DOI: 10.11844/cjcb.2025.08.0026
中国细胞生物学学报 Chinese Journal of Cell Biology 2025, 47(8): 2032–2047 CSTR: 32200.14.cjcb.2025.08.0026

慢性压力影响肿瘤发生发展机制的研究进展

蒋皓宇[1,2] 蒋贝贝[2] 金伟波[1] 张大伟[2]* 张瑾[2,3]*

([1]浙江理工大学生命科学与医药学院, 杭州 310018; [2]嘉兴大学生物与化学工程学院, 嘉兴 314001; [3]嘉兴爱博生物科技有限公司, 嘉兴 314050)

摘要 慢性压力(chronic stress)通过神经内分泌系统干扰体内激素平衡, 是导致肿瘤患者预后不良的重要因素。肿瘤患者在病程进展及治疗过程中常伴随焦虑、烦躁等负面情绪的反复发作, 这种慢性压力状态会加速疾病进展并降低临床疗效。近年研究表明, 处于激活状态的神经内分泌系统不仅直接作用于肿瘤细胞, 还能调节肿瘤微环境(tumor microenvironment, TME)中非癌细胞的生理状态。该文首先总结了压力信号响应特征和其介导的细胞内信号通路激活过程; 接着阐述了慢性压力通过调控肿瘤细胞自主性效应(包括增殖迁移、自噬调控及代谢重编程)、重塑TME[涉及免疫特征改变、血管新生及上皮–间充质转化(epithelial-mesenchymal transition, EMT)], 以及破坏肠道菌群稳态三方面促进肿瘤进展的机制; 最后基于现有肿瘤与慢性压力的临床治疗及药物研发进展, 总结了靶向神经内分泌系统的药理学干预策略, 为肿瘤合并压力患者的综合治疗提供了潜在方向。

关键词 慢性压力; 肿瘤; 抗肿瘤免疫; 代谢; 肠道菌群; 肿瘤治疗

Research Progress on the Mechanisms of Chronic Stress Affecting Tumor Development

JIANG Haoyu[1,2], JIANG Beibei[2], JIN Weibo[1], ZHANG Dawei[2]*, ZHANG Jin[2,3]*

([1]*College of Life Sciences and Medicine, Zhejiang Sci-Tech University, Hangzhou 310018, China*; [2]*School of Biological and Chemical Engineering, Jiaxing University, Jiaxing 314001, China*; [3]*Jiaxing i-Bio Biotechnology Co., Ltd, Jiaxing 314050, China*)

Abstract Chronic stress disrupts hormonal balance via the neuroendocrine system and is increasingly recognized as a critical factor contributing to poor prognosis in tumor patients. Cancer patients often experience recurrent negative emotions such as anxiety and irritability throughout disease progression and treatment, and this persistent chronic stress state can accelerate tumor progression and compromise therapeutic efficacy. Emerging evidence suggests that neuroendocrine activation not only exerts direct effects on tumor cells but also modulates the physiological behavior of non-cancerous cells in the tumor microenvironment. This review first outlines the process of stress signal transduction underlying stress and subsequent intracellular pathway activation. It then discusses how chronic stress facilitates tumor progression through regulating tumor cell autonomous effects (including proliferation, migration, autophagy modulation, and metabolic reprogramming), remodeling the tumor microenvironment (involving changes in immune characteristics, angiogenesis, and epithelial-mesenchymal transition), and disrupt-

收稿日期: 2025-04-18 接受日期: 2025-05-26
浙江省自然科学基金(批准号: LZ23C170002、LQ21C060007)和嘉兴市儿童疾病诊断与研究重点实验室开放基金(批准号: JXER-KJK-2025-1-0069)资助的课题
*通信作者。Tel: 0573-83643695, E-mail: cfzhangdw@zjxu.edu.cn; zhangjin7688@163.com
Received: April 18, 2025 Accepted: May 26, 2025
This work was supported by the Zhejiang Provincial Natural Science Foundation of China (Grant No.LZ23C170002, LQ21C060007) and the Jiaxing Key Laboratory of Children's Disease Diagnosis & Research Laboratory Open Fund (Grant No.JXER-KJK-2025-1-0069)
*Corresponding authors. Tel: +86-573-83643695, E-mail: cfzhangdw@zjxu.edu.cn; zhangjin7688@163.com

ing gut microbiota homeostasis. Finally, based on the existing clinical treatment and drug development progress of tumors and chronic stress, the review summarizes pharmacological intervention strategies targeting the neuroendocrine system, providing potential directions for the comprehensive treatment of cancer patients under chronic stress.

Keywords chronic stress; tumor; antitumor immunity; metabolism; gut microbiota; tumor treatment

慢性压力是个体在持续暴露于心理、生理或社会环境压力源时出现的适应性生理反应失调状态，已成为现代社会普遍存在的公共卫生问题[1]。慢性压力的成因具有多维性，主要涉及职业[2]、社会经济[3]、社会关系[4]以及健康[5]等方面。值得注意的是，这些压力源常呈现叠加效应，对健康造成多方面的影响。研究表明，慢性压力会削弱免疫系统功能，增加感染病毒和细菌的风险，并加速免疫系统衰退。同时，它还可导致代谢紊乱，增加肥胖、糖尿病及心血管疾病的风险，并引发认知能力下降、抑郁和焦虑等心理问题[6-8]。肿瘤患者面临的慢性压力主要来自疾病本身(如症状负担)、治疗过程(如长期治疗和反复就诊)以及心理与社会因素(如对疾病进展的担忧)。这些压力源共同导致持续的心理压力[9]。在慢性压力下，神经内分泌途径会影响肿瘤微环境(tumor microenvironment, TME)，导致免疫监视失效、促肿瘤信号通路激活，从而增加癌症复发风险和提高死亡率，具体表现为癌症复发风险增加1.73倍，2年相对生存率降低28.3%[10]。有研究注意到，慢性压力会引发神经、内分泌和免疫系统的变化，导致细胞微环境的改变、免疫监视的失效以及促肿瘤通路的激活，从而影响肿瘤的生长、转移和耐药性[11]。本综述首先总结了慢性压力的激活过程及其影响的信号通路，然后从多维度对慢性压力影响肿瘤发生发展的作用机制进行了探讨，接着对慢性压力相关肿瘤最新治疗药物的作用靶点与选用方面做出了分类说明。最后，本文对慢性压力与肿瘤关系的研究方向以及未来药物研发与使用策略提出了展望。

1 慢性压力的生物学作用机制

1.1 压力响应系统的激活特征

慢性压力状态下，机体通过激活下丘脑–垂体–肾上腺(hypothalamic-pituitary-adrenal, HPA)轴和交感神经系统(sympathetic nervous system, SNS)，分泌应激激素[如皮质醇(cortisol, COR)、肾上腺素(epinephrine, EPI)和去甲肾上腺素(norepinephrine, NE)]以应对短期压力[12]。然而，持续的压力会导致这些系统功能失调，进而对多种疾病的发生和发展产生深远影响[6]。研究表明，慢性压力可通过紊乱的神经内分泌信号影响肿瘤的进展[13](图1)，同时与胃肠道功能障碍(如肠易激综合征)和神经退行性疾病(如阿尔茨海默病)的发生密切相关[14-15]。此外，慢性压力诱导的免疫系统紊乱进一步加剧这些病理过程[16-17]。

HPA轴是机体应对压力的关键内分泌通路[18]。压力刺激促使下丘脑释放促肾上腺皮质激素释放激素(corticotropin-releasing hormone, CRH)，CRH通过下丘脑–垂体门脉系统运输到垂体前叶，驱动其分泌促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)。随后，ACTH进入血液循环，作用于肾上腺皮质，促使其分泌糖皮质激素(glucocorticoids, GCs)，主要是COR(在人类中)或皮质酮(在啮齿动物中)。GCs通过与广泛分布的糖皮质激素受体(glucocorticoid receptors, GRs)结合，调控基因表达，参与机体的代谢调控，影响蛋白质、脂肪和碳水化合物的代谢，以保障能量供应来应对压力[19]。此外，GCs还通过与中枢和外周神经系统中的受体结合，调节情绪和行为反应，从而影响机体对压力的综合反应[20]。

慢性压力导致SNS过度活跃，会引发儿茶酚胺类神经递质——EPI(epinephrine)和NE(norepinephrine)的大量释放[21]。这些儿茶酚胺在进入血液循环后，通过与不同细胞表面的肾上腺素能受体[adrenergic receptors, ARs; 主要是β-肾上腺素能受体(β-adrenergic receptor, β-AR)]结合来发挥生物学效应。例如，儿茶酚胺与免疫细胞表面β-AR结合，可抑制免疫细胞的活化和增殖，进而增强免疫抑制效应[22]; 与肿瘤细胞表面β-AR结合，激活肾上腺素能信号通路，影响肿瘤细胞的增殖、凋亡和转移[23]; 与平滑肌细胞、黏膜层上皮细胞等表面的β_2-肾上腺素能受体(β_2-adrenergic receptor, β_2-AR)结合，影响肠道蠕动和黏膜屏障功能，进而影响肠道功能[24]。以上研究提示，慢性压力导致的神经内分泌紊乱会加快机体的病理进程。

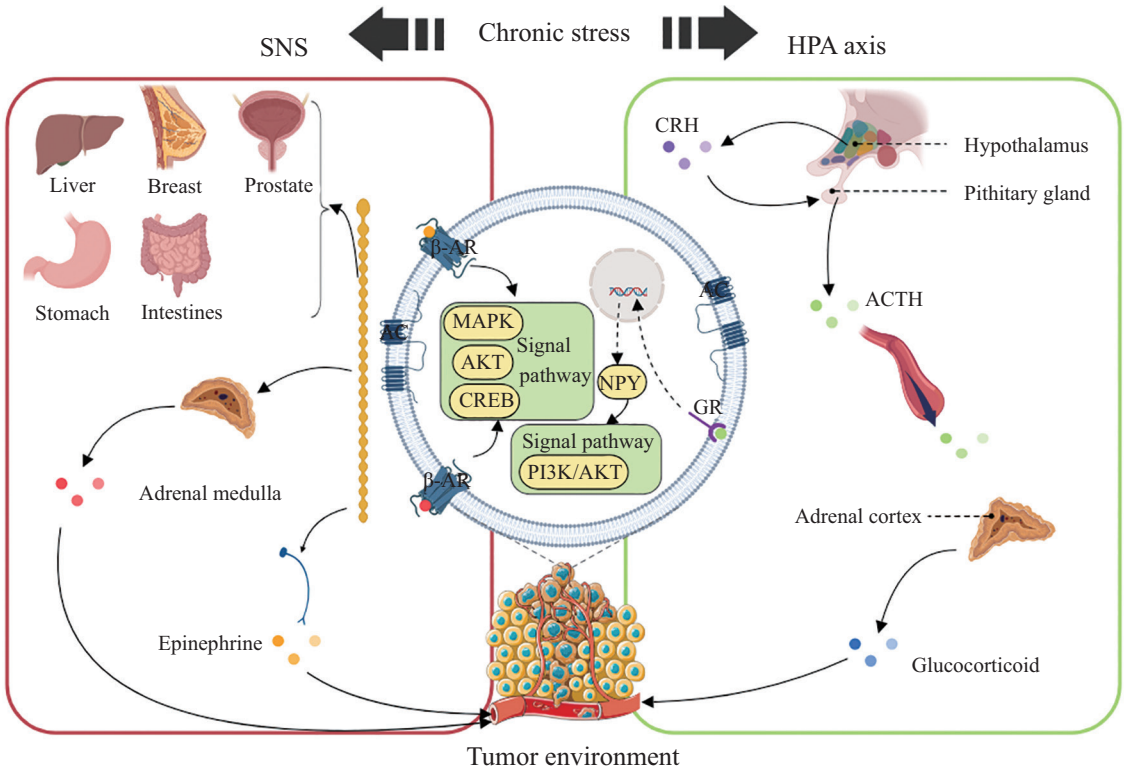

图1　慢性压力通过交感神经系统(SNS)和下丘脑–垂体–肾上腺(HPA)轴影响肿瘤环境

Fig.1　Chronic stress affects the tumor environment through the SNS (sympathetic nervous system) and the HPA (hypothalamic-pituitary-adrenal) axis

