

· 慢病专题:癌症 ·

慢性心理应激与肿瘤免疫的研究进展*

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[摘要] 压力、焦虑、失眠等慢性心理应激,近年来已成为促进肿瘤发生、发展的重要危险因素。应激反应介导的神经内分泌系统持续分泌应激相关激素和神经递质,对肿瘤有重要影响,包括促进肿瘤发生、侵袭、转移和免疫逃逸。除了对肿瘤细胞自身的影响外,慢性应激及其导致的心理应激也会影响肿瘤微环境中的免疫细胞,包括数量减少和功能抑制,显著促进多种肿瘤恶性进展。然而,慢性心理应激如何调控肿瘤相关免疫细胞或全身免疫细胞的机制仍是一个尚未完全解决的问题,靶向干预其中的潜在机制有望成为肿瘤免疫治疗新策略。该文主要针对现有的慢性心理应激与肿瘤免疫的相关研究作一综述。

[关键词] 慢性心理应激; 肿瘤免疫; 微环境; 免疫细胞; 综述

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Research progress on chronic psychological stress and tumor immunity*

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[Abstract] Chronic psychological stress such as stress, anxiety, and insomnia have become important risk factors for promoting the occurrence and development of tumors in recent years. The neuroendocrine system mediated by stress response continuously secretes stress-related hormones and neurotransmitters have important effects on tumors, including promoting tumor occurrence, invasion, metastasis, and immune escape. In addition to its impact on tumor cells themselves, chronic stress and the psychological stress it induces can also affect immune cells in the tumor microenvironment, including reduced numbers and functional inhibition, significantly promoting the malignant progression of various tumors. However, the mechanism by which chronic psychological stress regulates tumor associated immune cells or systemic immune cells remains an unresolved issue, and targeted interventions targeting these potential mechanisms have the potential to become a new strategy for tumor immunotherapy. This article mainly summarized the existing research on the correlation between chronic psychological stress and tumor immunity.

[Key words] Chronic psychological stress; Tumor immunity; Microenvironment; Immune cells; Review

在快节奏的现代化生活中,心理社会因素导致的健康问题日益突出。抑郁症是常见的慢性心理应激疾病之一,近 1/4 的女性和 1/6 的男性在一生中经历过抑郁症^[1]。一项对接受抑郁症治疗的患者随访研究显示,高达 64% 的个体在治疗期间抑郁症会再次发作^[2],持续影响人们的健康和生活质量。同时,肿瘤

等慢性疾病,也是导致患者产生慢性心理应激的常见因素。例如,癌症患者中抑郁症的患病率为 15%~30%,而一般人群的平均患病率约为 3.3%^[3]。

慢性心理应激会激活人体下丘脑-垂体-肾上腺(HPA)轴^[4]及交感神经系统(SNS)^[5],释放糖皮质激素和儿茶酚胺。在癌症中,儿茶酚胺可以增强前列

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腺、卵巢、乳腺和结肠肿瘤细胞的致癌特性^[6],糖皮质激素是免疫抑制剂,参与肿瘤细胞免疫调节^[7]。免疫系统在癌症的发展中起着重要作用,不同的免疫因子,如免疫细胞和各种白细胞介素,对肿瘤的发展过程和转移的出现有重要影响^[8-10]。

