中国科学: 生命科学
SCIENTIA SINICA Vitae
lifecn.scichina.com
《中国科学》杂志社
SCIENCE CHINA PRESS
评 述

NK细胞抗肿瘤转移的研究进展

董柯杉, 张阳, 杜欣珂, 谢成志, 韩佳寅*, 苏晓慧*, 李琦*

中国中医科学院中药研究所, 北京 100700
* 联系人, E-mail: jyhan@icmm.ac.cn; xhsu@icmm.ac.cn; qli@icmm.ac.cn

收稿日期: 2025-09-13; 接受日期: 2026-02-09; 网络版发表日期: 2026-04-28

摘要 肿瘤转移的发生高度依赖于免疫抑制性肿瘤微环境(tumor microenvironment, TME). 自然杀伤细胞(natural killer cells, NK cells)因其非特异性免疫杀伤特性, 在肿瘤转移各个阶段均发挥重要的抑制作用. NK细胞数量和功能活性与肿瘤转移呈负相关, 且基于NK细胞的免疫治疗在多种转移性肿瘤的治疗中展现出初步疗效. 然而, TME中免疫抑制细胞如调节性T细胞(regulatory T cells, Tregs)、肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)、髓系来源抑制性细胞(myeloid-derived suppressor cells, MDSCs), 及非免疫因素如肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)、血小板和代谢障碍等多重因素的共同作用, 会显著削弱NK细胞的浸润和效应功能, 限制其抗肿瘤转移能力. 目前, 大多数针对NK细胞的抗肿瘤转移治疗策略主要聚焦于其活性的增强, 却忽视了TME的系统性抑制, 导致临床疗效不理想. 因此, 本文系统综述了NK细胞在肿瘤转移中的抑制作用及其分子机制, 深入分析TME如何通过免疫细胞、基质细胞及代谢特征共同限制NK细胞功能, 提出"增强NK细胞活性并解除TME抑制"的双向发力治疗策略, 为NK细胞介导的抗肿瘤转移免疫治疗提供新的理论依据和治疗策略.

关键词 NK细胞, 肿瘤转移, 肿瘤微环境, 免疫治疗

肿瘤转移是导致肿瘤患者死亡的重要原因, 也是临床治疗的难题[1]. 肿瘤转移过程高度依赖于免疫抑制性肿瘤微环境(tumor microenvironment, TME), 肿瘤细胞依托于TME实现免疫逃逸, 从而成功实现肿瘤转移. 因此, TME被广泛认为是推动肿瘤转移的关键因素, 靶向TME也成为阻断肿瘤转移的重要治疗策略[2].

自然杀伤细胞(natural killer cells, NK cells)与肿瘤转移存在密切关系. 多项观察性研究表明, 在食管癌[3]、结直肠癌[4]和肾癌[5]等患者中, 循环或肿瘤浸润的NK细胞与肿瘤转移呈负相关; 同时, NK细胞数量及活性的改善与多种转移性肿瘤患者的良好预后密切相关[6]. 因此, 基于NK细胞的抗肿瘤转移治疗策略已成为热点, 并在临床治疗中呈现出一定的疗效. 一项前瞻性单臂Ⅰ期临床试验报告自体NK细胞输注在晚期肝癌患者中可实现高达80%的疾病控制率[7]. 当前治疗手段大多聚焦于NK细胞数量与活性的提升, 以增强NK细胞免疫疗法的抗肿瘤转移疗效[8,9].

然而, NK细胞在TME中出现的数量耗竭和功能缺陷已成为其发挥抗肿瘤转移效能的主要障碍. 在肺腺癌[10]、肝细胞癌[11]和黑色素瘤[12]等肿瘤中, 无论是临床患者样本还是实验小鼠模型均观察到NK细胞浸润

引用格式: 董柯杉, 张阳, 杜欣珂, 等. NK细胞抗肿瘤转移的研究进展. 中国科学: 生命科学
Dong K, Zhang Y, Du X, et al. Research progress on NK cell anti-tumor metastasis (in Chinese). Sci Sin Vitae, doi: 10.1360/SSV-2025-0314

© 2026《中国科学》杂志社

程度较低, 数量显著低于正常水平; 在结直肠癌和黑色素瘤中, NK细胞进入TME的24 h后, IFN-γ的释放能力和脱颗粒能力就迅速下调, 随即失去抗肿瘤转移能力[13]. 另外, NK细胞活化因子IL-2和自体NK细胞共输注临床治疗中, TME中免疫抑制细胞调节性T细胞(regulatory T cells, Tregs)与NK细胞竞争结合IL-2, 并被优先激活, 从而抑制NK细胞的功能, 使得该治疗策略疗效受限[14,15]. 可见, 仅依赖于强化NK细胞功能而忽视TME的免疫抑制状态, 难以系统性激发其抗转移潜力.

因此, 本文在系统阐述NK细胞抗肿瘤转移作用机制的基础上, 聚焦TME对NK细胞功能的影响, 并结合现有靶向NK细胞的临床治疗策略, 提出"增强NK细胞活性并解除TME抑制"双向发力的治疗策略.

1 NK细胞抗肿瘤转移的作用

NK细胞通过多机制协同作用发挥其抗肿瘤转移作用, 主要包括以下三种途径: (ⅰ) 直接细胞毒效应: NK细胞通过释放穿孔素和颗粒酶等效应分子, 并在细胞表面表达死亡配体(如FASL和TRAIL), 直接诱导肿瘤细胞发生凋亡. (ⅱ) 细胞因子介导的免疫调节作用, 即NK细胞可分泌IFN-γ, TNF-α等细胞因子, 不仅能直接抑制肿瘤细胞生长, 还能激活树突状细胞、T细胞等其他免疫效应细胞, 形成协同抗肿瘤转移免疫网络[16]. (ⅲ) 抗体依赖性细胞介导的细胞毒作用(antibody-dependent cell-mediated cytotoxicity, ADCC), 即NK细胞能通过表面受体CD16或低亲和力Fcγ受体ⅢA与免疫球蛋白的Fc区结合, 产生抗体依赖性细胞毒性[17], 这一机制在单克隆抗体治疗中具有重要临床意义. 值得关注的是, NK细胞发挥其抗肿瘤转移功能主要受其激活受体(NKARs)和抑制受体(NKIRs)的信号整合过程所调控. 激活受体(如NKG2D, CD16及天然细胞毒性受体NCRs家族成员NKp46/NKp30/NKp44)通过识别肿瘤细胞表面异常表达的配体(如MHC I类分子下调或缺失的"missing self"现象)实现对肿瘤细胞的识别与杀伤[18]. 而抑制受体则通过识别正常细胞表面MHC I类分子维持自身免疫耐受. 其中NK细胞常见的NKARs和NKIRs可见表1.

NK细胞通过其受体介导的特异性杀伤效应, 在肿瘤转移的多环节均发挥重要作用(图1). 首先, NK细胞干预肿瘤细胞上皮-间充质转化(epithelial-mesenchymal transition, EMT)过程抑制肿瘤转移, 而肿瘤细胞通过EMT脱离原发肿瘤是肿瘤转移的起始步骤[34]. 研究表明, EMT过程可上调肿瘤细胞NKG2D配体的表达, 增强NK细胞的识别与杀伤能力[35]. 此外, EMT过程能

表 1 NK细胞表面常见激活性受体与抑制性受体

Table 1 Common activating and inhibitory receptors on the surface of NK cells

受体分类	受体	配体	参考文献
NKARs	CD226	NECTIN2	[19]
	CD244	CD48	[20]
	NKG2C(KLRC2)	HLA-E	[21]
	NKG2D(KLRK1)	H60A, MICA, MICB, ULBPs	[22,23]
	NKp46(NCR1)	HS GAGs, CFP, ecto-CRT	[23~25]
	NKp44(NCR2)	HS GAGs, MLL5, NKp44L, PCNA, BAT3, PDGF-DD, Nidogen-1	[23,25,26]
	NKp30(NCR3)	HS GAGs, B7-H6, Galectin-3	[23,25,27]
	Nkp65	Keratinocyte-associated C-type lectin	[23,25,28]
	CD16(FCGR3A)	Fc-γ	[23]
NKIRs	CD96	NECTIN2, PVR(CD155)	[29,30]
	KIR2DL1	HLA-B, HLA-C	[23,31]
	KIR2DL2	HLA-A, HLA-C	[23]
	KIR2DL3	HLA-C	[23]
	KIR2DL4	HLA-G	[23]
	KLRC1(NKG2A)	HLA-E, H2-T23	[23]
	PD-1	PD-L1	[32]
	TIGIT	PVR(CD155), NECTIN2	[23,33]

