纳米药物递送系统调控干细胞样记忆T细胞在抗肿瘤治疗中的应用

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摘要: 干细胞样记忆T细胞 (stem cell-like memory T cells, T_{SCM}) 是一类兼具记忆细胞和干细胞功能特性的T细胞亚群, 在受到抗原刺激后能够快速分泌免疫细胞因子并分化为具有肿瘤杀伤能力的效应性T细胞, 为抗肿瘤免疫应答提供持久动力。因此, 诱导T_{SCM}产生提升T细胞抗耗竭能力增强肿瘤免疫治疗效果成为目前研究的新热点。纳米药物递送系统 (nano-based drug delivery system, NDDS) 具备体内靶向递送、促进药物渗透等特质, 为诱导T_{SCM}策略应用于临床提供潜在可行性。基于此, 本文系统阐述了T_{SCM}的特性, 综述了目前诱导并维持T_{SCM}功能的调控方法, 总结了纳米药物递送系统调控T_{SCM}用于抗肿瘤治疗的研究进展, 以期为诱导T_{SCM}产生策略应用于临床提供参考和思路。

关键词: 干细胞样记忆T细胞; 纳米药物递送系统; 肿瘤免疫治疗; 细胞治疗

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The application of nano-based drug delivery system in regulating stem cell-like memory T cells in anti-tumor therapy

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Abstract: Stem cell-like memory T cells (T_{SCM}), a subpopulation of T cells that combines features of both memory cells and stem cells, are capable of rapidly secreting immune cytokines and differentiating into effector T cells with tumor-killing ability after antigenic stimulation, thereby providing a lasting impetus for the anti-tumor immune response. Therefore, inducing T_{SCM} generation to bolster T cells' resistance to exhaustion, thereby improving tumor immunotherapy efficacy, has emerged as a major research focus. Nano-based drug delivery system (NDDS) possesses the qualities of *in vivo* targeted delivery and facilitated drug penetration, which provides the potential feasibility of inducing T_{SCM} strategy for clinical application. Based on this, this paper systematically describes the characteristics of T_{SCM}, reviews the current regulatory methods to induce and maintain T_{SCM} function, and summarizes the research progress of nano-based drug delivery system in regulating T_{SCM} for anti-tumor therapy, to provide reference and ideas for the application of induced T_{SCM} generation strategies in the clinic.

Key words: stem cell-like memory T cell; nano-based drug delivery system; anti-tumor immunotherapy; cell therapy

近年来, 基于T细胞的过继性免疫疗法和免疫检查点阻断 (immune checkpoint blockade, ICB) 疗法在临床实践中取得了突破性进展, 显著改善了癌症患者的生存预后[1-3]。然而, T细胞耗竭仍是限制抗肿瘤免疫治疗效果的核心问题[4,5]。在持续的抗原刺激及肿瘤微环境的免疫抑制压力下, 效应T细胞功能耗竭, 逐渐丧失增殖能力与杀伤功能, 导致免疫应答失效和肿瘤免疫逃逸[6,7], 成为当前肿瘤免疫治疗策略亟待突破的瓶颈。干细胞样记忆T细胞 (stem cell-like memory

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T cells, T_{SCM}) 凭借其快速应答、自我更新、多能分化能力及更好的肿瘤微环境适应性, 有望突破传统T细胞疗法的局限性, 是抗肿瘤免疫治疗的理想工具。本文对T_{SCM}特性、T_{SCM}的调控策略以及纳米药物递送系统 (nano-based drug delivery system, NDDS) 调控T_{SCM}用于抗肿瘤治疗进行综述, 以探讨其在抗肿瘤免疫治疗中的应用前景。

1 T_{SCM}的生物学特性

1.1 T_{SCM}的起源与分布

2005年, 研究人员在移植物抗宿主病小鼠模型中首次发现具备自我更新能力和多潜能的长寿记忆T细胞亚群, 将其命名为T_{SCM}, 这一发现打破了记忆T细胞传统的分化模式。2011年, 在人类外周血中证实了T_{SCM}的存在[8], 并在后续研究中通过体外培养体系分离、扩增获得[9]。近些年来, T_{SCM}受到研究人员持续关注, 旨在提高肿瘤免疫治疗效果。

初始T细胞 (naive T cells, T_N) 在淋巴结受到特异性抗原刺激后, 能够增殖分化为功能各异的两类细胞, 即效应T细胞 (effector T cells, T_{EFF}) 和记忆T细胞 (memory T cells, T_M)。效应T细胞通过识别体内被病原体入侵的细胞, 与靶细胞特异性结合后释放穿孔素、颗粒酶B等介导杀伤作用。记忆T细胞则在体内长期存在, 为机体提供长久的免疫保护[10]。根据表型、功能、转录因子等, T_M细胞可进一步分为T_{SCM}、中央记忆T细胞 (central memory T cells, T_{CM})、效应记忆T细胞 (effector memory T cells, T_{EM}) 和组织驻留记忆T细胞 (tissue resident memory T cells, T_{RM}), 其体内分布如图1所示。