1 慢性心理应激

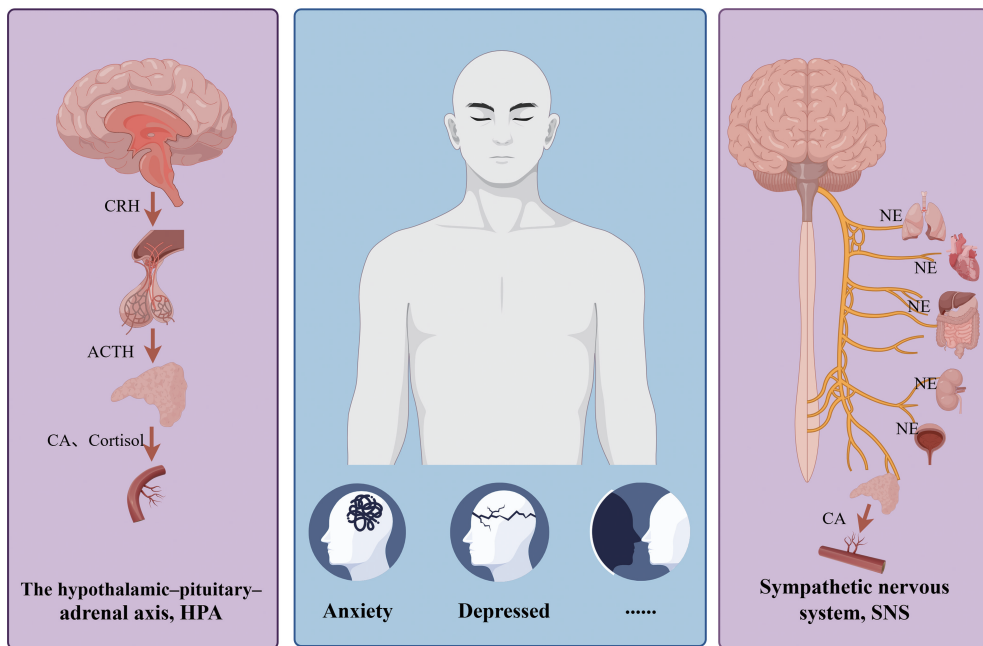
压力是生活中不可缺少的一部分,长期暴露于具有威胁性的环境中会产生有害影响,可能是包括癌症在内的许多慢性疾病的诱因或加重因素^[11]。持续的心理压力可能导致免疫监视功能的丧失^[12]。流行病学研究表明,慢性心理应激在癌症的发生、进展和转移中起积极作用,而在抗肿瘤免疫功能和治疗反应中起消极作用^[13]。

应激反应的神经内分泌系统主要由 HPA 轴和 SNS 构成^[14]。长期应激状态下,应激相关激素和神

经递质的持续分泌对肿瘤有重要影响,包括促进肿瘤发生、肿瘤增殖、肿瘤侵袭、肿瘤血管生成和逃避免疫监视^[15]。

1.1 HPA 轴 HPA 轴是神经内分泌系统的重要组成部分,由下丘脑、垂体前叶和肾上腺 3 个内分泌腺组成。在压力的条件下,下丘脑释放促肾上腺皮质激素释放激素(CRH),其触发垂体前叶分泌促肾上腺皮质激素(ACTH),ACTH 刺激肾上腺释放应激激素,如儿茶酚胺(肾上腺素、去甲肾上腺素)和皮质醇。这些激素通过体循环到达目标器官,从而引起生理反应^[16]。

1.2 SNS SNS 是调节压力相关级联反应的主要参与者。SNS 刺激肾上腺髓质分泌儿茶酚胺进入血液或直接向交感神经支配的靶器官释放去甲肾上腺素,从而促进肿瘤生长^[16]。心理应激反应的 2 条神经内分泌网络见图 1。



注:CRH 为促肾上腺皮质激素释放激素;ACTH 为促肾上腺皮质激素;CA 为儿茶酚胺;Cortisol 为皮质醇;Anxiety 为焦虑症;Depressed 为抑郁症;NE 为去甲肾上腺素。

图 1 心理应激反应的 2 条神经内分泌网络(由 Figdraw 绘制)

