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·专家论坛·

肿瘤免疫治疗耐药机制与克服策略

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[摘 要] 免疫治疗已成为肿瘤治疗的主要手段之一,但耐药率高是限制其临床应用的主要因素。尽管大量研究已揭示了免疫治疗耐药发生的众多机制,但面对错综复杂的肿瘤免疫微环境,仍是冰山一角。如何判定不同肿瘤类型免疫治疗耐药的主要机制,并精准制定逆转免疫治疗耐药的高效策略是当前肿瘤免疫治疗领域亟需解决的关键问题。本文系统阐述免疫治疗耐药机制及应对策略的相关研究进展,以期为临床清晰地认识免疫治疗耐药发生过程,以及发掘新型逆转耐药策略提供新的思路。

[关键词] 肿瘤;免疫治疗;耐药机制;应对策略
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Mechanism and respone strategies of resistance in tumor immunotherapy

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[Abstract] Immunotherapy is a major strategy of antitumor therapy, whereas it still faces many challenges in clinical application. Although a large number of studies have revealed numerous mechanisms for the occurrence of immunotherapy resistance, it is still the tip of the iceberg in the face of the complex immune microenvironment. How to determine the main mechanisms of immunotherapy resistance in different tumor types and developing efficient strategies for reversing immunotherapy resistance are key issues that need to be addressed in the field of current tumor immunotherapy. Systematically discuss the research progress of immunotherapy resistance mechanisms and response strategies, in order to provide new ideas for better clinical understanding of the process of immunotherapy resistance and discovering novel reversal strategies.

[Key words] tumor; immunotherapy; resistance mechanism; response strategy
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近年来,以PD-1/PD-L1抗体为代表的肿瘤免疫治疗已在黑色素瘤、NSCLC、头颈部肿瘤等实体瘤的治疗中取得了令人瞩目的临床疗效,成为肿瘤治疗史上里程碑式的突破,为肿瘤患者点亮了“生命的曙光”。然而,一部分肿瘤患者在初始治疗时就表现出治疗抵抗,初始治疗响应者中20%~30%的患者最终也会出现复发和进展,能维持长期获益的患者屈指可数[1-2]。由此可见,耐药的发生是免疫治疗持续获益的“绊脚石”。深入阐明肿瘤免疫治疗耐药机制、探寻逆转免疫治疗耐药的应对策略是肿瘤精准免疫治疗的当务之急。

免疫系统有效识别和杀伤肿瘤细胞受多种因素影响,故其耐药机制也纷繁复杂。本文将从肿瘤细胞、$CD8^+$ T细胞、肿瘤微环境(TME)及全身性因素等四个方面详细阐述当前肿瘤免疫治疗耐药机制及应对策略的相关研究进展并提出潜在的研究方向,以期

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深刻认识免疫治疗的本质,更好地迎接免疫治疗面临的挑战。

1　耐药机制

1.1　肿瘤细胞层面

1.1.1　肿瘤新抗原的丢失　肿瘤新抗原是由肿瘤细胞基因突变而产生的肿瘤特异性抗原(tumor specific antigen,TSA),可诱导机体的特异性抗肿瘤免疫反应。若肿瘤新抗原表达较低,不足以激活免疫细胞启动抗肿瘤免疫反应将导致免疫治疗无效[3-4]。肿瘤突变负荷(tumor mutation burden, TMB)、微卫星不稳定性(microsatellite instability, MSI)和DNA错配修复(mismatch repair,MMR)是影响肿瘤新抗原产生的主要因素。低TMB、微卫星稳定(microsatellite stability,MSS)、错配修复完整(mismatch repair proficient, pMMR)的肿瘤其新抗原产生较少,肿瘤免疫原性降低,可能会促进免疫治疗耐药。例如:前列腺癌等低TMB的肿瘤常常表现出免疫治疗耐药[5],而NSCLC等高TMB的肿瘤则对免疫治疗更敏感[6]。对于微卫星高度不稳定性(MSI-high,MSI-H)/错配修复缺失(deficiency of MMR,dMMR)的患者,其TMB约为pMMR患者的10倍,因此其新抗原表达较高,对免疫治疗应答率更高[7]。

