

中药活性成分调控 $\gamma\delta$ T细胞抗肿瘤免疫功能的研究进展^Δ

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摘 要 $\gamma\delta$ T细胞兼具先天性与适应性免疫特征,其抗原识别不依赖经典的主要组织相容性复合体呈递,可直接识别肿瘤代谢异常,在免疫低浸润肿瘤中具有独特应用潜力。本文系统梳理 $\gamma\delta$ T细胞的生物学特性及其抗肿瘤免疫功能特点,重点综述中药活性成分调控 $\gamma\delta$ T细胞抗肿瘤免疫功能的相关机制,发现甘草多糖、黄芪多糖可通过促进多种细胞因子表达、调节肠道菌群、改善免疫抑制状态等,增强 $\gamma\delta$ T细胞的抗肿瘤免疫功能;槲皮素和葛根素可通过调节 $\gamma\delta$ T细胞的增殖、细胞毒效应分子表达及相关信号通路活性,增强 $\gamma\delta$ T细胞介导的肿瘤细胞杀伤作用;川楝素可通过下调肿瘤细胞中抗凋亡蛋白表达,增强 $\gamma\delta$ T细胞对肿瘤细胞的杀伤作用;青蒿琥酯可通过增强 $\gamma\delta$ T细胞效应功能并减弱肿瘤细胞免疫逃逸能力,促进 $\gamma\delta$ T细胞介导的抗肿瘤免疫效应。未来可重点探索中药活性成分与 $\gamma\delta$ T细胞免疫治疗联合应用的协同效应及相关分子机制,明确 $\gamma\delta$ T细胞发挥抗肿瘤免疫功能的关键靶点。

关键词 $\gamma\delta$ T细胞; 中药; 活性成分; 抗肿瘤; 免疫治疗; 免疫逃逸

Research progress on regulation of antitumor immune function of $\gamma\delta$ T cells by active ingredients of traditional Chinese medicine

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ABSTRACT $\gamma\delta$ T cells possess both innate and adaptive immune characteristics. Their antigen recognition is independent of major histocompatibility complex presentation, and they can directly recognize abnormal tumor metabolism, showing unique application potential in tumors with low immune infiltration. This paper systematically sorts out the biological characteristics and antitumor immune functions of $\gamma\delta$ T cells, and mainly reviews the relevant mechanisms by which active ingredients of traditional Chinese medicine regulate $\gamma\delta$ T cells to exert antitumor immune functions. *Glycyrrhiza* polysaccharide and *Astragalus* polysaccharide can enhance the antitumor immune function of $\gamma\delta$ T cells by promoting the expression of various cytokines, regulating intestinal flora and alleviating immunosuppressive state. Quercetin and puerarin can strengthen $\gamma\delta$ T cell-mediated tumor cell killing by regulating the proliferation of $\gamma\delta$ T cells, the expression of cytotoxic effector molecules and related signaling pathways. Toosendanin can potentiate $\gamma\delta$ T cell-induced tumor cell killing by down-regulating the expression of anti-apoptotic protein in tumor cells. Artesunate can boost $\gamma\delta$ T cell-mediated antitumor immune responses by enhancing the effector function

of $\gamma\delta$ T cells and weakening tumor immune escape. Future research shall focus on exploring the synergistic effects and molecular mechanisms of the combined application of active ingredients of traditional Chinese medicine and $\gamma\delta$ T cell immunotherapy, and identifying the key targets for $\gamma\delta$ T cells to exert antitumor immune functions.

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在肿瘤发生和进展过程中,肿瘤细胞可通过多种机制逃避免疫监视,包括抗原呈递缺陷、免疫抑制性微环境形成以及免疫细胞功能耗竭等,这些机制均会影响机体对肿瘤的免疫清除能力^[1-2]。近年来,肿瘤免疫治疗在以免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)和过继性T细胞治疗为代表的治疗策略中取得了突破性进展,也在部分肿瘤患者中实现了长期生存率的提高^[3-4]。当前临床研究较多的嵌合抗原受体T细胞(chimeric antigen receptor T cells, CAR-T)、T细胞受体工程化T细胞(T cell receptor-engineered T cells, TCR-T)及肿瘤浸润淋巴细胞(tumor-infiltrating lymphocytes, TILs)治疗多以 $\alpha\beta$ T细胞为主要效应细胞,这些治疗虽然显著拓展了实体瘤和血液肿瘤的治疗边界^[4-5],但是 $\alpha\beta$ T细胞易受到肿瘤细胞主要组织相容性复合体(major histocompatibility complex, MHC)下调或抗原逃逸的影响,从而限制了其在复杂肿瘤免疫微环境中的持续效应^[6]。 $\gamma\delta$ T细胞在外周血中占比较小但功能独特,兼具先天性免疫和适应性免疫功能,其T细胞受体(T cell receptor, TCR)不依赖经典的MHC分子呈递,可直接识别肿瘤相关代谢异常产物及应激分子,快速启动细胞毒效应并分泌多种细胞因子,因此 $\gamma\delta$ T细胞在免疫低浸润或抗原呈递功能受限的肿瘤中仍可能发挥抗肿瘤效应^[7-8]。