1.2 T_{SCM}的分化与标志物

T_N作为未经历抗原刺激的初始T细胞, 在胸腺发育成熟后, 通过趋化因子及归巢受体的调控, 经淋巴循环和血液循环迁移至脾脏、淋巴结等次级淋巴器官并长期驻留[11]。T_{SCM}是T_N经抗原激活后形成的早期分化亚群, 其转录组与T_N仅存在75个基因的差异[12], 且具有自我更新能力及分化为其他记忆T细胞的潜能。表型上 (表1), T_{SCM}不仅保留T_N的标志$CCR7^+$、$CD45RA^+$、$CD45RO^-$、$CD27^+$、$CD28^+$、$CD127^+$等, 还表达记忆T细胞特征分子$CD95^+$、$CD122^+$等, 并高表达抗凋亡蛋白BCL2和介导骨髓归巢的趋化因子受体CXCR4[8]。当机体再次受到相同抗原刺激时, T_{SCM}能够产生其他几种记忆T细胞及效应T细胞。在外周循环的T_{CM}和T_{EM}抗原响应性分泌白细胞介素-2 (interleukin-2, IL-2) 及效应细胞因子如γ干扰素 (interferon-γ, IFN-γ)、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 等, 但T_{CM}因

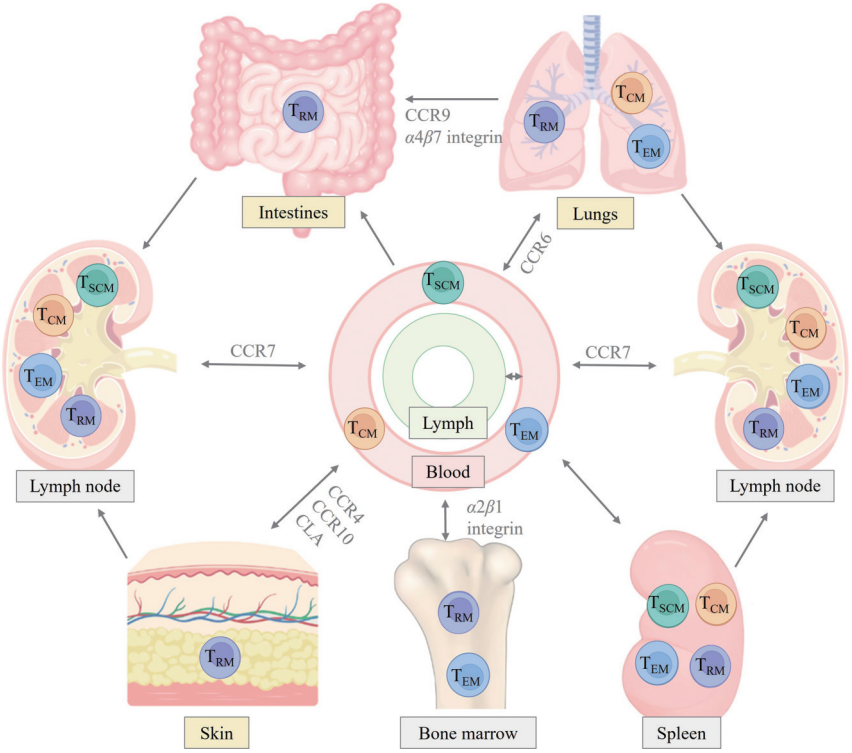


Figure 1 The tissue distribution and the migration patterns of the major memory T cell subsets. The individual organs are defined as the circulation (red or green), of lymphoid origin (grey) or as peripheral tissues (yellow). T_{RM}: Tissue resident memory T cells; T_{EM}: Effector memory T cells; T_{CM}: Central memory T cells; T_{SCM}: Stem cell-like memory T cells; CCR: C-C chemokine receptor; CLA: Cutaneous lymphocyte antigen

表达淋巴归巢受体具备向次级淋巴器官迁移和高增殖的能力, 而T_{EM}则凭高分泌效应分子介导快速免疫杀伤[13]。此外, T_{RM}长期定位于皮肤、黏膜等非淋巴组织, 通过释放调节性细胞因子如IL-10、转化生长因子-β (transforming growth factor-β, TGF-β) 等在局部维持免疫保护与组织稳态的平衡[14] (表2)。

Table 1 Characteristic surface markers of different T cell subsets. +/−: Only a portion of the subsets; −: No expression; +: Very low expression; T_N: Naive T cells; CD: Cluster of differentiation; LFA: Lymphocyte function-associated antigen; FAS: Factor-related apoptosis; IL: Interleukin

Surface marker	T_N	T_{SCM}	T_{CM}	T_{EM}
CD11a (LFA-1)	+/−	+	+	+
CD27	+	+	+	+/−
CD28	+	+	+	+/−
CD45RA	+	+	−	−
CD45RO	−	−	+	+
CD62L	+	+	+	−
CD69	−	−	+	+/−
CD95 (FAS)	−	+	+	+
CD122 (IL-2Rβ)	−	+	+	+
CD127 (IL-7Rα)	+	+	+	+

Table 2 Comparison among T_N, T_{SCM}, T_{CM}, T_{EM}. ++: Low expression; +++: Medium expression; ++++: High expression; IFN: Interferon; TNF: Tumor necrosis factor; EOMES: Eomesodermin; BCL: B cell lymphoma; ID: Inhibitor of DNA binding; STAT: Signal transducer and activator of transcription