1.1.2　肿瘤抗原提呈缺陷　研究证实,MHC-Ⅰ类抗原提呈受损与免疫治疗耐药密切相关[8]。β2微球蛋白(β2-microglobulin,β2M)是参与MHC-Ⅰ类分子折叠及运输的关键蛋白,肿瘤细胞发生β2M缺失或突变会使MHC-Ⅰ类分子表达受损,影响肿瘤抗原提呈,发生免疫治疗耐药。全外显子组测序显示,免疫治疗耐药的结直肠患者存在β2M双等位基因缺失和截短突变[9-10]。在17名免疫治疗后进展的恶性黑色素瘤患者组织中也检测到5名(29.4%)患者存在β2M缺失[11]。

1.1.3　IFN-γ信号通路异常　IFN-γ主要由活化的$CD8^+$ T细胞分泌,是启动和维持有效抗瘤免疫反应最重要的细胞因子。IFN-γ与Ⅱ型IFN受体IFNGR1/IFNGR2结合后可激活JAK1/JAK2-STAT1信号通路,启动下游靶分子的转录,从而通过促进肿瘤细胞凋亡、诱导肿瘤细胞MHC-Ⅰ类分子表达、促进Th1免疫反应等发挥抗肿瘤作用[12]。研究发现,多种肿瘤中均存在IFN-γ通路的异常,并显著影响免疫治疗疗效。约75%的对抗CTLA-4治疗原发耐药的黑色素瘤患者存在IFN-γ通路相关基因突变[13]。在小鼠黑色素瘤模型中,敲除IFNGR1可降低肿瘤细胞对抗CTLA-4治疗的敏感性;与之相印证的是,在对16名接受抗CTLA-4治疗的黑色素瘤患者(4名应答者,12名无应答者)进行肿瘤全外显子组测序分析后也发现,原发耐药的患者存在IFN-γ通路的基因缺失(IFNGR1、IRF-1、JAK2和IFNGR2)[14]。6%~12%的浸润性乳腺癌、肺癌、前列腺癌和结直肠癌患者存在JAK1/2的缺失突变,导致免疫治疗的原发性耐药[15]。需注意的是,JAK纯合性缺失的患者对IFN-γ抵抗,而JAK杂合性缺失患者其MHC-Ⅰ类分子及PD-L1的表达不受影响,表现出对IFN-γ的高响应性[16]。

1.2　$CD8^+$ T细胞层面

1.2.1　$CD8^+$ T细胞浸润减少　以抗PD-1/PD-L1抗体为代表的免疫治疗旨在重激活肿瘤特异性$CD8^+$ T细胞以增强机体的抗瘤能力,然而,不同瘤种、甚至同一瘤种不同部位中的免疫细胞浸润程度显著不同,表现出高度异质性。目前,研究者根据免疫细胞浸润程度将肿瘤分为炎症型(热肿瘤)、免疫豁免型和免疫沙漠型(冷肿瘤)。由于"冷肿瘤"内无$CD8^+$ T细胞浸润或浸润比例较低,抗PD-1/PD-L1抗体几乎无法发挥作用,从而导致免疫治疗原发耐药的发生[17]。已发现肿瘤内多种信号通路的异常可导致$CD8^+$ T细胞的浸润减少,如PTEN缺失可导致PI3K-Akt信号通路激活,从而促进免疫抑制性分子IDO1、HIF-1α、CCL2和CSF1等的表达,抑制$CD8^+$ T细胞的募集进而促进肿瘤细胞免疫逃逸[18-19],参与前列腺癌及三阴性乳腺癌的免疫治疗耐药[20-21]。MAPK通路的异常激活可促进PD-L1、VEGF及IL-8等的表达,抑制$CD8^+$ T细胞的浸润及功能,从而抑制抗肿瘤免疫反应[22-23]。在黑色素瘤中的研究发现,Wnt/β-catenin信号通路活化可抑制趋化因子CCL4的表达,从而导致$CD103^+$ DC浸润减少、初始$CD8^+$ T细胞活化障碍,因此肿瘤浸润$CD8^+$ T细胞也相应减少[24]。