中药是我国传统医学的重要组成部分,其活性成分可影响免疫细胞的增殖、分化及功能状态,并可调节细胞因子网络^[9]。相关研究发现,中药活性成分不仅可增强机体的整体免疫功能,还可间接影响 $\gamma\delta$ T细胞的活化状态及抗肿瘤能力,为 $\gamma\delta$ T细胞介导的肿瘤免疫应答提供支持^[10]。然而,目前有关中药活性成分调控 $\gamma\delta$ T细胞发挥抗肿瘤作用的系统研究仍然有限,其具体作用机制尚有待进一步梳理。因此,本文基于 $\gamma\delta$ T细胞的生物学特性及其抗肿瘤免疫功能特点,重点综述中药活性成分调控 $\gamma\delta$ T细胞发挥抗肿瘤免疫功能的相关机制,以期对肿瘤免疫治疗提供新的研究思路。

1 $\gamma\delta$ T细胞概述

1.1 $\gamma\delta$ T细胞的分布特征及抗肿瘤效应

成熟的 $\gamma\delta$ T细胞广泛分布于外周血和多种组织器官中。在人外周血中, $\gamma\delta$ T细胞占T淋巴细胞总数的1%~10%,其中V γ 9V δ 2 T细胞是人外周血中最主要的 $\gamma\delta$ T细胞亚群,具有较强且反应快速的T细胞效应^[11]。研究表明,V γ 9V δ 2 T细胞可识别肿瘤细胞代谢异常相

关的磷酸抗原,从而增强其对肿瘤细胞的杀伤作用^[12-13]。V δ 1 T细胞是富集于肠道、肺、皮肤等黏膜与上皮屏障部位的 $\gamma\delta$ T细胞亚群,其常与上皮细胞、基质细胞及局部抗原呈递细胞协同构建局部免疫微环境^[14]。V δ 1 T细胞可通过自然杀伤细胞受体2D等识别肿瘤细胞表面的主要组织相容性复合体I类链相关蛋白A/B等配体实现快速应答,并释放 γ 干扰素(interferon- γ , IFN- γ)、肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)等细胞因子,从而发挥抗肿瘤效应^[15-17]。

1.2 $\gamma\delta$ T细胞的促肿瘤效应及功能重塑

V δ 1 T细胞不仅具有抗肿瘤效应,在抗原持续刺激、免疫抑制性细胞因子富集等肿瘤免疫微环境因素的影响下,V δ 1 T细胞的功能亦可发生重塑并呈现促肿瘤效应^[18]。 $\gamma\delta$ T细胞的促肿瘤效应主要与功能极化异常、免疫抑制表型形成和效应功能衰减有关——(1)功能极化异常:在肿瘤相关炎症环境中, $\gamma\delta$ T细胞可向分泌白介素17(interleukin-17, IL-17)的 $\gamma\delta$ T17细胞亚群极化^[19-20];IL-17一方面可直接促进肿瘤细胞增殖,另一方面可通过招募髓源性抑制性细胞及中性粒细胞,促进肿瘤生长、侵袭及转移^[21-22]。(2)免疫抑制表型形成:部分 $\gamma\delta$ T细胞可在肿瘤免疫微环境刺激下呈现类似调节性T细胞的功能特征^[23],从而分泌免疫抑制性细胞因子或影响抗原呈递过程,抑制CD8⁺T细胞及树突状细胞功能,进而削弱机体抗肿瘤免疫功能^[24]。(3)效应功能衰减:在抗原持续刺激和免疫检查点信号持续激活的条件下, $\gamma\delta$ T细胞可能出现功能衰减(表现为细胞毒性下降及IFN- γ 、颗粒酶B、穿孔素等效应分子分泌减少),使得其抗肿瘤效应减弱,促肿瘤效应增强^[25]。

