肝转移是结肠癌主要死因之一，与慢性应激引起的儿茶酚胺水平升高有关，而β受体拮抗剂被证明可以逆转这一不良影响[23]。胃作为应激激素的重要靶器官，经常受到应激损伤的影响。慢性应激状态下，胃癌小鼠血浆及胃组织模型中去甲肾上腺素水平上调从而诱导胃癌细胞自噬激活。目前，关于自噬的肿瘤促进或抑制观点仍存在争议，此研究不仅首次揭示了胃癌细胞自噬对于其发生演进过程的促进作用，也是第一个提供临床前证据证明慢性应激在胃癌发生与演进中发挥重要作用的研究[24]。慢性应激激活SNS后，可通过肿瘤微环境中巨噬细胞的环氧化酶2（COX2）炎症信号使肿瘤细胞分泌血管内皮生长因子受体，从而影响肿瘤淋巴血管系统的重塑，为阻止肿瘤的淋巴转移途径提供了一种可能的策略[25]。综上所述，慢性应激对肿瘤转移的调控可发生在多个层面，包括肿瘤细胞自身转移潜能的调控以及肿瘤微环境的调控[26-27]。

有研究报道，慢性应激可引起大鼠肠道菌群的改变[28-29]，而肠道菌群作为肠道微环境的重要调节因子，在肿瘤转移过程中发挥重要作用。研究发现转移相关分泌蛋白组织蛋白酶K（CTSK）是肠道菌群失衡和结直肠癌（CRC）转移之间的重要中介[30]，肠道菌群失调引起的内毒素释放促进肿瘤细胞侵袭转移[31]。尽管目前缺乏慢性应激引起肠道菌群失调导致肿瘤转移的直接证据，但上述研究表明了其间存在的可能相关性。

## 3　慢性应激重塑肿瘤微环境

### 3.1　慢性应激重塑肿瘤免疫微环境

慢性应激对于癌症患者免疫系统的影响不容忽视。研究表明，慢性应激可通过加速免疫细胞衰老、减少免疫

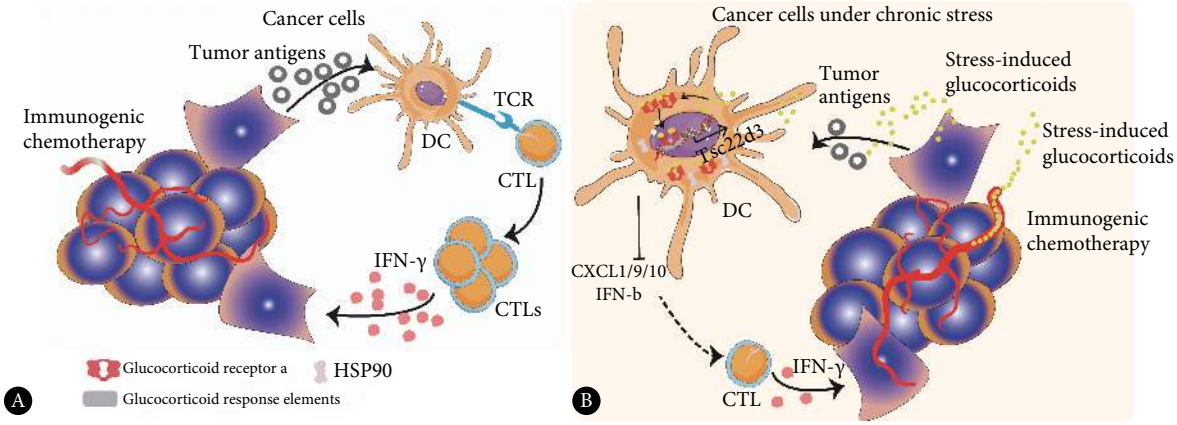


**图 2　慢性应激抑制免疫应答，重塑肿瘤免疫微环境**

**Fig 2　Chronic stress inhibits the immune response and reshapes the tumor tomor immune microenvironment**

A: Immunotherapy can induce tumor cells releasing tumor-associated antigens, which subsequently activate dendritic cells (DCs) and cytotoxic T lymphocytes (CTLs) and ultimately kill tumor cells; B: Under chronic stress, glucocorticoids inhibit secretion of tumor-associated antigens and cytotoxic function of CTLs through multiple mechanisms, including down-regulation of interferon β and chemokine lignad 1/9/10 (CXCL1/9/10), etc.. HSP90: Heat shock proteins 90; IFN-γ: Interferon-γ.