1.2　压力信号转导的关键通路

压力信号主要通过β-AR、GR以及神经肽Y(neuropeptide Y, NPY)等信号通路传导。β-AR属于G蛋白偶联受体(G protein-coupled receptor, GPCR)家族，广泛分布于心血管系统、平滑肌、肝脏、脂肪组织以及免疫细胞和肿瘤细胞中[25-26]。NE和EPI等儿茶酚胺类物质通过与β-AR结合，激活腺苷酸环化酶(adenylate cyclase, AC)，使细胞内环磷酸腺苷(cyclic adenosine monophosphate, cAMP)水平升高，进而激活蛋白激酶A(protein kinase A, PKA)，调节包括MAPK、AKT和CREB在内的多种细胞内信号通路，从而影响细胞的增殖、凋亡和代谢过程[21]。GR作为一种广泛分布于细胞内的核受体，能够在与COR结合后被招募到DNA上的GC反应元件(glucocorticoid response element, GRE)上，从而调控免疫、代谢和细胞应激反应相关基因的表达[27]。此外，GR还可以通过非Hippo依赖途径，例如酪氨酸磷酸化，直接激活YAP1，进而影响细胞的增殖和存活[28]。NPY作为一种在中枢和外周神经系统中广泛存在的神经肽，在慢性压力状态下，其表达水平显著上升[29]。这种上升受到多种机制的调控：一方面，GC通过与GR结合，增强NPY的转录活性[30]；另一方面，NPY表达水平的增加还与慢性压力改变的表观遗传修饰(包括DNA甲基化和组蛋白修饰)密切相关[31]。一旦NPY水平升高，它就会通过与Y1、Y2等受体的结合，激活PI3K/AKT信号通路，影响细胞的增殖、存活和代谢等多种生物学过程[32](图1)。

既往研究表明，在肿瘤发生发展的过程中，压力响应系统的过度激活及其引发的内分泌与神经系统紊乱，通过代谢调控、免疫调节、基因组稳定性和细胞行为改变等多个维度，深刻影响肿瘤的发生、发展和免疫逃逸过程。

2　慢性压力促进肿瘤发生的多维度机制

慢性压力通过激活HPA轴和SNS，促使大量神经内分泌因子释放。这些因子通过与肿瘤细胞和免疫细胞表面的受体结合，以及破坏肠道菌群的稳态，影响肿瘤的发生与发展。我们总结了慢性压力在以下三个方面对肿瘤的调控作用：肿瘤细胞的自主性

效应、TME的改变以及肠道菌群稳态的破坏。

2.1 肿瘤细胞自主性效应

2.1.1 *增殖与迁移* 在肿瘤发生和发展过程中, 细胞增殖与迁移的异常活化是驱动肿瘤恶性进展的核心机制[33]。乳腺癌研究领域的重要发现揭示, 血管紧张素II(angiotensin II, Ang II)处理会激活肿瘤局部肾素–血管紧张素系统(renin-angiotensin system, RAS), 进一步显著提升肿瘤组织内Ang II水平。该分子通过结合其受体AT1触发PARP1-FN1-黏着斑信号级联反应, 不仅促进乳腺癌细胞增殖转移, 还通过调控EMT关键分子[上调MMP2/9、N-钙黏蛋白(N-cadherin), 下调E-钙黏蛋白(E-cadherin)]重塑肿瘤侵袭表型[34]。机制研究进一步发现, EPI模拟的慢性压力通过激活cAMP/PKA信号轴, 在乳腺癌细胞中诱导缺氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)蛋白累积。这种缺氧诱导因子通过双重机制增强肿瘤干性: 一方面直接激活*Nanog*、*Oct-4*、*ABCG2*、*ALDH1*等干细胞特性相关基因; 另一方面与β-catenin形成复合物, 协同放大Wnt信号通路的促癌效应[35]。另外, 通过NE诱导的慢性压力模型会增加结肠癌细胞中β-catenin的蛋白水平, 进而上调细胞增殖相关基因(如*c-Myc*、*Cyclin D1*)、多药耐药蛋白(如ABCB1、ABCG2)的表达, 最终促进细胞增殖并增强耐药性[36-37]。在三阴性乳腺癌(triple-negative breast cancer, TNBC)研究中, 肝素酶(heparanase, HPSE)被证实是压力应答的关键效应分子。异丙肾上腺素(isoproterenol, ISO)刺激交感神经系统后, 通过cAMP/PKA/HIF-1α信号轴显著上调HPSE表达, 进而强化TNBC细胞的增殖迁移能力[38]。这种压力介导的促癌效应具有广谱性: ISO处理可诱导肝癌细胞(HepG2、Huh7)及乳腺癌细胞(MCF7、MDA-MB-231)中Src激酶磷酸化, 显著增强癌细胞侵袭潜能[39]; 在头颈癌细胞(CAL27、SCC25)中NE则通过LEPR-FOS-JUNB通路驱动异常增殖[40]。胶质瘤研究模型(U251、LN229)进一步拓展了压力激素的作用图谱: GC和NE处理模拟慢性压力状态, 会激活PI3K/AKT通路, 精密调控细胞周期相关蛋白(如Cyclin D1、CDK4等)的表达, 并促进细胞存活相关蛋白(如Bcl-2)的表达, 促使肿瘤细胞加速进入S期完成增殖循环[41]。以上这些压力激素相关的研究表明, 慢性压力所致的神经内分泌过程紊乱会使肿瘤细胞表现出持续生长和扩散的特征(图2)。

2.1.2 *自噬* 自噬(autophagy)是一种高度保守的细胞内降解途径, 通过清除受损的细胞器和不需要的蛋白质来维持细胞内稳态[42]。近年研究揭示, 慢性压力可通过多重机制干扰自噬调控网络: 在神经系统中, 其不仅诱导成体海马神经干细胞(neural stem cells, NSCs)发生自噬依赖性死亡, 还可通过激活多巴胺(dopamine, DA)能信号抑制自噬–溶酶体通路, 导致认知功能和学习记忆损伤[42-43]; 在免疫代谢层面, 慢性压力显著降低线粒体自噬关键调控元件MAVS蛋白及PINK1-Parkin通路活性, 引发线粒体质量控制失衡[44]。因此, 慢性压力能够通过调节细胞自噬水平影响不同疾病的发生或进程。

在肿瘤生物学中, 慢性压力可通过调控肿瘤细胞自噬水平来影响肿瘤发展。在胃癌中, 慢性压力通过激活β_2-AR信号通路, 进一步诱导AMPK-ULK1通路激活, 从而触发自噬并促进胃癌细胞增殖和存活[45]。有研究发现, 肿瘤细胞自身在慢性压力下呈现的自噬上调状态, 可能通过药物外排或促存活信号导致化疗耐药[46]。相反, 在乳腺癌中, 慢性压力通过激活肾上腺素能受体降低磷脂酰乙醇胺(phosphatidyl ethanolamine, PE)水平, 而PE是自噬体形成的关键成分。这导致自噬过程受阻, 反而促进肿瘤细胞的侵袭和迁移[47]。另外, 此研究也注意到普萘洛尔(一种β-受体阻滞剂)能够逆转EPI诱导的LC3 II/I值和p62的变化[47]。肝癌相关研究显示, 慢性压力下大自噬(macroautophagy)被下调, 细胞中p62异常积累, 引发炎症和氧化应激, 最终促进肿瘤发生[48]。除引起肿瘤细胞自身特征变化外, 压力相关自噬还通过改变TME调控肿瘤的发展进程。在肿瘤生物学领域, 慢性压力与自噬的相互作用呈现复杂的双刃剑效应。研究证实, 压力刺激可通过AMPK/mTOR信号轴增强髓系来源抑制细胞(myeloid-derived suppressor cells, MDSCs)的脂肪酸氧化(fatty acid oxidation, FAO)和氧化磷酸化(oxidative phosphorylation, OXPHOS), 进而激活代偿性自噬并促进前列腺素E2(prostaglandin E2, PGE2)分泌, 最终塑造免疫抑制微环境以助力肿瘤免疫逃逸[49]。同时, 压力诱导的肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)自噬活化可显著促进生长因子(如VEGF、FGF)及细胞外基质(extracellular matrix, ECM)重构相关蛋白的分泌, 为肿瘤细胞侵袭转移提供结构支持[50]。以上研究表明, 压力–自噬交互网络(图3)调