2 $\gamma\delta$ T细胞在肿瘤免疫治疗中的参与方式

$\gamma\delta$ T细胞在肿瘤免疫治疗中的参与方式主要包括体内免疫调控、体外扩增回输以及基因工程化改造——(1)体内免疫调控: $\gamma\delta$ T细胞在体内可用氨基双膦酸盐类药物联合IL-2进行激活,从而参与体内免疫调控。氨基双膦酸盐可通过影响甲羟戊酸代谢途径,促进磷酸抗原在肿瘤细胞内积累,从而增强V γ 9V δ 2 T细胞对肿瘤细胞的识别和活化功能;IL-2则可进一步促进V γ 9V δ 2 T细胞增殖,并增强细胞毒效应和细胞因子分泌能力^[26-30]。(2)体外扩增回输: $\gamma\delta$ T细胞可通过体外扩增回输的方式参与过继性T细胞免疫治疗,即以患者外周血细胞为来源,经体外刺激和扩增获得自体 $\gamma\delta$ T细胞后再输注,以提高体内抗肿瘤效应,相关I期临床研究已提

示其具有一定安全性和可行性^[31]。(3)基因工程化改造: $\gamma\delta$ T细胞可作为工程化免疫细胞,通过导入嵌合抗原受体(chimeric antigen receptor, CAR)增强其对特定肿瘤抗原的靶向识别和杀伤能力,同时保留 $\gamma\delta$ T细胞自身TCR介导的识别及抗原交叉提呈功能^[32]。近年来,非病毒多重基因工程化、多克隆CAR- $\gamma\delta$ T细胞扩增以及CAR工程化T细胞构建等策略^[33-34],为 $\gamma\delta$ T细胞免疫治疗提供了新思路。如CD19-CAR修饰的多克隆 $\gamma\delta$ T细胞可同时依赖内源性 $\gamma\delta$ T细胞受体和外源性CAR介导抗肿瘤效应,这体现了 $\gamma\delta$ T细胞在天然识别与人工靶向识别之间的协同潜力^[35-36]。

3 中药活性成分对 $\gamma\delta$ T细胞抗肿瘤免疫功能的调控及相关机制

中药活性成分种类多样,既包括多糖类大分子免疫活性物质,也包括槲皮素、葛根素等结构相对明确的中药单体成分。基于此,笔者归纳总结不同类型中药活性成分对 $\gamma\delta$ T细胞抗肿瘤免疫功能的调控及相关机制,具体如下。

3.1 中药多糖类成分

中药多糖类成分具有多靶点调控免疫应答的作用,可促进抗原呈递细胞成熟、增强共刺激信号并重塑细胞因子网络^[37]。研究发现,甘草多糖可诱导机体免疫激活,且在肠黏膜免疫系统中其可增强 $\gamma\delta$ T细胞相关免疫反应,并促进IFN- γ 等细胞因子分泌,从而参与黏膜免疫调控^[38]。在野生型雄性BALB/c小鼠中发现,甘草多糖可通过调节肠道菌群及Toll样受体/核因子 κ B(nuclear factor- κ B, NF- κ B)信号通路,调控 $\gamma\delta$ T细胞相关抗肿瘤免疫功能^[38]。研究发现,甘草多糖可显著抑制结肠癌荷瘤小鼠肿瘤生长,并提高小鼠胸腺指数和脾脏指数;还可促进CD4⁺T细胞、CD8⁺T细胞活化并上调IL-2、IL-6、IL-7等细胞因子表达,提示甘草多糖具有明显的免疫增强作用^[39]。另有研究显示,甘草多糖作为佐剂用于脂质体疫苗时,可通过淋巴结靶向调控DC-T细胞轴,增强抗肿瘤免疫应答^[40]。研究表明,黄芪多糖可促进荷瘤小鼠肠道上皮内 $\gamma\delta$ T细胞的增殖与活化,增强 $\gamma\delta$ T细胞免疫功能,上调IFN- γ 、TNF- α 、凋亡配体、颗粒酶B等表达^[41]。由此可知,中药多糖类成分可通过促进多种细胞因子表达、调节肠道菌群、改善免疫抑制状态等,从而增强 $\gamma\delta$ T细胞的抗肿瘤免疫功能。