综上所述,无论是 HPA 轴还是 SNS,应激介导癌症的发生、进展都与儿茶酚胺密切相关^[17]。在慢性应激条件下,癌症的进展主要是通过激活肾上腺素受体(ARs)和糖皮质激素受体(GRs)2 条信号通路来实现^[14-15]。例如,儿茶酚胺由 β_2 肾上腺素受体($ADR\beta_2$)发挥促肿瘤作用^[18-19]。在慢性应激小鼠模型中,糖皮质激素通过诱导血清和糖皮质激素调节的蛋白激酶(SGK1)增加负调节物小鼠双微体 2(MDM2)的活性并抑制 p53 功能,进而促进肿瘤的发生^[20]。

既往研究证明,儿茶酚胺表达含量增加促进了肿瘤的发生、进展。例如,儿茶酚胺促进了 $ADR\beta_2$ 依赖

性胰腺导管腺癌(PDAC)的发育、神经生长因子(NGF)的分泌,加速了肿瘤进展^[21]。慢性应激会通过 $ADRB2$ 激活 cyclic AMP(cAMP)-protein kinase A(PKA)信号通路导致组织儿茶酚胺水平升高、肿瘤负担加重和卵巢癌细胞侵袭性生长增加^[22]。此外,糖皮质激素也被证明在促进肿瘤进展中发挥重要作用。例如,糖皮质激素 GR-CDK1 信号诱导结肠癌细胞的增殖和侵袭^[23]。乳腺癌进展过程中应激激素的增加导致远处转移部位 GRs 的激活,增加了肿瘤定植和降低个体存活率^[24]。

2 慢性心理应激与肿瘤免疫

大量研究表明,慢性心理应激可调控机体的全身

免疫状态^[25-26]。慢性心理应激对 HPA 轴和 SNS 的激活产生积极作用,最终导致炎症上调,抑制细胞免疫毒性^[15]。在多种细胞因子的介导下,免疫细胞与肿瘤微环境(TME)中的癌细胞进行交流,调控肿瘤生长、血管生成和转移。慢性应激及其导致的心理应激也会影响 TME 中的免疫细胞,包括数量减少和功能抑制^[27]。

2.1 TME TME 是肿瘤生存的特殊环境,具有缺氧、酸性、缺乏营养和免疫抑制等特点,由脉管系统、免疫细胞、细胞外间质和蛋白质或代谢分子组成^[28]。HPA 轴和 SNS 的持续激活可通过介导应激性 TME 促进促癌免疫细胞和细胞因子数量增加,血管生成增多,上皮-间质转化增强,细胞外基质受损,最终加速肿瘤进展^[29]。

2.2 免疫细胞

2.2.1 T 细胞 T 细胞代谢在支持和塑造免疫反应及抗肿瘤免疫中起着核心作用^[30]。急性应激通过 β_2 肾上腺素介导的过程增加 T 细胞动员,而慢性应激会减弱这一过程,心理应激会削弱免疫系统的能力,从而使机体更容易受到感染^[31]。压力源和抑郁都与细胞毒性 T 细胞活动的减少有关,影响肿瘤的免疫监视等过程^[32]。一项研究表明,在人类免疫缺陷病毒-1 和人乳头瘤病毒合并感染的黑种人妇女中,有压力的负面生活事件和悲观情绪与自然杀伤细胞(NK)细胞毒性、T 细胞毒性/抑制细胞(CD8⁺ CD3⁺)百分比降低有关^[33]。在应激导致卵巢肿瘤小鼠腹水中检测到皮质酮、去甲肾上腺素,腹水微环境中 CD4⁺ PD-1⁺ / CD8⁺ PD-1⁺ T 细胞比率增加,是肿瘤相关炎症、T 细胞抑制和疾病进展的驱动因素^[34]。此外,应激降低了年轻前列腺癌小鼠肿瘤内 CD4⁺ 和 CD4⁺ FoxP3⁺ T 细胞数量^[35]。应激小鼠的肿瘤显示出 CD4⁺ T 细胞总数减少、调节性 T 细胞(Treg)增加、T 细胞与肿瘤细胞接触减少及 CD4⁺ T 细胞中 CTLA-4 减少的趋势^[36]。