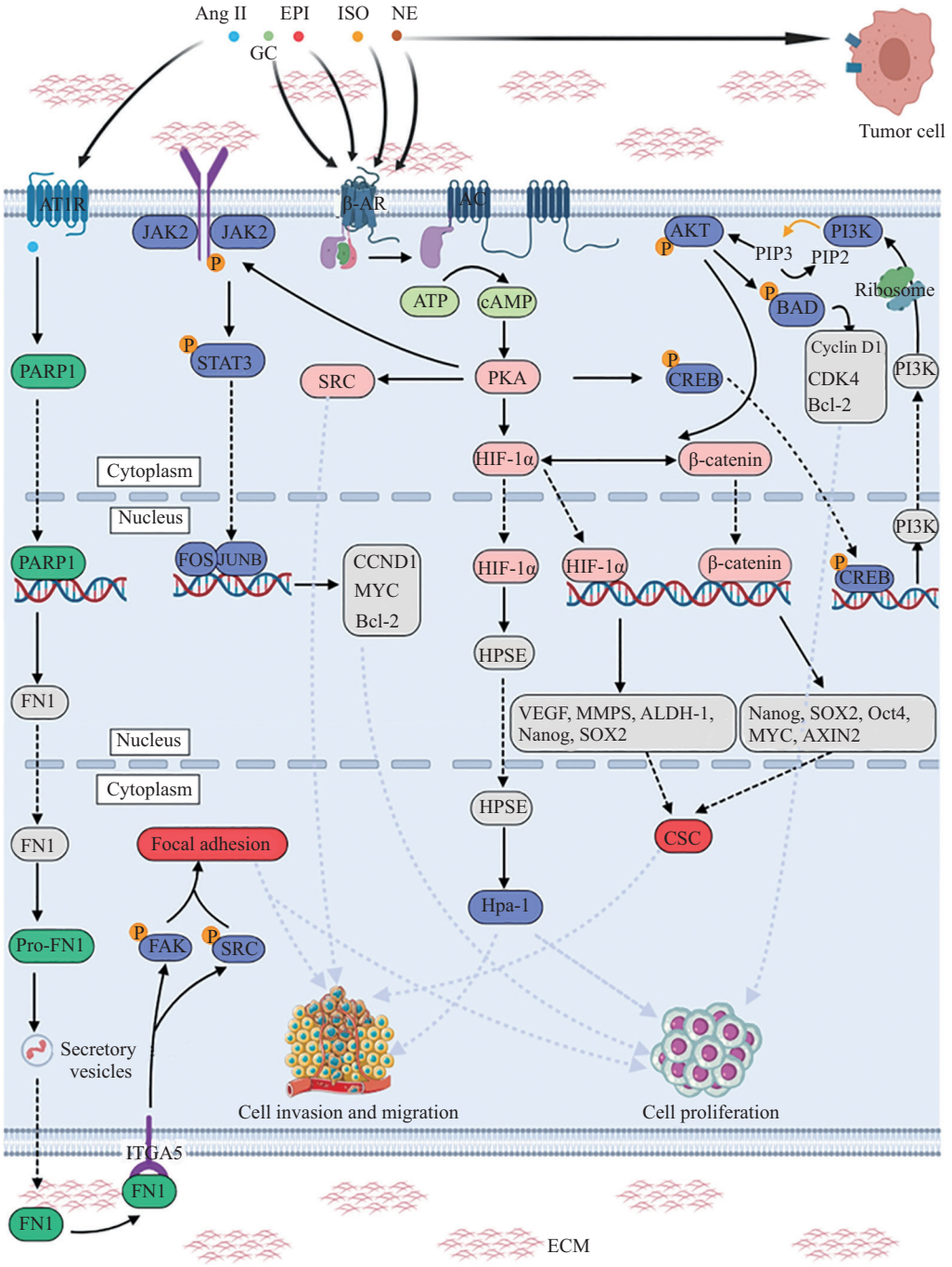

图 2　慢性压力通过肾上腺素能信号通路影响肿瘤细胞的增殖、侵袭和转移

Fig.2　Chronic stress affects the proliferation, invasion, and metastasis of tumor cells through adrenergic signaling pathways

控肿瘤发展时，不仅作用于肿瘤细胞本身，同时影响TME，且显示出双刃剑的作用效果。深入认识不同生理状态下肿瘤相关自噬通路的激活机制，将为开发靶向自噬调控节点的精准治疗策略提供新视角。

2.1.3　代谢重编程　肿瘤代谢重编程是肿瘤细胞为满足快速增殖需求而对代谢途径进行的调整，这种调整使肿瘤细胞能够适应营养匮乏、缺氧等恶劣微环境[51-52]。近年来的研究表明，在慢性压力下释放的压力激素通过结合GR、ADRB1和ADRB2受体，激活多条代谢相关信号通路(包括如cAMP/PKA、PI3K/AKT和MAPK通路等)，显著改变肿瘤细胞的代谢基因表达，从而促进肿瘤的发展[41,53-54]。研究发现，压力激素激活的cAMP/PKA信号通路使转录因子CREB1磷酸化，并与辅激活因子CBP/P300及CRTC2形成复合物，上调糖酵解关键分子葡萄糖转运蛋白1(glucose transporter 1,

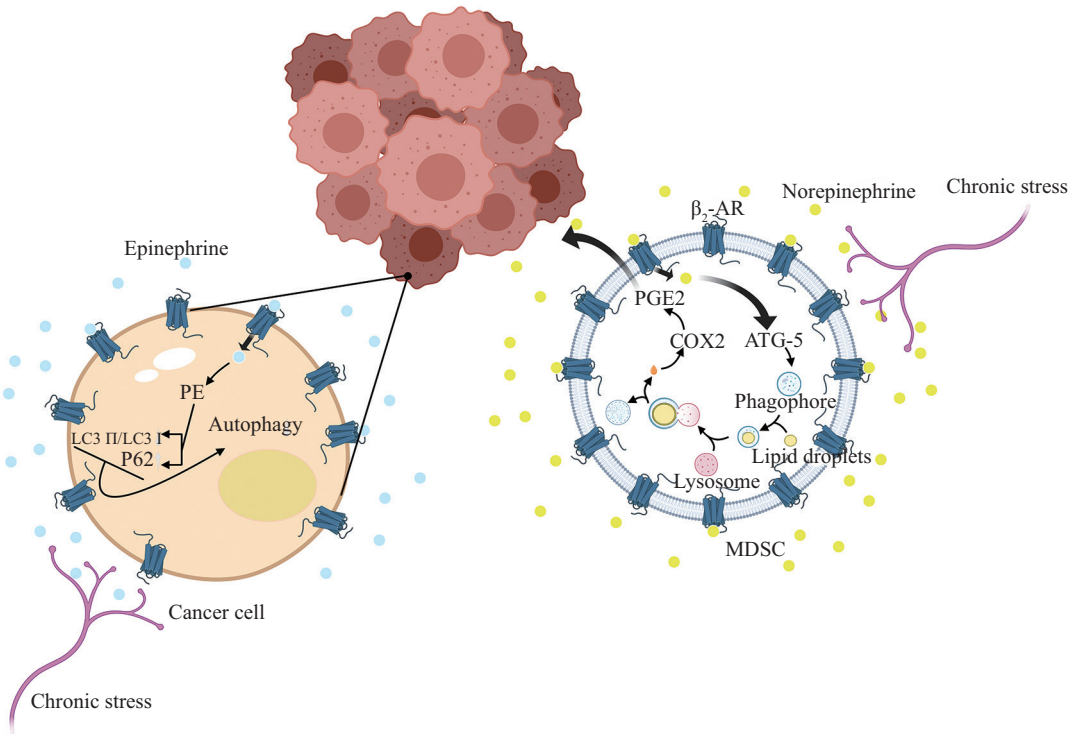

图3 慢性压力通过激活肾上腺素能信号通路增强肿瘤细胞的自噬和MDSC的免疫抑制功能

Fig.3 Chronic stress enhances tumor cell autophagy and the immunosuppressive function of MDSCs by activating adrenergic signaling pathways

GLUT1)、己糖激酶2(hexokinase 2, HK2)和磷酸果糖激酶(phosphofructokinase, PFK)的表达[55]; PI3K/AKT信号通路除直接调控这些基因表达外, 还通过稳定HIF-1α蛋白(尤其在缺氧条件下), 上调GLUT1和乳酸脱氢酶A(lactate dehydrogenase A, LDHA)表达[56]; 同样, p38 MAPK也通过上调HIF-1α表达, 促进GLUT1、LDHA的表达[57]。由此可见, 慢性压力显著增加肿瘤细胞的糖酵解通量, 而这也促进TME中乳酸的大量积累。此外, 慢性压力对脂肪和蛋白质代谢过程的影响也是促进肿瘤发展的因素。在乳腺癌微环境中, 压力激素EPI通过β-AR信号上调脂肪甘油三酯酶(adipose triglyceride lipase, ATGL)的表达和活性, 加速脂肪分解。而表达量与EPI水平呈正相关的去泛素化酶USP22则进一步放大ATGL活性, 从而使得肿瘤细胞内游离脂肪酸(free fatty acids, FFAs)激增, FFAs作为乳腺癌细胞的能量和生物分子来源, 促进癌细胞增殖、侵袭和转移[58]。此外, COR通过与GR结合, 经HMGB2-SREBF1-LDLR信号轴显著提升肿瘤细胞对低密度脂蛋白颗粒的摄取效率[59]。GCs信号还可特异性下调氨基酸转运蛋白SLC7A7等的表达, 促进精氨酸等非必需氨基酸的摄取和利用[60]。这些发现表明, 慢性压力通过这些机制共同构建了支持肿瘤快速增殖的能量与物质代谢网络。

除对肿瘤细胞能量供应和物质代谢的调节外, 慢性压力所致的中间代谢产物失衡也会改变TME。研究发现, 乳酸积累所形成的局部酸性环境会通过去泛素化酶USP28稳定转录因子MYC蛋白, 进而激活参与肿瘤细胞迁移和EMT的*SLUG*基因表达, 以增强肿瘤细胞干性[61]。在评估运动对乳腺癌风险的研究中, 13万名女性的数据显示较高的运动水平可以使乳腺癌的风险降低41%, 而这与运动产生的乳酸激活$CD8^+$ T细胞有一定关联[62-64]。然而, 病理性乳酸积累则导致组织酸中毒并引发免疫抑制: 一方面, 高浓度乳酸可降低T细胞增殖活性, 减少干扰素-γ等关键细胞因子的分泌; 另一方面, 乳酸通过竞争性阻断MHC分子与干扰素-γ的结合, 显著削弱T细胞的抗肿瘤免疫应答[65]。这种代谢微环境的动态平衡调控揭示了慢性压力影响肿瘤发生发展的深层机制。

2.2 肿瘤微环境重塑

2.2.1 *免疫微环境* 在肿瘤发生与发展的复杂进

程中，免疫微环境起着至关重要的调控作用。慢性压力不仅通过降低免疫细胞的活性和减弱其功能削弱机体的抗肿瘤免疫应答，还通过招募免疫抑制性细胞重塑TME，从而促进肿瘤的免疫逃逸和恶性进展。这里结合慢性压力对肿瘤中$CD8^+$ T细胞、$CD4^+$ T细胞、MDSCs、巨噬细胞以及其他类型免疫细胞的作用进行总结(图4)。

$CD8^+$ T细胞。在慢性压力状态下，交感神经系统因刺激而分泌高水平的EPI和5-羟色胺(5-hydroxytryptamine, 5-HT)。研究表明，EPI可通过β_1-肾上腺素能受体(β_1-adrenergic receptor, β_1-AR)依赖机制调控$CD8^+$ T细胞功能：一方面通过抑制丝氨酸蛋白酶Granzyme B(介导靶细胞凋亡)与跨膜糖蛋白CD38(参与免疫细胞活化)的共表达降低T细胞杀伤活性[66]；另一方面激活cAMP/PKA信号通路，降低$CD8^+$ T细胞中GLUT1的表达水平，抑制葡萄糖摄取和糖酵解同时介导线粒体的氧化磷酸化过程，最终干扰细胞能量代谢而削弱$CD8^+$ T细胞向TME的浸润能力[67]。值得注意的是，ADRB1的持续激活不仅抑制T细胞的增殖及IFN-γ、TNF-α等关键细胞因子的产生，还会促进$CD8^+$ T细胞向耗竭表型分化，并通过诱导耗竭型T细胞在交感神经周围的“神经邻近性”聚集，形成空间特异的免疫抑制微环境[68]。此外，慢性压力还通过多信号通路协同作用加剧$CD8^+$ T细胞相关的免疫抑制：Kisspeptin/GPR54通路激活可双重抑制$CD8^+$ T细胞功能，既减少IFN-γ、TNF-α等效应分子分泌，又上调PD-1、TIM-3和LAG-3等免疫检查点分子表达[17,69]；而高水平的5-HT则通过减少$CD8^+$ T细胞数量、抑制Granzyme B和IFN-γ表达及增强PD-1表达促进免疫负调控[70]；另外，COR还通过减弱树突状细胞(dendritic cells, DCs)的功能间接抑制$CD8^+$ T细胞的活化和细胞因子的分泌[71]。研究还注意到，慢性压力介导的肠道菌群失调导致了乙酸代谢物减少，进一步削弱了$CD8^+$ T细胞通过分泌IFN-γ发挥的抗肿瘤作用[72]。这些研究共同揭示了慢性压力通过抑制$CD8^+$ T细胞的活化、浸润及加速其耗竭

