

PD-1的免疫调控机制与肿瘤免疫治疗研究进展

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摘要: 程序性死亡蛋白1(PD-1)是免疫调控的关键分子,除抑制T细胞活化的经典功能外,新近研究发现其在巨噬细胞、NK细胞及肿瘤细胞中均发挥重要作用。本文系统阐述了PD-1在不同免疫细胞亚群中的调控机制,并且进一步讨论了肿瘤细胞自身表达PD-1的现象及其在肿瘤细胞中的功能,即肿瘤细胞固有PD-1通过非免疫途径介导肿瘤双向调控:一方面通过维持肿瘤干细胞干性、促进肿瘤细胞增殖等发挥促癌作用,另一方面可产生抑癌作用。尽管PD-1/PD-L1抑制剂在多种肿瘤中展现出差异化疗效,但仍面临客观缓解率不均一、耐药及超进展等临床挑战。本文结合上述机制与临床研究进展,进一步探讨了PD-1靶向治疗的联合策略与新型药物研发,旨在为开发靶向肿瘤细胞固有PD-1的精准疗法及优化免疫治疗策略提供理论依据。

关键词: PD-1;肿瘤细胞固有PD-1;免疫治疗耐药;联合治疗;非免疫功能

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Immune regulatory mechanisms of PD-1 and advances in tumor immunotherapy research

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Abstract: Programmed cell death protein 1 (PD-1) has emerged as a pivotal immunoregulatory molecule, whose influence extends far beyond its conventional role in inhibiting T cell activation. Recent groundbreaking research has uncovered its critical involvement in modulating the functions of various immune cell subsets, including macrophages and natural killer (NK) cells, and surprisingly, its direct expression and functional significance within tumor cells themselves. This comprehensive review aims to systematically elucidate the multifaceted regulatory mechanisms of PD-1 across diverse immune cell populations and critically examine the intriguing phenomenon of intrinsic PD-1 expression in tumor cells. We delve into how this tumor-intrinsic PD-1 can exert dual regulatory effects—either promoting or suppressing tumorigenesis—via non-immune pathways, such as influencing tumor stem cell properties, cellular proliferation, and apoptosis. Despite the transformative impact of PD-1/PD-L1 inhibitors in cancer therapy, their efficacy varies significantly across different tumor types, highlighting the complex interplay within the tumor microenvironment and the emergence of resistance mechanisms. This review synthesizes current understanding of these differential therapeutic outcomes and addresses key challenges, including primary and acquired resistance, and the risk of hyperprogressive disease (HPD). We discuss various resistance mechanisms, such as antigen presentation defects, the formation of suppressive tumor microenvironments, the activation of alternative immune checkpoints, and oncogenic pathway abnormalities. Furthermore, we explore innovative strategies to overcome these limitations, including combination therapies involving PD-1 antibodies with anti-angiogenic drugs, LAG-3 inhibitors, or bispecific antibodies targeting PD-1/VEGF, which hold immense promise in enhancing anti-