2.2.2 NK 细胞 NK 细胞通过其细胞毒性效应器功能及其与其他免疫细胞相互作用发挥抗肿瘤免疫反应的能力,在肿瘤免疫监测中起着关键作用^[37]。一项研究表明,在卵巢癌患者中,具有更强心理应激的人群肿瘤浸润淋巴细胞中有更多的 NK 细胞活性受损^[38]。另一项研究表明,在癌症相关的高水平心理应激患者中观察到的 NK 细胞溶解损伤可能是由于 NK 细胞抑制和激活受体的失调^[39]。此外,新诊断为癌症的女性及乳腺活检会引起焦虑、压力等情绪,进而导致 NK 细胞活性降低和细胞因子失调^[40-41]。动物实验表明,在暴露于精神压力的小鼠血清中应激激素水平升高,血液和肿瘤样本中 NK 细胞百分比降低,体内肿瘤生长加速^[42]。

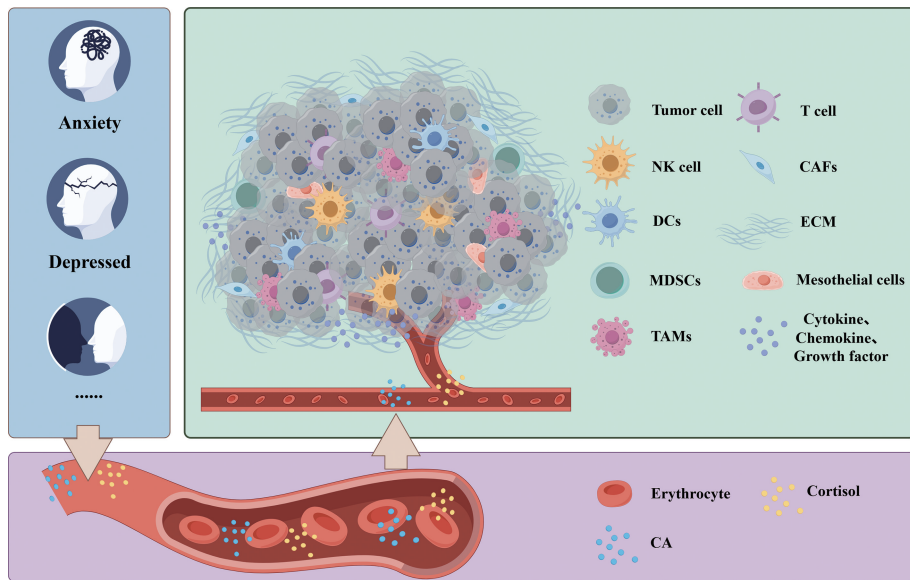
2.2.3 骨髓来源的抑制性细胞(MDSCs) MDSCs 是免疫抑制网络的一个主要组成部分,抑制 T 细胞的活性,利于恶性肿瘤的免疫逃逸^[43]。在一项研究中,应激相关的糖皮质激素升高增强了 TAM/CXCL1 信号传导,从而招募脾脏 MDSCs 通过 CXCR2 促进肿瘤转移前生态位的形成^[44]。慢性心理应激的小鼠模型增强了 MDSCs 对增殖 T 细胞的抑制活性,表明 MDSCs 等抑制性细胞在促进肿瘤生长中可能发挥了作用^[45]。此外,慢性应激增强了 MDSCs 中 CXCR2 和 pErk1/2 的表达,促进肝癌组织中趋化因子 CXCL5 表达增加,显著促进肝细胞癌的生长,以及骨髓中 MDSCs 向脾脏和肿瘤部位的动员^[46]。应激还降低了荷瘤小鼠血液中 CD3⁺ CD4⁺ T 细胞和 CD3⁺ CD8⁺ T 细胞的百分比,同时增加了 CD11b⁺ Gr-1⁺ MDSC 的百分比,促进肝细胞癌的生长,抑制荷瘤小鼠的抗肿瘤免疫^[47]。