细胞数量、抑制免疫细胞功能以及打破体内细胞因子平衡等方式,重塑肿瘤免疫微环境并抑制机体的免疫反应,从而导致肿瘤的发生与演进[32-33]。儿茶酚胺与GCs可通过多种途径参与慢性应激对免疫细胞的抑制作用(图2),例如破坏树突状细胞(DCs)激活T细胞的能力并阻止DCs成熟,促进骨髓源性抑制细胞(MDSC)在肿瘤部位的积累等[34-35]。手术作为肿瘤的主要治疗策略之一,所引起的慢性应激状态可导致乳腺癌小鼠肿瘤微环境中MDSC数量的增加,上调转化生长因子-β1(TGF-β1)、血管内皮生长因子(VEGF)和白介素-10(IL-10)的表达,从而诱导肿瘤细胞上皮-间充质转化(epithelial-mesenchymal transition, EMT),进而促进肿瘤转移[36]。该研究为临床预防乳腺癌术后转移的发生提供了新的研究方向——消耗MDSC的治疗策略,同时提示肿瘤患者在选择外科治疗时需更加谨慎。慢性应激显著抑制小鼠黑色素瘤疫苗的效果,是损害DC功能和$TCD8^+$启动介导的癌症免疫接种宿主免疫抑制的一个重要因素[37]。尽管小鼠是研究人类疾病模型和免疫反应的最佳生物,但研究人员在构建模型时忽略了在施加各种应激源之前小鼠的应激状态,实验过程中无法量化分组中单个小鼠的应激水平等问题的存在一定程度上限制了慢性应激相关研究的临床转化潜力[38]。

### 3.2 慢性应激重塑肿瘤炎性微环境

应激状态下所产生的促炎细胞因子被认为在肿瘤的发生与演进中发挥重要作用[39-40]。白介素-6(IL-6)是应激诱导细胞分泌的特征性细胞因子,既可以由肿瘤细胞产生也可以由浸润肿瘤组织的免疫细胞产生,是应激的生理反应标志之一[41]。促肾上腺皮质激素释放因子受体亚型1(CRF1)信号可正向调节应激诱导的肥大细胞脱粒促进肿瘤发生,*CRF1*基因敲除小鼠可通过调节白介素-1β(IL-1β)、IL-6、肿瘤坏死因子-α(TNF-α)的表达使得肠炎相关的肿瘤发生率明显下降[42]。未来需要深入探索应激、炎症与免疫以及肿瘤之间的关系,为肿瘤的防治策略开拓新视野。

## 4 应激管理策略的探索

目前,慢性应激直接导致人体肿瘤发生与演进的循证医学证据仍不明确。肿瘤患者出现的由疾病诊断、进展及治疗所引发的强烈情感变化(恐惧、绝望、悲观等)使机体处于慢性应激状态,进而下调机体免疫力、认知能力、记忆力等功能,降低患者的生活质量,导致不良的临床结局。同时,人们在慢性应激状态下更易存在吸烟、过量饮酒等不良嗜好,这种不健康的生活方式可能是慢性应激诱发肿瘤的重要原因。因此,应激管理策略的探索性研究极具挑战[43]。

