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溶瘤病毒助力肿瘤免疫治疗

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摘要 肿瘤的治疗手段包括手术治疗、放化疗、靶向治疗和免疫治疗等. 其中, 免疫治疗因为其应用范围广、效果好、副作用低等优势, 在肿瘤治疗领域广受关注. 但是一些肿瘤中存在免疫激活机制缺陷, 即我们常说的“冷肿瘤”, 限制了免疫治疗的效果. 溶瘤病毒是经基因改造后的一类发挥抗肿瘤作用的病毒, 因其具有优秀的免疫激活功能而广受关注, 可以使“冷”肿瘤转化为“热”肿瘤. 目前研究发现溶瘤病毒可以通过直接杀伤肿瘤细胞提升组织的免疫原性, 上调肿瘤细胞表面免疫检查点的表达, 以及通过溶瘤病毒的病毒特性激活免疫反应. 此外, 它们还可在基因工程技术的加持下进一步募集肿瘤浸润T细胞、促进树突状细胞成熟、诱导多能T细胞. 因此, 我们认为溶瘤病毒将是未来肿瘤免疫治疗的优秀协助者, 能很好地放大免疫治疗的抗肿瘤效果. 在这篇综述中, 我们总结了目前溶瘤病毒的免疫激活机制, 并结合临床试验结果展示了溶瘤病毒在免疫治疗中强大的抗肿瘤效果.

关键词 溶瘤病毒, 免疫逃逸, 免疫治疗, 免疫检查点抑制剂

肿瘤是目前横亘在人类健康面前的一大问题, 但值得庆幸的是, 如今我们拥有了靶向治疗、免疫治疗等更强大手段去对抗它. 肿瘤免疫治疗开启了肿瘤治疗的新纪元. 免疫疗法联合放疗、化疗、靶向治疗、过继细胞治疗(adoptive cell therapy, ACT)、免疫调节剂治疗等方案在肿瘤治疗领域大放异彩[1]. 但是, 由于肿瘤的异质性, 免疫治疗在实际情况中的效果并不乐观.

因为免疫活性程度不同, 肿瘤常常表现出“冷”与“热”的个体差异特性, 甚至在同一患者的肿瘤内部都可能存在“热”区和“冷”区[2]. 总的来说, “热”肿瘤有以下特征: 肿瘤微环境(tumor microenvironment, TME)中有大量肿瘤浸润性淋巴细胞(tumor infiltrating lymphocytes, TILs)、肿瘤相关免疫细胞高表达程序性死亡受体-1(programmed cell death-1, PD-1)、肿瘤突变负荷(tumor mutation burden, TMB)高, 且TME中预先存在抗肿瘤免疫反应. 相反, 那些TME中免疫细胞几乎不表达PD-1、TMB低、免疫原性差、低表达人类白细胞抗原(human leukocyte antigen, HLA)的肿瘤被称为“冷”肿瘤[3,4]. 免疫治疗在“热”肿瘤中效果相对显著, 但

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是在一些“冷”肿瘤中却存在明显的免疫耐药. 如何使“冷”肿瘤转化为“热”肿瘤是抗肿瘤免疫疗法中的一大挑战.

作为免疫激活剂的一种, 溶瘤病毒(oncolytic viruses, OVs)是一类天然或基因工程病毒, 可以直接或间接发挥抗肿瘤作用. 它可以激活机体局部的抗肿瘤免疫反应, 并通过旁观者效应诱导全身抗肿瘤免疫反应[5,6], 将非炎性的“冷”肿瘤转化成“热”肿瘤. 近年来, 有关OVs作为肿瘤免疫治疗辅助手段的文章层出不穷[7]. 但是, 鲜少有综述从免疫微环境的角度出发探讨OVs如何影响免疫治疗. 在这篇综述中, 我们讨论了OVs强大的抗肿瘤效果, 聚焦于OVs如何转化“冷”肿瘤中的抑制性TME, 并在与免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)或ACT等免疫疗法联用时触发强大的抗肿瘤效果.

1 OVs的概念和功能

天然地或在被改造后, OVs不会杀伤人体正常细胞但是可以特异性识别并感染肿瘤细胞. DNA或RNA病毒都可以作为构建OVs的基础. 常用的有腺病毒(*Adenoviridae*)、单纯疱疹病毒(*Simplexvirus*)、麻疹病毒(*Morbillivirus*)、牛痘病毒(*Orthopoxvirus vaccinia*)、呼肠孤病毒(*Sedoreoviridae*)、脊髓灰质炎病毒(*Enterovirus poliovirus*)和新城疫病毒(*Paramyxovirus newcastle disease virus*)等[5]. 在肿瘤治疗中, OVs可以通过感染和裂解肿瘤细胞使肿瘤细胞直接死亡. 此外, 它们也可以通过诱导局部或全身抗肿瘤免疫反应或抑制肿瘤新生血管生成间接发挥抗肿瘤作用[5,8,9](图1).