3.2 中药单体类成分

3.2.1 黄酮类单体成分

研究发现,槲皮素可通过调节颗粒酶B、穿孔素和IFN- γ 的表达,增强 $\gamma\delta$ T细胞的抗肿瘤免疫功能;还可通

过抑制Wnt/ β -catenin信号通路活性,强化 $\gamma\delta$ T细胞对人结直肠癌细胞的杀伤作用^[42]。另有研究发现,葛根素可通过提高 $\gamma\delta$ T细胞的扩增效率,促进 $\gamma\delta$ T细胞中穿孔素、颗粒酶B、CD107a、B细胞淋巴瘤2的表达和细胞外信号调节激酶1/2的磷酸化,从而增强 $\gamma\delta$ T细胞对肝癌SMMC-7721细胞的杀伤作用^[43]。由此可知,黄酮类中药单体可通过调节 $\gamma\delta$ T细胞增殖、细胞毒效应分子表达及相关信号通路,增强 $\gamma\delta$ T细胞介导的肿瘤细胞杀伤作用。

3.2.2 其他单体类成分

川楝素是一种三萜类成分,研究发现,川楝素可显著增强 $\gamma\delta$ T细胞对结直肠癌SW480细胞的杀伤作用;进一步机制研究表明,川楝素可通过下调结直肠癌SW480细胞中抗凋亡蛋白髓样细胞白血病1的表达,降低肿瘤细胞的抗凋亡能力,从而增强 $\gamma\delta$ T细胞对肿瘤细胞的杀伤作用^[44]。在肝癌HepG2细胞与 $\gamma\delta$ T细胞共培养体系中,青蒿琥酯一方面可上调 $\gamma\delta$ T细胞中颗粒酶B表达,增强其细胞毒活性;另一方面,青蒿琥酯可下调肝癌HepG2细胞中转化生长因子 β_1 表达,上调Fas表达;从而增强 $\gamma\delta$ T细胞对肝癌HepG2细胞的杀伤作用^[45]。由此可知,川楝素可通过下调肿瘤细胞中抗凋亡蛋白表达,增强 $\gamma\delta$ T细胞对肿瘤细胞的杀伤作用;青蒿琥酯可通过增强 $\gamma\delta$ T细胞效应功能并减弱肿瘤细胞免疫逃逸能力,促进 $\gamma\delta$ T细胞介导的抗肿瘤免疫效应。

4 结语

$\gamma\delta$ T细胞在人体内分布广泛,具有抗肿瘤与促肿瘤双重效应,其可通过氨基双磷酸盐类药物联合IL-2进行体内诱导激活,还可通过体外扩增进行过继性回输,或可通过CAR修饰及其他基因工程化改造增强其肿瘤靶向杀伤能力,从而参与肿瘤免疫治疗。中药活性成分种类多样,具有多靶点、多环节调节免疫应答的特点,可调控免疫细胞功能状态、细胞因子网络及肿瘤免疫相关过程,为 $\gamma\delta$ T细胞抗肿瘤免疫提供新思路。本文综述发现,中药活性成分(如多糖类成分甘草多糖和黄芪多糖、黄酮类成分槲皮素和葛根素等)可通过调节细胞因子网络、改善肿瘤免疫微环境、激活肠黏膜免疫及增强细胞毒效应等途径,影响 $\gamma\delta$ T细胞的抗肿瘤免疫功能。目前,相关研究仍以体外细胞实验和动物实验为主,针对人体 $\gamma\delta$ T细胞亚群及其功能变化的研究相对有限。未来可从以下方面进一步深入分析:(1)结合网络药理学、转录组学、蛋白质组学、代谢组学、空间组学及单细胞测序等技术,系统分析中药活性成分干预后 $\gamma\delta$ T细胞亚群组成、功能状态、代谢特征及其在肿瘤免疫微环境中的

空间分布变化;(2)厘清各类中药活性成分的作用机制,区分其是直接诱导 $\gamma\delta$ T细胞增殖、增强细胞毒效应,还是通过改变肿瘤细胞状态及肿瘤免疫微环境,提高肿瘤细胞对 $\gamma\delta$ T细胞杀伤作用的敏感性。后续可重点探索中药活性成分与 $\gamma\delta$ T细胞免疫治疗联合应用的协同效应及相关分子机制,明确 $\gamma\delta$ T细胞发挥抗肿瘤免疫功能的关键靶点。

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