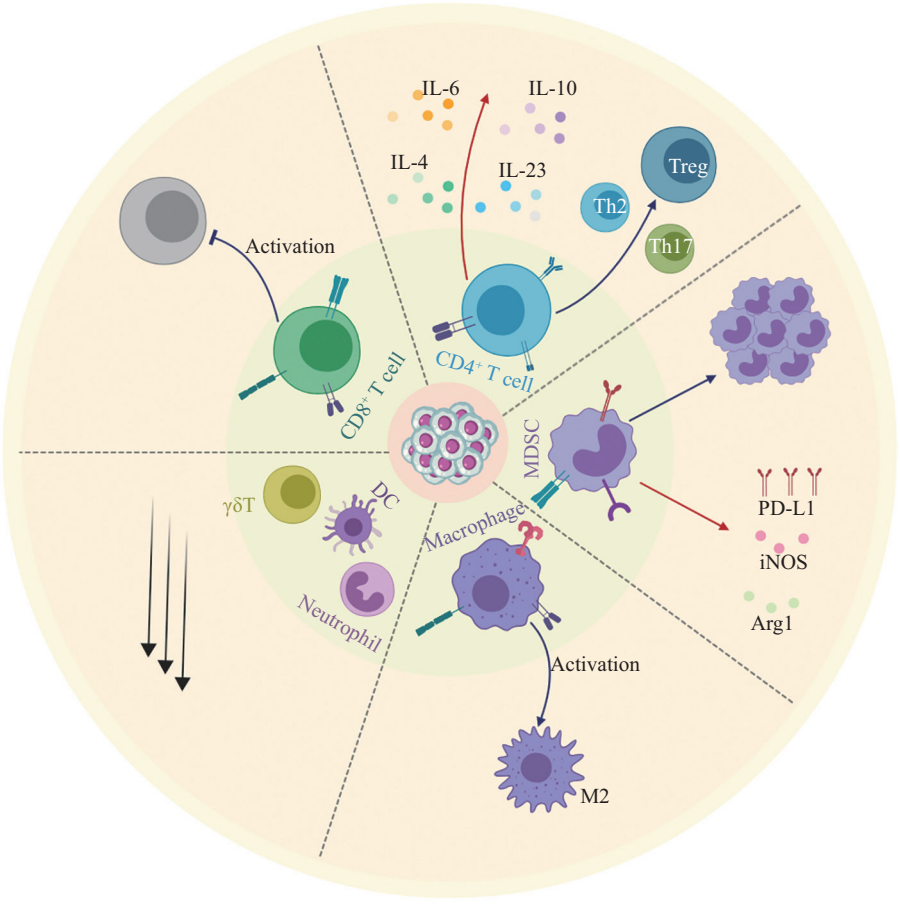

图4　压力激活的肾上腺素能信号调节免疫细胞的功能

Fig.4　Stress-activated adrenergic signaling regulates the function of immune cells

帮助肿瘤细胞实现免疫逃逸。

$CD4^+$ T细胞。在肿瘤免疫微环境研究中, $CD4^+$ T淋巴细胞[即辅助性T细胞(helper T cell, Th)]的异常分化与慢性压力存在显著关联。在多种肿瘤中已经证实, 慢性压力能够显著增加肿瘤中$CD4^+$ T细胞的比例[66,73]。研究发现, 慢性压力通过多种机制促进$CD4^+$ T细胞向具有促肿瘤作用的亚型分化。一方面, 慢性压力通过上调IL-4、IL-6、IL-10及IL-23等关键因子的表达, 促进$CD4^+$ T细胞向Th2(分泌IL-4、IL-13)和Th17(分泌IL-17)等促肿瘤亚型分化, 同时抑制具有抗肿瘤功能的Th1细胞(以IFN-γ为特征)发育[74]; 另一方面, 慢性压力通过上调TGF-β和IL-10等细胞因子, 促进调节性T细胞(regulatory T cells, Tregs)的生成并增强其功能; 而Tregs在TME中的异常聚集, 进一步抑制效应T细胞的抗肿瘤活性[74-75]。另外, IL-6也通过激活STAT3信号通路显著上调吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)表达, 导致色氨酸消耗和犬尿氨酸等代谢产物的积累, 进而抑制效应T细胞的活化和增殖, 以及通过犬尿氨酸-AhR信号轴正向调控Tregs的分化与功能, 形成持续性的免疫抑制环路。

MDSCs。在慢性压力状态下, β-AR信号的激活可显著调控MDSCs的动员、募集、增殖、分化及功能成熟[76]。肿瘤细胞和基质细胞在β-AR信号激活后分泌多种趋化因子(如CCL2、CXCL1、CXCL2、CXCL3、IL-8、CXCL8等), 这些趋化因子通过MDSCs表面的受体吸引其向肿瘤组织迁移, 其中CXCL2和CXCL3通过结合受体CXCR2发挥趋化作用[77-79]。研究发现β-AR信号激活还对MDSCs的增殖分化及功能成熟具有调控作用。当慢性压力导致血清中的NE水平升高后, β-AR信号促进肿瘤细胞分泌IL-6, 激活MDSCs内JAK-STAT3信号级联, 显著促进其扩增及免疫抑制表型的成熟[80]。此外, β_2-AR信号和GCs信号也通过代谢重编程增强MDSCs的免疫抑制功能: β_2-AR上调脂肪酸转运蛋白CPT1A(carnitine palmitoyltransferase 1A)和免疫抑制介质PGE2, 驱动MDSCs的FAO和OXPHOS[81-83]。这些研究揭示, 慢性压力通过空间募集、表型重塑、代谢重编程三层次机制, 系统性增强MDSCs的免疫抑制功能, 为肿瘤免疫逃逸创造有利条件。

肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)。在肿瘤免疫调控领域, 巨噬细胞极化失衡是介导肿瘤进展的关键环节。经典活化的M1型巨噬细胞通过分泌IL-1β、IL-12、TNF-α等促炎因子及活性氧(reactive oxygen species, ROS)发挥抗肿瘤作用, 而选择性活化的M2型巨噬细胞则通过分泌VEGF、TGF-β等促生长因子和精氨酸酶-1(arginase-1, Arg1)、IL-10等免疫抑制分子促进肿瘤细胞增殖、肿瘤血管生成和免疫逃逸[84]。研究发现, 慢性压力通过神经–内分泌网络激活, 显著上调IL-4、IL-10等M2型巨噬细胞极化相关因子的表达, 同时抑制IL-1β、IL-12、TNF-α等M1型巨噬细胞特征性细胞因子的表达, 驱动TAMs向促瘤型M2表型转化[85]。这种极化失衡导致促炎/抑炎因子比例失调, 形成有利于肿瘤进展的微环境。慢性压力也可诱导肿瘤组织高表达*CCL2*, 通过CCR2受体依赖机制促进单核细胞向肿瘤部位的募集, 继而使其分化为M2型TAMs[86]。在胶质瘤中, 慢性压力会减少CCL3的分泌, 从而抑制TAMs的招募, 尤其是具有免疫激活作用的M1型巨噬细胞的招募减少, 这会进一步增强胶质瘤免疫抑制微环境的抑制效应[87]。中枢神经系统中的CeM^{CRH}神经元(分布于杏仁核、下丘脑等脑区)表达CRH, 能够感知慢性压力信号并调节HPA轴功能及神经递质系统[88]。在4T1乳腺癌模型中, CeM^{CRH}神经元激活可特异性降低肿瘤内M1型巨噬细胞($CD11b^+F4/80^+CD86^+CD206^-$)比例及M1/M2值, 却不影响M2型($CD11b^+F4/80^+CD86^-CD206^+$)数量, 提示中枢神经系统通过精准调控巨噬细胞亚群分布促进肿瘤发展[89]。对于以上过程的调节而言, β-AR信号通路扮演核心角色, 其通过与CCL2/CCR2、mTOR、HIF-1α等信号通路相互作用得以实现这一功能[13,21]。以上研究表明, 慢性压力通过影响巨噬细胞极化、趋化和亚型分布三种方式打破肿瘤组织中M1、M2型巨噬细胞的比例平衡营造有利于肿瘤免疫逃逸的微环境。

其他免疫细胞。先天性T细胞(innate-like T cells)是T细胞家族中的一个特殊亚群, 起源于胎儿胸腺[90]。其中, γδ T细胞能够识别肿瘤细胞表面的磷抗原, 分泌多种细胞因子(如IFN-γ、TNF-α), 并通过与DC和自然杀伤细胞(natural killer cell, NK细胞)等免疫细胞的相互作用, 增强免疫系统对肿瘤的免疫反应[91]。研究发现, 压力激素GCs通过抑制TCR信号通路, 下调*IL-1β*、*TNF-α*等促炎基因表达, 导致先天性T细胞功能障碍及凋亡率升高, 肿瘤免疫监视能力降低, 导致癌细胞的发展和扩散加速[92]。DC作为具备抗原呈递和免疫激活功能的细胞, 在受到

GCs刺激时, 会过表达*TSC22D3*, 从而抑制肿瘤内DC的I型干扰素应答, 削弱DCs的抗原交叉递呈能力及共刺激分子表达, 最终导致抗肿瘤T细胞启动效率下降[93]。中性粒细胞则在GCs作用下形成和释放中性粒细胞外网(neutrophil extracellular traps, NETs)这一网状结构, 其携带的组蛋白-DNA复合物能够捕捉血液循环中的肿瘤细胞并提供一个附着和定植平台, 促进肿瘤细胞的扩散与转移[94]。此外, 压力激素NE能够与粒细胞上的受体结合, 上调粒细胞内精氨酸酶2(arginase 2, ARG2)、基质金属蛋白酶1(matrix metalloproteinase 1, MMP1)及转移相关的S100钙结合蛋白A4(S100 calcium binding protein A4, S100A4)表达, 增强其促血管生成及基质降解的能力[95]。这些发现揭示, 压力激素通过靶向调控先天性T细胞的效应功能、DCs的抗原递呈效能及中性粒细胞的促转移特性, 构建多层次的免疫抑制网络。这种跨细胞类型的协同作用, 最终导致肿瘤免疫监视系统的崩溃。