虽然用病毒治疗肿瘤的想法早已经存在, 但直到20世纪末才有科学家首次证明了基因工程病毒在肿瘤中的治疗作用[10]. 目前全球共有4款OVs在不同国家上市. 早期有Rigvir (2003年)和安柯瑞(H101, 2005年)两款OVs药物分别在拉脱维亚和中国上市, 但临床应用较少. 此后, 应用转基因技术的第二代溶瘤病毒T-VEC (talimogene laherparepvec, 2015年)和第三代溶瘤病毒G47delta (2021年)分别在美国和日本上市[11~13]. 这两种病毒均以单纯疱疹病毒HSV-1为基础, 可以表达转基因粒细胞集落刺激因子(granulocyte-macrophage colony stimulating factor, GM-CSF), 拥有更强的自我复制和肿瘤杀伤能力.

OVs的基因工程改造主要着力于以下三点: 第一, 使其靶向协助病毒吸附的肿瘤细胞表面受体; 第二, 使其仅能在肿瘤细胞内复制, 而不杀伤正常细胞; 第三, 向OVs基因组中插入特定基因以提高免疫激活或抑制新生血管生成的能力. 例如, 使OVs表达GM-CSF[14,15]、白介素15(interleukin 15, IL-15)[16]、IL-2[17]、CD40[18]、IL-24[19]等细胞因子, 从而通过多种机制激活免疫, 将免疫“冷”肿瘤转化成“热”肿瘤. 接下来, 我们将进一步总结OVs如何激活“冷”肿瘤中的免疫抑制性TME并分析探讨OVs在协助肿瘤免疫治疗中的作用.

2 OVs在肿瘤免疫治疗中的作用

2.1 OVs通过改造肿瘤微环境将“冷”肿瘤转化为“热”肿瘤

OVs产生的免疫激活效应比传统抗肿瘤疗法更强. 在传统抗肿瘤疗法中, 放化疗主要基于物理和化学原理杀伤肿瘤细胞, 常常与免疫治疗联用. 例如, 化疗联合免疫治疗在非小细胞肺癌[20]、肾细胞癌[21]、胰腺癌[22]中显示出增强的疗效. 同样, 放疗联合免疫治疗在非小细胞肺癌[23]、头颈部鳞状细胞癌[24]、鼻咽癌[25]中也有效.

但是, 囿于放化疗对肿瘤免疫的激活并不强, 并且可能对TME中的免疫细胞产生抑制作用[26], 无法稳定地将“冷”肿瘤转化成“热”肿瘤[27], 我们仍需探索针对“冷”肿瘤的新治疗方案. 例如, 在III期非小细胞肺癌放化疗后联用PD-1抑制剂, 能产生较为持久的疗效. 但是, 在局限期小细胞肺癌中, 放化疗联用ICIs未产生积极影响[28]. 并且, 在已有PD-1抑制剂耐药的非小细胞肺癌中, 放疗并没有改善其对ICIs的耐药[29].

相比之下, OVs是更高效和稳定的免疫治疗“伙伴”. 它们可以通过提高组织免疫原性、借助病毒抗原本身特性和转基因表达细胞因子产生强大的免疫激活作用, 具备稳定激活“冷”肿瘤的潜力.

OVs可以直接裂解肿瘤细胞, 提升组织免疫原性(图2). 不同的OVs可以诱导肿瘤细胞发生不同的死亡事件, 例如腺病毒主要使肿瘤细胞发生自噬、坏死性凋亡和细胞焦亡[30,31]; 溶瘤性副痘病毒(*Parapoxvirus*)通过焦孔素E(gasdermin E, GSDME)诱导细胞焦亡[32]. 肿瘤细胞裂解后, TME中产生大量的肿瘤相关抗原(tu-