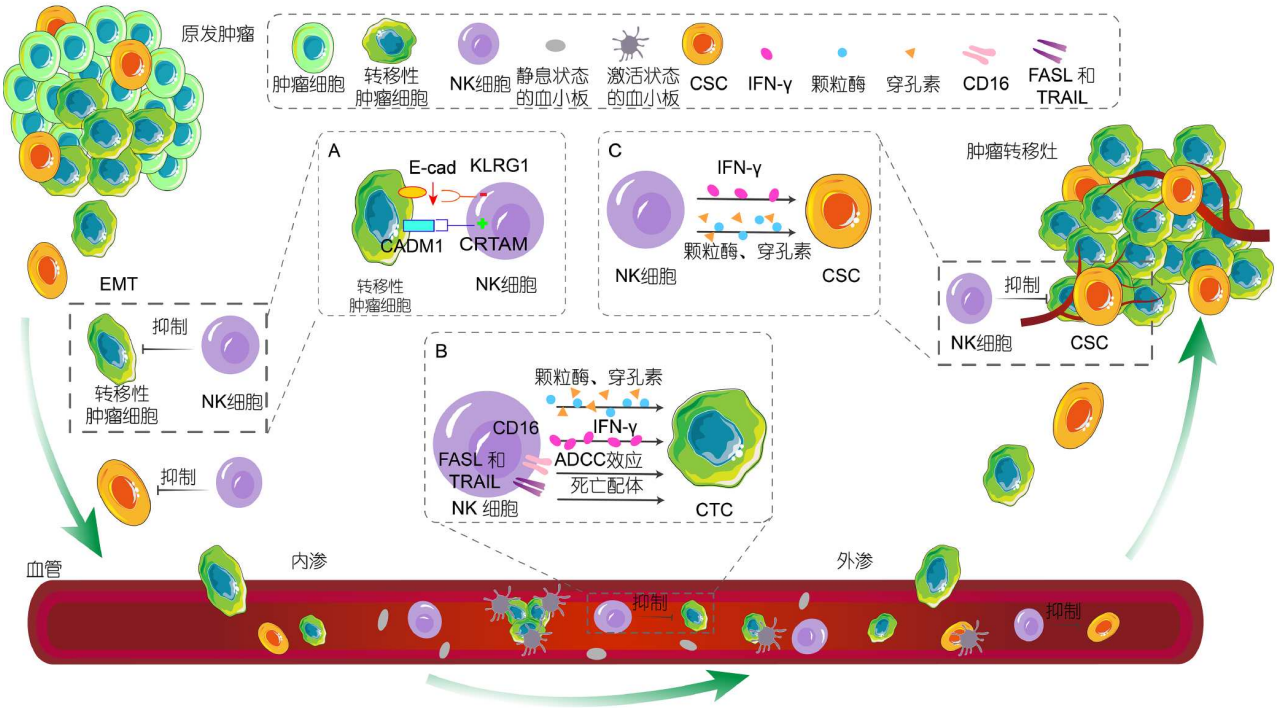

图 1 NK细胞抑制肿瘤转移的多步骤过程. A: NK细胞通过调控上皮-间质转化抑制肿瘤转移. EMT下调肿瘤细胞表面的E-钙黏蛋白, 上调CADM1, 进而激活NK细胞上的CRTAM, 介导对肿瘤细胞的杀伤. B: NK细胞靶向清除循环肿瘤细胞, 抑制血行转移过程. NK细胞通过穿孔素、颗粒酶和IFN-γ的分泌, CD16介导的抗体依赖性细胞毒性以及死亡配体(FASL和TRAIL)等途径诱导肿瘤细胞死亡. C: NK细胞靶向肿瘤干细胞以抑制转移灶形成, 其主要机制包括IFN-γ、穿孔素和颗粒酶的作用

Figure 1 NK cells inhibit the multi-step metastatic cascade. A: NK cells inhibit tumor metastasis by regulating epithelial-mesenchymal transition. EMT down-regulates E-cadherin on tumor cells, up-regulates CADM1, and activates CRTAM on NK cells, resulting in tumor cell killing. B: NK cells target and kill CTCs to inhibit the hematogenous metastasis process. NK cells induce tumor cell death through perforin, granzyme, and IFN-γ secretion, CD16-mediated ADCC, and death ligands (FASL and TRAIL). C: NK cells target CSCs to suppress metastasis formation, primarily via IFN-γ, perforin, and granzyme

够下调肿瘤细胞表面的上皮型钙黏蛋白(epithelial cadherin, E-cadherin), 同时上调其细胞黏附分子1(cell adhesion molecule 1, CADM1), 从而增加其对NK细胞介导的细胞毒作用的敏感性, 有效抑制肿瘤转移潜能[36,37]. 其次, NK细胞靶向杀伤循环肿瘤细胞(circulating tumor cells, CTCs)抑制血行转移过程. 发生EMT之后的肿瘤细胞离开原发肿瘤部位, 以CTCs的形式进入外周血. 进入外周血的CTCs是肿瘤转移的关键媒介, 其存在与患者不良预后呈负相关[38]. 临床研究显示, 在转移性乳腺癌和结肠癌患者中, CTCs阳性患者NK细胞毒性显著低于CTCs阴性患者[39]. 相较于T细胞, NK细胞对CTCs的杀伤作用更强[40], 如NK细胞依托穿孔素胞吐途径能够消除约80%的CTCs[41], 且短时间内NK细胞水平升高与CTCs减少相关[42]. 最后, NK细胞靶向杀伤肿瘤干细胞(cancer stem cells, CSCs)抑制转移灶的形成. CSCs参与EMT、肿瘤血管新生及转移灶的生成[43,44], 是肿瘤转移的重要驱动因素. 此外, NK细胞能够特异性识别并杀伤CSCs, 例如在胶质母细胞瘤干细胞(glioblastoma stem cells, GSCs)与NK细胞体外共培养体系中, GSCs高表达NK细胞活化配体, 对NK细胞介导的杀伤表现出高敏感性[45]. NK细胞不仅通过分泌穿孔素、颗粒酶直接杀伤CSCs, 还可释放IFN-γ和TNF-α等细胞因子诱导CSCs分化, 从而抑制肿瘤转移[46]. 综上, NK细胞通过调控EMT进程、高效清除CTCs及靶向杀伤CSCs, 在肿瘤转移的多个关键环节发挥关键抑制作用, 为抗肿瘤转移免疫治疗提供重要靶点.

2 TME抑制NK细胞的抗肿瘤转移作用

肿瘤微环境的免疫抑制特性是限制NK细胞抗肿瘤转移功能的关键因素. TME通过多种途径构建高度

免疫抑制的生态位. 一方面, 肿瘤细胞能够招募Tregs、肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)、髓系来源抑制性细胞(myeloid-derived suppressor cells, MDSCs)等免疫抑制性细胞及肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)和血小板等基质成分. 这些细胞及成分通过直接抑制、间接调控以及细胞间互作等方式抑制NK细胞功能, 促进肿瘤转移. 另一方面, TME的代谢特征, 如缺氧、酸性和营养匮乏(如葡萄糖、氨基酸)等也是造成NK细胞功能障碍的重要因素.

2.1 TME中免疫抑制细胞对NK细胞抑制肿瘤转移的影响

TME中存在着以Tregs, MDSCs和TAMs为代表的免疫抑制细胞网络, 这些细胞通过多途径协同作用抑制NK细胞的抗肿瘤转移功能, 为肿瘤转移创造有利条件(图2). 研究表明, 在乳腺癌小鼠体内模型中Tregs抑制NK细胞的活化, 从而促进肿瘤的淋巴结转移[47]; 在结肠癌小鼠体内模型中, 抑制Tregs能够恢复NK细胞的活性并抑制结肠癌转移[48]; 而在转移性肺癌患者的临床研究中发现, MDSCs在转移性肺肿瘤患者的外周血中大量富集, 并与NK细胞浸润呈现负相关, 且MDSCs能抑制NK细胞在循环系统中的肿瘤细胞杀伤能力, 促进血行转移[49].

Tregs, MDSCs和TAMs通过分泌细胞因子, 塑造免疫抑制微环境, 抑制NK细胞, 促进肿瘤转移. 转化生长因子-β(transforming growth factor beta, TGF-β)是三者共分泌的一种细胞因子, 能够通过下调NKARs的表达和IFN-γ、穿孔素、颗粒酶等的分泌, 抑制NK细胞功能. 在非小肺癌患者的肿瘤微环境中, Tregs通过TGF-β信号抑制NK细胞, 使用抗TGF-β抗体疗法能够恢复NK的细胞毒活性[50]. 在胃癌患者的肿瘤微环境中, TAMs通过TGF-β抑制NK细胞IFN-γ和TNF-α分泌, 该效应可被TGF-β阻断剂所逆转[51]. 在小鼠肝癌模型中, MDSCs通过TGF-β下调NKG2D和IFN-γ表达, 削弱NK细胞识别杀伤功能[52]. 此外, TAMs分泌IL-10、吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)、前列腺素E2(prostaglandin E2, PGE2)等抑制NK细胞功能[53]. TAMs分泌的免疫抑制趋化因子配体(如CCL5和CCL22)可以将Tregs募集到TME[54], 进一步抑制NK细胞功能. MDSCs则通过产生一氧化氮(NO)削弱NK细胞的ADCC效应[55].

除此之外, Tregs还能通过CD39/CD73将ATP/ADP转化为腺苷, 并与NK细胞上腺苷A2A受体(adenosine A2A receptor, A2AR)结合[56,57]抑制NK细胞活化成熟, 还能与NK细胞竞争结合IL-2[58]抑制NK细胞的发育成熟, 更能通过穿孔素和颗粒酶B对NK细胞进行直接细胞毒性作用[59]. 体外MDSCs和NK细胞共培养模型下发现MDSCs能通过增加精氨酸酶-1导致局部精氨酸耗竭, 抑制NK细胞的代谢, 从而减少IFN-γ的产生[60].