1.2.2　免疫抑制性分子的表达　免疫检查点作为免疫系统的"刹车钳",在控制免疫系统过度应答方面发挥重要作用。然而,肿瘤调控下的免疫检查点分子过表达可损伤效应$CD8^+$ T细胞识别和杀伤肿瘤细胞的能力,促进肿瘤进展及免疫治疗耐药[25]。随着研究的深入,除已被熟知的PD-1及CTLA-4外,还发现其他免疫检查点分子的过表达也可影响免疫治疗的反应,如TIM3、LAG-3、VISTA及TIGIT等。新近研究[26-27]发现,使用抗PD-1治疗可反馈性触发其他免疫抑制性分子的表达,导致获得性耐药的发生。如在NSCLC中,抗PD-1可上调$CD8^+$ T细胞表面的TIM-3,进而与髓源性抑制性细胞(MDSC)上的Galectin-9结合产生获得性耐药[28]。在小鼠卵巢癌模型中,抗CTLA-4或抗PD-1可诱导$CD8^+$ T细胞上LAG3的表达[29];在接受抗CTLA-4治疗的前列腺癌患者中,M2型

肿瘤相关巨噬细胞(TAM)表达VISTA增加[30],VISTA与其配体结合后可抑制效应T细胞的增殖和活化、诱导Treg细胞的分化[31]。

1.3 TME层面

TME是活化$CD8^+$ T细胞杀伤肿瘤的主要场所。然而,位于TME中的肿瘤细胞、免疫抑制细胞(MDSC、TAM、Treg细胞)等,以及这些细胞所产生的抑制性细胞因子共同组成免疫抑制性微环境,在诱导抗肿瘤免疫耐受及免疫治疗耐药中发挥关键作用。

1.3.1 免疫抑制性细胞增多 TME中的免疫抑制性细胞主要包括Treg细胞、TAM和MDSC等。这些免疫抑制性细胞通过表达共抑制分子、分泌免疫抑制性因子等途径抑制$CD8^+$ T细胞的活化、增殖及杀伤功能,最终导致肿瘤细胞免疫逃逸。Treg细胞可通过表达CD25竞争性结合IL-2、分泌IL-10、TGF-β等途径抑制效应$CD8^+$ T细胞的增殖和活化,从而促进免疫逃逸,导致免疫治疗耐药[32-33]。新近研究[34]表明,Treg细胞高表达PD-1,而$PD\text{-}1^+CD8^+$ T细胞与$PD\text{-}1^+$Treg细胞在肿瘤内的平衡决定了PD-1抗体的疗效。肿瘤浸润性TAM可通过分泌IL-6、IL-10、CCL17、CCL22等因子趋化Treg细胞抑制效应$CD8^+$T细胞的功能诱导免疫治疗耐药[35]。此外,TAM还可以通过产生类二十烷酸、犬尿氨酸等代谢产物诱导$CD8^+$ T细胞免疫抑制[36]。MDSC可通过分泌前列腺素E2(PGE2)、表达ARG1和分泌TGF-β等多种途径抑制效应$CD8^+$ T细胞的功能[37-38]。