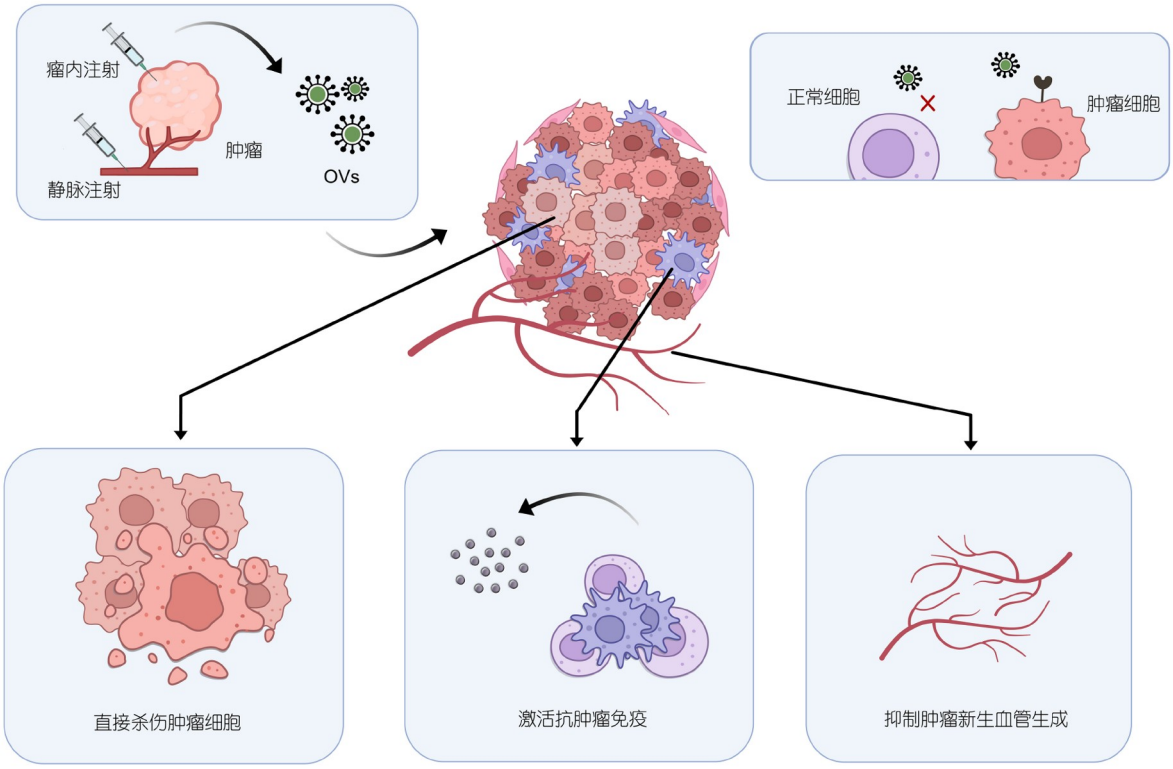

图 1　溶瘤病毒的特点. 溶瘤病毒(OVs)可通过瘤内注射或静脉注射开展治疗, 靶向肿瘤细胞表面受体, 不杀伤正常细胞. 在肿瘤微环境中, OVs可以通过杀细胞效应直接杀死肿瘤细胞, 此外, 还可以通过激活抗肿瘤免疫和抑制肿瘤新生血管形成发挥抗肿瘤作用. (图片使用 BioRender.com 创建)

Figure 1　Characterization of oncolytic viruses. Through intratumoral or intravenous injection, oncolytic viruses (OVs) selectively target tumor cell surface receptors without harming normal cells. Within the tumor microenvironment, OVs exert a cytocidal effect, directly eliminating tumor cells. Moreover, OVs contribute to an anti-tumor effect by activating anti-tumor immunity and suppressing tumor neovascularization. (Created in BioRender.com)

mor-associated antigens, TAA)、病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs)信号[5,31], 免疫细胞表面的模式识别受体(pattern recognition receptors, PRRs)识别这些信号, 进而激活先天免疫、获得性免疫或产生慢性炎症反应. 例如, 肿瘤细胞由OVs诱发免疫原性细胞死亡(immunogenic cell death, ICD)[33], 产生胞外钙网蛋白(calreticulin, CRT)、ATP和高迁移率族蛋白B1 (high mobility group protein B1, HMGB1)等DAMPs, 这3种分子分别与树突状细胞(dendritic cells, DCs)上的受体CD91、嘌呤能受体P2X7 (purinergic receptor P2X 7, P2RX7)和Toll样受体4 (Toll-like receptor 4,TLR4)结合[34], 促进DCs的募集和成熟, 并募集大量$CD8^+$ T细胞[35,36], 促使“冷”肿瘤转化为“热”肿瘤[37].

OVs具有病毒的基本特性, 因此可以不依赖于杀伤肿瘤细胞而激活部分免疫细胞(图2). OVs可以感染DCs而诱导和激活NK细胞[38]. 在B细胞淋巴瘤中, 溶瘤性柯萨奇病毒A21(*Enterovirus coxsackieviruses* A21)除了直接杀伤肿瘤B细胞外, 还可以通过激活NK细胞杀伤耐药的肿瘤B细胞[39]. 脊髓灰质炎溶瘤病毒不诱导显著的肿瘤杀伤, 但是可以通过感染TME中的巨噬细胞诱导先天免疫系统的活化. 此外, 它可以刺激产生更优质的多功能T细胞[40]. 单纯疱疹病毒抗原可以直接通过TLR/核因子κB(nuclear factor κ-B, NF-κB)信号通路使NK细胞释放干扰素γ(Interferon-γ, IFN-γ)[41], 增强抗肿瘤免疫, 并通过NK细胞进一步激活$CD4^+$ T细胞[42]. 牛痘溶瘤病毒抗原可以通过激活碱性亮氨酸拉链转录因子ATF样蛋白3(basic leucine zipper transcriptional factor ATF-like 3, Batf3)依赖性

