

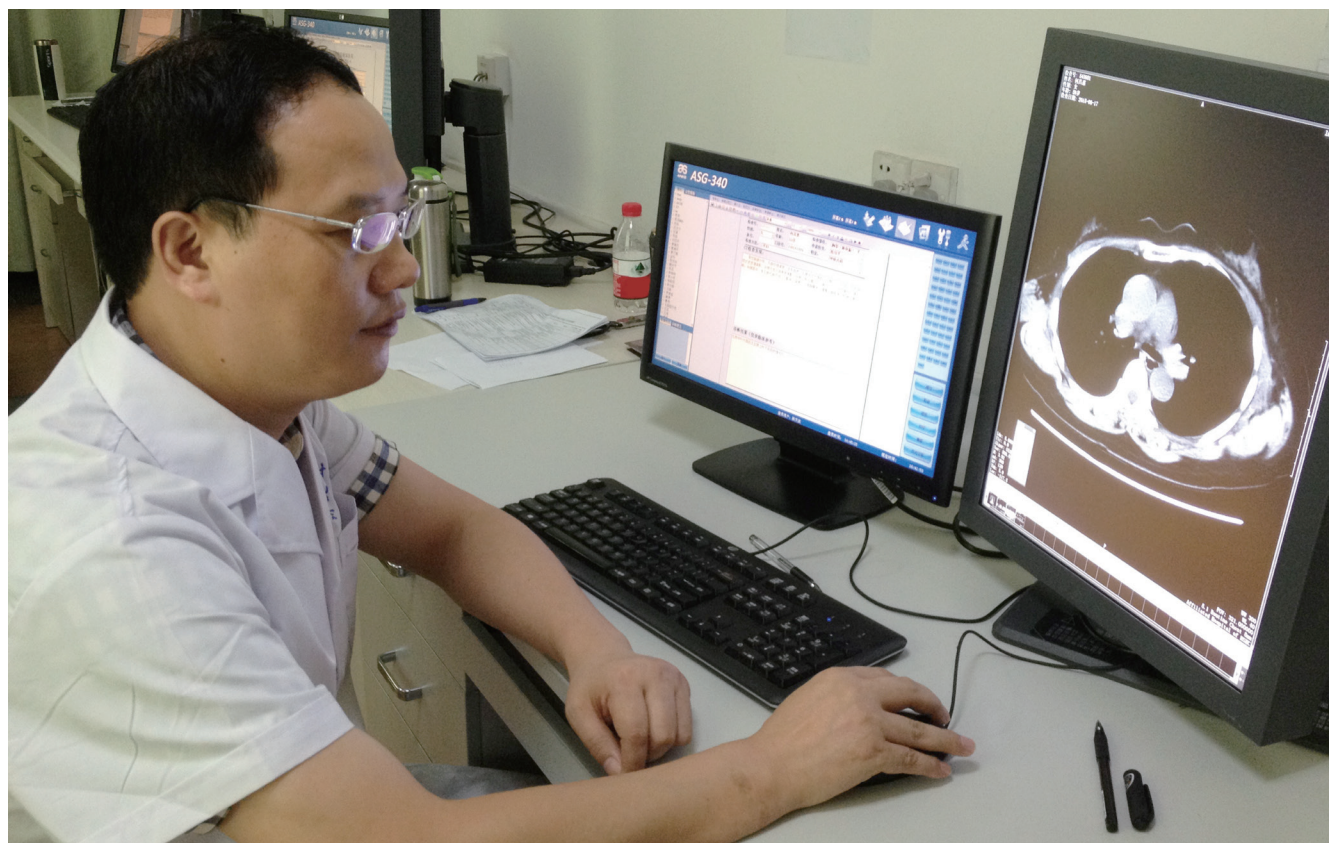
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CD8+ T细胞干细胞样亚群在肿瘤免疫治疗中的应用前景

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Application prospect of stem cell-like subpopulations of CD8+ T cells in tumor immunotherapy

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Abstract

Immunotherapy brings certain clinical benefits, but it still needs to be explored. Immune cell subsets are essential for tumor control in immunotherapy. Stem cell-like subpopulations of CD8+ T cells own the potential to self-proliferate and differentiate into effector cells so as to produce a prolonged antitumor immune response. Here, we will discuss stem cell-like subpopulations of CD8+ T cells with regard to the immune response mechanism of immune checkpoint inhibitor immunotherapy, its molecular and functional characteristics and relationship with immunotherapy efficacy, and its application strategies in tumor immunotherapy. This review will highlight the potential therapeutic implications of inducing or utilizing stem cell-like subpopulations of CD8+T cells for tumor immunotherapy.