2.2.4 树突状细胞(DCs) DCs 是宿主免疫应答的关键“哨兵”,是启动和维持有效的 T 细胞介导抗肿瘤免疫应答的关键因素,TME 中 DCs 的存在和功能可能决定癌症免疫疗法及常规癌症治疗的功效^[48]。一项研究表明,社会压力会激活 DCs,增加 DCs 分泌 Toll 特异性刺激的细胞因子,并使 DCs 对糖皮质激素产生抵抗,抑制 DCs 的活化和功能^[49]。

2.2.5 肿瘤相关巨噬细胞(TAMs) TAMs 是肿瘤进展、转移和抗治疗的关键驱动因素,TME 中抗肿瘤 M1 类和促肿瘤 M2 类 TAMs 共存,M1/M2 亚群直接影响改善抗肿瘤免疫反应的策略^[50]。在一项研究中,慢性应激抑制了 TAMs 和其他免疫细胞的募集,特别是 M1 型 TAMs 和 CD8⁺ T 细胞,并降低胶质瘤中促炎性细胞因子的水平,导致免疫抑制微环境和胶质瘤进展^[51]。心理应激状态下的 TME 构成见图 2。

3 中医视角下慢性应激导致肿瘤发生、发展的机制

近年来,中医从自身角度解释了慢性应激导致肿瘤发生、发展的机制,即情志失调导致肝气郁结,引起机体糖代谢、脂质代谢、氨基酸代谢水平紊乱,从而使 TME 的动态平衡被打破^[52]。气、血、津液失调是情志致病主要病理过程:七情内伤致气机逆乱,引发血、津液代谢障碍,气滞可致血瘀、津停,形成湿、痰、饮等;脏腑受损或功能不全,使气、血、津液不归正化,酿生病理产物。气机长期失调,病理产物蓄积,易生癌毒^[53]。此外,中医认为,肝主疏泄是心理应激反应的核心,肝郁脾虚也为心理应激相关性疾病常见中医证候^[54]。针对致病机制,中医药在应激导致的肿瘤发生、发展治疗中得到应用。有研究证明,四逆散可以通过降低有氧糖酵解抑制慢性心理应激介导的乳腺癌生长转移^[55]。



注:CA 为儿茶酚胺;Cortisol 为皮质醇;Erythrocyte 为红细胞;NK cell 为自然杀伤细胞;DCs 为树突状细胞;MDSCs 为髓源性抑制细胞;TAMs 为肿瘤相关巨噬细胞;CAFs 为肿瘤相关成纤维细胞;ECM 为细胞外基质;Mesothelial cells 为间皮细胞;Cytokine 为细胞因子;Chemokine 为趋化因子;Growth factor 为生长因子。

图 2 心理应激状态下的 TME 构成(由 Figdraw 绘制)

4 小结与展望

应激反应的神经内分泌系统主要由 HPA 轴和 SNS 构成。长期应激状态下,应激相关激素和神经递质的持续分泌对肿瘤有重要影响,包括促进肿瘤发生、肿瘤增殖、肿瘤侵袭、肿瘤血管生成和逃避免疫监视。TME 是目前肿瘤领域的热门话题,而免疫细胞又是 TME 中的重要组成部分。慢性应激及其导致的心理应激影响 TME 中的免疫细胞,包括数量减少和功能下降。目前的研究主要集中在某些特定的肿瘤类型(如乳腺癌)和心理应激状态(如抑郁和焦虑),对其他肿瘤类型和心理应激状态的研究相对较少。此外,对于不同人群(如儿童、老年人、不同性别等)的心理应激与肿瘤免疫关系的了解也有限。尽管已经发现了一些与心理应激和肿瘤免疫相关的生物标志物(如血清皮质醇、儿茶酚胺等),但这些生物标志物的特异性和灵敏性仍需进一步提高,以便更好地用于临床诊断和预测。

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