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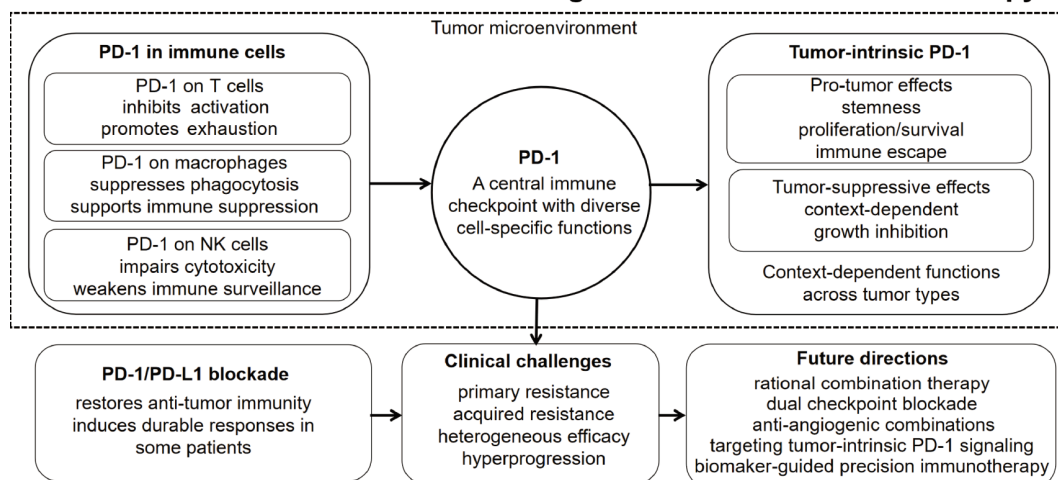
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tumor immunity and combating resistance. The review also highlights emerging research directions, particularly targeting tumor-intrinsic PD-1 with small molecule inhibitors to inhibit tumor stemness and proliferation via downstream signaling pathways. We emphasize the potential of multi-modal approaches combining PD-1 antibodies with small molecule inhibitors or mTOR pathway inhibitors to synergistically modulate both tumor cells and the immune microenvironment. Moving forward, a deeper understanding of the PD-1 signaling networks within specific cancer types and cell subtypes is crucial. We propose that future research should focus on deciphering these intricate networks to develop highly specific targeted therapies and combination regimens, coupled with the establishment of predictive biomarker systems. This approach will be instrumental in advancing tumor immunotherapy towards more broad-spectrum, efficient, and precise clinical applications, ultimately benefiting a wider patient population by overcoming current therapeutic hurdles and fostering sustained anti-tumor responses.

Multifaceted roles of PD-1 in immune regulation and tumor immunotherapy



Key words: PD-1; tumor-intrinsic PD-1; immunotherapy resistance; combination therapy; non-immune function

1 引言

程序性细胞死亡蛋白1(programmed cell death protein 1, PD-1, 又称CD279)是关键免疫检查点分子,自20世纪90年代被发现以来,已成为肿瘤免疫治疗领域的核心靶点^[1]。PD-1主要表达于活化T细胞表面,通过与配体PD-L1(programmed death ligand 1)或PD-L2(programmed death 1 ligand 2)结合,传递抑制性信号,从而维持外周免疫耐受并防止自身免疫反应的发生^[2]。近年来,以PD-1/PD-L1为靶点的免疫疗法在多种癌症治疗中取得显著进展,但其总体有效率仍限于20%~40%,且在不同肿瘤类型及个体间差异显著^[3]。因此,深入探究PD-1的调控机制对提升临床疗效、扩大受益人群具有重要意义。与此同时,联合治疗策略及新型药物(如PD-1/VEGF双特异性抗体)的探索为克服耐药、提高治疗响应提供了新方向。近年研究还进一步证实,PD-1的表达具有广泛细胞谱系特征,除经典T细胞外,在巨噬细胞、自然杀伤(NK)细胞^[4]以及部分肿瘤细胞^[5]中亦有表达。尤为重要的是,肿瘤细胞固有PD-1可经mTOR-mtROS等信号通路直接促进肿瘤生长^[5],这

一发现突破了PD-1作为纯免疫抑制受体的传统认知框架。目前,PD-1在不同免疫细胞亚群中的表达谱系已有初步描绘,但其在各类细胞中的精确调控网络及功能异质性仍待系统解析。为全面理解PD-1在肿瘤免疫中的多维功能,并为开发更精准的免疫治疗策略奠定理论基础,本文系统综述PD-1在适应性免疫细胞与天然免疫细胞中的表达动态与功能差异,重点探讨肿瘤细胞固有PD-1的生物学特性、其在免疫逃逸与治疗抵抗中的作用机制,以及PD-1信号通路的细胞特异性调控网络对免疫检查点阻断疗法响应的影响,以期拓展靶向治疗新视角提供理论支撑。

2 PD-1简介

PD-1又称为CD279,是一种抑制性共刺激分子,由日本免疫学家本庶佑(Tasuku Honjo)及其团队首次发现,因其在程序性细胞死亡过程中表达上调,故命名为“程序性死亡蛋白1”(PD-1)^[1]。PD-1主要在活化的T细胞、B细胞、髓系细胞、自然杀伤细胞中表达,并通过与程序性细胞死亡1配体(PD-L1或