### 4.1 阻遏慢性应激的药物治疗探索

流行病学研究表明,服用β受体拮抗剂的患者罹患几种肿瘤的概率较低[44-45]。β2-肾上腺素能信号通路的激活可以增强慢性应激下胃癌细胞的发生演进及肿瘤血管生成[46],提示β2受体拮抗剂可用于控制肿瘤的临床进展,改善患者预后。β肾上腺素能信号激活会依赖LKB1/CREB/IL-6途径促进非小细胞肺癌使用表皮生长因子受体抑制剂(EGFR-TKI)的耐药反应[47],因此,β受体拮抗剂与EGFR-TKI的联合使用可能成为解决耐药反应的一种新策略。此外,β受体拮抗剂与其他肿瘤治疗方案之间可能的协同作用也值得我们关注,例如普萘洛尔与放疗联合可以降低人胃腺癌细胞的克隆生存能力[48],普萘洛尔联合顺铂对于头颈部鳞状细胞癌的治疗可能有效[49]等。综上,β受体拮抗剂的"抑癌"活性及其机制以及与不同联合治疗方案的选择等问题是我们今后探索研究的重要方向。

### 4.2 逆转慢性应激的干预措施

肿瘤治疗早已进入综合治疗的时代。有研究提示,在肿瘤患者治疗的过程中加入医学与心理干预(medical and psychological intervention, MPI)以及认知行为压力管理(cognitive-behavioral stress management, CBSM)可降低患者的应激水平,改善其生活质量,从而进一步提高临床疗效[50-51]。良性应激往往带来有利的影响,恶性肿瘤也不例外。体育运动诱导的肾上腺素、IL-6水平升高可通过NK细胞的动员与再分配可抑制肿瘤生长[52-53]。一项动物实验结果展示了丰富胰腺癌和肺癌模型小鼠生存环境(社交和运动)可以通过交感神经的激活稳定NK细胞中CCR5和NKG2D的表达水平从而增强其抗肿瘤效应,除此之外,也抑制了黑色素瘤肺转移小鼠模型的肿瘤转移作用[54]。临床研究表明,正念冥想、瑜伽等模式是减轻慢性应激和提高癌症患者生活质量的有效策略[55-57]。总之,健康的生活方式、积极的生活态度与专业的应激管理指导对肿瘤的防治来说至关重要。

## 5 展望

慢性应激与肿瘤的发生与演进过程辅牙相倚,极大地影响着我们的生活。越来越多的证据表明,慢性应激可以促进肿瘤的发生与演进,抑制机体免疫反应,重塑肿瘤免疫微环境;但考虑到人们尚未系统、全面地揭示慢性应激促进肿瘤发生与演进的机制,因此,仍需深入探讨并进一步阐明作用机理,为肿瘤的防治策略带来新的希望。临床上,慢性应激的出现总会伴随神经功能紊乱与失调,在癌症患者的个性化治疗过程中,我们应该更加密

切关注患者的应激状态, 提出科学合理的应激管理策略。

## 参 考 文 献


[1] TAO W, LUO X, CUI B, *et al*. Practice of traditional Chinese medicine for psychobehavioral intervention improves quality of life in cancer patients: a systematic review and meta-analysis. Oncotarget, 2015, 6(37): 39725–39739.

[2] ANTONI M, DHABHAR F. The impact of psychosocial stress and stress management on immune responses in patients with cancer: stress, stress management, and immunity. Cancer, 2019, 125(9): 1417–1431.

[3] MRAVEC B, TIBENSKY M, HORVATHOVA L. Stress and cancer. Part I: Mechanisms mediating the effect of stressors on cancer. J Neuroimmunol, 2020, 3(346): 577311[2020-10-12]. https://doi.org/10.1016/j.jneuroim.2020.577311.

[4] KRIZANOVA O, BABULA P, PACAK K. Stress, catecholaminergic system and cancer. Stress, 2016, 19(4): 419–428.

[5] HUANG T, POOLE E, OKEREKE O, *et al*. Depression and risk of epithelial ovarian cancer: results from two large prospective cohort studies. Gynecol Oncol, 2015, 139(3): 481–486.

[6] HALBERT C H, JEFFERSON M S, DANIELSON C, *et al*. An observational study and randomized trial of stress reactivity in cancer disparities. Health Psychol, 2020, 39(9): 745–757.