2.2 TME中非免疫成分对NK细胞抑制肿瘤转移的影响

研究表明, TME中的非免疫成分与肿瘤细胞之间存在着双向通讯网络, 这种通讯网络在肿瘤转移过程中发挥着重要作用. 其中, 最具代表性的为肿瘤微环境核心基质细胞CAFs和参与TME调控的循环功能性细胞血小板. 二者在物理屏障方面, 能够形成保护性结构阻碍免疫细胞的识别和浸润; 在化学调控方面, 通过分泌多种生物活性因子来调节免疫细胞功能, 从而削弱机体的抗肿瘤免疫应答[61], 以促进肿瘤的转移进程(图2).

研究显示, CAFs促进M2型巨噬细胞向肿瘤组织中的募集, 但对NK细胞的浸润并无显著影响[62], 提示CAFs对NK细胞的作用主要体现在功能调控而非直接抑制. 在三阴性乳腺癌患者中, 尽管NK细胞在CAFs区域呈富集状态, 但其细胞毒功能却受到显著抑制, 导致肿瘤细胞逃避免疫监视[63]. 同时, CAFs能通过分泌IL-6, TGF-β, CXCL12, IDO和PGE2等, 下调NKARs的表达, 从而促进肿瘤转移[61,64]. 其中, FAK/Src信号通路的激活被认为是CAFs抑制NK细胞功能的关键机制[65]. CAFs中Netrin G1表达上调, 释放大量谷氨酸盐、谷氨酰胺等代谢产物, 为肿瘤细胞提供营养支持的同时, 显著降低NK细胞介导的肿瘤细胞杀伤效应[66].

血小板主要通过两方面对NK细胞抑制肿瘤血行转移进行调控. 一方面, 血小板与肿瘤细胞形成复合物(以下简称"T-P"复合物), 来干扰NK细胞的识别过程. 这一过程涉及多种分子互作: 包括血小板表面的GPVI、平足蛋白、GPIIb-IIIa和P-选择素与肿瘤细胞上Galectin3、P选择素配体、CLEC2和整合素αvβ3等的特异性结合[67]. 这种物理屏障不仅直接遮蔽肿瘤抗原, 还能通过转移MHC I类分子到肿瘤细胞表面, 进一

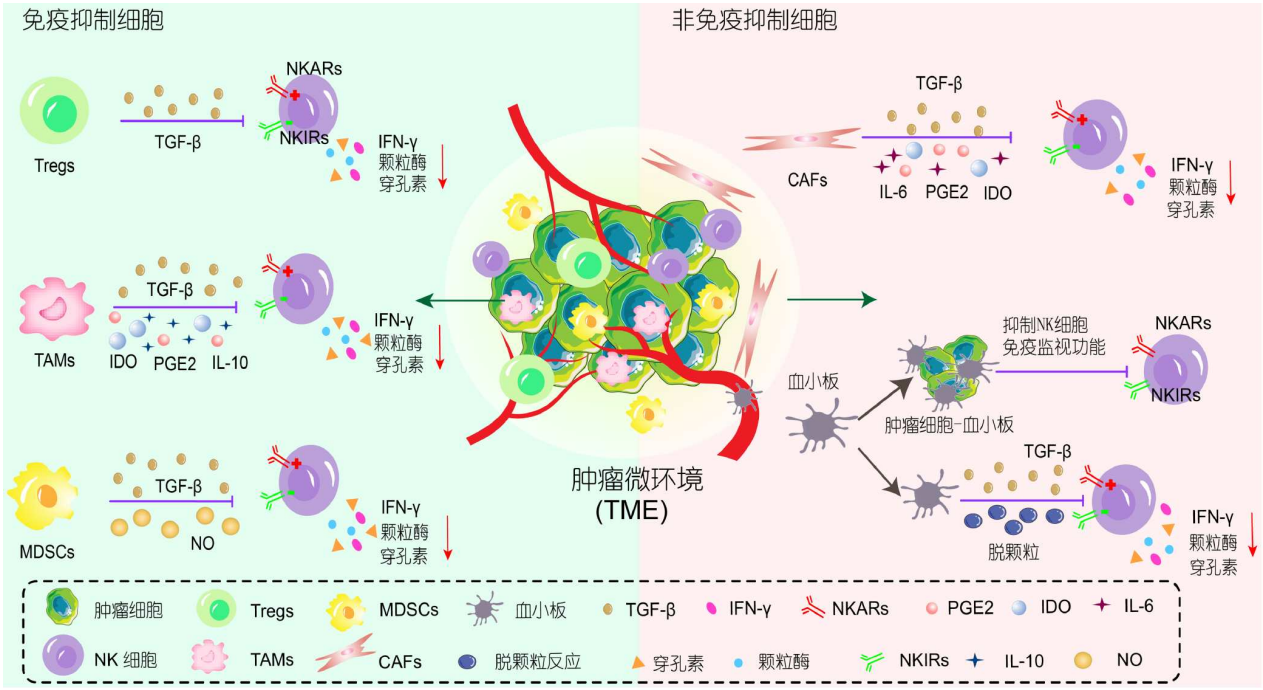

图 2 肿瘤微环境中的细胞对NK细胞的抑制作用. 左图: 免疫抑制细胞介导的NK细胞抑制. 在肿瘤微环境中, 调节性T细胞、肿瘤相关巨噬细胞和髓源抑制细胞主要通过分泌TGF-β, IDO, PGE2, IL-10和一氧化氮等因子, 下调NK细胞表面激活受体的表达, 并抑制其IFN-γ、穿孔素和颗粒酶的分泌. 右图: 非免疫细胞介导的NK细胞抑制. 癌相关成纤维细胞通过释放TGF-β, IL-6, IDO和PGE2等因子抑制NK细胞的细胞毒性. 血小板则通过两种机制抑制NK细胞功能: 一是通过黏附作用与肿瘤细胞形成复合物, 从而干扰免疫监视; 二是直接通过释放TGF-β和脱颗粒作用对NK细胞功能进行抑制

Figure 2 The inhibitory effect of cells in the tumor microenvironment on NK cells. Left: Immunosuppressive cells in the tumor microenvironment—Tregs, TAMs, and MDSCs—inhibit NK cells by downregulating NKAR expression and impairing the production of IFN-γ, perforin, and granzymes, largely via secretion of TGF-β, IDO, PGE2, IL-10, and NO. Right: Non-immune cell-mediated inhibition of NK cells in the tumor microenvironment. CAFs suppress NK cytotoxicity via TGF-β, IL-6, IDO, and PGE2. Platelets inhibit NK function both by forming tumor cell complexes through adhesion (disrupting immune surveillance) and through direct suppression via TGF-β and degranulation

步增强对NK细胞免疫识别的干扰. 同时, 研究者通过构建肿瘤细胞-血小板-NK细胞三元互作体外模型, 发现血小板来源的ADAM10和ADAM17蛋白酶能够特异性切割肿瘤细胞表面的NKG2D配体, 从而抑制NKG2D介导的免疫监视[68], 此外, 在T-P复合物形成过程中, 血小板还大量分泌TGF-β1等免疫抑制因子, 通过下调NKG2D受体表达抑制NK细胞活化, 最终促进肿瘤的血行转移[67].

2.3 TME代谢特征对NK细胞抑制肿瘤转移的影响

2.3.1 缺氧微环境对NK细胞的影响

缺氧微环境可诱导NK细胞发生抑制性表型重编程, 显著削弱其肿瘤浸润能力及杀伤功能[69]. 在缺氧过程中, NK细胞通过上调缺氧诱导因子1α(hypoxia-inducible factor 1α, HIF-1α)以适应缺氧环境. 然而, 持续的缺氧状态会导致HIF-1α的异常激活, 进而持续抑制NK细胞的趋化迁移能力, 并显著降低其分泌IFN-γ和TNF-α等关键效应细胞因子的能力[70], 这为肿瘤细胞逃脱免疫监视并发生转移创造了条件, 从而削弱了机体关键的抗肿瘤转移免疫防御. 同时, 缺氧微环境还可通过诱导NK细胞线粒体损伤和功能障碍, 进一步降低NK细胞毒性, 促进肿瘤细胞免疫逃逸, 导致肝癌患者的不良预后[71]. 缺氧微环境可下调多发性骨髓瘤中NK细胞的颗粒酶B和穿孔素等的表达, 从而抑制NK细胞的杀伤功能[72]. 此外, 在缺氧微环境下, 肿瘤细胞分泌的细胞外囊泡能将TGF-β1转移到NK细胞, 下调NKG2D的表达, 从而抑制NK细胞的功能及其抗肿瘤转移反应[73].

2.3.2 低糖和低氨基酸微环境对NK细胞的影响

在低糖条件下, 糖酵解或氧化磷酸化(oxidative

phosphorylation, OXPHOS)水平降低均可抑制NK细胞活性, 而抑制糖酵解对NK细胞受体介导的细胞毒性似乎更为关键, 主要表现为, 糖酵解受抑制时NK细胞的杀伤能力、NK细胞脱颗粒作用及死亡配体的表达均显著下降[74]. 研究表明, 在小鼠肺癌模型中, NK细胞的糖酵解能力被TME抑制, 其细胞毒性和细胞因子(IFN-γ和TNF-α)的分泌能力也相应下降[75].