PD-L2)结合调控人体免疫应答^[2]。PD-1由288个氨基酸构成,包括胞外区、跨膜区和胞内区三部分。其中,胞外区包含免疫球蛋白可变区(IgV)样结构域,跨膜区起到连接和锚定作用,而胞内区则包含C端和N端氨基酸残基,且存在2个独立的磷酸化位点,分别是免疫受体酪氨酸抑制基序(immunoreceptor tyrosine based inhibitory motif, ITIM)和免疫受体酪氨酸转换基序(immunoreceptor tyrosine based switch motif, ITSM)^[3],是PD-1传递抑制信号,发挥免疫抑制功能的重要结构基础(图1)。PD-1轴能负向调控T细胞活化,精准把控T细胞反应的强度与持续时长,从而在生理及病理状态下,有效限制组织损伤,维护自我耐受^[4]。

3 PD-1的免疫调控机制

3.1 PD-1在T细胞中的功能

3.1.1 抑制T细胞活化

T细胞是适应性免疫的核心执行者,也是PD-1的经典表达细胞,在细胞免疫与免疫调节中发挥关键作用^[6-9]。其完全活化依赖于双信号:第一信号由抗原肽-MHC复合物与T细胞受体(TCR)结合所提供;第二信号来源于抗原呈递细胞(APC)表面的共刺激分子与TCR的相互作用,后者依据功能可分为激活型与抑制型^[10,11]。PD-1属于共抑制信号分子,对T细胞活化具有重要的负向调控功能^[9]。PD-1的免疫抑制作用主要依赖于胞内区Src同源2结构域蛋白酪氨酸磷酸酶(SHP2)的介导^[12]。SHP2由593

个氨基酸构成,包含N端SH2(N-SH2)、C端SH2(C-SH2)结构域、蛋白酪氨酸磷酸酶催化结构域及C端酪氨酸磷酸化位点(Tyr542、Tyr580)^[13]。当PD-1与配体PD-L1结合后,其胞内ITIM和ITSM发生磷酸化,进而募集SHP2至细胞膜。其中,ITSM以高亲和力结合C-SH2结构域,而ITIM与N-SH2结构域结合,诱导后者从催化中心解离,从而解除自抑制、激活SHP2磷酸酶活性^[14,15]。活化的SHP2进而对TCR近端信号分子(如ZAP70、CD3)进行去磷酸化,抑制下游MAPK与PI3K通路,导致IL-2、IFN- γ 等关键细胞因子的合成与分泌减少,最终削弱T细胞功能^[16]。值得关注的是,既往研究多强调PD-1对TCR信号通路的直接抑制;而近期证据表明,PD-1/SHP2轴主要通过介导共刺激受体CD28的去磷酸化来发挥抑制作用,提示共刺激通路在效应T细胞功能调节及PD-1/PD-L1阻断治疗响应中具有核心地位^[17](图2a)。

3.1.2 促进T细胞耗竭

T细胞耗竭(T cell exhaustion)是指在肿瘤微环境或慢性感染等持续性抗原刺激下,T细胞逐渐丧失效应功能及自我更新能力的一种功能失调状态^[18]。其典型特征包括效应细胞因子(如IL-2、TNF- α 、IFN- γ)分泌减少、抑制性受体(如PD-1、LAG-3、TIGIT)持续高表达与共表达,以及转录因子NFAT、TOX、BATF等表达失调^[18,19]。PD-1是T细胞耗竭的核心驱动因子,其与PD-L1结合后传递抑制信号,不仅直接抑制T细胞功能,亦促进耗竭表型的巩固,从而防止免疫应答过度活化^[12](图2a)。该