2.2.2 *肿瘤血管生成* 慢性压力通过β-AR信号网络诱导的促血管生成效应已成为研究焦点。动物实验证实, 慢性压力可显著提高荷瘤小鼠肿瘤组织的平均血管密度(mean vessel density, MVD), 而β-AR非选择性拮抗剂普萘洛尔能逆转此现象[75], 这一现象表明, 慢性压力激活的β-AR信号通路可促进TME中的血管生成, 其机制与刺激肿瘤细胞分泌血管内皮生长因子-A(vascular endothelial growth factor-A, VEGF-A)密切相关[96]。研究发现, 慢性压力激活的β-AR信号通过双重转录调控机制促进VEGF-A分泌[97-98]: 一方面其持续激活(如通过激动剂ISO)会抑制转录因子PAX6表达, 解除PAX6对*TGF-β1*基因的抑制作用, 促进TGF-β1的生成, 从而激活Smad依赖性信号通路; 另一方面慢性压力激活的β-AR通过激活PKA依赖的EGFR/AKT/ERK通路, 抑制HIF-1α的泛素化降解, 提升其与VEGF-A启动子的结合效率。同时, TGF-β1与HIF-1α形成正向调控环路——TGF-β1通过PI3K/AKT/mTOR通路增加HIF-1α转录活性, 而HIF-1α又可反馈增强TGF-β1受体表达, 形成持续放大的促血管生成信号[99]。此外, β-AR信号也能够通过以下三种机制协同发挥作用: 首先, 通过cAMP/PKA通路激活CREB转录因子[100]; 其次, 通过MAPK/ERK1/2磷酸化ETS家族转录因子[101]; 最后, 通过PI3K/AKT通路抑制GSK-3β对HIF-1α的降解作用[102]。这三种通路的协同作用确保了VEGF-A在TME中的持续高表达。同时, 分泌的VEGF-A通过Plexin A1/VEGFR2受体复合物激活JAK2-STAT3信号轴, 不仅直接促进内皮细胞增殖迁移, 还能以自分泌方式增强肿瘤细胞自身的VEGF-A合成能力, 形成促血管生成的“信号放大器”[103]。以上研究表明, VEGF-A是慢性压力调节肿瘤血管生成的核心效应分子。

2.2.3 *EMT* EMT是上皮细胞获得间充质特征的动态过程, 使细胞失去极性和细胞间黏附, 获得迁移和侵袭能力, 是恶性肿瘤侵袭转移的关键环节[104]。研究发现, 慢性压力与EMT调控网络存在显著关联。在慢性压力模型中, 研究者以ISO处理胃癌细胞MGC-803和SGC-7901, 发现负责细胞黏附的E-cadherin表达下调, 而标志细胞间充质特性的N-cadherin和α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)表达水平增加, 从而促进胃癌细胞的EMT。这一过程与ISO激活Plexin A1/VEGFR2受体复合物进一步触发JAK2-STAT3信号磷酸化级联反应密切相关[105]。此外, β_2-AR特异性激动剂沙丁胺醇通过激活ERK1/2通路, 诱导转录因子Snail核转位, 调控N-cadherin和E-cadherin表达, 增强EMT[106]。慢性压力不仅影响胃癌的EMT过程, 还被发现能够增强黑色素瘤和乳腺癌的EMT能力。在黑色素瘤及乳腺癌中, 多巴胺D2受体(dopamine receptor D2, DRD2)激活可招募E3泛素连接酶VHL, 阻断其对HIF-1α的泛素化降解。HIF-1α的累积通过TWIST1/Snail信号轴下调上皮连接蛋白(如Claudins), 同时上调基质金属蛋白酶(MMP2、MMP9), 促进细胞基底膜侵袭[107]。肝癌研究发现, EPI通过ADRB2激活原癌基因*c-Myc*, 后者直接转录调控泛素特异性蛋白酶10(ubiquitin specific peptidase 10, USP10)。USP10通过去泛素化稳定PLAGL2(pleiomorphic adenoma gene-like 2)蛋白, 进而激活ZEB1/2介导的EMT转录程序[108]。以上研究表明, 慢性压力会打破EMT的动态平衡, 为肿瘤细胞侵袭转移提供分子基础, 而靶向压力相关EMT调控节点(如STAT3、HIF-1α、USP10)或可成为抑制肿瘤转移的新策略(图5)。

2.3 肠道菌群

在慢性压力状态下, 激活的HPA轴会促使肾上腺分泌COR等GR, 引起肠道分泌性免疫球蛋白A(secretory immunoglobulin A, SIgA)和黏液减少, 削

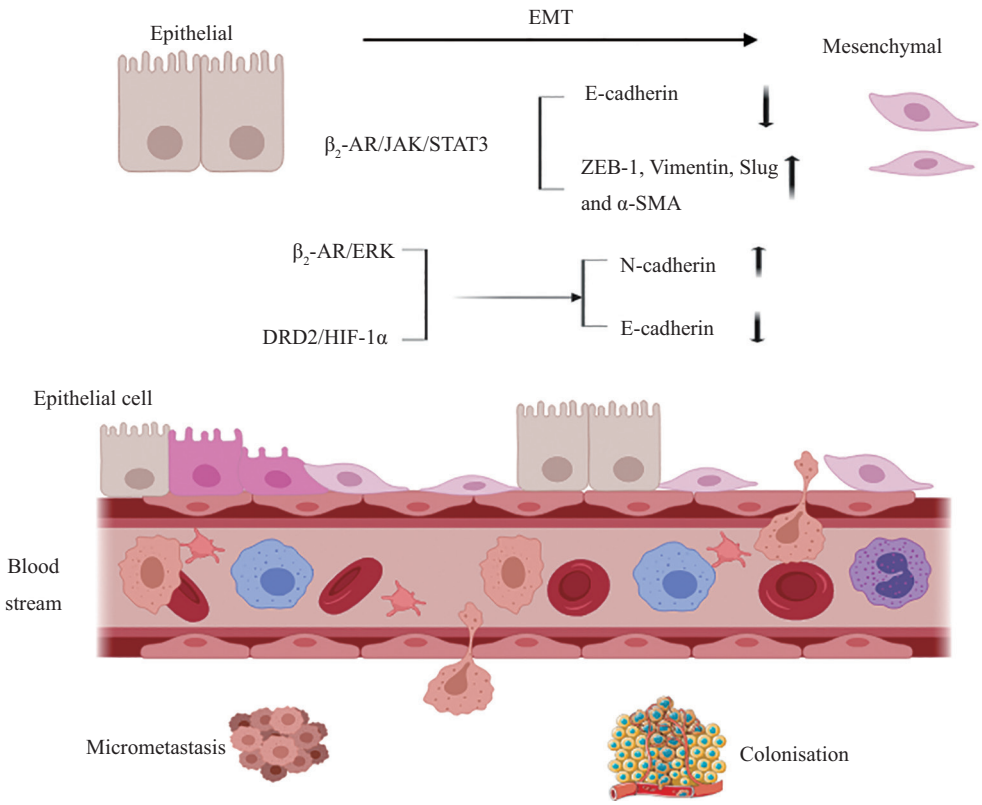

图5 慢性压力通过肾上腺素能信号影响上皮–间充质转化(EMT)和肿瘤转移的过程

Fig.5 Chronic stress influences EMT (epithelial-mesenchymal transition) and tumor metastasis through adrenergic signaling

弱黏膜免疫屏障功能, 使病原菌更易定植; 同时, 压力通过交感神经输出也会改变肠道运动节律, 加速肠道蠕动, 使乳杆菌等需定植时间的菌群因养分获取不足而减少[109-111]。这一生理状态下, 观察到肠道菌群的组成发生显著改变, 表现为有益菌(如双歧杆菌和乳杆菌)数量减少, 而潜在有害菌(如大肠杆菌、肠球菌)数量增加, 进而导致肠道菌群的代谢产物谱失衡[17,112]。研究发现, 短链脂肪酸(short-chain fatty acids, SCFAs)、胆汁酸(bile acids, BAs)和三甲胺N-氧化物(trimethylamine N-oxide, TMAO)等代谢产物可通过调节肿瘤细胞活性或者免疫系统功能, 影响包括结直肠癌、肝癌和乳腺癌在内的多种肿瘤的发生与发展过程。丁酸作为一种由肠道菌群产生的短链脂肪酸, 能够通过降低组蛋白去乙酰化酶(histone deacetylase, HDAC)活性, 促进肿瘤抑制基因(如*p21*、*PTEN*)的表达[113]; 同时, 其还可增强Tregs的分化与增殖, 并提升NK细胞的活性, 从而提高机体对肿瘤细胞的免疫监视与杀伤能力[114]。相比之下, 胆汁酸[如熊去氧胆酸(ursodeoxycholic acid, UDCA)和石胆酸(lithocholic acid, LCA)]则通过诱导氧化应激、DNA损伤及炎症反应, 促进肿瘤细胞增殖与存活[115], 并且可通过调节Th17细胞、Tregs和NK细胞的数量与功能来控制机体免疫反应[116]。此外, TMAO作为一种由肠道菌群参与合成的代谢产物, 其血液水平升高与结直肠癌、乳腺癌和前列腺癌等癌症转移风险呈正相关(HR=1.84)[117-118]。研究表明, TMAO可通过NLRP3炎症小体促进巨噬细胞向促炎M1表型极化, 由此形成的持续炎症微环境虽可抑制部分肿瘤生长, 但通过PD-L1/CTLA-4轴诱导T细胞耗竭, 最终促进肿瘤细胞的免疫逃逸[119]。此外, 肠道菌群还能够合成多种神经递质(如5-HT、DA和NE), 它们通过迷走神经传入中枢, 增强HPA轴活性, 形成“压力信号–菌群失调–代谢异常”的正反馈环路, 显著降低PD-1抑制剂等的免疫治疗应答率[120]。这些研究揭示, 慢性压力引起的肠道菌群紊乱促进肿瘤恶性生态的形成, 靶向菌群代谢干预将有助于压力相关肿瘤的治疗。

3 靶向压力通路的干预策略

现有研究表明, 慢性压力可通过多种机制加快肿瘤的发生与发展进程, 而这一作用也增强肿瘤

表1 慢性压力相关肿瘤药物

Table 1 Chronic stress-related cancer drugs

序号 Order No.	压力药物 Stress-relieving medications	联合药物 Concomitant medications	作用机制 Mechanisms of action	癌症类型 Types of cancer
1	OLZ (olanzapine)	GEM (gemcitabine)	OLZ inhibits GEM resistance caused by ADRB activation	Lung cancer (Kras mutant, LLC1 model)[123]
2	CAR (carvedilol)	DOX (doxorubicin)	CAR blocks β-ARs. DOX induces apoptosis, inhibits HIF-1α and β-catenin, downregulates ALDH-1 and SOX2, and inhibits CSCs enrichment. Combined therapy offsets DOX resistance caused by β-ARs activation	Triple-negative breast cancer[35]
3	PRO (propranolol)	Anti-PD-1 (RMP1-14) and Anti-CTLA-4 (9H10)	PRO blocks ADRB1 and ADRB2, reduces T-cell exhaustion, enhances T-cell function, and synergizes with immune checkpoint blockade to enhance antitumor efficacy	Pancreatic cancer[68,124]
4	PRO	Trabectedin	PRO inhibits stress response and blocks β-ARs. Trabectedin disrupts DNA repair. Combined therapy offsets trabectedin resistance caused by β-ARs activation	Cervical cancer[125]
5	PIMO (pimozide)	TMZ (temozolomide)	PIMO inhibits TMZ resistance caused by DR activation	GBM (glioblastoma)[126]
6	Quercetin	-	Acts on β_2-AR and ERK1/2 signaling pathways, inhibits tumor cell proliferation and migration	TNBC (triple-negative breast cancer)[127]
7	ICI-118551	Sorafenib	ICI-118551 inhibits ADRB2 signaling-mediated autophagic degradation of HIF-1α, thereby inhibiting sorafenib resistance	Liver cancer[128]
8	Mangiferin	-	Acts on β_2-AR and WAVE2 signaling pathways, inhibits tumor cell growth	CLM (colorectal liver metastasis)[129]
9	Jujuboside B	-	Inhibits CREB, PI3K, AKT, and MAPK signaling pathways, inhibits tumor cell growth	Various cancers (e.g., breast cancer, colorectal cancer)[54]
10	Blautia supplement	Acetate	Acts on $CD8^+$ T cells, enhances $CD8^+$ T cell antitumor immunity	Breast cancer[112]
11	Akk (Akkermansia muciniphila) supplement	Butyrate	Acts on LRP5, inhibits stress, activates T cells, and reverses cancer stemness	Breast cancer[113]
12	XYS (Xiao Yao San)	-	Modulates the abundance of *Bacteroides*, *Lactobacillus*, and *Desulfovibrio*, improves gut dysbiosis, thereby inhibiting tumor cell proliferation	Colorectal cancer[130]

-: 没有联合用药。

-: no concomitant medication used.