1.3.2 抑制性细胞因子增多 TME中抑制性细胞因子增多是导致免疫治疗耐药的重要原因。肿瘤细胞通过分泌CCL5、CCL7、CXCL8和CXCL12等趋化因子招募MDSC及Treg细胞等免疫抑制细胞进入肿瘤,这些免疫抑制细胞进一步产生免疫抑制性细胞因子如TGF-β、IL-6等,抑制$CD8^+$ T细胞功能,诱导免疫治疗耐药[39]。另有报道[40]显示,与抗PD-1敏感患者相比,抗PD-1耐药患者VEGF表达更高,VEGF可通过趋化Treg细胞、上调$CD8^+$ T细胞上的抑制性受体如PD-1、TIM3等抑制$CD8^+$ T细胞的浸润及杀伤功能,促进免疫治疗耐药。在“冷肿瘤”中,TGF-β表达异常升高,提示其可抑制$CD8^+$ T细胞向肿瘤内浸润。TGF-β还可通过诱导Foxp3的表达来促进并维持Treg细胞的分化,发挥免疫抑制作用,导致免疫治疗耐药[41]。

1.4 全身层面相关因素

1.4.1 肠道菌群失调 肠道微生物被称为人类的第二基因组。肠道微生物可通过诱导慢性炎症反应、释放毒素及影响激素水平等多种方式参与包括乳腺癌、肝癌、胃癌、结直肠癌在内的多种肿瘤的发生、发展。近年的研究[42]发现,肠道微生物还可影响肿瘤免疫治疗的疗效。肠道内富含双歧杆菌、肠球菌的患者更容易从免疫治疗中获益[43],移植脆弱拟杆菌可增加对抗CTLA-4治疗的响应性[44]。而在黑色素瘤中,肠道微生物多样性减少与抗PD-1疗效不佳密切相关[45]。此外,抗生素的使用会诱发肠道菌群失调,最终促进免疫治疗耐药的发生[46]。

1.4.2 贫血 贫血是晚期肿瘤最常见的并发症,初诊肿瘤患者中贫血比例高达40%。据报道[47],合并贫血的肿瘤患者难以从抗PD-1治疗中获益,贫血是阻碍免疫检查点抑制剂(ICI)疗效的独立因素。接受免疫治疗的胃癌及NSCLC临床回顾性研究发现,贫血患者的中位PFS及OS均显著低于不贫血的患者[48-49]。近年来,贫血在诱导免疫耐受以及免疫治疗抵抗的作用机制逐渐得到认识。研究[50]发现,肿瘤患者合并贫血状态下,为满足机体的造血需求,弥补骨髓造血功能的不足,肿瘤会重新启动髓外造血,蓄积一群$CD45^+$的红系前体细胞($CD45^+$EPC);该群$CD45^+$EPC失去红系发育潜能,在GM-CSF作用下转向分化为具有更强免疫抑制功能的红系来源髓系细胞(erythroid-derived myeloid cell,EDMC)。小鼠体内外实验证实,EDMC可抑制$CD8^+$ T细胞的功能,促进肿瘤进展,参与免疫治疗抵抗。在多个独立临床队列中发现,EDMC/活化效应$CD8^+$ T细胞(ActCD8)比例较高的肿瘤患者往往对免疫治疗耐药,提示贫血诱导的EDMC是免疫治疗耐药的机制之一[47]。

2 应对策略

2.1 肿瘤细胞层面

2.1.1 促进肿瘤抗原释放 促进肿瘤抗原释放是提高免疫治疗疗效的重要途径之一。研究表明,化疗可引起免疫原性细胞死亡(immunogenic cell death,ICD),上调HLA-A、-B及-C的表达,促进免疫应答。在复发/难治性经典霍奇金淋巴瘤中,地西他滨联合卡瑞利珠单抗可将卡瑞利珠单抗治疗的CR率由32%提高至71%[51]。放疗可增加损伤相关分子模式(damage-associated molecular pattern,DAMP)释放、增加肿瘤细胞MHC-Ⅰ类分子的表达,进而增强$CD8^+$ T细胞的杀伤能力。PEMBO-RT研究[53]显示,放疗联合帕博利珠单抗可将免疫单药客观缓解率从18%提高至36%[52]。溶瘤病毒治疗是另一种促进肿瘤抗原释放的方法,其可诱发$CD8^+$ T细胞对肿瘤新抗原的特异性免疫反应,克服免疫治疗耐药。