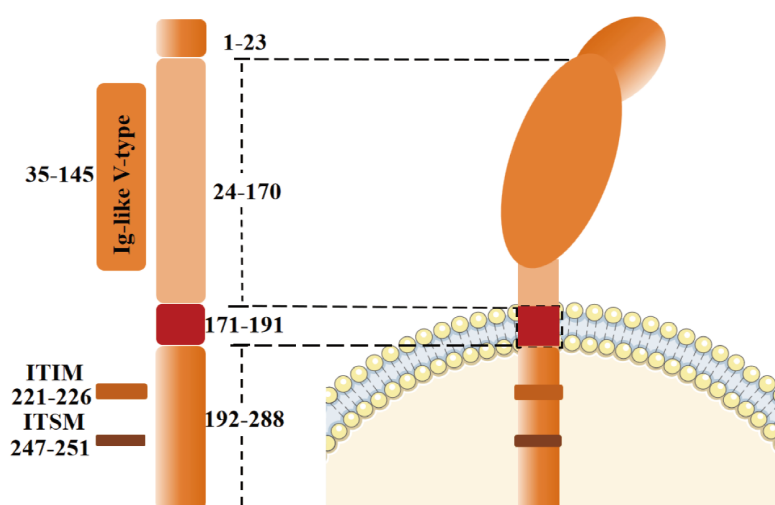


图1 PD-1蛋白一级结构示意图

Figure 1 Schematic diagram of the primary structure of the PD-1 protein

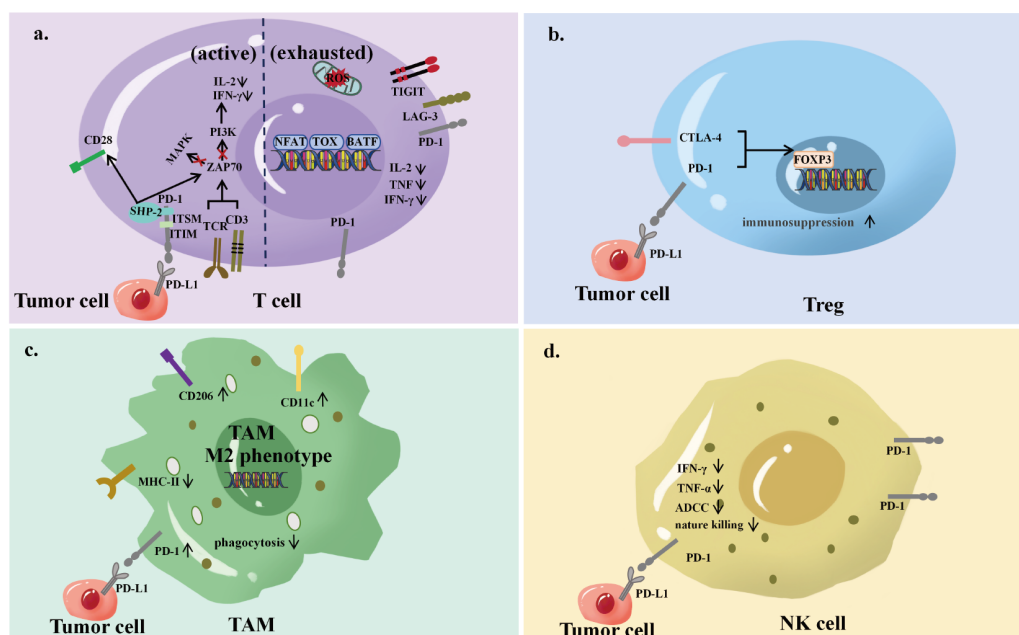


图2 PD-1对不同免疫细胞的调控

PD-1在T细胞、调节性T细胞、肿瘤相关巨噬细胞、NK细胞中表达上调。a: PD-1与肿瘤细胞表面PD-L1结合后,其胞内区ITSM和ITIM结构域发生磷酸化,进而招募并激活SHP2磷酸酶。活化的SHP2介导TCR近端信号分子CD3和ZAP70去磷酸化,并抑制CD28共刺激信号,从而削弱下游TCR信号通路及IL-2等细胞因子的分泌,最终导致T细胞功能抑制。此外,PD-1信号也参与促进T细胞耗竭(Tex)。Tex细胞表现为效应细胞因子(如IL-2、TNF- α 、IFN- γ)分泌减少、抑制性受体(如PD-1、LAG-3、TIGIT)共表达上升,以及转录因子NFAT、TOX、BATF表达失调和代谢异常。PD-1/PD-L1通路通过传递抑制信号,直接抑制T细胞效应功能,并在持续抗原刺激下推动T细胞功能衰退,限制过度免疫反应。b: PD-1/PD-L1信号通过抑制天冬氨酰内肽酶介导的FOXP3蛋白降解,稳定FOXP3表达,进而协同CTLA-4增强Tregs的免疫抑制功能,维持免疫耐受状态。c: PD-1促进TAMs向M2表型极化,表现为CD206、CD11c高表达和MHCII低表达,导致其吞噬功能下降,从而促进肿瘤进展。d: 活化的NK细胞高表达PD-1,其与肿瘤细胞表面PD-L1结合后,可抑制NK细胞脱颗粒(如穿孔素和颗粒酶B释放)及IFN- γ 、TNF- α 等细胞因子的分泌,从而削弱其对肿瘤的杀伤能力,促进免疫逃逸。