治疗过程的耐药性。研究发现GCs信号通过结合*PD-L1*基因的启动子区域, 激活其转录过程, 导致PD-L1在细胞表面显著上调, 增加肿瘤对免疫检查点抑制剂(如PD-1/PD-L1抗体)的耐药性; 相反, GR的耗竭或药物抑制(如米非司酮)可显著降低PD-L1水平[121]。研究也证实GCs会诱导肿瘤细胞内顺铂耐药关键基因*MAST1*的转录[122]。考虑到慢性压力可对肿瘤治疗产生消极影响, 可从以下三个药理学干预层面制定策略: 其一, 靶向干预肿瘤的自主性效应, 包括抑制肿瘤细胞增殖、诱导凋亡以及调节代谢重编程; 其二, 改善TME, 主要通过优化免疫微环境及抑制肿瘤血管生成来实现; 其三, 调节肠道微生物群落的组成或代谢功能。我们聚焦于压力信号通路调节相关的药物分子或联合用药方式, 对它们的抗肿瘤类型与机制进行归纳(表1), 旨在为肿瘤治疗提供创新性参考。

4 总结与展望

慢性压力是一种对外界刺激的反应, 伴随着神经内分泌变化, 主要通过HPA和SNS轴介导压力信号的传导。在慢性压力下, EPI、NE和GCs等压力激素被释放, 作用于TME, 调控细胞代谢, 促进血管形成和EMT转化, 同时抑制抗肿瘤免疫反应, 从而促进肿瘤细胞的增殖、侵袭和转移。尽管已从多方面研究慢性压力与肿瘤发生发展的关系, 但更为精准的治疗靶点仍有待明确。代谢组学和单细胞测序等技术可能是发现这些靶点的有力工具。目前已有ARs调节剂(如普萘洛尔)在肿瘤的治疗中显示出潜力, 其机制包括增强免疫检查点抑制剂疗效、增加肿瘤浸润性T细胞、减少肿瘤血管生成、减少免疫抑制性细胞的浸润及减弱其功能等。然而, 仍需进一步探索这些压力信号调节剂在不同肿瘤类型中的疗效和作用机制, 以及它们在长期使用和高剂量应用中的潜在副作用; 同时, 也需要继续研发新的调节剂。肿瘤治疗过程中患者往往承受较大压力, 因此, 明确药物与心理干预手段的协同使用, 不失为控制慢性压力相关肿瘤进展的有效途径。此外, 肠道菌群稳态的失调与慢性压力密切相关, 这一变化可能影响肿瘤的治疗效果, 因此通过调节肠道菌群的方式可能减弱慢性压力对肿瘤的促进作用。然而, 相关菌种、使用剂量和组合策略仍需不断研究。此外, 从慢性压力的角度考虑肿瘤耐药性也是一个值得深入研究的方向。综上所述, 基于慢性压力调节肿瘤发展过程的机制研究, 探索肿瘤治疗的新策略, 将对改善肿瘤预后具有积极意义。

参考文献 (References)

[1] MONROE S M, ANDERSON S F, HARKNESS K L. Life stress and major depression: the mysteries of recurrences [J]. Psychol Rev, 2019, 126(6): 791-816.

[2] SUN R, LÜ K, HE Z, et al. The mediating role of worker-occupation fit in the relationship between occupational stress and depression symptoms in 1988 medical workers: a cross-sectional study [J]. Front Public Health, 2022, 10: 843845.

[3] CONGER R D, RUETER M A, ELDER G H, Jr. Couple resilience to economic pressure [J]. J Pers Soc Psychol, 1999, 76(1): 54-71.

[4] HOSTINAR C E. Recent developments in the study of social relationships, stress responses, and physical health [J]. Curr Opin Psychol, 2015, 5: 90-5.

[5] NORDBY G, EKEBERG O, KNARDAHL S, et al. A double-blind study of psychosocial factors in 40-year-old women with essential hypertension [J]. Psychother Psychosom, 1995, 63(3/4): 142-50.

[6] KIVIMÄKI M, BARTOLOMUCCI A, KAWACHI I. The multiple roles of life stress in metabolic disorders [J]. Nat Rev Endocrinol, 2023, 19(1): 10-27.

[7] BILTZ R G, SAWICKI C M, SHERIDAN J F, et al. The neuroimmunology of social-stress-induced sensitization [J]. Nat Immunol, 2022, 23(11): 1527-35.

[8] KLOPACK E T, CRIMMINS E M, COLE S W, et al. Social stressors associated with age-related T lymphocyte percentages in older US adults: evidence from the US Health and Retirement Study [J]. Proc Natl Acad Sci USA, 2022, 119(25): e2202780119.

[9] 任若佳, 黄凡凡, 赵天宇, 等. 慢性躯体疾病共病抑郁障碍及其生物心理影响因素的研究进展[J]. 神经疾病与精神卫生(REN R J, HUANG F F, ZHAO T Y, et al. Biopsychological factors and current status of comorbidity between chronic medical disease and depressive disorder [J]. Journal of Neuroscience and Mental Health), 2024, 24(9): 609-14.

[10] ZENG Y, HU C H, LI Y Z, et al. Association between pretreatment emotional distress and immune checkpoint inhibitor response in non-small-cell lung cancer [J]. Nat Med, 2024, 30(6): 1680-8.

[11] ECKERLING A, RICON-BECKER I, SORSKI L, et al. Stress and cancer: mechanisms, significance and future directions [J]. Nat Rev Cancer, 2021, 21(12): 767-85.

[12] 李丽, 谢光荣. 心理弹性的心理社会及生物学机制[J]. 医学与哲学(LI L, XIE G R. The psychosocial and biological mechanism of resilience [J]. Medicine & Philosophy), 2012, 33(2): 32-3.

[13] WANG C, SHEN Y, NI J, et al. Effect of chronic stress on tumorigenesis and development [J]. Cell Mol Life Sci, 2022, 79(9): 485.

[14] WEI W, LIU Y, HOU Y, et al. Psychological stress-induced microbial metabolite indole-3-acetate disrupts intestinal cell lineage commitment [J]. Cell Metab, 2024, 36(3): 466-83,e7.

[15] WALLENSTEN J, LJUNGGREN G, NAGER A, et al. Stress, depression, and risk of dementia-a cohort study in the total population between 18 and 65 years old in Region Stockholm [J]. Alzheimers Res Ther, 2023, 15(1): 161.

[16] MILLIGAN ARMSTRONG A, PORTER T, QUEK H, et al. Chronic stress and Alzheimer's disease: the interplay between the hypothalamic-pituitary-adrenal axis, genetics and microglia [J]. Biol Rev Camb Philos Soc, 2021, 96(5): 2209-28.

[17] CHANG H, PERKINS M H, NOVAES L S, et al. Stress-sensitive neural circuits change the gut microbiome via duodenal glands [J]. Cell, 2024, 187(19): 5393-412,e30.

[18] SPIGA F, WALKER J J, TERRY J R, et al. HPA axis-rhythms [J]. Compr Physiol, 2014, 4(3): 1273-98.

[19] MILLER D B, O'CALLAGHAN J P. Neuroendocrine aspects of the response to stress [J]. Metab, 2002, 51(6 Suppl 1): 5-10.

[20] 袁川评, 王玮, 柳巨雄, 等. 神经–内分泌–免疫网络与炎症性肠病[J]. 世界华人消化杂志(YUAN C P, WANG W, LIU J X, et al. Neuro-endocrine-immune network and inflammatory bowel disease [J]. World Chinese Journal of Digestology), 2010, 18(19): 2024-8.

[21] ZHANG H, YANG Y, CAO Y, et al. Effects of chronic stress on cancer development and the therapeutic prospects of adrenergic signaling regulation [J]. Biomed Pharmacother, 2024, 175:

116609.
[22] NAYAK T K, PARASANIA D, TILLEY D G. Adrenergic orchestration of immune cell dynamics in response to cardiac stress [J]. J Mol Cell Cardiol, 2024, 196: 115-24.
[23] DONG Z K, WANG Y F, LI W P, et al. Neurobiology of cancer: Adrenergic signaling and drug repurposing [J]. Pharmacol Ther, 2024, 264: 108750.
[24] STRAUB R H, WIEST R, STRAUCH U G, et al. The role of the sympathetic nervous system in intestinal inflammation [J]. Gut, 2006, 55(11): 1640-9.
[25] 李晓燕, 李亚星, 贾漪涛. β-肾上腺素能受体在肿瘤发生和发展中的研究进展[J]. 肿瘤(LI X Y, LI Y X, JIA Y T. Effect on the occurrence and development of tumor of β-adrenergic receptor [J]. Tumor), 2021, 41(9): 650-6.
[26] JOHNSON M. Molecular mechanisms of β2-adrenergic receptor function, response, and regulation [J]. J Allergy Clin Immunol, 2006, 117(1): 18-24.
[27] AUGER J P, ZIMMERMANN M, FAAS M, et al. Metabolic rewiring promotes anti-inflammatory effects of glucocorticoids [J]. Nature, 2024, 629(8010): 184-92.
[28] SORRENTINO G, RUGGERI N, ZANNINI A, et al. Glucocorticoid receptor signalling activates YAP in breast cancer [J]. Nat Commun, 2017, 8: 14073.
[29] ZHANG Y, SHEN J, XIE F, et al. Feedforward inhibition of stress by brainstem neuropeptide Y neurons [J]. Nat Commun, 2024, 15(1): 7603.
[30] ZHANG K, RAO F, MIRAMONTES-GONZALEZ J P, et al. Neuropeptide Y (NPY): genetic variation in the human promoter alters glucocorticoid signaling, yielding increased NPY secretion and stress responses [J]. J Am Coll Cardiol, 2012, 60(17): 1678-89.
[31] SUN Q, ZHU J, ZHAO X, et al. Mettl3-m6A-NPY axis governing neuron-microglia interaction regulates sleep amount of mice [J]. Cell Discov, 2025, 11(1): 10.
[32] ZHANG S, LU Y, LI Y, et al. Brain-derived neurotrophic factor (BDNF) activates PI3K-AKT-mTOR signaling via hypothalamic TrkB receptors to reduce feeding in Siberian sturgeon (*Acipenser baerii*) [J]. Aquaculture, 2024, 579: 740196.
[33] DE VISSER K E, JOYCE J A. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth [J]. Cancer Cell, 2023, 41(3): 374-403.
[34] CUI Y, ZHUANG M, HUANG Z, et al. An antihypertensive drug-AT1 inhibitor attenuated BRCA development promoted by chronic psychological stress via Ang II/PARP1/FN1 pathway [J]. Biochim Biophys Acta Mol Basis Dis, 2024, 1870(3): 167031.
[35] ATTIA Y, HAKEEM A, SAMIR R, et al. Harnessing adrenergic blockade in stress-promoted TNBC *in vitro* and solid tumor *in vivo*: disrupting HIF-1α and GSK-3β/β-catenin driven resistance to doxorubicin [J]. Front Pharmacol, 2024, 15: 1362675.
[36] HAN J, JIANG Q, MA R, et al. Norepinephrine-CREB1-miR-373 axis promotes progression of colon cancer [J]. Mol Oncol, 2020, 14(5): 1059-73.
[37] STEIN U, FLEUTER C, SIEGEL F, et al. Impact of mutant β-catenin on ABCB1 expression and therapy response in colon cancer cells [J]. Br J Cancer, 2012, 106(8): 1395-405.
[38] QIU J, SHEN Z, JIANG G, et al. Isoproterenol-induced upregulation of HPSE accelerates triple-negative breast cancer cell proliferation and migration through enhancing the transcriptional activity of HIF-1α [J]. Anticancer Agents Med Chem, 2023, 23(4): 470-7.
[39] JEONG J H, PARK H J, PARK S H, et al. β2-adrenergic receptor signaling pathway stimulates the migration and invasion of cancer cells via Src activation [J]. Molecules, 2022, 27(18): 5940.
[40] ZHU J, LIU Q, NIE S, et al. LEPR/FOS/JUNB signaling pathway contributes to chronic restraint stress-induced tumor proliferation [J]. Biochem Biophys Res Commun, 2024, 719: 150042.
[41] ZHANG Z Q, WANG X, XUE B H, et al. Chronic stress promotes glioma cell proliferation via the PI3K/Akt signaling pathway [J]. Oncol Rep, 2021, 46(3): 202.
[42] YAMAMOTO H, ZHANG S, MIZUSHIMA N. Autophagy genes in biology and disease [J]. Nat Rev Genet, 2023, 24(6): 382-400.
[43] JUNG S, CHOE S, WOO H, et al. Autophagic death of neural stem cells mediates chronic stress-induced decline of adult hippocampal neurogenesis and cognitive deficits [J]. Autophagy, 2020, 16(3): 512-30.
[44] DUAN K, GU Q, PETRALIA R S, et al. Mitophagy in the basolateral amygdala mediates increased anxiety induced by aversive social experience [J]. Neuron, 2021, 109(23): 3793-809,e8.
[45] 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 [J]. Int J Oncol, 2019, 54(5): 1625-38.
[46] 徐然, 邵弘, 朱静. 自噬在肿瘤发生发展中的调控作用以及通过靶向自噬抑制肿瘤的研究进展[J]. 生命科学(XU R, SHAO H, ZHU J. Regulation of autophagy in tumor cells and application of targeting autophagy in cancer [J]. Chinese Bulletin of Life Sciences), 2018, 30(7): 723-31.
[47] ZHU Z, YU R, YANG C, et al. Stress-related hormone reduces autophagy through the regulation of phosphatidylethanolamine in breast cancer cells [J]. Ann Transl Med, 2021, 9(2): 149.
[48] KARAMPA A D, GOUSSIA A C, GLANTZOUNIS G K, et al. The role of macroautophagy and chaperone-mediated autophagy in the pathogenesis and management of hepatocellular carcinoma [J]. Cancers, 2022, 14(3): 760.
[49] MOHAMMADPOUR H, MACDONALD C R, MCCARTHY P L, et al. β2-adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived suppressor cell function within the TME [J]. Cell Rep, 2021, 37(4): 109883.
[50] CHEN C, LIU J, LIN X, et al. Crosstalk between cancer-associated fibroblasts and regulated cell death in tumors: insights into apoptosis, autophagy, ferroptosis, and pyroptosis [J]. Cell Death Discov, 2024, 10(1): 189.
[51] DEY P, KIMMELMAN A C, DEPINHO R A. Metabolic codependencies in the tumor microenvironment [J]. Cancer Discov, 2021, 11(5): 1067-81.
[52] HAO X, REN Y, FENG M, et al. Metabolic reprogramming due to hypoxia in pancreatic cancer: Implications for tumor formation, immunity, and more [J]. Biomed Pharmacother, 2021, 141: 111798.
[53] THAKER P H, HAN L Y, KAMAT A A, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma [J]. Nat Med, 2006, 12(8): 939-44.
[54] YANG Z, CAI W, CHEN Y, et al. Jujuboside B reverse cums-promoted tumor progression via blocking PI3K/Akt and MAPK/ERK

and dephosphorylating CREB signaling [J]. J Immunol Res, 2022, 2022: 5211368.

[55] GUAN Y, YAO W, YU H, et al. Chronic stress promotes colorectal cancer progression by enhancing glycolysis through β2-AR/CREB1 signal pathway [J]. Int J Biol Sci, 2023, 19(7): 2006-19.

[56] XIE Y, SHI X, SHENG K, et al. PI3K/AKT signaling transduction pathway, erythropoiesis and glycolysis in hypoxia [J]. Mol Med Rep, 2019, 19(2): 783-91.

[57] SIMOES-SOUSA S, LITTLER S, THOMPSON S L, et al. The p38α stress kinase suppresses aneuploidy tolerance by inhibiting HIF-1α [J]. Cell Rep, 2018, 25(3): 749-60,e6.

[58] ZHOU Y, CHU P, WANG Y, et al. Epinephrine promotes breast cancer metastasis through a ubiquitin-specific peptidase 22-mediated lipolysis circuit [J]. Sci Adv, 2024, 10(33): eado1533.

[59] WANG T, WANG X, WANG K, et al. Chronic stress-induced cholesterol metabolism abnormalities promote ESCC tumorigenesis and predict neoadjuvant therapy response [J]. Proc Natl Acad Sci USA, 2025, 122(5): e2415042122.

[60] XU W J, GUO K, SHI J L, et al. Glucocorticoid regulates the synthesis of porcine muscle protein through m^6A modified amino acid transporter SLC7A7 [J]. Int J Mol Sci, 2022, 23(2): 661.

[61] CUI B, LUO Y, TIAN P, et al. Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells [J]. J Clin Invest, 2019, 129(3): 1030-46.

[62] DIXON-SUEN S C, LEWIS S J, MARTIN R M, et al. Physical activity, sedentary time and breast cancer risk: a mendelian randomisation study [J]. Br J Sports Med, 2022, 56(20): 1157-70.

[63] FENG Q, LIU Z, YU X, et al. Lactate increases stemness of $CD8^+$T cells to augment anti-tumor immunity [J]. Nat Commun, 2022, 13(1): 4981.

[64] MA J, TANG L, TAN Y, et al. Lithium carbonate revitalizes tumor-reactive $CD8^+$ T cells by shunting lactic acid into mitochondria [J]. Nat Immunol, 2024, 25(3): 552-61.

[65] DUBROT J, DU P P, LANE-RETICKER S K, et al. *In vivo* crispr screens reveal the landscape of immune evasion pathways across cancer [J]. Nat Immunol, 2022, 23(10): 1495-506.

[66] AQUINO-ACEVEDO A N, KNOCHENHAUER H, CASTILLO-OCAMPO Y, et al. Stress hormones are associated with inflammatory cytokines and attenuation of T-cell function in the ascites from patients with high grade serous ovarian cancer [J]. Brain Behav Immun Health, 2022, 26: 100558.

[67] SWITZER B, PUZANOV I, GANDHI S, et al. Targeting beta-adrenergic receptor pathways in melanoma: how stress modulates oncogenic immunity [J]. Melanoma Res, 2024, 34(2): 89-95.

[68] GLOBIG A M, ZHAO S, ROGINSKY J, et al. The β1-adrenergic receptor links sympathetic nerves to T cell exhaustion [J]. Nature, 2023, 622(7982): 383-92.

[69] ZHANG S, YU F, CHE A, et al. Neuroendocrine regulation of stress-induced T cell dysfunction during lung cancer immunosurveillance via the Kisspeptin/GPR54 signaling pathway [J]. Adv Sci, 2022, 9(13): e2104132.

[70] ZHOU S, YE D, XIA H, et al. Sertraline inhibits stress-induced tumor growth through regulating $CD8^+$ T cell-mediated antitumor immunity [J]. Anticancer Drugs, 2022, 33(9): 935-42.

[71] ZHAO Q, PRAMANIK J, LU Y, et al. Perturbing local steroidogenesis to improve breast cancer immunity [J]. Nature Commun, 2025, 16(1): 3945.

[72] MILLER K D, O'CONNOR S, PNIEWSKI K A, et al. Acetate acts as a metabolic immunomodulator by bolstering T-cell effector function and potentiating antitumor immunity in breast cancer [J]. Nature Cancer, 2023, 4(10): 1491-507.

[73] ZENGA J, AWAN M J, FREI A, et al. Chronic stress promotes an immunologic inflammatory state and head and neck cancer growth in a humanized murine model [J]. Head Neck, 2022, 44(6): 1324-34.

[74] YANG Z, LI Z, GUO Z, et al. Antitumor effect of fluoxetine on chronic stress-promoted lung cancer growth via suppressing kynurenine pathway and enhancing cellular immunity [J]. Front Pharmacol, 2021, 12: 685898.

[75] LIU Z L, CHEN H H, ZHENG L L, et al. Angiogenic signaling pathways and anti-angiogenic therapy for cancer [J]. Signal Transduct Target Ther, 2023, 8(1): 198.

[76] ZHENG Y, WANG N, WANG S, et al. Chronic psychological stress promotes breast cancer pre-metastatic niche formation by mobilizing splenic MDSCs via TAM/CXCL1 signaling [J]. J Exp Clin Cancer Res, 2023, 42(1): 129.

[77] YUE D, LIU S, ZHANG T, et al. NEDD9 promotes cancer stemness by recruiting myeloid-derived suppressor cells via CXCL8 in esophageal squamous cell carcinoma [J]. Cancer Biol Med, 2021, 18(3): 705-20.

[78] JIANG W, LI Y, LI Z Z, et al. Chronic restraint stress promotes hepatocellular carcinoma growth by mobilizing splenic myeloid cells through activating β-adrenergic signaling [J]. Brain Behav Immun, 2019, 80: 825-38.

[79] CAO M, HUANG W, CHEN Y, et al. Chronic restraint stress promotes the mobilization and recruitment of myeloid-derived suppressor cells through β-adrenergic-activated CXCL5-CXCR2-ERK signaling cascades [J]. Int J Cancer, 2021, 149(2): 460-72.

[80] AN J, FENG L, REN J, et al. Chronic stress promotes breast carcinoma metastasis by accumulating myeloid-derived suppressor cells through activating β-adrenergic signaling [J]. Oncoimmunology, 2021, 10(1): 2004659.