	Feature	T_N	T_{SCM}	T_{CM}	T_{EM}
Cytokines	IL-2	+/−	+++	++	+/−
	IFN-γ	−	+	++	+++
	TNF-α	−	+	++	+++
	Perforin	−	+	++	+++
	Granzyme B	−	−	−	+
Transcription factors	EOMES	+++	++	+	+/−
	BCL-6	+++	++	+	−
	ID3	+++	++	+	+/−
	STAT3	+++	++	+	+/−
	T-bet	+/−	+	++	+++
	ID2	+/−	+	++	+++
	STAT4	+/−	+	++	+++
Function	Longevity	++++	+++	++	+
	Memory cell potential	+++	++	+	+/−
	Multipotency	+++	++	+	−
	Proliferative potential	++++	+++	++	+/−
	Effector function	−	+	++	+++

T_{SCM}虽表现出淋巴组织趋向性[15], 但其在体内的解剖定位及微环境调控网络尚未完全阐明。在肿瘤患者的三级淋巴结构、肿瘤及肿瘤引流淋巴结中发现有T_{SCM}存在[16], 但其在肿瘤微环境中抗肿瘤的确切机制仍需进一步研究。在肿瘤抗原持续刺激及免疫抑制性微环境的双重压力下, $CD8^+$ T细胞进入功能耗竭状态[17], 干性标志物如转录因子7 (transcription factor 7, TCF7)、B淋巴细胞瘤-2 (B cell lymphoma-2, BCL-2) 表达下调, 耗竭标志物如程序性死亡受体-1 (programmed cell death protein-1, PD-1)、T细胞免疫球蛋白-3 (T cell immunoglobulin and mucin domain-3, TIM-3) 表达升高, 效应细胞因子分泌减少, 出现代谢异常如线粒体功能障碍, 此外, 其表观遗传重塑与转录失调, 进一步削弱抗肿瘤活性。与$CD8^+$ T细胞相似, 在各类肿瘤中$CD4^+$ T细胞也会出现耗竭状态, 产生功能障碍。因此, 通过改变T细胞的代谢或表观遗传诱导T_{SCM}, 已逐渐成为抗肿瘤免疫治疗中克服T细胞耗竭的新研究热点。

2 T_{SCM}的功能特性

2.1 T_{SCM}的自我更新和多分化潜能

T_{SCM}具备持续的多能分化和自我更新潜能, 在抗肿瘤免疫应答中发挥关键作用。未受到肿瘤抗原刺激时, T_{SCM}维持静息状态, 在接受抗原提呈细胞 (antigen-presenting cells, APC) 的肿瘤抗原递呈后, 其能够不对称分裂, 一方面自我复制为T_{SCM}以维持干细胞池的稳定性, 另一方面分化为T_{EFF}并迁移至肿瘤部位发挥效应功能。随着肿瘤负荷降低及抗原刺激减弱, T_{SCM}重新恢复静息态以建立长效免疫记忆[18]。Gattinoni等[8]研究表明, 白细胞介素-15 (interleukin-15, IL-15) 能够诱导约60%的T_{SCM}维持干性表型, 并在抗原再次刺激时迅速应答, 4 h内即可分泌高水平的IFN-γ、IL-2和TNF-α等效应细胞因子, 展现出强大的免疫应答能力。Cieri等[19]通过肿瘤特异性抗原刺激T_N细胞进一步验证, 尽管部分T_{SCM}在激活后分化为T_{CM}和T_{EM}, 但仍有显著比例的T_{SCM}保留$CD45RA^+CD62L^+$的原始表型, 且结果显示其扩增能力超过T_{CM}和T_{EM}, 证明T_{SCM}具备优异的多能分化和自我更新潜能。

2.2 T_{SCM}的长期寿命

T_{SCM}兼具干细胞特性, 展现出显著的抗凋亡能力和长寿特性。研究发现, 由黄热病疫苗诱导产生的$CD8^+$ T_{SCM}能够在人体中稳定存在超过25年[20]。尽管多项研究表明, T_{SCM}在整个生命周期中以稳定的频率存在[21], 但其维持稳定性的基础机制尚未完全明确。Ahmed等[22]提出了两种可能: 其一, T_{SCM}能够在休眠的条件下存活并延长存活时间; 其二, T_{SCM}能够通过持续的增殖和细胞更新来维持平衡态。研究人员通过同位素标记法观察体内T_{SCM}的周转情况, 发现无论在年轻还是年老的受试者中, T_{SCM}均通过持续增殖而达到动态平衡状态, 且这一过程与T_{SCM}中活性端粒酶抑制端粒侵蚀密切相关。

3 抗肿瘤治疗中T_{SCM}调控方法

T细胞是免疫治疗中的关键执行者, 抗肿瘤疗效

也依赖于T细胞的持久性杀伤作用[23-26]。然而, T_{SCM}数量较少, 在外周循环的T细胞中仅占2%～3%, 而在脐带血中的比例更是低于1%[8], 极大地限制了其临床应用。因此, 现有研究已有多种调控策略包括调控T_{SCM}相关信号通路 (表3[27-34])、加入细胞因子诱导剂、重塑表观遗传等聚焦于诱导T_{SCM}的数量增加, 以期促进T_{SCM}在抗肿瘤免疫治疗中的应用[35]。