[7] COKER A L, BOND S, MADELEINE M M, *et al*. Psychosocial stress and cervical neoplasia risk. Psychosom Med, 2003, 65(4): 644–651.

[8] KIRSI L, VERKASALO P, JAAKKO K, *et al*. Stressful life events and risk of breast cancer in 10 808 women: a cohort study. Am J Epidemiol, 2003, 157(5): 415–423.

[9] BLANC L A, ROUSSEAU M C, PARENT M E. Perceived workplace stress is associated with an increased risk of prostate cancer before age 65. Front Oncol, 2017, 13(7): 269[2020-10-12]. https://doi.org/10.3389/fonc.2017.00269.

[10] AFRISHAM R, PAKNEJAD M, SOLIEMANIFAR O, *et al*. The influence of psychological stress on the initiation and progression of diabetes and cancer. Int J Endocrinol Metab, 2019, 17(2): e67400[2020-10-12]. https://doi.org/10.5812/ijem.67400.

[11] BRAADLAND P, RAMBERG H, GRYTLI H, *et al*. The β2-adrenergic receptor is a molecular switch for neuroendocrine transdifferentiation of prostate cancer cells. Mol Cancer Res, 2019, 17(11): 2154–2168.

[12] XIA Y, ZHAN C, FENG M, *et al*. Targeting CREB pathway suppresses small cell lung cancer. Mol Cancer Res, 2018, 16: 825–832.

[13] HASSAN S, KARPOVA Y, BAIZ D, *et al*. Behavioral stress accelerates prostate cancer development in mice. J Clin Invest, 2013, 123(2): 874–886.

[14] HONG Q Z, QING B K, JIAO W, *et al*. Complex roles of cAMP-PKA-CREB signaling in cancer. Exp Hematol Oncol, 2020, 9: 32[2020-11-01].https://doi.org/10.1186/s40164-020-00191-1.

[15] CHO E A, KIM E J, KWAK S J, *et al*. cAMP signaling inhibits radiation-induced ATM phosphorylation leading to the augmentation of apoptosis in human lung cancer cells. Molecular Cancer, 2014, 13(1): 36–36.

[16] XU L, LI S, ZHOU W, *et al*. p62/SQSTM1 enhances breast cancer stem-like properties by stabilizing *MYC* mRNA. Oncogene, 2017, 36(3): 304–317.

[17] TAM W, LU H, BUIKHUISEN J, *et al*. Protein kinase C α is a central signaling node and therapeutic target for breast cancer stem cells. Cancer Cell, 2013, 24(3): 347–364.

[18] BOWEN Z, CHENZHOU W, WEN C, *et al*. The stress hormone norepinephrine promotes tumor progression through β2-adrenoreceptors in oral cancer. Arch Oral Biol, 2020, 113: 104712[2020-11-01]. https://doi.org/10.1016/j.archoralbio.2020.104712.

[19] CUI B, LUO Y, TIAN P, *et al*. Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells. J Clin Invest, 2019, 129(3): 1030–1046.

[20] DAN L, XIANG C, MING S, *et al*. Chronic psychological stress promotes lung metastatic colonization of circulating breast cancer cells by decorating a pre-metastatic niche through activating β-adrenergic signaling. J Pathol, 2018, 244(1): 49–60.

[21] DAI S, MO Y, WANG Y, *et al*. Chronic stress promotes cancer development. Front Oncol, 2020, 10: 1492[2020-11-01]. https://doi.org/10.3389/fonc.2020.01492.

[22] OBRADOVIC M, HAMELIN B, MANEVSKI N, *et al*. Glucocorticoids promote breast cancer metastasis. Nature, 2019, 567(7749): 540–544.

[23] ZHAO L, XU J, LIANG F, *et al*. Effect of chronic psychological stress on liver metastasis of colon cancer in mice. PLoS One, 2015, 10(10): e0139978[2020-11-01]. https://doi.org/10.1371/journal.pone.0139978.