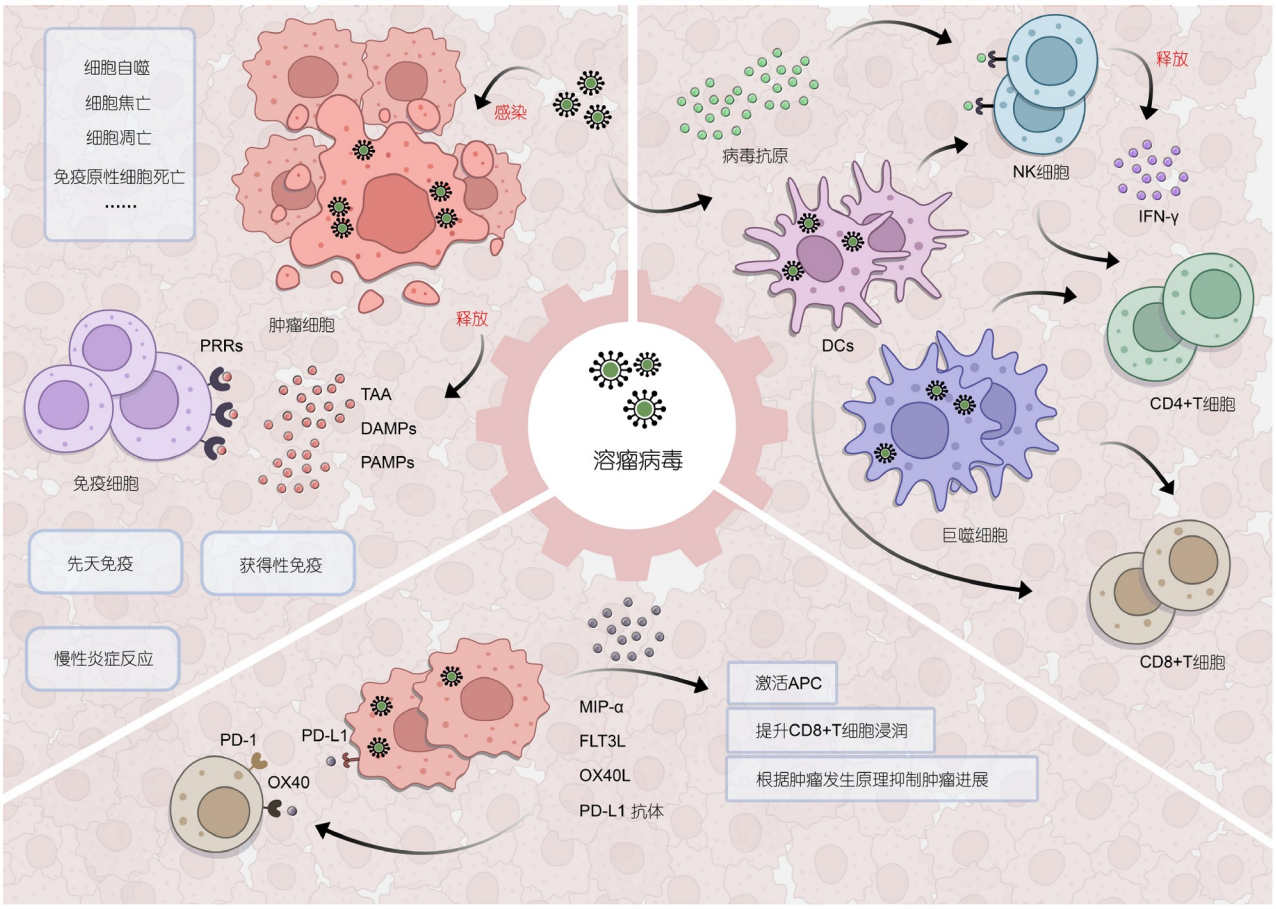

图 2 溶瘤病毒改造肿瘤微环境的免疫机制. 溶瘤病毒通过杀细胞效应感染并直接杀死肿瘤细胞, 死亡的肿瘤细胞释放大量TAA、PAMPs和DAMPs, 这些分子与多种PRRs结合, 激活获得性免疫、先天免疫和导致慢性炎症. OVs因为具有病毒的基本特性, 也可以不依赖于杀伤肿瘤细胞而激活DCs、巨噬细胞、NK细胞、T细胞等免疫细胞. 通过基因工程技术, OVs表达多种免疫因子, 例如MIP-1α, FLT3L, OX40L和PD-L1抗体, 进一步强化上述免疫过程, 激活抗原提呈细胞、促进$CD8^+$ T细胞浸润, 激活冷肿瘤. 还可以基于肿瘤发生机制设计OVs, 使其发挥更强的肿瘤抑制功能. (图片使用 BioRender.com 创建)

Figure 2 Modulation of tumor microenvironment by oncolytic viruses. OVs infect and directly eliminate tumor cells through cytocidal effects. The resulting dead tumor cells release abundant TAAs, PAMPs, and DAMPs, which bind to various PRRs. This interaction activates acquired immunity, innate immunity, and triggers chronic inflammation. Leveraging their viral nature, OVs can independently activate immune cells such as DCs, macrophages, NK cells, and T cells, irrespective of tumor cell killing. Through genetic engineering technology, OVs can be designed to produce a variety of immune factors like MIP-1α, FLT3L, OX40L, and PD-L1 antibodies, further enhancing immune processes. This includes activating antigen-presenting cells, promoting CD8+ T cell infiltration, and reversing the "cold" tumor phenotype. Additionally, it is feasible to design OVs based on tumorigenic mechanisms, allowing them to exert a more potent tumor suppressor function. (Created in BioRender.com)

$CD103^+$的DCs产生先天免疫和适应性免疫反应[43]. 此外, OVs激活NK细胞的功能后还可以进一步被强化以产生更强的细胞毒活性[44]. 以脊髓灰质炎-鼻病毒嵌合体为基础的OVs对DCs具有天然噬性, 因此它们可以招募和激活DCs, 有效地激活抗肿瘤$CD8^+$ T 细胞, 并诱导$CD8^+$ T细胞迁移[45].