Table 3 Mechanism of signaling pathway modulators in regulating T_{SCM}. GSK: Glycogen synthase kinase; NF: Nuclear factor; mTOR: Mammalian target of rapamycin; FAO: Fatty acid oxidation; ACD: Asymmetric cell division

Strategy	Mechanism	Ref.
GSK-3β inhibition	Regulate stemness-related pathways such as Wnt-β-Catenin, Notch, NF-κB to block the terminal differentiation of T cells	[27-30]
mTOR inhibition	Reprogram T cell metabolism to FAO; maintain ACD; activate Wnt-β-Catenin signaling	[31,32]
Notch activation	Up-regulate the expression of stemness-related genes; inhibit the expression of differentiation-related genes; reprogramming metabolism to FAO	[33,34]

3.1 T_{SCM}相关通路调节调控分化途径

3.1.1 激活Wnt-β-Catenin通路 糖原合成酶激酶-3β (glycogen synthase kinase-3, GSK-3β) 是一种多功能丝氨酸/苏氨酸蛋白激酶, 其抑制剂能够通过阻断T细胞终末分化来维持T_{SCM}的特性, 从而持续生成具有抗肿瘤活性的T_{EFF}。Gattinoni等[27]发现, GSK-3β抑制剂TWS119能抑制β-连环蛋白 (β-Catenin) 磷酸化降解, 促进其快速积累, 从而激活Wnt/β-Catenin信号轴, 最终诱导$CD44^{low}CD62L^{high}Sca1^{high}CD122^{high}Bcl\text{-}2^{high}CD8^{+}$ T_{SCM}的扩增 (stem cell antigen 1, Sca1), 并阻止其向T_{EFF}的继续分化, 且该亚群的增殖和抗肿瘤能力超过T_{CM}和T_{EM}亚群。Zhang等[28]发现GSK3β抑制剂能够通过上调颗粒酶B、IFN-γ、凋亡相关因子等相关效应蛋白的表达, 增强分化后$CD8^{+}$ T_{SCM}的细胞毒性, 从而在胃癌模型中显著抑制肿瘤进展。此外, GSK-3β抑制剂还能够调控其他与T细胞干性相关的信号通路, 如Notch信号通路、NF-κB信号通路等, 协同维持T细胞干性[29,30]。然而, GSK-3β作为调控细胞增殖、代谢重编程及凋亡的关键节点分子, 其抑制可能引发免疫稳态失衡或代谢异常, 因此需通过剂量优化及靶向递送策略平衡疗效与安全性。

3.1.2 抑制mTOR通路 mTOR作为关键的丝氨酸/苏氨酸激酶, 通过复合体mTORC1和mTORC2整合多重信号通路[36], 其抑制剂能够重编程T_{SCM}代谢方式及维持其不对称分裂, 进而调控T_{SCM}的功能特性。研究表明, T_{SCM}与低分化的T_N及T_{CM}依赖FAO途径生成三磷酸腺苷 (adenosine triphosphate, ATP) 以维持静息状态, 而活化T细胞则通过有氧糖酵解快速供能以支持增殖与效应功能。Scholz等[31]证实, mTOR抑制剂雷帕霉素可将T细胞代谢表型从糖酵解重编程为FAO主导模式, 并在高度纯化的T_N细胞亚群中高效诱导出T_{SCM}, 这些药物诱导的T_{SCM}在过继转移后表现出显著的体内持久性和再繁殖能力。值得注意的是, mTOR信号与Wnt/β-Catenin通路存在功能性串扰, 小分子化合物TWS119通过协同抑制mTORC1与激活Wnt信号, 显著提升T_{SCM}生成效率, 提示联合靶向策略的潜在价值。此外, T细胞通过ACD在分化早期即T_N/T_{CM}阶段产生功能异质的子代细胞, 而终末分化的效应T细胞受限于对称分裂模式, 导致自我更新能力丧失。Borsa等[32]发现雷帕霉素瞬时处理可通过维持$CD8^{+}$ T细胞的ACD特性, 使其子代细胞的记忆相关基因表达量增加, 并在过继免疫治疗中展现出更强的扩增能力。然而, mTOR抑制剂的调控作用可能因不同的药物、剂量和疾病背景有所差异, 因此, 基于疾病类型、药物代谢动力学参数及个体化风险评估的精准给药策略至关重要。

3.1.3 激活Notch通路 T_{SCM}具有区别于耗竭T细胞的独特表观遗传特征, 其中Notch信号通路在调控其细胞命运中起关键作用。Notch信号通路通过调控靶基因的转录以发挥生物学功能, 其激动剂能维持T细胞干性相关基因表达或抑制T细胞分化相关基因表达, 从而维持T_{SCM}的表观遗传特征。与通过干扰Wnt信号促使T_N分化为T_{SCM}的策略不同, Notch信号激动剂能够将完全激活或分化程度更高的记忆细胞逆向重编程为T_{SCM}表型。Wilkens等[33]证实, Notch1激动剂处理可显著增强CAR-T细胞干性维持能力促进效应细胞因子分泌, 增强$CD4^{+}$ CAR-T的能力, 促进$CD8^{+}$ CAR-T的增殖并在体内发挥持久的抗肿瘤作用。Kondo等[34]采用Notch配体修饰的基质细胞与活化T细胞共培养, 成功诱导出具有长寿命、强自我更新能力且免疫检查点分子如PD-1、细胞毒T淋巴细胞相关抗原-4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4) 等低表达的T_{SCM}亚群, 该亚群经抗原再刺激后能分化为大量肿瘤特异性效应细胞。值得注意的是, 相较于TWS119介导的Wnt信号激活方案, Notch通路诱导产生的T_{SCM}虽然在表型特征和肿瘤杀伤效率方面无明显差异, 但其细胞得率显著提升。此外, Notch信号能通过其下游转录因子叉头盒MI (forkhead box protein M1, FOXM1) 调控线粒体生物合成关键基因和脂肪酸代谢酶的表达, 进而促进T_{SCM}的代谢重构。然