[24] ZHI X, LI B, LI Z, *et al*. Adrenergic modulation of AMPK-dependent autophagy by chronic stress enhances cell proliferation and survival in gastric cancer. Int J Oncol, 2019, 54(5): 1625–1638.

[25] LE P, NOWELL C, KIM C, *et al*. Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. Nat Commun, 2016, 1: 10634[2020-11-01]. https://doi.org/10.1038/ncomms10634.

[26] KIM F, LE C, PIMENTEL M, *et al*. Chronic stress accelerates pancreatic cancer growth and invasion: a critical role for beta-adrenergic signaling in the pancreatic microenvironment. Brain Behav Immun, 2014, 40: 40–47.

[27] CLAIRE M. Autonomic nerve development contributes to prostate cancer progression. Science, 2013, 341(6142): 1236361[2020-11-01]. https://doi.org/10.1126/science.1236361.

[28] WEI L, LI Y, TANG W, *et al*. Chronic unpredictable mild stress in rats induces colonic inflammation. Front Physiol, 2019, 10: 1228[2020-11-01]. https://doi.org/10.3389/fphys.2019.01228.

[29] MURAKAMI T, KAMADA K, MIZUSHIMA K, *et al*. Changes in intestinal motility and gut microbiota composition in a rat stress model. Digestion, 2017, 95(1): 55–60.

[30] ROOKS M, GARRETT W. Gut microbiota, metabolites and host immunity. Nat Rev Immunol, 2016, 16(6): 341–352.

[31] ZHANG Y, ZANOS P, JACKSON I, *et al*. Psychological stress enhances tumor growth and diminishes radiation response in preclinical model of lung cancer. Radiother Oncol, 2020, 146: 126–135.

[32] KANG Y, NAGARAJA A, ARMAIZ P, *et al*. Adrenergic stimulation of DUSP1 impairs chemotherapy response in ovarian cancer. Clin Cancer Res, 2016, 22(7): 1713–1724.

[33] MUTHUSWAMY R, OKADA N J, JENKINS F J, *et al*. Epinephrine promotes COX-2-dependent immune suppression in myeloid cells and cancer tissues. Brain Behav Immun, 2017, 62: 78–86.

[34] YANG H, XIA L, CHEN J, *et al*. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. Nat Med, 2019, 25(9): 1428–1441.

[35] MATYSZAK M, CITTERIO S, RESCIGNO M, *et al*. Differential effects of corticosteroids during different stages of dendritic cell maturation. Eur J Immunol, 2000, 30(4): 1233–1242.

[36] MA X, WANG M, YIN T, *et al*. Myeloid-derived suppressor cells promote metastasis in breast cancer after the stress of operative removal of the primary cancer. Front Oncol, 2019, 10(9): 855[2020-11-01].https://doi.org/10.3389/fonc.2019.00855.

[37] SOMMERSHOF A, SCHEUERMANN L, KOERNER J, *et al*. Chronic

stress suppresses anti-tumor TCD8$^+$ responses and tumor regression following cancer immunotherapy in a mouse model of melanoma. Brain Behav Immun, 2017, 10(65): 140–149.

[38] HYLANDER B, GORDON C, REPASKY E. Manipulation of ambient housing temperature to study the impact of chronic stress on immunity and cancer in mice. J Immunol, 2019, 202(3): 631–636.

[39] BARITAKI S, BREE E, CHATZAKI E, *et al*. Chronic stress, inflammation, and colon cancer: a CRH system-driven molecular crosstalk. J Clin Med, 2019, 8(10): 1669[2020-11-01].https://doi.org/10.3390/jcm8101669.

[40] NIRAULA A, WITCHER K, SHERIDAN J, *et al*. Interleukin-6 induced by social stress promotes a unique transcriptional signature in the monocytes that facilitate anxiety. Biol Psychiatry, 2019, 85(8): 679–689.

[41] POWELL N, TARR A, SHERIDAN J, *et al*. Psychosocial stress and inflammation in cancer. Brain Behav Immun, 2013(Suppl): S41–S47[2020-11-01].https://doi.org/10.1016/j.bbi.2012.06.015.