在肿瘤治疗中, 免疫因子因其"双刃剑"特性——可以激活抗肿瘤免疫, 也可能诱发严重的细胞因子风暴, 往往难以直接运用于临床. 而由基因工程OVs编码的细胞因子的不良事件发生率较低, 可以触发更强的抗肿瘤免疫反应[46](图2). 编码非分泌型IL-12(non-secreting interleukin 12, nsIL-12)的溶瘤腺病毒Ad-TD-nsIL-12可以产生适量的IL-12以激活TME, 并且在动物实验中表现出较好的安全性和肿瘤治疗效果[47].

在激活抗原提呈细胞(antigen-presenting cells, APC)方面, 巨噬细胞炎性蛋白1α(macrophage inflam-

matory protein 1α, MIP-1α)[48]和Fms样酪氨酸激酶-3 (FMS-related tyrosine kinase 3 ligand, FLT3L)[49]可以分别吸引未成熟的DCs和促进DCs成熟. 基因工程OVs可以通过表达这两种分子以解决“冷”肿瘤中DCs成熟度低的问题[30,50]. 由于DCs是$CD8^+$ T细胞免疫的主要诱导因子, 因此当DCs被完全激活时, $CD8^+$ T细胞的激活会变得更加容易.

在提升$CD8^+$ T细胞浸润方面, 表达肿瘤坏死因子受体4配体(OX40 ligand, OX40L)的基因工程OVs可以通过结合$CD8^+$ T细胞表面的肿瘤坏死因子受体4 (OX40)来促进$CD8^+$ T细胞的增殖和活化[35]. 插入程序性死亡配体1 (programmed cell death-L1, PD-L1)抗体基因的OVs通过阻断效应使T细胞颗粒酶B释放增强[51], 消除了抑制$CD8^+$ T细胞活化的穿孔蛋白[52], 增强$CD8^+$ T细胞的募集.

此外, OVs也可以根据肿瘤发生原理表达相应治疗性分子. 例如, 相互依赖性的胆固醇代谢促使胶质母细胞瘤中的巨噬细胞吞噬功能障碍. 编码胆固醇反向转运蛋白——人载脂蛋白A1(human apolipoprotein A-I, ApoA1)的溶瘤腺病毒可以协助胆固醇外排, 并恢复抗肿瘤免疫[53].

以上这些OVs激活免疫以改造“冷”肿瘤的机制在肿瘤治疗中具有重要意义, 或许我们可以借此破解目前免疫治疗耐药的困境.

2.2　OVs协助免疫检查点抑制剂达到免疫治疗目的

目前常见的免疫治疗主要是ICIs和ACT. ICIs通过消除TME中免疫检查点的免疫抑制作用发挥抗肿瘤功能, 以临床应用广泛且副作用较小为特征. ICIs在非小细胞肺癌、黑色素细胞瘤、尿路上皮癌、膀胱癌、局部晚期基底细胞癌、胆道癌等肿瘤中具有相当可观的临床治疗效果[54~61]. 然而, 免疫检查点抑制剂主要在免疫检查点高表达的“热”肿瘤中发挥疗效[62]. 为了解决“冷”肿瘤中的免疫耐受问题, 多药联合策略常被采用, 例如联合多种免疫检查点抑制剂或联合免疫抑制因子抑制剂、免疫激活剂和放化疗[63~66].

OVs是一种优秀的免疫激活剂, 可以直接裂解肿瘤细胞, 提升组织免疫原性; 激活DCs、$CD4^+$ T细胞、$CD8^+$ T细胞等免疫细胞, 上调免疫检查点, 还可以通过基因工程技术使OVs表达细胞因子, 这些特点都说明OVs在免疫治疗中的强大作用[67].

通过联合基因工程OVs, ICIs展现出比单药治疗更强的治疗效果[45,46]. 例如, 通过与编码IL-12的OVs联用, PD-1抑制剂在晚期结肠癌小鼠中表现出百分之百的治愈率[68]; 通过与编码IL-15的OVs联用, PD-1抑制剂产生具有更强T细胞诱导能力的成熟DCs[69]; 通过与编码IL-2[70]和 肿瘤坏死因子α(tumor necrosis factor α, TNFα)[71]的OVs联用, PD-1抑制剂成功刺激T细胞并促进T细胞浸润[72]. 通过与编码IL-7和IL-12的OVs联用, PD-1和细胞毒性T淋巴细胞相关蛋白4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)抑制剂激活肿瘤的炎症免疫状态, 并在小鼠中实现肿瘤完全消退[73].