而, Notch激动剂对T_{SCM}的多维度调控网络仍存在诸多未解之谜, 需深入探究其时空特异性调控规律及临床转化潜力。

3.2 γ链细胞因子诱导T_{SCM}分化

γ链细胞因子家族包括IL-2、IL-7、IL-15、IL-21等通过激活JAK-STAT及PI3K-AKT-mTOR信号网络, 在T_{SCM}的生成与维持中发挥调控作用。当$CD8^+$ T细胞在强效T细胞受体 (T cell receptor, TCR) 信号与IL-2共刺激下被激活时, 可短暂获得干性特征[37], 但连续多次IL-2刺激可使T细胞持久性降低, 并伴随耗竭标志物比例上升[38]。IL-7作为T细胞稳态存活的关键调节因子, 在体外培养体系中可使CD19 CAR-T细胞中富含T_{SCM}亚群, 该亚群高表达干性相关转录因子, 低表达耗竭标志物, 并极大提升肿瘤清除率[39]。临床前试验中, Li等[40]开发的IL-21/抗PD-1抗体融合蛋白靶向肿瘤特异性T细胞, 在多种细胞模型中极大提高T_{SCM}生成效率, 同时显著延长抗肿瘤应答持续时间。此外, 细胞因子联用也用于调控T_{SCM}特性, 且多种细胞因子如IL-7、IL-15和IL-21的联用具有协同作用。研究表明, 在CD3/CD28抗体刺激下, 联用IL-7、IL-15可以富集T_{SCM}, 且与单独使用IL-2相比, 暴露于IL-7和IL-15中的CAR-T细胞在连续抗原刺激下具有更高的存活率[41]。细胞因子虽已用于调节T_{SCM}功能特性, 然而其调控网络的时空动态特征及与表观遗传修饰的交互作用仍需系统解析。

3.3 表观遗传重塑调控T细胞命运

不同亚群T细胞转录谱不同, 因此通过改变表观遗传调控T_{SCM}以改进T细胞疗法是有效途径。Chaudhry等[42]发现锌指蛋白转录抑制因子GFI1是维持T_{SCM}功能特性的核心调控因子, 能够启动T细胞增殖相关基因, 抑制TOX、PD-1等相关耗竭通路, 通过表观遗传重塑维持T_{SCM}线粒体功能和代谢适应性。胞外酸性微环境作为关键应激源, 通过代谢–表观遗传调控机制维持T细胞干性。长期胞外酸处理T细胞, 可以促进线粒体代谢适应性, 同时通过抑制MYC-SLC7A5轴抑制甲硫氨酸摄入和一碳代谢, 从而重编程T细胞的表观遗传图谱, 维持T细胞干性[43]。肠道菌群与宿主代谢互作通过表观遗传重编程$CD8^+$ T细胞干性[44], 决定ICB疗法应答效率。研究表明直接补充约氏乳杆菌或者增加其体内代谢产物吲哚-3-丙酸均可以调控$CD8^+$ T细胞的干性程序, 增加H3K27在TCF7超级增强子区域的乙酰化, 促进耗竭前体T细胞的产生, 从而提高机体对免疫疗法的反应性[45,46]。此外, 溴结构域和末端外蛋白抑制剂JQ1可以通过抑制与T细胞分化相关的转录因子即碱性亮氨酸拉链ATF样转录因子 (human basic leucine zipper transcription factor, BATF) 进而增强沉默信息调节因子来促进T_{SCM}生成[47]。然而表观遗传的改变可能间接影响基因组稳定性, 有基因突变或染色体异常等风险。

3.4 其他

免疫细胞之间相互作用也会影响T_{SCM}特性, 抗原提呈细胞富集区将T_{SCM}与促进分化的炎性环境隔离, 形成支持T_{SCM}的生态位以维持其特性[48]。Zhang等[49]制备了加载雷喹莫特的过表达甲胎蛋白的工程化微粒(R848@M2pep-MPs), 将肿瘤相关巨噬细胞重编程为抗原呈递细胞, 为T_{SCM}功能的维持提供肿瘤内生态位。机械信号传导在细胞增殖和分化中起着至关重要的作用, 已有研究表明3D纤维蛋白凝胶介导的机械力信号传导只驱动肿瘤细胞增殖而不分化并能诱导分化细胞转化为未分化表型[50], Lv等[51]将活化$CD8^+$ T细胞置于其中培养, 细胞扩增效率较传统方式提高5.5倍, 且有50.5%细胞表现出$CD62L^+CD45RO^-CD45RA^+CCR7^+CD27^+CD127^+CD95^+$ T_{SCM}表型, 进一步研究发现机械力信号能够磷酸化β2整合素, 降解YAS相关蛋白, 从而上调干性相关基因。转录因子在很大程度上影响T细胞命运, 研究表明T_{SCM}中高表达的转录因子TCF1有利于T_{SCM}生成并维持其干性以促进自我更新[52]。此外, 除mTOR抑制剂影响T细胞分裂方式外, TCR信号强度也参与不对称分裂, 适当的刺激强度有利于诱导T_{SCM}产生, 随着强度增大记忆潜能反而降低[53]。