低水平的氨基酸同样会抑制NK活性. 例如, 临床前研究发现肿瘤手术后的应激会导致精氨酸的低利用率, 从而抑制NK细胞的免疫监视功能, 而通过膳食补充恢复精氨酸水平, 可显著逆转NK细胞的活性, 并有效抑制肿瘤转移[76]. 在肿瘤患者体内发现TAMs, CAFs可通过分泌IDO和色氨酸-2,3-双加氧酶(tryptophan-2,3-dioxygenase, TDO)加速色氨酸转化为犬尿氨酸, 导致TME中色氨酸耗竭, 从而抑制NK细胞的抗肿瘤转移免疫效应[77]. 此外, 体外实验发现, IDO衍生的犬尿氨酸不仅可通过活性氧依赖性途径诱导NK细胞凋亡, 还能显著下调NK细胞表面活化受体(如NKG2D和NKp46)的表达, 进一步削弱其免疫监视功能[78]. 一项临床前研究表明, 肌成纤维细胞型肿瘤相关成纤维细胞(myofibroblastic cancer-associated fibroblasts, my-CAFs)来源的外泌体PWAR6可通过增强肿瘤细胞对谷氨酰胺的摄取, 促进NK细胞的凋亡, 从而加速结直肠癌的肝转移进程[79].

2.3.3 酸性微环境对NK细胞的影响

在酸性TME中, 乳酸可直接影响NK细胞的功能. 例如, 小鼠NK细胞吸收乳酸会导致细胞内酸化并引起能量代谢受损(以细胞内ATP水平衡量); 在肝脏驻留NK细胞中, 用乳酸处理也出现了类似结果, NK细胞内pH和ATP降低, 促进NK细胞凋亡[77]. 在酸性环境下, 乳酸通过SLC16A1和SLC16A3转运蛋白至NK细胞中, 导致NK细胞内酸化, 使pH从6.8降至6.0, 同时下调颗粒酶B和穿孔素mRNA表达水平[80]. 此外, 在结直肠癌肝转移模型中, 乳酸介导的酸性微环境可引发NK细胞线粒体应激, 进而诱导细胞凋亡, 最终导致NK细胞丧失抑制肿瘤转移的能力[81]. 除直接抑制NK细胞外, 乳酸还可通过间接机制促进免疫抑制性微环境的形成. 例如, 乳酸水平升高还可促进Tregs细胞分化、诱导TAMs向M2型极化以及增强MDSCs的募集等, 进一步协同抑制NK细胞的杀伤功能, 从而促进肿瘤免疫逃逸[82].

3 NK细胞抗肿瘤转移治疗策略及未来展望

在临床实践中, 以抗肿瘤转移为目标的NK细胞免疫疗法主要包括过继NK细胞疗法, NK cell engagers, 以及免疫检查点抑制剂等(表2). 其中, 过继NK细胞疗法的NK细胞有多种来源, 包括体外扩增自体、异体或其他来源的NK细胞和构建表达嵌合抗原受体或特异性活化受体的CAR-NK细胞. 上述这些策略主要的核心目标均为通过提升NK细胞数量、活化状态与靶向杀伤能力, 增强其在转移各个环节(包括EMT, CTCs, CSCs等关键环节)的抗肿瘤转移功能. 然而, 现有临床试验设计的终点评价主要围绕疗效与安全性两大维度. 在疗效评估中, 无进展生存期和无病生存率等指标常作为评估受试物能否控制肿瘤转移的关键点, 客观缓解率则作为初期疗效的主要评价点; 在安全性方面, 不良事件、剂量限制毒性和最大耐受剂量是评价重点. 值得注意的是, 直接以转移率作为评价终点的试验较为罕见, 因其评估需要更长的随访期且受多因素影响. 当前, 以抗肿瘤转移为目标的NK细胞免疫疗法仍存在巨大挑战. 其一, 疗法自身存在较大的风险和局限性. 细胞因子(尤其是IL-2/IL-15联用)可能诱发严重的细胞因子风暴[83]; CAR-NK疗法存在潜在的脱靶毒性和引发自身免疫相关不良反应的风险; 过继回输疗法中NK细胞在体内的存活与持久性不稳定. 其二, 更重要的是, 这些疗法未能同步干预TME的免疫抑制作用, NK细胞在患者体内往往面临浸润不足、功能耗竭、持续性差等问题, 导致临床响应差异显著. TME中免疫抑制细胞(如Tregs, MDSCs, TAMs)及抑制因子(如TGF-β, PGE_2, IDO等)通过多途径、多层面削弱NK细胞的活化与杀伤功能, 形成免疫屏障[84,85]. 单纯“把NK细胞变强”难以长期奏效, 需同时提升NK数量/效能/定向性, 并系统解除TME的免疫与代谢抑制. 这提示未来NK细胞抗肿瘤转移免疫治疗需采取“增强NK细胞功能+解除TME抑制”的双向发力策略.

当前, 部分新兴治疗策略已探索通过增强NK细胞功能和解除TME抑制实现抗肿瘤转移. 例如, 靶向TME中Tregs的免疫检查点阻断疗法(如CTLA-4抗体)[86], 通过抑制血小板与NK细胞免疫检查点轴(CD155-TIGIT)干扰肿瘤转移[87], 或利用纳米酶催化肿瘤中过氧化氢分解生成氧气以缓解缺氧[88], 均旨在为NK细胞浸润及细胞毒效应创造更优的微环境. 然

表 2 NK细胞免疫疗法在肿瘤治疗的临床试验汇总[a)]

Table 2 Summary of Clinical trials of NK cell immunotherapy in tumor therapy[a)]

NK免疫治疗策略	肿瘤类型	靶标	终点	临床阶段	状态	编号
异体TGFβi NK细胞输注策略	黑色素瘤脑转移	/	无进展生存期及总体生存期等	Ⅳ期	招募	NCT05588453
CAR-NK策略	晚期实体肿瘤(结肠癌等)肝转移	NKG2D	总体生存率等	Ⅰ期	招募	NCT07021534
自体NK细胞输注策略	黑色素瘤和肾癌	/	客观反映等	Ⅱ期	终止	NCT00328861
CAR-NK策略	复发/转移性胃癌或头颈癌	PD-L1	临床反应率、无进展生存期等	Ⅱ期	不招募	NCT04847466
异体NK细胞输注策略	转移性乳腺癌	/	不良事件和总体反应率等	Ⅰ期	终止	NCT05385705
自体NK细胞输注策略	转移性鼻咽癌	/	安全性等	Ⅰ期	完工	NCT00717184
异体NK细胞输注策略	转移性结肠癌等	/	安全性与耐受性等	Ⅰ期	停止	NCT05400122
异体NK细胞输注策略	急性骨髓系白血病	/	安全性与总体反应率等	Ⅰ期	完工	NCT02316964
NK细胞输注策略	白血病和淋巴瘤等	/	无进展生存期等	Ⅱ期	招募	NCT02727803
CAR-NK策略	复发/难治性B细胞恶性肿瘤	CD19	安全性与总体响应率等	Ⅰ期	未知	NCT05410041
CAR-NK策略	复发或难治性急性骨髓性白血病	NKG2D	安全性与最大耐受剂量等	Ⅰ期	终止	NCT05247957
CAR-NK策略	血液恶性肿瘤	CD7	安全性与耐受性等	Ⅰ期	尚未招募	NCT07117175
CAR-NK策略	复发或难治性B细胞恶性肿瘤	CD19	剂量限制毒性与客观响应率等	Ⅰ期	未知	NCT05645601
CAR-NK策略	复发/难治性非小细胞肺癌	Trop2	安全性与客观响应率等	Ⅰ/Ⅱ期	尚未招募	NCT06454890
CAR-NK策略	复发/难治性急性骨髓性白血病	C123	安全性与耐受性等	Ⅰ期	招募	NCT06690827
NK细胞输注策略	复发性实体肿瘤	/	局部缓解度、无进展生存期和总体生存期等	Ⅱ期	完工	NCT02853903
NK细胞输注策略	白血病	/	无病生存率等	Ⅰ/Ⅱ期	未知	NCT05143125
CAR-NK策略	T细胞淋巴瘤和急性髓系白血病	CD70	剂量限制毒性的发生率与类型等	Ⅰ期	尚未招募	NCT06696846
CAR-NK策略	复发/难治性弥漫性大B细胞淋巴瘤	CD19	剂量限制毒性发生率与治疗急性不良事件发生率等	Ⅰ期	未知	NCT05673447

a) 表格数据均来源于美国Clinical Trials网站数据库(https://clinicaltrials.gov/)

而, 这些策略多聚焦于单一抑制因素(特定细胞、分子或代谢特征), 难以从整体撼动由多种免疫抑制细胞、炎症因子及代谢异常共同构成的高度复杂抑制网络.