在临床试验中, 目前进展较快的主要是PD-L1抑制剂[14,15]或CTLA-4[74]抑制剂联用单纯疱疹溶瘤病毒T-VEC的方案. 在2期临床试验中, 相比于只使用CTLA-4抑制剂, CTLA-4抑制剂联用T-VEC的客观缓解率(objective remission rate, ORR)由16%升高到了37.5%[75]; PD-L1抑制剂联用T-VEC的ORR也达到了35%[15]. 此外, 由呼肠孤病毒改造的OVs与PD-L1抑制剂联用也进入了一期临床阶段, 并表现出了较好的长期益处[76]. 编码ICIs的基因工程OVs也能产生类似OVs联用ICIs的效果[77,78]. 使用编码PD-1/PD-L1抗体[79~82], 或编码针对免疫检查点单链可变片段(single-chain variable fragment, scFv)的OVs[83~85]进行肿瘤治疗, 普遍获得了较好的前期结果[86~89](表1).

OVs也可以利用非典型ICIs. 与PD-1/PD-L1类似, 阻断NK细胞表面的抑制性受体——自然杀伤细胞凝集素样受体亚家族C成员1 (NK cell lectin-like receptor subfamily C member 1, NKG2A), 可以提升肿瘤对NK细胞的敏感性[90]. OVs可以上调NKG2A和肿瘤表面的配体HLA-E[91], 暗示NKG2A/HLA-E检查点抑制剂联合OVs的方案具有潜在可行性.

OVs还可以在特征性突变肿瘤中提升免疫检查点抑制剂疗效. 第10号染色体同源丢失性磷酸酶张力蛋白基因(phosphatase and tensin homolog deleted on chromosome ten, PTEN)在约40%的胶质母细胞瘤中存在突变, 并通过激活PI3K-AKT (胞内磷脂酰肌醇激酶, phosphoinositide 3-kinase, PI3K; 蛋白激酶B, protein kinase B, AKT)通路产生抑制性TME. PI3K抑制剂联用PD-1抗体能抑制5/7小鼠的肿瘤生长, 但仅3/7出现了肿瘤完全消退[92]. 借助PTEN突变干扰肿瘤抗病毒先天免疫的特点[93], 将OVs, PI3K抑制剂和PD-1抑制剂

表 1 OVs与ICIs联用或通过转基因技术编码ICIs

Table 1 OVs in combination with ICIs or encoding ICIs by genetic engineering techniques

病毒种类	溶瘤病毒	ICIs联用	转基因修饰	肿瘤
腺病毒	TILT-123[17]	PD-1	编码TNFa和IL-2	黑色素瘤
	OBP-502[36]	PD-1	\	结肠癌和胰腺癌
	Ad-Cab[85]	\	编码靶向PD-L1的Fc融合肽(fragment crystallizable, Fc)	肾细胞癌
	ZD55-IL-24[19]	PD-1	编码IL-24	黑色素瘤
	VALO-D102[18]	PD-1	编码CD40L和OX40L	黑色素瘤
	OBP-702[86]	PD-1	\	胰腺导管腺癌
	AdC68-spE1A-αPD-1[82]	\	编码PD-1抗体	结肠直肠癌、结肠腺癌和肝癌
	XVir-N-31[87]	PD-1	\	胶质母细胞瘤
	Delta-24-ACT[88]	PD-L1	编码4-1BB配体	胶质母细胞瘤
单纯疱疹病毒	T-VEC	CTLA-4[74]	编码GM-CSF	晚期或无法切除的黑色素瘤
		PD-L1[14]	编码GM-CSF	复发性或转移性头颈部鳞状细胞癌
		PD-L1[15]	编码GM-CSF	晚期或转移性肉瘤
	OVH-aMPD-1[83]	TIGIT	编码表达针对PD-1的scFv	肝癌
	PD-L1-BiTE-oHSV-1[78]	\	具有交联PD-L1和CD3ε的双特异性T细胞捕获结构	结直肠腺癌
麻疹病毒	MV-s-NAP[80]	PD-1	编码幽门螺杆菌中性粒细胞激活蛋白	胶质母细胞瘤
	MeVac[79]	\	编码PD-1/PD-L1 抗体	结直肠腺癌
牛痘病毒	vvDD-IL15-Rα[16]	PD-1	编码IL-15和IL-15α	结肠癌或卵巢癌
	VV-scFv-TIGIT[84]	PD-1或LAG-3	编码靶向T细胞免疫球蛋白和ITIM结构域的scFv	结肠癌
	(VV)-iPDL1/GM[77]	\	编码PD-L1抗体和GM-CSF	骨肉瘤、腺癌、 黑色素瘤、淋巴瘤
呼肠孤病毒	Pelareorep[76]	PD-L1	\	晚期胰腺腺癌
新城疫病毒	rNDV-抗-PD-1[81]	\	编码PD-1抗体	黑色素瘤
	rNDV-抗-PD-L1[81]	\	编码PD-L1抗体	黑色素瘤
	NDVhuGM-CSF[89]	PD-1/PD-L1	编码GM-CSF	泛癌

联用, 最终使5/8小鼠的肿瘤完全消退[94].