Figure 2 Regulation of various immune cells by PD-1

PD-1 is upregulated in T cells, regulatory T cells, tumor-associated macrophages, and NK cells. a: Upon binding to PD-L1 on the surface of tumor cells, the ITSM and ITIM domains of PD-1 undergo phosphorylation, which subsequently recruits and activates the SHP2 phosphatase. Activated SHP2 mediates the dephosphorylation of TCR-proximal signaling molecules CD3 and ZAP70 and inhibits CD28 co-stimulatory signaling, thereby attenuating downstream TCR signaling pathways and the secretion of cytokines such as IL-2, ultimately leading to T cell functional suppression. In addition, PD-1 signaling also participates in promoting T cell exhaustion (Tex). Tex cells are characterized by reduced secretion of effector cytokines (such as IL-2, TNF- α , and IFN- γ), increased co-expression of inhibitory receptors (such as PD-1, LAG-3, and TIGIT), as well as dysregulation of transcription factors NFAT, TOX, and BATF and metabolic abnormalities. The PD-1/PD-L1 pathway directly suppresses T-cell effector function by transmitting inhibitory signals and promotes T-cell functional decline under sustained antigen stimulation, thereby limiting excessive immune responses. b: PD-1/PD-L1 signaling stabilizes FOXP3 expression by inhibiting aspartyl endopeptidase-mediated degradation of the FOXP3 protein, thereby synergizing with CTLA-4 to enhance the immunosuppressive function of Tregs and maintain a state of immune tolerance. c: PD-1 promotes the polarization of TAMs toward the M2 phenotype, characterized by high expression of CD206 and CD11c and low expression of MHCII, leading to reduced phagocytic function and thereby promoting tumor progression. d: Activated NK cells highly express PD-1; upon binding to PD-L1 on the surface of tumor cells, PD-1 signaling suppresses NK cell degranulation, including the release of perforin and granzyme B, as well as the secretion of effector cytokines such as IFN- γ and TNF- α , thereby weakening their antitumor cytotoxic capacity and promoting immune evasion.

现象在肿瘤微环境与慢性病毒感染中广泛存在。研究显示,在HIV感染者耗竭CD8⁺T细胞中,PD-1信号通过上调BATF表达,抑制T细胞增殖及IL-2、IFN- γ 等细胞因子的分泌^[20]。在肿瘤模型中,PD-1在耗

竭CD8⁺T细胞中的持续高表达显著削弱其抗原特异性杀伤能力^[21]。值得注意的是,PD-1介导的T细胞抑制具有一定可逆性,帕博利珠单抗等PD-1单抗可在部分患者中重新激活耗竭CD8⁺T细胞^[21,22],但

受表观遗传等因素限制,其功能无法完全恢复^[23]。除PD-1外,其他抑制性受体也参与调控T细胞耗竭。研究发现,LAG-3通过维持转录因子TOX(thymocyte selection-associated high mobility group box)表达,调控CD94/NKG2抑制通路,进而影响耗竭CD8⁺T细胞的自然杀伤受体表达与细胞毒性^[24]。LAG-3与PD-1在CD8⁺T细胞上具有协同抑制作用,共同促进耗竭表型并抑制IFN- γ 自分泌依赖的抗肿瘤免疫^[25]。联合阻断LAG-3与PD-1可协同增强T细胞功能,促使细胞毒性相关基因上调、耗竭相关基因下调,从而更有效地恢复抗肿瘤免疫应答^[26]。此外,PD-1信号与TCR刺激、微环境压力共同诱导肿瘤浸润T细胞发生线粒体功能障碍,导致生物能量代谢失衡,进而加剧T细胞功能衰竭^[27]。综上,PD-1在T细胞耗竭中居于核心地位,但与其与LAG-3等协同抑制受体、表观遗传调控及代谢紊乱共同构成复杂网络,提示多靶点干预策略可能是重建T细胞功能的关键。