[42] AYYADURAI S, GIBSON A, DCOSTA S, *et al*. Frontline science: corticotropin-releasing factor receptor subtype 1 is a critical modulator of mast cell degranulation and stress-induced pathophysiology. J Leukoc Biol, 2017, 102(6): 1299–1312.

[43] MRAVEC B, TIBENSKY M, HORVATHOVA L. Stress and cancer. Part II: Therapeutic implications for oncology. J Neuroimmunol, 2020, 3(346): 577312[2020-11-01]. https://doi.org/10.1016/j.jneuroim.2020.577312.

[44] FITZGERALD J. Beta blockers, norepinephrine, and cancer: an epidemiological viewpoint. Clin Epidemiol, 2012, 4: 151–156.

[45] JANSEN L, HOFFMEISTER M, ARNDT V, *et al*. Stage-specific associations between beta blocker use and prognosis after colorectal cancer. Cancer, 2014, 120(8): 1178–1186.

[46] ZHANG X, ZHANG Y, HE Z, *et al*. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. Cell Death Dis, 2019, 10(11): 788[2020-11-01]. https://www.nature.com/articles/s41419-019-2030–2. doi: 10.1038/s41419-019-2030-2.

[47] NILSSON M, SUN H, DIAO L, *et al*. Stress hormones promote EGFR inhibitor resistance in NSCLC: implications for combinations with β-blockers. Sci Transl Med, 2017, 9(415): 4307[2020-11-01].https://doi.org/10.1126/scitranslmed.aao4307.

[48] LIAO X, CHE X, ZHAO W, *et al*. Effects of propranolol in combination with radiation on apoptosis and survival of gastric cancer cells. Radiat Oncol, 2010, 5: 98[2020-11-01].https://doi.org/10.1186/1748-717X-5-98.

[49] WOLTER N, WOLTER J, ENEPEKIDES D, *et al*. Propranolol as a novel adjunctive treatment for head and neck squamous cell carcinoma. J Otolaryngol Head Neck Surg, 2012, 41(5): 334–344.

[50] BARRE P V, PADMAJA G, RANA S, *et al*. Stress and quality of life in cancer patients: medical and psychological intervention. Indian J Psychol Med, 2018, 40(3): 232–238.

[51] WANG A W, BOUCHARD L C, GUDENKAUF L M, *et al*. Differential psychological effects of cognitive-behavioral stress management among breast cancer patients with high and low initial cancer-specific distress. J Psychosom Res, 2018, 113: 52–57.

[52] PEDERSEN L, IDORN M, OLOFSSON G H, *et al*. Voluntary running suppresses tumor growth through epinephrine- and il-6-dependent NK cell mobilization and redistribution. Cell Metab, 2016, 23(3): 554–562.

[53] IDORN M, HOJMAN P. Exercise-dependent regulation of nk cells in cancer protection. Trends Mol Med, 2016, 22(7): 565–577.

[54] YANF, GAN Y, QANG Q, *et al*. Enriching the housing environment for mice enhances their NK cell antitumor immunity via sympathetic nerve-dependent regulation of NKG2D and CCR5. Cancer Res, 2017, 77(7): 1611–1622.

[55] ARAUJO R, FERNANDES A, NERY I, *et al*. Meditation effect on psychological stress level in women with breast cancer: a systematic review. Rev Esc Enferm USP, 2019, 53: e03529[2020-11-01].https://doi.org/10.1590/S1980-220X2018031303529.

[56] RUSH S E, SHARMA M. Mindfulness-based stress reduction as a stress management intervention for cancer care: a systematic review. J Evid Based Complementary Altern Med, 2017, 22(2): 348–360.

[57] SCHELLEKENS M P J, PRINS J B, DONDERS A R T, *et al*. Mindfulness-based stress reduction added to care as usual for lung cancer patients and/or their partners: a multicentre randomized controlled trial. Psychooncology, 2017, 26(12): 2118–2126.

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