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Key Words: CD8+ T cells; Stem-cell like; Immunotherapy; PD1; PD-L1

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摘要

免疫治疗带来一定的临床获益, 仍需探索。免疫细胞亚群对于免疫治疗中的肿瘤控制至关重要。CD8+ T细胞干细胞样亚群具有自我增殖和向效应细胞分化的潜能从而产生持久的抗肿瘤免疫反应。本文将从免疫检查点抑制剂免疫治疗中免疫细胞应答的机制、分子功能特性, 与免疫治疗疗效的相关性以及肿瘤免疫治疗中的应用策略等方面来阐述CD8+ T细胞

干细胞样亚群在肿瘤免疫治疗中的应用前景.

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关键词: CD8+ T淋巴细胞; 干细胞样; 免疫治疗; PD1; PD-L1

核心提要: 本篇文章综合阐述了具有自我增殖能力和多分化潜能的CD8+ T细胞干细胞样亚群在肿瘤免疫治疗中的研究进展, 强调该亚群作为新型潜在靶点在肿瘤免疫治疗中的应用前景.

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0 引言

利用人体自身免疫细胞进行治疗已经成为新型肿瘤治疗方法, 这种免疫疗法可以诱导晚期肿瘤患者产生持久的抗肿瘤反应. 但并非所有人都对肿瘤免疫治疗产生反应, 靶向肿瘤的细胞毒性CD8+ T细胞的持久性和增殖能力与机体抗肿瘤反应能力有关, 因而对于肿瘤免疫疗法的有效性至关重要.

1 对免疫检查点抑制剂抑制应答的免疫机制

PD1/PD-L1免疫检查点抑制剂(immune checkpoint inhibitor, ICI)免疫治疗疗效在很大程度上取决于直接阻断失调的CD8+ T细胞表面的免疫检查点分子, 从而重新激活其效应功能^[1]. 免疫检查点分子的表达驱动了CD8+ T细胞终末效应细胞(effector T cells, TE)进入功能衰竭T细胞(T cell exhaustion, TEX), 而这种状态可能与T细胞在肿瘤微环境中长时间暴露于肿瘤抗原有关, 而免疫检查点阻断介导了肿瘤浸润淋巴细胞(tumor infiltrating lymphocyte, TILs)的增殖反应, 但对其应答的免疫细胞亚群尚有争议^[2]. CD8+ T细胞是杀伤肿瘤细胞的主要免疫细胞, 研究表明, PD1+TE和/或TEX细胞由于其表型稳定且不能被ICI逆转, 所以该亚群产生长期持续的效应能力有限, 而ICI诱导肿瘤微环境中PD1-CD8+ T细胞亚群发生了动态变化^[1], 提示ICI免疫治疗可能并不直接作用于效应性亚群. 此外, 另一项关于黑色素瘤的研究也发现ICI免疫治疗不是依赖于CD8+ T细胞的疲惫状态的逆转而是依赖于肿瘤浸润免疫细胞中的干细胞样亚群的增殖^[3], 提示CD8+ T细胞干细胞样亚群可能是ICI免疫治疗的初始反应T细胞亚群. 因此, 目前免疫治疗领域开始关注具有自我更新和多能分化潜能的CD8+ T细胞干细胞样亚群.

2 CD8+ T细胞干细胞样亚群的分子特征

由于肿瘤细胞具有持续增殖能力, 所以靶向肿瘤的杀伤性CD8+ T细胞同样需要具有持续增殖能力. 研究显示CD8+ T细胞的寿命越长, 持久能力越强, 患者在接受免疫治疗时效果就越好^[4]. 因此, 具有长寿的高增殖能力的CD8+ T细胞对于有效的免疫治疗至关重要. 干细胞样记忆T细胞(stem cell memory T cells, TSCM)具有较强的自我更新能力, 增殖能力以及多分化潜能, 因而介导更强的抗肿瘤免疫^[5,6]. 目前研究认为TSCM的分子特征为CD45RA+CD45RO-CCR7+CD62L+且表达CD122, CD95和CXCR3表面分子; TSCM能够进一步分化成中心记忆T细胞(central memory T cells, TCM)和效应记忆T细胞(effector memory T cells, TEM)^[5,7-9]. 本文观点认为T细胞记忆亚群向效应阶段的分化是一个连续的动态的过程, 即按照TSCM, TCM, TEM, TE, TEX的顺序逐渐由低分化向高分化发展, 处于低分化阶段的细胞亚群其干细胞性和寿命增加, 而处于高分化阶段的细胞亚群的效应性增强但其增殖能力和寿命降低. 在过继T细胞免疫治疗(adoptive cell transfer, ACT)方面, 处于低分化阶段的TSCM和/或TCM应该是理想的过继细胞亚群; 在ICI方面, 对PD1/PD-L1免疫治疗产生免疫应答的理想CD8+ T细胞亚群应该是具有PD1低度和/或中度表达水平同时具有干细胞性的CD8+ T细胞亚群. 值得注意的是, 单细胞转录组学已鉴定出干细胞样T细胞亚群同时共表达干细胞性与效应性基因, 即为干细胞性和效应性的杂交状态, 且表观遗传学分析鉴定出效应基因保留表观遗传的位置, 同时具有有限的转录活性, 从而解释了该亚群具有迅速召回的效应反应潜能^[10,11]. 而另外两项研究也确定了干细胞样CD8+ T细胞在形成TE细胞时逐渐表达出更高水平的免疫检查点分子, 并最终获得疲惫状态^[3,12]. 长期暴露于肿瘤抗原而产生的高TCR刺激会限制T细胞的效应反应, 从而导致TEX^[13]. 由于T细胞特异性转录因子1(transcription factor T cell factor 1, TCF1)蛋白作为Wnt/β-catenin信号通路的下游转录因子, 在维持T细胞的干细胞样状态, 自我更新和保持记忆特性中发挥重要作用^[14-16], 因而PD1+TCF1+的细胞亚群被认为是TEX细胞的祖细胞, 该亚群具有部分疲惫的特征, 但保留了干细胞样特性(TCF1+, 类似TSCM和TCM), 可增强对PD1阻断的反应^[15,17]. 因此, PD1+TCF1+CD8+ T细胞亚群可能作为PD1/PD-L1免疫治疗应答的主要CD8+ T细胞亚群, 从而凸显了靶向该亚群以增强ICI治疗获益的重要性.