4 纳米药物递送系统调控T_{SCM}

目前使用上述调节策略在体外编辑T_{SCM}已经在过继T细胞疗法中进行研究, 并在多种肿瘤模型中得到验证[54-56]。然而, 体外细胞编辑技术存在制造成本高、生产周期长等弊端, 极大限制了患者可及性及商业化进程, 体内编辑技术直接在患者体内完成细胞改造, 具备治疗流程相对简单、等待时间短、降低成本等优势[57]。目前T_{SCM}体内调控策略大多直接注射游离药物, 虽然能够增加体内T_{SCM}数量, 但可能诱导效率较低。NDDS能够保护药物免受递送过程及递送终点肿瘤微环境(tumor mircroenvironment, TME)中酶或其他物质降解以减少损耗, 同时通过改变组分比例或修饰靶向配体等提高靶向性, 最终将更多的药物递至靶向部位以诱导更高比例的T_{SCM}[58-60]。此外, NDDS可携带不同类型的调控分子如mRNA、CRISPR组件、小分子药物等, 具有较高的灵活性, 为诱导T_{SCM}并应用于抗肿瘤免疫治疗提供潜在可行性。因此, 通过纳米递送系统递送药物以提高T_{SCM}诱导效率极具前景 (图2、表4[58-64])。

随着对免疫反应和肿瘤微环境的深入理解及纳米技术的不断发展, 除提高靶向性外, 研究人员不断构建

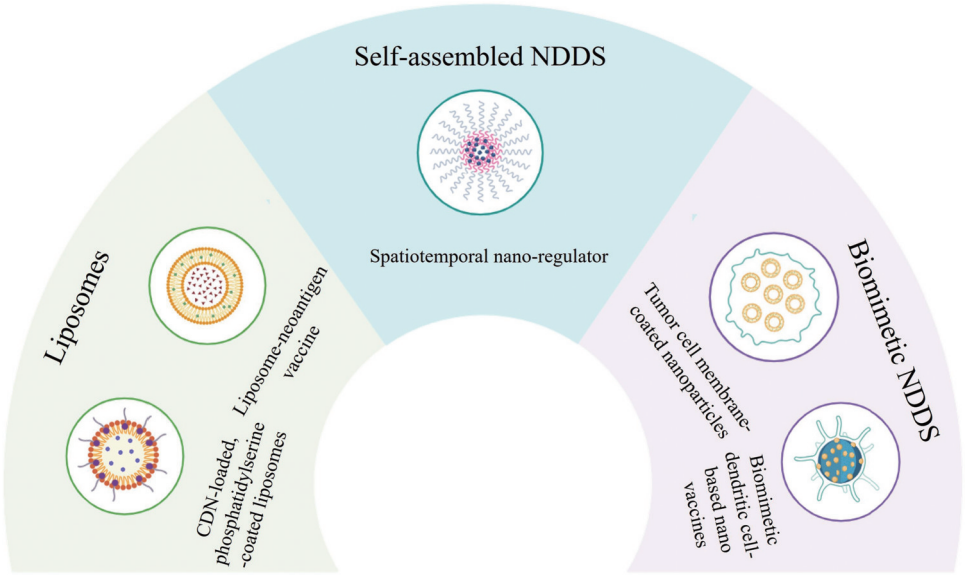


Figure 2 The application of NDDS in regulating T_{SCM} in anti-tumor therapy. NDDS: Nano-based drug delivery system

Table 4 NDDS for regulating T_{SCM} in anti-tumor therapy. FCM: Flow cytometry; CDN: Cyclic dinucleotide; LNP: Lipid nanoparticle; LNP-CDN: FCM, LNP-CDN was labelled with DiR; C-N-LNPs-vax^{D18}: FCM, LNP was labelled with DiR; DNR: FCM, DNR contained Cy5-labeled non-functional siRNA; ICP: Inhibitory immune checkpoint; ICP-MS: Inductively coupled plasma-mass spectrometry; PX+CS-J@CM/6: ICP-MS, each mouse was injected with 200 μL of CS-J@CM/6 NPs solution; PS: Phosphatidylserine; MPE: Malignant pleural effusion; TDLNs: Tumor-draining lymph nodes; TCF: Transcription factor; Vax: Vaccine; DC: Dendritic cell; TCR: T cell receptor; TAM: Tumor-associated macrophage; APC: Antigen-presenting cell; PLNs: Popliteal lymph nodes; ILNs: Inguinal lymph nodes; CS: Copper selenides