总的来说, 相比于ICIs单药治疗或者OVs单药治疗, OVs联合ICIs极大促进了疗效. 在溶瘤脊髓灰质炎病毒单药治疗的临床试验中, 其结果暗示OVs可能在同ICIs联合时取得更好的疗效[46]. 更重要的是, OVs刺激免疫系统产生的高浓度细胞因子, 例如IFN-γ, 会转而攻击OVs自己, 使OVs病毒感染率下降并影响治疗效果[95]. 而在OVs同免疫治疗联用时, 其产生的巨大免疫效能可能使得肿瘤消退比病毒消除更早. 因此, OVs更适合联合免疫治疗发挥功能[36,74].

2.3 OVs通过协助过继细胞疗法实现肿瘤免疫治疗

ACT是通过改造T细胞并回输体内发挥抗肿瘤作用的免疫治疗. ACT在血液系统肿瘤中展现出惊人的疗效, 但是在实体瘤中却因为存在移植不良反应、持久性不足以及抑制性TME等情况收效甚微.

OVs有望打破ACT在实体瘤中的疗效限制. 例如, 编码IL-12和PD-L1抗体的溶瘤病毒CAdTrio与嵌合抗原受体T细胞免疫疗法(chimeric antigen receptor T-cell immunotherapy, CAR-T)联用, 在小鼠异种移植物模型中表现出持久的抗肿瘤活性[96]. 类似的方案在黑色素瘤和胶质瘤[97,98]中也表现甚佳. 在胶质瘤中, 编码CXC趋化因子配体11 (chemokine ligand C-X-C motif chemokine ligand 11, CXCL11)的溶瘤腺病毒促进了肿瘤中T细胞的浸润, 并在与靶向免疫检查点B7H3 (B7 homolog 3, B7H3)的CAR-T细胞联用时表现出了持久

的抗肿瘤反应[99]. 在肾细胞癌中, 编码CC趋化因子配体5 (C chemokine ligand 5, CCL5)和IL-12的溶瘤腺病毒增强了CAR-T疗效[100]. 这是因为OVs为TILs提供了激活信号, 协助解决了CAR-T在肿瘤组织中缺乏浸润和难以持续存在的问题. 此外, OVs在CAR-T治疗前期可协助诱导出更优质的TILs, 再进行T细胞分离和体外扩增等程序[101].

但是并不是所有OVs都在同ACT的联合中显示出积极的结果. 有研究人员发现在临床治疗中出现了一种拮抗机制. 原本意在通过表达IFN系统以实现靶向肿瘤细胞的OVs[102]可以通过I型IFN导致治疗性CAR-T细胞凋亡[103].

3　OVs在肿瘤免疫治疗中存在的问题与应用前景

作为一种可复制和具有肿瘤特异性的病毒载体, OVs在直接诱导肿瘤细胞死亡的同时还可以表达转基因细胞因子, 并通过病毒复制保证药物浓度, 同其他免疫激活剂相比具有独特优势. 但是, 在临床推广过程中还有许多细节需要完善, 例如安全性、给药方式和耐药性等问题.

目前, 多种不同的OVs在早期临床试验中表现出较好的安全性, 常见的不良事件(adverse event, AE)为发热、恶心和呕吐. 在重组溶瘤腺病毒YSCH-01的一期临床试验中, AE的总发生率为92.3%, 但没有观察到剂量限制性毒性(dose-limiting toxicity, DLT), 并且肿瘤有减小的趋势, 总体情况较好[104]. 表达癌胚抗原(carcinoembryonic antigen, CEA)的溶瘤麻疹病毒衍生物MV-CEA在I期临床试验最大剂量下未观察到DLT, 并且表现出较好的治疗效果[105]. 在溶瘤牛痘病毒JX-594与环磷酰胺节拍化疗和PD-L1抑制剂阿维鲁单抗的联合治疗II期临床试验中, 观察到较好的安全性以及对晚期软组织肉瘤免疫耐受患者TME的免疫激活[106].

目前虽然在临床试验中鲜少有针对OVs安全性的负面报道, 但是有临床前研究发现溶瘤腺病毒可以在胶质母细胞瘤中促进胶质瘤干细胞的形成[107], 这可能对抗肿瘤治疗产生负面影响, 也提示我们需要更加深入地研究OVs对肿瘤细胞的影响.

给药方式可能会对OVs的疗效产生影响. OVs主要有瘤内注射和静脉注射两种方案. 在静脉注射OVs时, 机体血清中的抗体和凝血因子将阻碍OVs向肿瘤定位, 从而减弱OVs的效果, 并且被捕获的OVs还可能导致肝毒性[108]. 溶瘤病毒M1可以采用静脉注射进行抗肿瘤治疗[109,110], 并且在非人灵长类动物的实验中未发现上述先天免疫因子的不良影响[111]. 但是, 更多的OVs不具备此类特性, 因此需要采用瘤内注射的方式开展治疗. 瘤内注射的缺点是容易受限于肿瘤内部的物理阻隔, 影响OVs在瘤内的扩散, 并且在面对分散性小病灶时难以处理. 在腹膜癌的治疗中, 腹腔注射OVs比静脉注射更有效[112], 说明不同肿瘤和OVs的给药方案不同, 需要根据实际情况进行调整.