2.1.2 促进肿瘤抗原提呈 联合应用低剂量的DNA甲基转移酶抑制剂地西他滨可以通过促进MHC复合物的表达,改善肿瘤抗原提呈,增强免疫治疗疗效,为MSS及pMMR的结直肠癌患者带来福音[54]。在晚期

黑色素瘤中，Toll样受体激动剂SD-101联合帕博利珠单抗可通过促进肿瘤内DC的浸润增强抗原提呈，提高免疫治疗疗效[55]。阳离子纳米级金属-有机框架可促进肿瘤抗原提呈、促进DC成熟，与ICI联合可协同抗癌，联合治疗组肿瘤消退率可达97%[56]。

2.1.3　恢复对IFN-γ信号通路的敏感性　临床前研究[57]结果显示肿瘤内应用STING激活剂可诱导IFN-γ的产生，启动适应性免疫应答，从而增强免疫治疗的疗效。在针对晚期实体瘤或淋巴瘤的Ⅰ期临床试验[55]中，STING激动剂MK-1454与帕博利珠单抗联用可获得24%的ORR。TLR-9激动剂SD-101可通过动员NK细胞和提高肿瘤内CXCL9和CXCL10的水平，从而激活固有和适应性免疫应答，克服JAK1/2敲除引发的免疫治疗耐药。

2.2　促进CD8$^+$T细胞浸润并增强其细胞功能

2.2.1　过继T细胞治疗　过继性回输体外扩增的肿瘤浸润淋巴细胞(TIL)和CAR-T细胞是将“冷肿瘤”转变为“热肿瘤”的有效方法。一项TIL联合纳武利尤单抗治疗晚期NSCLC的单臂Ⅰ期临床试验[58]发现，在13名可评估的患者中有2名患者获得了CR。CAR-T细胞免疫疗法在治疗血液系统恶性肿瘤方面取得了巨大成功，但其在实体瘤中的临床疗效却远不如人意，主要障碍为包括PD-1介导的免疫抑制及CAR-T细胞向肿瘤内浸润障碍。因此，通过联合ICI和CAR-T细胞治疗可达到协同抗瘤效应[59-60]。此外，2021年研究[61]发现嗜酸性粒细胞的缺失是导致CAR-T细胞肿瘤内浸润减少的重要机制之一，通过放疗增加嗜酸性粒细胞的比例可促进CAR-T细胞向肿瘤组织的浸润，有效控制肿瘤进展[62]。

2.2.2　促进记忆性CD8$^+$T细胞的形成　肿瘤内浸润的效应CD8$^+$T细胞决定了初始免疫治疗的反应性，而记忆性CD8$^+$T细胞才是维持长期疗效的关键[63]。研究[64]表明，IL-15不仅可刺激CD8$^+$T细胞的活化，还可维持和扩增记忆性CD8$^+$T细胞。纳武利尤单抗联合IL-15激动剂ALT-803治疗转移性NSCLC的Ⅰ期临床试验安全性可耐受，联合治疗效果期待后续的研究报道[65]。

2.2.3　抗血管治疗　CD8$^+$T细胞浸润不足与肿瘤血管异常密切相关。应用抗血管生成药物使肿瘤血管正常化，可改善CD8$^+$T细胞在肿瘤内的浸润。美国FDA已批准贝伐珠单抗联合阿替利珠单抗及化疗用于一线治疗无驱动基因突变的转移性NSCLC[66]。一项信迪利单抗联合安罗替尼一线治疗晚期NSCLC的Ⅰ期临床研究[67]显示，总入组的22名患者中，16名患者达到部分缓解，客观缓解率为72.7%，疾病控制率为100.0%。