Type	Strategy	Target	Delivery efficiency	Mechanism	Challenge of clinical translation	Ref.
Liposomes	CDN-loaded, PS-coated liposomes (LNP-CDN)	MPE	DiR^+ cells%: MPE, 60−80; tumor, 50−80; TDLNs, 60−80	Increase the expression of TCF1	Poor blood stability; short cycle life; special storage conditions	[58,59,61]
	Liposome-neoantigen vaccine (C-N-LNPs-vax^{D18})	Spleen; tumor tissues	DiR^+ cells in spleen%: DC, 5−10; macrophage, 5−10; T cells, 5−10	Add neoantigen peptide to improve tumor immunogenicity and TCR signaling; activate splenic DCs and increase the population of M1-TAMs to provide more suitable APC niche		
Self-assembled NDDS	Spatiotemporal nano-regulator (DNR)	TDLNs	$Cy5^+CD11c^+$ cells in TDLNs%: 10−30	Alleviate DC tolerance to promote T cell activation and expansion; reduce the expression of ICP to prevent T cell exhaustion	*In vivo* stability limited by self-assembly forces; unclear mechanism of self-assembly formation	[60,62]
Biomimetic NDDS	Tumor cell membrane-coated nanoparticles (CS-J@CM/6)	Tumor tissues	Cu concentrations in the tumor tissue: 2−3 μg·g^{-1}	Inhibit T cell differentiation to promote T_{SCM} production; reduce the expression of ICP to improve the exhaustion of T cells	Cumbersome preparation; limited characterization methods; special storage conditions	[63,64]

新的NDDS以突破TME中多重生物屏障来实现更高效的递送[65]。纤维化屏障与肿瘤发展密切相关，一方面肿瘤纤维化为肿瘤增殖扩散提供物理支持，另一方面纤维化增加会影响免疫细胞浸润和药物渗透[66]。已有研究通过抑制纤维化中关键通路TGF-β信号转导[67]、抑制肿瘤相关成纤维细胞 (cancer-associated fibroblasts, CAFs) 活化[68]、直接杀伤CAFs[69]等策略来瓦解纤维化屏障或将屏障改造为药物储库[70]来实现药物在肿瘤部位的大量积累。TME中血管通透性增加及淋巴引流受损引起的局部高间质压 (elevated interstitial fluid pressure, IFP) 是另一挑战，这加剧了药物随间质液向周围组织的流失，同时流动引起的剪切应力促进肿瘤侵袭和转移。现有NDDS通过使用水解酶消除瘤内多余液体[71]、血管正常化[72]、改变纳米颗粒内在

特性如构建梭形纳米颗粒[73]等应对这一挑战。开发能够穿越TME生物屏障的新型NDDS将极大提高T_{SCM}诱导效率。

4.1 脂质体

脂质体是将药物包封于类脂质双分子层内而形成的微型囊泡。使用脂质体递送T_{SCM}调控药物能够增加靶器官蓄积, 同时可以保护生物大分子免受核酸酶或蛋白酶降解。为避免药物被恶性胸腔积液中的蛋白酶降解并表现出更好的肺部保留, Liu等[58]设计出一种负载STING通路激动剂环二核苷酸 (cyclic dinucleotide, CDN) 的磷脂酰丝氨酸 (phosphatidylserine, PS) 包被的脂质体LNP-CDN, 其中PS介导的凋亡信号促进单核巨噬细胞的摄取, 与磷酸钙复合后CDN能够响应pH变化从内体释放到细胞质基质发挥作用。具体来说, CDN能够驱动I型IFN信号转导, 通过增加TCF1表达促进初始T细胞分化为T_{SCM}亚群。单细胞测序结果显示, LNP-CDN能很大程度上扩增$TCF7^+CCR7^+Pdcd1^+Sca1^+Hoxa1^+Lpxn^+Il2rb^+Cxcr3^+CD8^+$ T_{SCM}亚群, 减少$Pdcd1^+Lag3^+Ctla4^+CD8^+$耗竭T细胞, 促使$F4/80^+Arg1^+$ M2样巨噬细胞复极化为$F4/80^+iNOS^+$ M1样巨噬细胞, 同时ELISA测定显示TME中IL-2、IL-15、IFN-γ等因子含量上升, 这同样有利于T_{SCM}的生成和维持。体内数据显示, LNP-CDN能将免疫抑制性骨髓细胞重编程为促炎表型并重塑MPE中的免疫景观, 达到良好的抗肿瘤目的。

此外, 脂质体因与生物膜具有高度相似的结构, 有更好的细胞亲和性和生物相容性, 能够提高药物体内递送效率以诱导更多的T_{SCM}。在此基础上, Xu等[59]通过改变制剂中各组分比例筛选了一系列阳离子脂质体, 最终得到一种无需额外修饰配体就能靶向脾脏和肿瘤部位APC的脂质体, 能够将肿瘤新抗原疫苗高效递送至循环中的APC并增强APC对新抗原的摄取。T_{SCM}的命运与肿瘤免疫原性以及TCR信号强度密切相关, 适宜的抗原刺激有利于$TCF-1^+CD8^+$ T_{SCM}细胞生成[74]。同时脂质体中包载Toll样受体9激动剂CpG-ODN促进单核细胞髓源性抑制细胞 (monocytic myeloid-derived suppressor cells, MDSCs) 分化为M1型巨噬细胞并刺激树突状细胞 (dendritic cell, DC) 的成熟与活化, 为T_{SCM}的增殖分化提供适宜的APC生态。单细胞测序结果表明该疫苗增加了肿瘤部位IFN-γ^+CD8^+ T细胞和$TCF1^+CD8^+$ T_{SCM}, 上调$CD11b^+CD80^+CD86^+$ M1样巨噬细胞, 下调$CD11b^+CD206^+$ M2样巨噬细胞及调节性T细胞 (regulatory T cell, Treg), 重塑免疫抑制性微环境, 能够显著抑制肿瘤生长并为持续性免疫提供基础。