为了对抗上文提到的免疫系统对静脉注射OVs的抑制作用, 基于细胞载体的递送方案或许可以解决这个问题. 间充质干细胞(mesenchymal stem cells, MSCs)可以穿过血脑屏障并且具有肿瘤归巢特性, 是针对脑部肿瘤的理想生物载体[113]. 在弥漫性内源性脑桥胶质瘤中, MSCs装载的OVs避免了过早被免疫系统攻击并成功在肿瘤中广泛传播[114]. 神经干细胞(neural stem cells, NSCs)也可以作为协助溶瘤病毒通过血脑屏障的有效工具. 以NSCs为载体的基因工程溶瘤病毒NSC-CRAd-S-pk7在I期剂量递增临床试验中展现出较好的安全性和递送效果[115]. 借助抗原抗体的相互作用, 溶瘤腺病毒-T细胞嵌合体成功提高了OVs向肿瘤细胞的递送效率, 同时也提示了OVs与CAR-T疗法结合的新方案[116].

除了调整给药方式和使用细胞载体递送OVs, 还可以通过基因工程技术协助OVs逃避免疫攻击. SJ-600溶瘤牛痘病毒使受感染细胞的细胞膜上掺入人宿主补体调节蛋白CD55, 使产生的病毒外包膜具有抗补体特性, 并且可以持续作用直到肿瘤完全缓解[117]. 基因工程水疱性口炎病毒rVSV-LCMVG使用淋巴细胞性脉络丛脑膜炎病毒(*Lymphocytic choriomeningitis mammarenavirus*, LCMV)的G蛋白替代自身原本的G蛋白, 降低了中和抗体对病毒的影响, 并且在与ACT联用治疗实体瘤时显著提升了肿瘤内的细胞因子和免疫细胞浸润水平[118].

也有研究发现可以使用外源抑制剂协助OVs逃脱免疫攻击. 在神经胶质瘤中, 溶瘤性单纯疱疹病毒oHSV刺激胰岛素样生长因子2 mRNA 结合蛋白3 (insulin like growth factor 2 mRNA binding protein 3,

IGF2BP3)促进肿瘤产生中性粒细胞胞外陷阱(neutrophil extracellular traps, NETs), 使得oHSV被阻断. 具有肿瘤增殖抑制能力的BET抑制剂(bromodomain and extraterminal, BET)通过阻断IGF2BP3抑制NETs形成, 增强oHSV的溶瘤活性[119]. 依此机制, 若将BET抑制剂相关功能通过基因工程手段整合到oHSV中, 对于oHSV维持病毒复制和溶瘤效果有较大意义.

除了开发新的OVs, 针对已上市的OVs开发新的免疫联合治疗方案或许更为重要. 已在中国上市的用于治疗鼻咽癌的溶瘤病毒H101在针对难以治疗的恶性肿瘤并发症——恶性腹水的II期临床试验中展现出了肿瘤抑制效果, 并且提示H101产生的免疫激活效果为抗PD-1/PD-L1治疗奠定了基础, 提示二者联用增强疗效的可能[120].

在未来, 针对不同肿瘤患者TME的个性化OVs将更好地为精准免疫治疗服务[121], 纳米技术有望为OVs免疫联合方案的安全性和给药方式等问题提供更完美的解决方案[122,123]. 我们相信, 在不久的将来, OVs将作为精准免疫治疗的高效协助者, 为全球肿瘤患者带去新的光明.

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Oncolytic viruses facilitate tumor immunotherapy

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Tumor immunotherapy, distinguished by its broad applicability, positive outcomes, and minimal side effects, has garnered significant attention recently. However, some tumors exhibit immune escape mechanisms, referred to as “cold” tumors, which curtail the efficacy of immunotherapy. Oncolytic viruses, genetically modified viruses with potent anti-tumor effects, have emerged surprisingly and prominently due to their remarkable immune-activating properties, capable of transforming “cold” tumors into “hot” ones. Current research underscores that oncolytic viruses can enhance tissue immunogenicity by directly eliminating tumor cells, upregulating immune checkpoints on the tumor cell surface, and activating immunity through innate viral properties. Furthermore, through genetic engineering technology, these viruses prompt tumor-infiltrating lymphocyte recruitment, facilitate dendritic cells maturation, and induce T cell activation. The consensus is that oncolytic viruses hold immense potential as facilitators of tumor immunotherapy, amplifying the anti-tumor effects of immunotherapies. This review provides an overview of the current immune activation mechanisms of oncolytic viruses, highlighting their robust anti-tumor effects in clinical applications.

oncolytic viruses, immune escape, immunotherapy, immune checkpoint inhibitors

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