2.2.4　联合放疗　PACIFIC研究结果[68]显示，对于不可切除的Ⅲ期NSCLC患者，放化疗联合纳武利尤单抗免疫治疗可获得持续OS及PFS获益。放疗引起的免疫应答不仅涉及到促进抗原的释放增加，还包括诱导CD8$^+$T细胞向肿瘤内的浸润。放疗后嗜酸性粒细胞增多引起的CXCL9及CXCL10分泌增加被认为是放疗募集CD8$^+$T细胞的新发现机制[62]。

2.2.5　联合免疫治疗　CD8$^+$T细胞表面除了表达PD-1以外，还会表达其他多种负性免疫调控作用的分子，如LAG-3、TIM-3及TIGIT等[69]。在小鼠卵巢癌模型中，单独抑制LAG-3可能触发PD-1、CTLA-4和TIM-3的表达升高，从而导致免疫治疗耐药。因此，联合不同类型的ICI可能获得协同抗瘤效果。抗PD-1联合抗TIM-3或抗TIGIT治疗可获得更好的临床疗效[70-71]，且抗TIM-3、抗PD-1及抗LAG-3抗体的联合三联阻断的抑瘤效果远大于任意两种组合[72]。

2.2.6　增强T细胞共刺激信号　共刺激分子4-1BB、OX-40和CD40由活化的T细胞、NK细胞、B细胞及DC表达，激活共刺激分子可以极大地促进CD8$^+$T细胞的增殖和活化。4-1BB激动剂已在多种肿瘤模型中被证明可增强CD8$^+$T细胞的功能，B7-H3×4-1BB双特异性抗体也正在研发中[73]。OX-40具有与4-1BB相似的功能，全球已有十余款OX-40激动剂迈入临床试验阶段。ICOS信号通路活化可促进组织驻留记忆性CD8$^+$T细胞的产生，从而获得持续抗肿瘤作用[74]。ICOS激动剂相关临床研究也正在开展。

2.3　逆转肿瘤免疫抑制微环境

2.3.1　靶向免疫抑制性细胞　鉴于免疫抑制性细胞对免疫治疗疗效的负面影响，目前已有大量研究集中于如何减少免疫抑制性细胞的浸润或抑制其功能，从而提高免疫治疗疗效。CXCR2-CXCL5/CXCL8、CXCR4-CXCL12及CCR5-CCL5等信号轴在MDSC的募集中发挥重要作用，靶向上述趋化因子受体可抑制TME中MDSC的浸润。已证实，CXCR4拮抗剂BL-8040可显著减少胰腺癌中MDSC的浸润，CXCR4及CXCR2的阻断剂与抗PD-1抗体具有协同抗癌作用[75-76]。研究[77]表明，补体C5a可通过促进MDSC表达ROS、iNOS及Arg-1增强其免疫抑制活性，联合C5a/C5aR抑制剂与ICI治疗有望提高免疫治疗疗效。

使用CD25受体抑制剂αCD25-m2a可以显著减少CD25$^+$Treg细胞的浸润，在抗PD-1治疗前使用αCD25-m2a可使78.6%的小鼠肿瘤消退[78]。

靶向CSF-1和/或其受体(CSF-1R)是消除M2型TAM的有效策略[79]。在胰腺癌中，CSF-1R阻断联合抗PD-1或CTLA-4抗体可提高免疫治疗疗效、促进肿瘤消退[80]。此外，肿瘤细胞内高表达补体C3，其裂解产

物C3a可通过C3a-C3aR-PI3Kγ途径调控TAM向M2型极化,从而抑制$CD8^+$T细胞免疫应答。C3缺陷型小鼠对ICI治疗敏感性显著增加,因此,靶向肿瘤细胞中的C3或可能逆转免疫治疗耐药[81]。