在此背景下, 中医药的整体观和辨证论治思想为调控TME的复杂动态网络提供了独特的视角. 中医将肿瘤的核心病机概括为“癌毒”, 认为其非单一邪气, 而是由痰、瘀、热、湿等多种病理产物(毒邪)交织互结、耗伤正气所形成的. 在这一理论框架下, 癌毒并非孤立存在, 它与其赖以生存和发展的“土壤”——TME密不可分. 王玉如等人[89]提出TME是气滞、痰凝、血瘀、热毒等病邪盘踞的场所; 贺佳文等人[90]进一步指出, 癌毒导致的热、瘀、痰、湿等病理状态, 与TME所呈现的慢性炎症、低氧、酸性及免疫抑制等复杂内环境具有高度相似性. 例如, 中医学“气”的功能与细胞能量枢纽——线粒体的活动密切相关, “正气亏虚”相关的代谢失调(如线粒体功能障碍)可促使肿瘤细胞转向糖酵解, 从而参与塑造TME的缺氧与酸化核心特征.

基于上述理论, 越来越多的基础研究揭示, 中医药可通过多靶点协同作用, 构建以NK细胞为关键效应枢纽的“解除抑制-增强功能”双向调控网络, 从而重塑TME、抑制肿瘤转移(图3). 首先, 中医药通过改善免疫抑制性TME为NK细胞功能发挥创造条件. 例如, 中药复方如肺炎宁合剂通过抑制Tregs细胞数量, 增强肿瘤免疫反应, 缓解肺癌进展[91]; 归芪益元膏通过抑制JAK3/STAT6信号通路减少M2型巨噬细胞极化, 改善

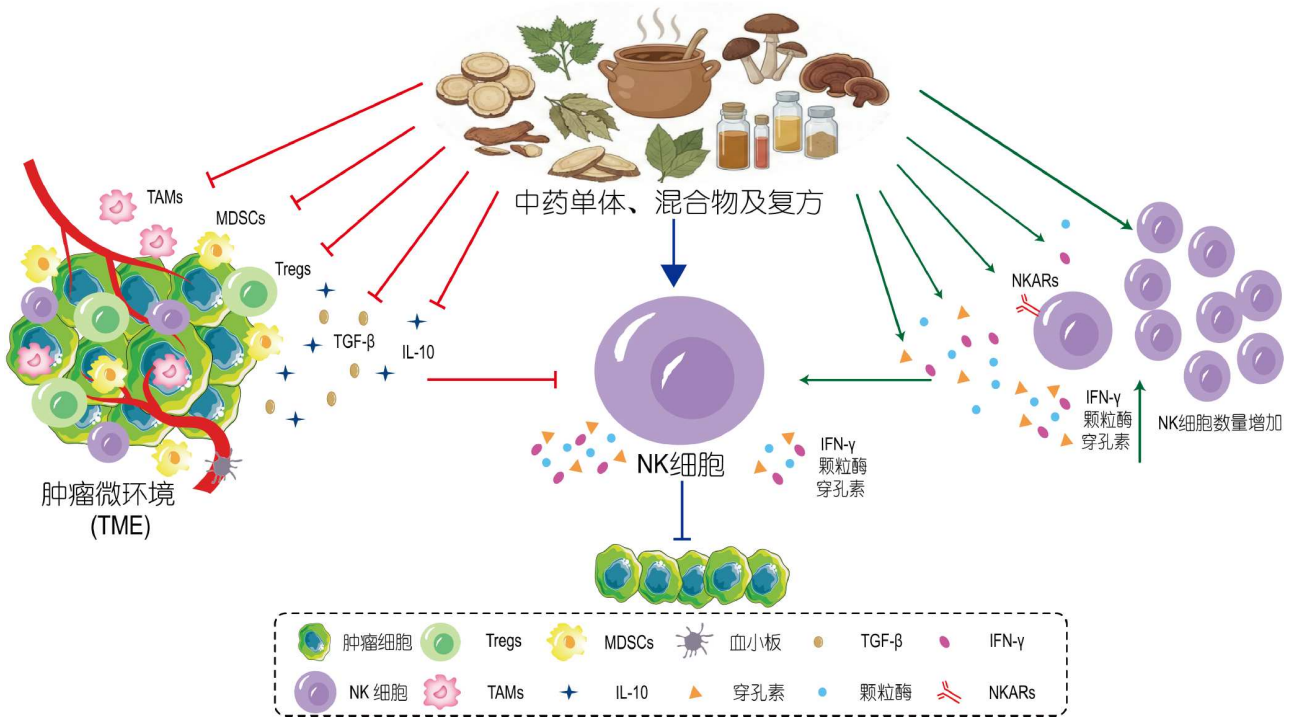

图 3 中医药重塑肿瘤微环境并增强NK细胞活性的进展. 左图: 肿瘤微环境中存在的免疫抑制细胞(TAMs, Tregs和MDSCs等)和相关因子(TGF-β和IL-10)可削弱NK细胞的免疫监视和杀伤功能, 中药单体、混合物及其复方可通过抑制TME, 恢复NK细胞正常免疫功能. 右图: 中药单体、混合物及其复方还可直接增加NK细胞数量、提升其激活受体表达及促进杀伤物质分泌

Figure 3 Advances in traditional Chinese medicine for reshaping the tumor microenvironment and enhancing NK cell activity. Left: The TME contains immunosuppressive cells (such as TAMs, Tregs, and MDSCs) and related factors (e.g., TGF-β and IL-10) that impair the immune surveillance and killing functions of NK cells. Chinese herbal monomers, mixtures, and compound prescriptions can restore the normal immune function of NK cells by suppressing the TME. Right: Chinese herbal monomers, mixtures, and compound prescriptions can also directly increase NK cell numbers, enhance the expression of activating receptors, and promote the secretion of killing substances

免疫抑制微环境, 缓解肺癌小鼠的顺铂耐药[92]. 其次, 中医药能直接激活并增强NK细胞的免疫效能, 该效能在“扶正”类补益中药及复方中尤为突出. 例如, 补气类的灵芝激活NKG2D/NCR受体通路, 玉屏风散提升NK细胞数量; 补血类的川芎增强NK细胞活性及相关细胞因子分泌, 当归补血汤提升NK细胞数量与活性; 补阴类的地黄通过激活ERK/p38 MAPK通路增强NK细胞功能, 生脉饮可提高NK细胞数量; 补阳类的附子抑制TME中TGF-β, IL-10等免疫抑制因子, 增强NK细胞活性, 小柴胡汤提升NK细胞数量与活性[93]. 此外, 一些中药活性成分及复方更具备“既能改善TME, 又能增强NK细胞免疫效应”的双重调控特点. 例如, 丹参的活性成分能够改善肿瘤免疫抑制性微环境并提升NK细胞杀伤活性. 丹参素能降低肿瘤患者外周血中免疫抑制因子TGF-β1的表达并增强NK细胞的免疫功能[94], 丹酚酸B和15,16-二氢丹参酮 I 可通过抑制中性粒细胞向转移灶募集, 阻断肿瘤血行转移[95], 丹参酮IIA通过调节基质金属蛋白酶(matrix metalloproteinase, MMP)的活性, 抑制血管内皮生长因子(vascular endothelial growth factor, VEGF), 干预肿瘤的侵袭和转移[96]. 黄芩中黄芩苷和黄芩素既能够调节TME中Tregs和MDSCs的活性, 还能促使TAMs向M1型极化, 改善TME中免疫抑制状况[97], 同时直接作用于NK细胞[98,99], 促进其细胞毒性因子, 实现免疫微环境重塑与效应细胞激活的双重效应. 人参中人参皂苷Rh2一方面下调VEGF和MMP2的表达, 抑制肿瘤血管新生, 另一方面抑制内质网蛋白5(endoplasmic reticulum protein 5, ERp5)表达、调控NKG2D-MICA信号轴增强NK细胞的免疫监视功能[100]. 中药复方亦表现出类似特点, 如川芎精油则通过抑制HIF-1α信号通路逆转缺氧所致的化疗耐药, 从而改善缺氧对NK细胞的抑制作用[101]; 阳和汤不仅能促进TME中NKT细胞和$CD4^+$ T细胞的

浸润, 还能减少免疫抑制细胞MDSCs的募集[102]. 这些研究共同表明, 中医药可通过多维度、系统性干预模式, 既削弱抑制信号, 又强化NK效应, 为突破TME构筑的免疫屏障提供了全新的思路.

但是, 中医药与NK细胞、TME相结合的临床研究尚处于起步阶段, 中药对于NK细胞及TME相关研究仍然以实验研究为主, 大样本, 多中心的注册临床研究较少, 且成果转化率低, 这可能与TME的复杂性网络性和动态性等因素相关[103]. 现有证据以小样本探索性研究和临床观察为主, 例如一些临床观察提示, 康艾注射液[104]、抗癌平丸[105]、消癌解毒方[106]、当归四君子汤[107]等可改善肿瘤患者外周血NK细胞数量与活性, 并可能与生活质量、无进展生存期等临床结局改善相关. 这些临床结果多以免疫指标为主, 直接以调控TME和增强NK细胞功能为核心的前瞻性研究仍较为缺乏.

综上, 未来的NK细胞抗肿瘤转移治疗可考虑将中医药作为免疫微环境调控的重要组成部分, 与现代NK细胞免疫疗法及TME靶向策略相结合, 形成多靶点、多路径的综合治疗体系. 该体系向临床转化过程中, 仍有一些方面需要进一步探索与完善, 例如: 中药调控TME的具体作用机制有待深入阐释; 复方制剂的质量标准化与稳定性也需要持续优化; 此外, 个体化用药方案的设计与实施同样面临一定复杂性. 未来研究可聚焦于开展机制导向的临床研究, 结合单细胞测序等前沿技术, 在临床样本中系统验证中医药对TME及NK细胞功能的影响; 同时推动复方生产工艺与质量标准的现代化. 通过这一系列努力, 有望推动该领域向循证、精准和规范化的方向发展, 最终提升抗肿瘤转移免疫治疗的疗效与可持续性.