[81] LU Y, LIU H, BI Y, et al. Glucocorticoid receptor promotes the function of myeloid-derived suppressor cells by suppressing HIF1α-dependent glycolysis [J]. Cell Mol Immunol, 2018, 15(6): 618-29.

[82] MOHAMMADPOUR H, MACDONALD C R, QIAO G, et al. β2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells [J]. J Clin Invest, 2019, 129(12): 5537-52.

[83] JOSHI S, SHARABI A. Targeting myeloid-derived suppressor cells to enhance natural killer cell-based immunotherapy [J]. Pharmacol Ther, 2022, 235: 108114.

[84] GE W, WU W. Influencing factors and significance of tumor-associated macrophage polarization in tumor microenvironment [J]. Chin J Lung Cancer, 2023, 26(3): 228-37.

[85] YANG Y, HU Y E, HUANG Y Q, et al. Tongxie Yaofang regulates tumor-associated macrophage polarization in colorectal cancer under chronic stress [J]. Chin J Trad Chin Med, 2023, 48(22): 6142-53.

[86] YANG J, WEI W, ZHANG S, et al. Chronic stress influences the macrophage M1-M2 polarization balance through β-adrenergic signaling in hepatoma mice [J]. Int Immunopharmacol, 2024,

138: 112568.

[87] WANG X, ZHANG L, ZHOU Y, et al. Chronic stress exacerbates the immunosuppressive microenvironment and progression of gliomas by reducing secretion of CCL3 [J]. Cancer Immunol Res, 2024, 12(5): 516-29.

[88] PARETKAR T, DIMITROV E. The central amygdala corticotropin-releasing hormone (CRH) neurons modulation of anxiety-like behavior and hippocampus-dependent memory in mice [J]. Neuroscience, 2018, 390: 187-97.

[89] XIONG S Y, WEN H Z, DAI L M, et al. A brain-tumor neural circuit controls breast cancer progression in mice [J]. J Clin Invest, 2023, 133(24): e167725.

[90] PELLICCI D G, KOAY H F, BERZINS S P. Thymic development of unconventional T cells: how NKT cells, MAIT cells and γδ T cells emerge [J]. Nat Rev Immunol, 2020, 20(12): 756-70.

[91] 刘义, 王慧, 马春玲. γδ T细胞的生物学特征及在抗肿瘤免疫治疗中的研究进展[J]. 世界肿瘤研究(LIU Y, WANG H, MA C L. Research progress of biological characteristics and anti-tumor immunotherapy of γδ T cells [J]. World Journal of Cancer Research), 2021, 11(3): 83-90.

[92] RUDAK P T, CHOI J, PARKINS K M, et al. Chronic stress physically spares but functionally impairs innate-like invariant T cells [J]. Cell Rep, 2021, 35(2): 108979.

[93] YANG H, XIA L, CHEN J, et al. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity [J]. Nat Med, 2019, 25(9): 1428-41.

[94] HE X Y, GAO Y, NG D, et al. Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment [J]. Cancer Cell, 2024, 42(3): 474-86,e12.

[95] ZHU Y, CHEN J, LI J, et al. Ginsenoside Rg1 as a promising adjuvant agent for enhancing the anti-cancer functions of granulocytes inhibited by noradrenaline [J]. Front Immunol, 2023, 14: 1070679.

[96] MATSUNO H, TSUCHIMINE S, O'HASHI K, et al. Association between vascular endothelial growth factor-mediated blood-brain barrier dysfunction and stress-induced depression [J]. Mol Psychiatry, 2022, 27(9): 3822-32.

[97] ZHANG J, DENG Y T, LIU J, et al. Role of transforming growth factor-β1 pathway in angiogenesis induced by chronic stress in colorectal cancer [J]. Cancer Biol Ther, 2024, 25(1): 2366451.

[98] CHEN M, SINGH A K, REPASKY E A. Highlighting the potential for chronic stress to minimize therapeutic responses to radiotherapy through increased immunosuppression and radiation resistance [J]. Cancers, 2020, 12(12): 3853.

[99] LIANG H, YIN G, SHI G, et al. Echinacoside regulates PI3K/AKT/HIF-1α/VEGF cross signaling axis in proliferation and apoptosis of breast cancer [J]. Anal Biochem, 2024, 684: 115360.

[100] JEON S H, CHAE B C, KIM H A, et al. The PKA/CREB pathway is closely involved in VEGF expression in mouse macrophages [J]. Mol Cells, 2007, 23(1): 23-9.

[101] LIN X, HE J, LIU F, et al. β-adrenergic receptor activation promotes the proliferation of HepG2 cells via the ERK1/2/CREB pathways [J]. Oncol Lett, 2023, 26(6): 519.

[102] FEI Y, ZHAO B, ZHU J, et al. XQ-1H promotes cerebral angiogenesis via activating PI3K/Akt/GSK3β/β-catenin/VEGF signal in mice exposed to cerebral ischemic injury [J]. Life Sci, 2021, 272: 119234.

[103] LU Y, ZHAO H, LIU Y, et al. Chronic stress activates PlexinA1/VEGFR2-JAK2-STAT3 in vascular endothelial cells to promote angiogenesis [J]. Front Oncol, 2021, 11: 709057.

[104] BAKIR B, CHIARELLA A M, PITARRESI J R, et al. EMT, MET, plasticity, and tumor metastasis [J]. Trends Cell Biol, 2020, 30(10): 764-76.

[105] LIU Y, HAO Y, ZHAO H, et al. PlexinA1 activation induced by β2-AR promotes epithelial-mesenchymal transition through JAK-STAT3 signaling in human gastric cancer cells [J]. J Cancer, 2022, 13(7): 2258-70.

[106] LU Y, ZHANG Y, ZHAO H, et al. Chronic stress model simulated by salbutamol promotes tumorigenesis of gastric cancer cells through β2-AR/ERK/EMT pathway [J]. J Cancer, 2022, 13(2): 401-12.

[107] LIU H, YANG J, ZHANG Y, et al. Psychologic stress drives progression of malignant tumors via DRD2/HIF1α signaling [J]. Cancer Res, 2021, 81(20): 5353-65.

[108] WANG C, NI J, ZHAI D, et al. Stress-induced epinephrine promotes hepatocellular carcinoma progression via the USP10-PLAGL2 signaling loop [J]. Exp Mol Med, 2024, 56(5): 1150-63.

[109] BORRE Y E, MOLONEY R D, CLARKE G, et al. Microbial endocrinology: the microbiota-gut-brain axis in health and disease [J]. Adv Exp Med Biol, 2014, 817: 177-94.

[110] WEI W, LIU Y, HOU Y, et al. Psychological stress-induced microbial metabolite indole-3-acetate disrupts intestinal cell lineage commitment [J]. Cell Metab, 2024, 36(3): 466-83,e7.

[111] MARIN I A, GOERTZ J E, REN T, et al. Microbiota alteration is associated with the development of stress-induced despair behavior [J]. Sci Rep, 2017, 7(1): 43859.

[112] YE L, HOU Y, HU W, et al. Repressed *Blautia*-acetate immunological axis underlies breast cancer progression promoted by chronic stress [J]. Nat Commun, 2023, 14(1): 6160.

[113] CUI B, LUO H, HE B, et al. Gut dysbiosis conveys psychological stress to activate LRP5/β-catenin pathway promoting cancer stemness [J]. Signal Transduct Target Ther, 2025, 10(1): 79.

[114] YANG Q, WANG B, ZHENG Q, et al. A review of gut microbiota-derived metabolites in tumor progression and cancer therapy [J]. Adv Sci, 2023, 10(15): e2207366.

[115] VARANASI S K, CHEN D, LIU Y, et al. Bile acid synthesis impedes tumor-specific T cell responses during liver cancer [J]. Science, 2025, 387(6730): 192-201.

[116] CAI J, SUN L, GONZALEZ F J. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis [J]. Cell Host Microbe, 2022, 30(3): 289-300.

[117] CHO C E, CAUDILL M A. Trimethylamine-N-oxide: friend, foe, or simply caught in the cross-fire [J]? Trends Endocrinol Metab, 2017, 28(2): 121-30.

[118] WANG H, RONG X, ZHAO G, et al. The microbial metabolite trimethylamine N-oxide promotes antitumor immunity in triple-negative breast cancer [J]. Cell Metab, 2022, 34(4): 581-94,e8.

[119] MIRJI G, WORTH A, BHAT S A, et al. The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer [J]. Sci Immunol, 2022, 7(75): eabn0704.

[120] CHEN Y, XU J, CHEN Y. Regulation of neurotransmitters by the

gut microbiota and effects on cognition in neurological disorders [J]. Nutrients, 2021, 13(6): 2099.

[121] DENG Y, XIA X, ZHAO Y, et al. Glucocorticoid receptor regulates PD-L1 and MHC-I in pancreatic cancer cells to promote immune evasion and immunotherapy resistance [J]. Nat Commun, 2021, 12(1): 7041.

[122] PAN C, KANG J H, HWANG J S, et al. Cisplatin-mediated activation of glucocorticoid receptor induces platinum resistance via MAST1 [J]. Nat Commun, 2021, 12(1): 4960.

[123] LU J, ZHANG X, SU K, et al. Olanzapine suppresses mPFC activity-norepinephrine releasing to alleviate CLOCK-enhanced cancer stemness under chronic stress [J]. Cell Commun Signal, 2024, 22(1): 375.

[124] GENG Q, LI L, SHEN Z, et al. Norepinephrine inhibits $CD8^+$ T-cell infiltration and function, inducing anti-PD-1 mAb resistance in lung adenocarcinoma [J]. Br J Cancer, 2023, 128(7): 1223-35.

[125] DI FONTE R, STRIPPOLI S, GAROFOLI M, et al. Cervical cancer benefits from trabectedin combination with the β-blocker propranolol: *in vitro* and *ex vivo* evaluations in patient-derived organoids [J]. Front Cell Dev Biol, 2023, 11: 1178316.

[126] WANG Y, WANG X, WANG K, et al. Chronic stress accelerates glioblastoma progression via DRD2/ERK/β-catenin axis and dopamine/ERK/TH positive feedback loop [J]. J Exp Clin Cancer Res, 2023, 42(1): 161.

[127] ZHANG J, TENG F, WU T, et al. Quercetin inhibits chronic stress-mediated progression of triple-negative breast cancer by blocking β2-AR/ERK1/2 pathway [J]. Biomed Pharmacother, 2024, 177: 116985.

[128] WU F Q, FANG T, YU L X, et al. ADRB2 signaling promotes HCC progression and sorafenib resistance by inhibiting autophagic degradation of HIF1α [J]. J Hepatol, 2016, 65(2): 314-24.

[129] TAO Y, TIAN X, LUO J, et al. Mangiferin inhibits chronic stress-induced tumor growth in colorectal liver metastases via WAVE2 signaling pathway [J]. Heliyon, 2023, 9(3): e13753.

[130] ZHANG Z, SHAO S, ZHANG Y, et al. Xiaoyaosan slows cancer progression and ameliorates gut dysbiosis in mice with chronic restraint stress and colorectal cancer enografts [J]. Biomed Pharmacother, 2020, 132: 110916.