2.3.2 细胞因子 在转移性尿路上皮癌中,抗TGF-β联合抗PD-L1治疗可显著提高肿瘤内效应$CD8^+$T细胞比例,增强免疫治疗疗效[82]。PD-L1/TGF-β双靶点融合蛋白M7824在I期临床试验[83]中显示出令人鼓舞的临床疗效,被视为多种难治性癌症的新型免疫治疗策略,但近期多项相关临床研究均以失败告终。IL-2激动剂NKTR-214联合纳武利尤单抗治疗转移性尿路上皮癌的ORR为35%、CR为19%[84];但在2022年ESMO会议中,黑色素瘤、肾癌两项Ⅲ期临床数据显示,联合治疗未表现出协同抗癌作用。新近研究[85]证实,IL-15激动剂NIZ985可有效提高胰腺肿瘤组织中效应$CD8^+$T细胞比例,增强其对免疫治疗的敏感性。针对IL-8及IL-10的调节制剂联合免疫治疗方案正在研究中。

2.4 调节患者全身状态

2.4.1 调节肠道菌群 研究[43]表明,将免疫治疗有效患者的肠道微生物移植到无菌小鼠身上,可明显提高其对免疫治疗的响应性。一项评估粪便微生物群移植联合抗PD-1抗体治疗$PD\text{-}1^+$难治性黑色素瘤患者的安全性和有效性的临床研究结果[86]显示,15名患者中有6名取得了临床获益,获益者肠道微生物丰度增加,$CD8^+$T细胞活性增强。上述研究提示,改善肠道微生物的组成有可能改善肿瘤免疫治疗耐药。此外,在免疫治疗的临床应用中还应密切监控或限制抗生素的使用。使用丁酸菌减轻接受抗生素治疗患者肠道微生物失调的影响或有益于免疫治疗[87]。

2.4.2 改善患者贫血状态 重组人促红细胞生成素(rhEPO)和促红细胞生成刺激剂等治疗手段虽然能有效改善贫血,但在合并贫血的肿瘤患者中并未延长癌症患者生存期,其可能原因在于这些治疗手段加速了$CD45^+$EPC的生成,且被肿瘤利用于促肿瘤的髓系细胞生成[47]。靶向清除EDMC或抑制$CD45^+$EPC重编程可能提供一种有效的ICI联合治疗策略,以提高ICI的肿瘤治疗疗效。迫切需要阐明肿瘤阻止$CD45^+$EPC向红系发育的分化机制,开发相应的药物用于治疗肿瘤相关性贫血,通过减少EDMC生成而提高免疫治疗的疗效。

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尽管以抗PD-1/PD-L1抗体为代表的免疫治疗为抗肿瘤治疗带来了划时代的变革,但高耐药率的发生成为阻碍其临床疗效发挥的最大障碍。深入了解免疫治疗耐药的发生机制对于制定合理的应对策略至关重要。随着越来越多免疫治疗反应性和抵抗性机制被发现,如何综合评估影响免疫治疗疗效的因素和针对性地制定应对策略成为困扰临床医师的一大难题。2016年,BLANK等[88]就根据肿瘤-免疫交互作用绘制了肿瘤免疫图谱,提出了影响免疫治疗的7大因素。近日,CDMBES等[89]绘制了包括12种不同类型肿瘤的泛肿瘤免疫特征图谱,为深入理解肿瘤与免疫细胞间的相互作用提供了重要思路。但鉴于免疫耐药机制错综复杂,拮抗单一机制不足以实现持久的免疫应答,因此需结合肿瘤类型、肿瘤转录图谱及肿瘤免疫图谱等进行个性化治疗的选择。例如,对于“冷肿瘤”可采用CAR-T细胞或TIL联合ICI治疗,而对于“热肿瘤”可采用抗血管生成药物联合ICI治疗等。未来期望研发程序化算法通过综合评估肿瘤转录图谱、肿瘤免疫图谱、微生物组学,并结合免疫治疗过程中新生抗原演变[90]等制定“个体化”精准联合治疗策略。相信随着肿瘤免疫学、微生物组学及生物信息学的飞速发展,各种新的治疗策略将被积极探讨,有望为克服免疫治疗耐药提供新的方向。

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