3 CD8+ T细胞干细胞样亚群在免疫治疗中的作用

研究显示表达TCF1的CD8+ T细胞的黑色素瘤患者在接

受ICI免疫治疗后其临床疗效会更好, 表明如果肿瘤中含有干细胞样T细胞, 则无法通过手术切除肿瘤的人可能会受益于阻断免疫检查点分子的疗法^[18]。而最近一项研究同样发现在人类肾脏肿瘤的肿瘤浸润T细胞中存在干细胞样亚群, 该亚群有助于促进有效的抗肿瘤免疫反应, 且与患者具有更好的生存率呈正相关性, 而评估免疫检查点蛋白PD-L1的表达, 并未显示与无进展的癌症存活率有明显相关性; 同时细胞基因表达谱分析显示干细胞样T细胞中趋化因子和趋化因子结合受体的表达高于正常水平, 可能与免疫细胞通过淋巴管有关, 而且表达更高水平的关键共刺激分子, 可能与向终末效应阶段分化产生细胞毒性CD8⁺ T细胞有关^[19]。据此, 产生对CD8⁺ T细胞疲惫状态固有抗性的干细胞性和/或效应性的杂交状态的CD8⁺ T干细胞性记忆亚群对改善ICI或ACT免疫治疗具有十分重要的治疗价值。

4 诱导CD8⁺ T细胞干细胞样亚群的方法

目前越来越多的研究致力于通过长寿的CD8⁺ T细胞干细胞样记忆亚群来增强肿瘤免疫治疗的疗效, 影响该亚群细胞的产生和持久性的因素就变得十分重要。CD8⁺ T细胞的表现遗传修饰可能会影响其干细胞样记忆亚群发挥作用的能力, 而表现遗传修饰可能会受到肿瘤微环境中各种因素的影响^[20,21]。例如, 肿瘤中钾离子的浓度可以调节表现遗传修饰, 从而影响T细胞是否处于干细胞样状态, 这是它们产生终末效应细胞毒性CD8⁺ T细胞所需的^[20]。因此, 肿瘤微环境对T细胞发育的影响将成为肿瘤免疫研究的重点之一。关于ACT免疫治疗方面的研究逐渐显示抗肿瘤免疫反应的持久性在很大程度上不取决于转移时CD8⁺ T细胞的杀伤能力, 而取决于转移时细胞的持久性^[22]。大量的临床前和临床数据也支持这样一种概念, 即具有干细胞性的T细胞优先发挥抗肿瘤潜力^[23,24]。目前的ACT方案更倾向于生成这些分化程度较低的细胞亚群, 而不是分化程度更高的亚群^[25]。此外通过利用IL-7, IL-15或IL-21代替IL-2减少TCR刺激^[26], 促进Notch信号传导^[27]或限制抗氧化剂处理后的活性氧代谢^[24]等策略通过抑制与终末效应分化有关的基因或蛋白表达, 促进维持干细胞样基因(如编码TCF1和LEF1的基因)^[28]从而获得具有改善的持久性和抗肿瘤活性的CD8⁺ T细胞干细胞样记忆亚群。因此通过各种方式来利用干细胞样和/或效应性且具有持久性的免疫细胞亚群来提高免疫治疗潜力, 无疑将是未来研究的重要领域。

5 结论

CD8⁺ T细胞干细胞样亚群具有多能分化潜能, 可以同时产生效应性亚群并具有长寿记忆能力, 从而对先前暴露的肿瘤抗原产生有效的免疫应答。围绕该亚群进行的

共存特性分析, 诱导扩增及与治疗相关性研究, 将在深入了解CD8⁺ T细胞分化的细胞和分子机制的同时, 有助于优化或开发基于T细胞介导的特异性, 持久性免疫的理想的肿瘤免疫治疗方法, 具有十分重要的临床转化意义。

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