4.2 自组装纳米药物递送系统

自组装纳米药物递送系统是指通过分子间作用力如疏水相互作用、氢键、静电作用等驱动载体材料或药物分子自发形成有序纳米结构的递送系统[62], 与单独递送基因药物相比, 自组装NDDS装载能抵抗其降解, 提高细胞摄取效率和溶酶体逃逸, 并且能够共载多种RNA或其他功能性分子以实现协同治疗。Wang等[60]开发出一种由咪唑喹啉前药和抑制性免疫检查点siRNA自组装构建成的时空纳米调节剂DNR, 其外涂被甘露聚糖促进DNR静脉注射后通过白蛋白搭便车淋巴反流到TDLN, 随后Toll样受体激活控制和维持DC的功能, siRNA下调抑制性免疫检查点TIM-3和PD-L1以缓解DC耐受性, 这缓解了T细胞耗竭并为$CD8^+$ T_{SCM}维持提供生态位。体内外实验表明, DNR的使用改善了$CD8^+$ T细胞的增殖活化, 增加了活化DC和M1样巨噬细胞的比例, 同时显著性下调MDSC, 且该调节剂和疫苗联合使用能够有效抗肿瘤并建立长期的免疫记忆。

4.3 仿生纳米药物递送系统

仿生纳米药物递送系统是一类利用天然生物成分或其合成衍生物构建的纳米递送载体, 通过模拟生物体的结构、功能或行为特性实现药物在复杂生理环境中的高效递送与精准释放, 已有研究利用免疫细胞膜或肿瘤细胞膜的天然特性或进行基因改造来调控T细胞功能以达到抗肿瘤目的。Wang等[63]开发了一种由CD6功能化的肿瘤细胞膜包裹的NDDS, 能够通过同源肿瘤靶向将GPCR抑制剂帕罗西汀 (paroxetine, PX) 和JQ1高效递送至肿瘤微环境。其中PX能增加肿瘤中T细胞的浸润, JQ1则抑制BATF来促进T_{SCM}生成, 并同步下调T细胞表面抑制性受体PD-1和TIM-3的表达, 有效逆转T细胞的功能耗竭状态, 显著提升其抗肿瘤活性。体内流式细胞术检测发现, 该系统能够增加TME中抗肿瘤细胞如$CD8^+$ T、$CD4^+$ T和T_{EM}浸润, 减少Treg, 显示优异的抗肿瘤功效。Wang等[64]将放疗诱导的免疫原性抗原及肿瘤衍生的外泌体和骨髓来源的DC混合以呈递全肿瘤抗原, 随后提取该细胞膜包被在纳米颗粒外以制备仿生纳米疫苗。该系统能够延长抗原在免疫系统中的持续时间并提供适当的的TCR信号刺激, 有利于T_{SCM}的激发和扩增。单细胞测序发现, HybridDC能够重塑TME, 显著增加CD8效应或记忆T细胞和M1巨噬细胞, 同时减少CD8耗竭T细胞、M2巨噬细胞以及PD-L1巨噬细胞, 逆转免疫抑制微环境。体内实验显示该系统在免疫原性差的胶质瘤模型中表现出显著的治疗作用, 能够增强ICB疗效并诱导出记忆性T细胞的长期保护性免疫。

5 总结与展望

随着对T_{SCM}研究的不断深入，T_{SCM}在抗肿瘤免疫治疗中的巨大潜力已被证实，诱导或维持T_{SCM}功能以增强抗肿瘤疗效极具发展前景。本文介绍了T_{SCM}的生物学特性及功能特性，综述了信号通路调节剂、细胞因子以及NDDS包载不同药物调控T_{SCM}的研究进展。但是目前大多数治疗策略仍处于早期开发阶段，临床转化与产业化发展仍存在很多问题[75-77]：NDDS本身或其降解产物并非药理学上的惰性物质，可能与有害的体内生物过程相关，此外脱靶的纳米制剂也会导致安全性问题，因此亟需开发可生物降解和生物相容性良好的纳米递送载体；不同患者肿瘤相关血管分布、间质压力、pH、免疫细胞浸润等TM存在差异，必须开发能够高度模块化和定制化的NDDS；NDDS微观构造及组成复杂，制备可重复性差，缺乏统一标准，从实验室小批量制备到大规模工业化生产同样具有挑战，因此在生产过程中需要对粒径、电位等特性进行持续控制并建立统一的质量标准及评价方法。相信随着纳米制剂制备工艺的不断完善及单细胞测序、AI算法等科学技术的发展，对T_{SCM}的研究和应用将进一步深化，为T_{SCM}应用于临床抗肿瘤免疫治疗提供新范式。

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