参考文献

1 Valastyan S, Weinberg R A. Tumor metastasis: molecular insights and evolving paradigms. Cell, 2011, 147: 275–292

2 Ghajar C M. Metastasis prevention by targeting the dormant niche. Nat Rev Cancer, 2015, 15: 238–247

3 Xu S J, Luo Y F, Huang J, et al. Prognostic value of immunosuppression scores in patients with esophageal squamous cell carcinoma: a multicenter study. Front Immunol, 2024, 15: 1517968

4 Zu S, Lu Y, Xing R, et al. Changes in subset distribution and impaired function of circulating natural killer cells in patients with colorectal cancer. Sci Rep, 2024, 14: 12188

5 Xu W, Birch G, Meliki A, et al. Progressive natural killer cell dysfunction in advanced-stage clear-cell renal cell carcinoma and association with clinical outcomes. ESMO Open, 2025, 10: 104105

6 Diao J, Wei Z, Pei Y, et al. Association of lymphocyte subsets percentage with prognosis for recurrent or metastatic nasopharyngeal carcinoma patients receiving PD-L1 inhibitors. Cancer Immunol Immunother, 2025, 74: 129

7 Bae W K, Lee B C, Kim H J, et al. A phase I study of locoregional high-dose autologous natural killer cell therapy with hepatic arterial infusion chemotherapy in patients with locally advanced hepatocellular carcinoma. Front Immunol, 2022, 13: 879452

8 Zhang Z, Liu S, Yao W, et al. Maimendong decoction inhibits lung cancer metastasis by increasing the proportion and killing activity of NK cells. J EthnoPharmacol, 2025, 338: 119127

9 Nakamura T, Sato T, Endo R, et al. STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis via NK cell activation. J Immunother Cancer, 2021, 9: e002852

10 Tian H, Li K, Chen J, et al. Impaired natural killer cell maturation in lung adenocarcinoma driven by FABP4 and SPON2 downregulation through disrupted lipid metabolism. Transl Lung Cancer Res, 2025, 14: 1660–1676

11 Huang Y, Xie Y, Zhang Y, et al. Single-cell transcriptome reveals the reprogramming of immune microenvironment during the transition from MASH to HCC. Mol Cancer, 2025, 24: 177

12 Bi J, Huang C, Jin X, et al. *TIPE2* deletion improves the therapeutic potential of adoptively transferred NK cells. J Immunother Cancer, 2023, 11: e006002

13 Dean I, Lee C Y C, Tuong Z K, et al. Rapid functional impairment of natural killer cells following tumor entry limits anti-tumor immunity. Nat Commun, 2024, 15: 683

14 Shimizu K, Ueda S, Kawamura M, et al. Combination of cancer vaccine with CD122-biased IL-2/anti-IL-2 Ab complex shapes the stem-like effector NK and $CD8^+$ T cells against tumor. J Immunother Cancer, 2023, 11: e006409

15 Gasteiger G, Hemmers S, Firth M A, et al. IL-2-dependent tuning of NK cell sensitivity for target cells is controlled by regulatory T cells. J Exp Med, 2013, 210: 1167–1178
16 Shi Y J. The role and mechanism of FBXO38 in promoting anti-tumor activities of natural killer cells (in Chinese). Dissertation for Doctoral Degree. Hefei: University of Science and Technology of China, 2024 [石永靖. FBXO38分子促进NK细胞抗肿瘤免疫应答的机制研究. 博士学位论文. 合肥: 中国科学技术大学, 2024]
17 Caligiuri M A. Human natural killer cells. Blood, 2008, 112: 461–469
18 Douka S, Papamoschou V, Raimo M, et al. Harnessing the power of NK cell receptor engineering as a new prospect in cancer immunotherapy. Pharmaceutics, 2024, 16: 1143
19 Molfetta R, Milito N D, Zitti B, et al. The ubiquitin-proteasome pathway regulates Nectin2/CD112 expression and impairs NK cell recognition and killing. Eur J Immunol, 2019, 49: 873–883
20 Mou J, Xie L, Xu Y, et al. 2B4 inhibits the apoptosis of natural killer cells through phosphorylated extracellular signal-related kinase/B-cell lymphoma 2 signal pathway. Cytotherapy, 2023, 25: 1080–1090
21 Petersdorf E W, McKallor C, Malkki M, et al. The association of HLA-E ligand and NKG2 receptor variation with relapse and mortality after haploidentical related donor transplantation. Transplant Cell Ther, 2025, 31: 137–156
22 Ding B, Li J, Yan J L, et al. Resveratrol contributes to NK cell-mediated breast cancer cytotoxicity by upregulating ULBP2 through miR-17-5p downmodulation and activation of MINK1/JNK/c-Jun signaling. Front Immunol, 2025, 16: 1515605
23 López-Soto A, Gonzalez S, Smyth M J, et al. Control of metastasis by NK cells. Cancer Cell, 2017, 32: 135–154
24 Sen Santara S S, Lee D J, Crespo Â, et al. The NK cell receptor NKp46 recognizes ecto-calreticulin on ER-stressed cells. Nature, 2023, 616: 348–356
25 Wu S Y, Fu T, Jiang Y Z, et al. Natural killer cells in cancer biology and therapy. Mol Cancer, 2020, 19: 120
26 Sun Y, Sedgwick A J, Palarasah Y, et al. A transcriptional signature of PDGF-DD activated natural killer cells predicts more favorable prognosis in low-grade glioma. Front Immunol, 2021, 12: 668391
27 Fournier L, Arras P, Pekar L, et al. Enhancing NK cell-mediated tumor killing of B7-H6^{+} cells with bispecific antibodies targeting allosteric sites of NKp30. Mol Ther Oncol, 2025, 33: 200917
28 Mariuzza R A, Singh P, Karade S S, et al. Recognition of self and viral ligands by NK cell receptors. Immunol Rev, 2025, 329: e13435
29 Zhang X, Zhang L, Li B, et al. Identification of epinastine as CD96/PVR inhibitor for cancer immunotherapy. BMC Biol, 2025, 23: 27
30 Hu S, Han P, Wang M, et al. Structural basis for the immune recognition and selectivity of the immune receptor PVRIG for ligand Nectin-2. Structure, 2024, 32: 918–929.e4
31 Halimi H, Mirzazadeh S, Kalantar K, et al. Activating KIR/HLA-I combinations as a risk factor of adult B-ALL. Hum Immunol, 2024, 85: 110750
32 Liu Y, Gong L, Feng J, et al. Co-delivery of axitinib and PD-L1 siRNA for the synergism of vascular normalization and immune checkpoint inhibition to boost anticancer immunity. J Nanobiotechnol, 2025, 23: 194
33 Lü X, Wei X, Wang C, et al. Identification of the therapeutic potential of novel TIGIT/PVR interaction blockers based advanced computational techniques and experimental validation. Biophys Chem, 2025, 318: 107383
34 Zhang Y, Weinberg R A. Epithelial-to-mesenchymal transition in cancer: complexity and opportunities. Front Med, 2018, 12: 361–373
35 Lo H C, Xu Z, Kim I S, et al. Resistance to natural killer cell immunosurveillance confers a selective advantage to polyclonal metastasis. Nat Cancer, 2020, 1: 709–722
36 Chockley P J, Chen J, Chen G, et al. Epithelial-mesenchymal transition leads to NK cell-mediated metastasis-specific immunosurveillance in lung cancer. J Clin Invest, 2018, 128: 1384–1396
37 Okita R, Shimizu K, Nakata M. Epithelial-mesenchymal transition-induced metastasis could be a bait for natural killer cells. J Thorac Dis, 2018, 10: S3143–S3146
38 Lawrence R, Watters M, Davies C R, et al. Circulating tumour cells for early detection of clinically relevant cancer. Nat Rev Clin Oncol, 2023, 20: 487–500
39 Green T L, Cruse J M, Lewis R E. Circulating tumor cells (CTCs) from metastatic breast cancer patients linked to decreased immune function and response to treatment. Exp Mol Pathol, 2013, 95: 174–179
40 Liu X, Song J, Zhang H, et al. Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell

surveillance. Cancer Cell, 2023, 41: 272–287.e9
41 Dianat-Moghadam H, Mahari A, Heidarifard M, et al. NK cells-directed therapies target circulating tumor cells and metastasis. Cancer Lett, 2021, 497: 41–53
42 Liu X, Chen Q, Yan J, et al. MiRNA-296-3p-ICAM-1 axis promotes metastasis of prostate cancer by possible enhancing survival of natural killer cell-resistant circulating tumour cells. Cell Death Dis, 2013, 4: e928
43 Zheng C L, Wang C Z, Yang Z Y, et al. Regulation of gastrointestinal tumor stem cells by traditional Chinese medicine: a review (in Chinese). Chin J Exp Tradit Med Formulae, 2025, 31: 280–287 [郑成垒, 王成志, 杨振耀, 等. 中医药调控消化道肿瘤干细胞的研究进展. 中国实验方剂学杂志, 2025, 31: 280–287]
44 Zhou L, Wen R, Bai C, et al. Spatial transcriptomic revealed intratumor heterogeneity and cancer stem cell enrichment in colorectal cancer metastasis. Cancer Lett, 2024, 602: 217181
45 Shaim H, Shanley M, Basar R, et al. Targeting the αv integrin/TGF-β axis improves natural killer cell function against glioblastoma stem cells. J Clin Invest, 2021, 131: e142116
46 Jewett A, Kos J, Fong Y, et al. NK cells shape pancreatic and oral tumor microenvironments; role in inhibition of tumor growth and metastasis. Semin Cancer Biol, 2018, 53: 178–188
47 Kos K, Aslam M A, van de Ven R, et al. Tumor-educated Tregs drive organ-specific metastasis in breast cancer by impairing NK cells in the lymph node niche. Cell Rep, 2022, 38: 110447
48 Jiang Y, Gao S, Sun H, et al. Targeting NEDD8 suppresses surgical stress-facilitated metastasis of colon cancer via restraining regulatory T cells. Cell Death Dis, 2024, 15: 8
49 Tumino N, Besi F, Martini S, et al. Polymorphonuclear myeloid-derived suppressor cells are abundant in peripheral blood of cancer patients and suppress natural killer cell anti-tumor activity. Front Immunol, 2021, 12: 803014
50 Liu W, Wei X, Li L, et al. CCR4 mediated chemotaxis of regulatory T cells suppress the activation of T cells and NK cells via TGF-β pathway in human non-small cell lung cancer. Biochem Biophys Res Commun, 2017, 488: 196–203
51 Peng L S, Zhang J Y, Teng Y S, et al. Tumor-associated monocytes/macrophages impair NK-cell function via TGFβ1 in human gastric cancer. Cancer Immunol Res, 2017, 5: 248–256
52 Li H, Han Y, Guo Q, et al. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-β1. J Immunol, 2009, 182: 240–249
53 Zhu Z C, He L Y, Qi C J. Regulating effect of macrophages on NK cells in tumor microenvironment (in Chinese). Chin J Immunol, 2023, 39: 849–854 [朱志超, 何流漾, 戚春建. 肿瘤微环境中巨噬细胞对NK细胞的调控作用. 中国免疫学杂志, 2023, 39: 849–854]
54 Noy R, Pollard J W. Tumor-associated macrophages: from mechanisms to therapy. Immunity, 2014, 41: 49–61
55 Kim J, Thomas S N. Opportunities for nitric oxide in potentiating cancer immunotherapy. Pharmacol Rev, 2022, 74: 1146–1175
56 Bozward A G, Warricker F, Oo Y H, et al. Natural killer cells and regulatory T cells cross talk in hepatocellular carcinoma: exploring therapeutic options for the next decade. Front Immunol, 2021, 12: 643310
57 Li C, Jiang P, Wei S, et al. Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects. Mol Cancer, 2020, 19: 116
58 Xiong Q, Zhang H, Ji X, et al. A novel membrane-bound interleukin-2 promotes NK-92 cell persistence and anti-tumor activity. Oncoimmunology, 2022, 11: 2127282
59 Zimmer J, Andrès E, Hentges F. NK cells and Treg cells: a fascinating dance cheek to cheek. Eur J Immunol, 2008, 38: 2942–2945
60 Goh C C, Roggerson K M, Lee H C, et al. Hepatitis C virus-induced myeloid-derived suppressor cells suppress NK cell IFN-γ production by altering cellular metabolism via arginase-1. J Immunol, 2016, 196: 2283–2292
61 Ielpo S, Barberini F, Dabbagh Moghaddam F, et al. Crosstalk and communication of cancer-associated fibroblasts with natural killer and dendritic cells: new frontiers and unveiled opportunities for cancer immunotherapy. Cancer Treat Rev, 2024, 131: 102843
62 Zhang R, Qi F, Zhao F, et al. Cancer-associated fibroblasts enhance tumor-associated macrophages enrichment and suppress NK cells function in colorectal cancer. Cell Death Dis, 2019, 10: 273
63 Ben-Shmuel A, Gruper Y, Halperin C, et al. Cancer-associated fibroblasts serve as decoys to suppress NK cell anticancer cytotoxicity in breast cancer. Cancer Discov, 2025, 15: 1247–1269
64 Cifaldi L, Prencipe G, Caiello I, et al. Inhibition of natural killer cell cytotoxicity by interleukin-6: implications for the pathogenesis of

macrophage activation syndrome. Arthritis Rheumatol, 2015, 67: 3037–3046
65 Fanijavadi S, Thomassen M, Jensen L H. Targeting triple NK cell suppression mechanisms: a comprehensive review of biomarkers in pancreatic cancer therapy. Int J Mol Sci, 2025, 26: 515
66 Francescone R, Barbosa Vendramini-Costa D, Franco-Barraza J, et al. Netrin G1 promotes pancreatic tumorigenesis through cancer-associated fibroblast-driven nutritional support and immunosuppression. Cancer Discov, 2021, 11: 446–479
67 Schlesinger M. Role of platelets and platelet receptors in cancer metastasis. J Hematol Oncol, 2018, 11: 125
68 Maurer S, Kropp K N, Klein G, et al. Platelet-mediated shedding of NKG2D ligands impairs NK cell immune-surveillance of tumor cells. Oncoimmunology, 2018, 7: e1364827
69 Zhou Y, Cheng L, Liu L, et al. NK cells are never alone: crosstalk and communication in tumour microenvironments. Mol Cancer, 2023, 22: 34
70 Parodi M, Raggi F, Cangelosi D, et al. Hypoxia modifies the transcriptome of human NK cells, modulates their immunoregulatory profile, and influences NK cell subset migration. Front Immunol, 2018, 9: 2358
71 Zheng X, Qian Y, Fu B, et al. Mitochondrial fragmentation limits NK cell-based tumor immunosurveillance. Nat Immunol, 2019, 20: 1656–1667
72 Sarkar S, Germeraad W T V, Rouschop K M A, et al. Hypoxia induced impairment of NK cell cytotoxicity against multiple myeloma can be overcome by IL-2 activation of the NK cells. PLoS One, 2013, 8: e64835
73 Berchem G, Noman M Z, Bosseler M, et al. Hypoxic tumor-derived microvesicles negatively regulate NK cell function by a mechanism involving TGF-β and miR23a transfer. Oncoimmunology, 2016, 5: e1062968
74 Wang Z, Guan D, Wang S, et al. Glycolysis and oxidative phosphorylation play critical roles in natural killer cell receptor-mediated natural killer cell functions. Front Immunol, 2020, 11: 202
75 Cong J, Wang X, Zheng X, et al. Dysfunction of natural killer cells by FBP1-induced inhibition of glycolysis during lung cancer progression. Cell Metab, 2018, 28: 243–255.e5
76 Angka L, Tanese de Souza C, Baxter K E, et al. Perioperative arginine prevents metastases by accelerating natural killer cell recovery after surgery. Mol Ther, 2022, 30: 3270–3283
77 Terrén I, Orrantia A, Vitallé J, et al. NK cell metabolism and tumor microenvironment. Front Immunol, 2019, 10: 2278
78 Chiesa M D, Carlomagno S, Frumento G, et al. The tryptophan catabolite l-kynurenine inhibits the surface expression of NKp46- and NKG2D-activating receptors and regulates NK-cell function. Blood, 2006, 108: 4118–4125
79 Fang H, Dai W, Gu R, et al. Correction: myCAF-derived Exosomal PWAR6 accelerates CRC liver metastasis via altering glutamine availability and NK cell function in the tumor microenvironment. J Hematol Oncol, 2025, 18: 31
80 Scott K E N, Cleveland J L. Lactate wreaks havoc on tumor-infiltrating T and NK cells. Cell Metab, 2016, 24: 649–650
81 Harmon C, Robinson M W, Hand F, et al. Lactate-mediated acidification of tumor microenvironment induces apoptosis of liver-resident NK cells in colorectal liver metastasis. Cancer Immunol Res, 2019, 7: 335–346
82 Miao L, Lu C, Zhang B, et al. Advances in metabolic reprogramming of NK cells in the tumor microenvironment on the impact of NK therapy. J Transl Med, 2024, 22: 229
83 Yang Y, Lundqvist A. Immunomodulatory Effects of IL-2 and IL-15; implications for cancer immunotherapy. Cancers, 2020, 12: 3586
84 Russick J, Torset C, Hemery E, et al. NK cells in the tumor microenvironment: prognostic and theranostic impact. Recent advances and trends. Semin Immunol, 2020, 48: 101407
85 Chen Y Q, Zuo A X, Su M X. Research progress of NK cell therapy in brain glioma immunotherapy (in Chinese). Chin Clinical Oncol, 2025, 30: 302–306 [陈永琼, 左安学, 苏牟潇. NK细胞疗法在脑胶质瘤免疫治疗中的研究进展. 临床肿瘤学杂志, 2025, 30: 302–306]
86 Shapiro R M, Sheffer M, Booker M A, et al. First-in-human evaluation of memory-like NK cells with an IL-15 super-agonist and CTLA-4 blockade in advanced head and neck cancer. J Hematol Oncol, 2025, 18: 17
87 Sun Y, Li T, Ding L, et al. Platelet-mediated circulating tumor cell evasion from natural killer cell killing through immune checkpoint CD155-TIGIT. Hepatology, 2025, 81: 791–807
88 Liu Y, Chen J, Tian J, et al. Engineered CAR-NK cells with tolerance to H_2O_2 and hypoxia can suppress postoperative relapse of triple-negative breast cancers. Cancer Immunol Res, 2024, 12: 1574–1588
89 Wang Y R, Li H J, Liu Z D. Exploring the biological basis of collateral disease pathogenesis in cancer pain from the perspective of tumor microenvironment (in Chinese). J Anhui Univ Chin Med, 2024, 43: 9–12 [王玉如, 李慧杰, 刘寨东. 基于肿瘤微环境探讨癌性疼痛络病病机

的生物学基础. 安徽中医药大学学报, 2024, 43: 9–12]
90 He J W, Han B, Lu J X, et al. Exploring the mechanism of Fuzheng Jiedu Therapy in tumor treatment from the perspective of tumor microenvironment remodeling (in Chinese). Global Tradit Chin Med, 2024, 17: 273–276 [贺佳文, 韩冰, 卢佳萱, 等. 从肿瘤微环境的重塑探索扶正解毒法治疗肿瘤的机制. 环球中医药, 2024, 17: 273–276]
91 Chen F, Li J, Wang H, et al. Anti-tumor effects of Chinese medicine compounds by regulating immune cells in microenvironment. Front Oncol, 2021, 11: 746917
92 Zou X Y, Tian P, Li J, et al. Guiqi Yiyuan Ointment reduces M2 macrophage polarization and enhances sensitivity of Lewis lung cancer mice to cisplatin by inhibiting JAK3/STAT6 signaling pathway (in Chinese). China J Chin Mater Med, 2025, 50: 6072–6080 [邹晓雨, 田萍, 李娟, 等. 归芪益元膏通过抑制JAK3/STAT6信号通路减少M2型巨噬细胞极化提高Lewis肺癌小鼠对顺铂的敏感性. 中国中药杂志, 2025, 50: 6072–6080]
93 Duan Y Y, Wu B X, Li J H, et al. Summary and evaluation of representative traditional Chinese medicine and health foods based on enhanced NK cell activity (in Chinese). J Pharm Res, 2025, 44: 394–402 [段阳阳, 吴槟辛, 李君菡, 等. 增强NK细胞活性的代表性中药及保健食品综述与评价. 药学研究, 2025, 44: 394–402]
94 Zhang T T. the mechanism of Tanshinol regulating the killing effect of NK cells on breast cancer based on TGF-β1 (in Chinese). Dissertation for Master's Degree. Nanjing: Nanjing University of Chinese Medicine, 2019 [张婷婷. 基于TGF-β1探讨丹参素调节NK细胞对乳腺癌的杀伤作用及机制. 硕士学位论文. 南京: 南京中医药大学, 2019]
95 Tao L, Xu M, Dai X, et al. Polypharmacological profiles underlying the antitumor property of *Salvia miltiorrhiza* root (Danshen) interfering with NOX-dependent neutrophil extracellular traps. Oxid Med Cell Longev, 2018, 2018: 4908328
96 Mao Y, Meng L, Liu H, et al. Therapeutic potential of traditional Chinese medicine for vascular endothelial growth factor. J Zhejiang Univ Sci B, 2022, 23: 353–364
97 Liu S, An Q, Sun Q, et al. Research progress in the modulation of tumor microenvironment by traditional Chinese medicine (in Chinese). J Oncol Chin Med, 2025, 7: 13–25 [刘珊, 安倩, 孙琼, 等. 中药调控肿瘤微环境研究进展. 中医肿瘤学杂志, 2025, 7: 13–25]
98 Xu L, Wang Y, Chen F X, et al. The effect of wogonin on NK cell cytotoxicity against gastric cancer MKN45 cells *in vitro* and the mechanism (in Chinese). Immunol J, 2014, 30: 804–808 [许琳, 王营, 陈复兴, 等. 汉黄芩素对人NK细胞杀伤胃癌MKN45细胞的影响及其机制研究. 免疫学杂志, 2014, 30: 804–808]
99 Wu W P, Wang W Z. The effect of baicalin on the killing activity of NK cells in mice (in Chinese). China Mod Doctors, 2007, 14: 28–30 [吴维平, 王婉真. 黄芩苷对小鼠NK细胞杀伤活性的作用. 中国现代医生, 2007, 14: 28–30]
100 Li X X, Cheng A M, Yang R, et al. Research progress on the antitumor effects of ginsenoside Rh2 (in Chinese). Prog Physiol Sci, 2025, 1–16 [李秀秀, 程爱民, 杨睿, 等. 人参皂苷Rh2在抗肿瘤中的作用研究进展. 生理科学进展, 2025, 1–16]
101 Ke G, Hu P, Xiong H, et al. Enhancing temozolomide efficacy in GBM: the synergistic role of chuanxiong rhizoma essential oil. Phytomedicine, 2025, 140: 156575
102 Mao D, Feng L, Gong H, et al. The antitumor and immunomodulatory effect of Yanghe Decoction in breast cancer is related to the modulation of the JAK/STAT signaling pathway. Evid-Based Complement Alternat Med, 2018, 1: 8460526
103 Li Y, Huang J, Chen T, et al. Research progress on chinese medicine intervention in immune cells in tumor microenvironment (in Chinese). World Chin Med, 2023, 18: 566–571 [李悦, 黄菁, 陈婷, 等. 中药干预肿瘤微环境中免疫细胞的研究进展. 世界中医药, 2023, 18: 566–571]
104 Xiao M, Liu Y, Tian W S, et al. Kang Ai injection chemotherapy for locally advanced colorectal cancer immune function and the effect of TCM symptoms (in Chinese). Contemp Med, 2017, 23: 9–12 [肖敏, 刘瑛, 田武生, 等. 康艾注射液联合化疗对中晚期结直肠癌免疫功能及中医症候的影响. 当代医学, 2017, 23: 9–12]
105 Zhang H, Yu J W, Lu H Z, et al. Clinical study on Kang'aiping Pills combined with SOX chemotherapy regimen in treatment of advanced gastric cancer (in Chinese). Drugs Clinic, 2026, 41: 139–144 [张煌, 余嘉文, 鲁恒珍, 等. 抗癌平丸联合SOX化疗方案治疗晚期胃癌的临床研究. 现代药物与临床, 2026, 41: 139–144]
106 Chen H B, Zhou H G, Cheng H B, et al. Immune function of Xiaoaijiedufang on patients with advanced malignant tumor (in Chinese). Acta Univ Med Nanjing (Nat Sci), 2009, 29: 1257–1259 [陈海彬, 周红光, 程海波, 等. 消癌解毒方对中晚期恶性肿瘤患者免疫功能的影响. 南京医科大学学报(自然科学版), 2009, 29: 1257–1259]
107 Chen R W, Teng R, Zhou K X, et al. Efficacy of Danggui Sini Decoction combined with strontium chloride injection in treatment of metastatic bone tumors (in Chinese). J Hubei Univ of Chin Med, 2024, 26: 69–71 [陈若万, 滕然, 周可芯, 等. 当归四逆汤联合氯化锶注射液治疗转移性骨肿瘤临床疗效观察. 湖北中医药大学学报, 2024, 26: 69–71]

Research progress on NK cell anti-tumor metastasis

DONG KeShan, ZHANG Yang, DU XinKe, XIE ChengZhi, HAN JiaYin*, SU XiaoHui* & LI Qi*

Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
** Corresponding authors, E-mail: jyhan@icmm.ac.cn; xhsu@icmm.ac.cn; qli@icmm.ac.cn*

The process of tumor metastasis is highly dependent on the immunosuppressive tumor microenvironment (TME). Natural killer (NK) cells play an important inhibitory role at all stages of tumor metastasis due to their non-specific immune killing characteristics. The quantity and functional activity of NK cells are negatively correlated with tumor metastasis, and NK cell-based immunotherapy has shown preliminary efficacy in various solid tumors. However, the tumor microenvironment (TME) harbors various immunosuppressive components. These include cells such as regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), as well as non-immune components like cancer-associated fibroblasts (CAFs). The combined effect of these factors, along with others such as platelets and metabolic disorders, significantly weakens the infiltration and effector functions of NK cells, thereby restricting their ability to resist tumor metastasis. At present, most anti-tumor treatment strategies targeting NK cells mainly focus on enhancing their activity, but neglect the systemic inhibition of the TME, resulting in unsatisfactory clinical efficacy. Therefore, this article systematically reviews the inhibitory effect of NK cells in tumor metastasis and its molecular mechanism, deeply analyzes how TME jointly restricts the function of NK cells through immune cells, stromal cells, and metabolic characteristics, and proposes a bidirectional therapeutic strategy of “enhancing NK cell activity and relieving TME inhibition”. Provide new theoretical basis and therapeutic strategies for NK cell-mediated anti-tumor metastasis immunotherapy.

NK cells, tumor metastasis, tumor microenvironment, immunotherapy

doi: 10.1360/SSV-2025-0314