3.1.3 促进调节性T细胞免疫抑制

调节性T细胞(regulatory T cells, Tregs)是CD4⁺T细胞中具有免疫抑制功能的亚群,通过维持自身免疫耐受在免疫稳态中发挥关键作用^[28]。Tregs特征性表达转录因子叉头框蛋白P3(FOXP3),并同时组成性表达PD-1与CTLA-4等抑制性受体^[29]。FOXP3不仅是Tregs的标志性分子,更在其细胞表型建立与功能维持中起核心作用^[30]。在稳态条件下,PD-1与CTLA-4在部分活化型FOXP3⁺Tregs中发挥协同调控功能^[31]。具体而言,PD-1与PD-L1结合后可抑制内吞溶酶体蛋白酶——天冬氨酰内肽酶对FOXP3的降解,从而间接稳定FOXP3蛋白水平,增强Tregs的免疫抑制能力^[32](图2b)。在发育层面,PD-1缺失会削弱Tregs的TCR信号转导,并促进胸腺细胞分泌IL-2,进而改变Tregs的发育微环境^[33]。在功能层面,PD-1对Tregs的调控呈现明显的背景依赖性:在肿瘤微环境(TME)中,PD-1阻断虽可恢复耗竭性CD8⁺T细胞功能,但同时可能增强PD-1⁺Tregs的免疫抑制活性^[34]。然而,PD-1缺失或抑制也可通过削弱Tregs的谱系稳定性与代谢适应性,从而增强机体抗肿瘤免疫力^[35]。其机制可能与PD-1缺失导致PI3K-AKT信号减弱,进而增强Tregs抑制能力有关^[36]。值得注意的是,PD-1阻断介导的肿瘤消退主要依赖于对效应CD8⁺T细胞的重新激活,而非对Tregs的直接作用^[34]。在自身免疫背景下,如非肥胖糖尿病模型

中,Tregs特异性缺失PD-1可增强其抑制功能,缓解实验性自身免疫性脑脊髓炎并阻止糖尿病发生^[36],提示PD-1在自身免疫病中负向调控Tregs功能。

在肿瘤免疫治疗中,PD-1/PD-L1阻断疗法可影响Tregs的增殖与功能,甚至诱导耐药及超进展性疾病(HPD)^[37]。例如,在转移性透明细胞肾细胞癌中Tregs的PD-1表达与抗PD-1治疗耐药相关,提示联合靶向Tregs可能提升疗效^[38]。相反,在部分胃癌患者中,抗PD-1单抗治疗可促进PD-1⁺Tregs增殖,增强其免疫抑制活性,进而诱发HPD^[39]。此外,在黑色素瘤模型及患者中,PD-1抑制剂可激活CD8⁺T细胞分泌IL-2,进而通过IL-2/ICOS轴上调Tregs抗凋亡蛋白ICOS表达,导致Tregs扩增;而干预该轴可增强PD-1阻断疗效^[40]。综上,PD-1通过调控Tregs的发育、功能稳定性及代谢适应能力,在肿瘤免疫与自身免疫中扮演双重角色。尽管PD-1/PD-L1阻断疗法具有显著临床价值,但仍需重视其可能引发的Tregs介导的耐药与HPD风险,未来需探索精准联合策略以优化治疗获益。

3.2 PD-1在巨噬细胞中的功能

巨噬细胞作为先天免疫系统的核心组分,具有高度可塑性与功能多样性,在免疫防御、组织稳态及疾病进展中发挥关键作用^[41]。肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)是TME中最丰富的免疫细胞群之一,其极化状态与肿瘤进程密切相关^[42]。根据微环境信号的不同,TAMs可分为经典活化的M1型与替代活化的M2型:M1型具有抗肿瘤作用,而M2型则促进肿瘤生长、血管生成、转移及治疗耐药^[42]。近年研究发现,TAMs中PD-1表达水平与肿瘤恶性进展呈正相关。在结直肠癌小鼠模型中,TAMs的PD-1表达呈时间依赖性上升;临床样本分析进一步显示,PD-1⁺M2型TAMs的浸润程度与结直肠癌临床分期正相关^[43]。类似现象亦见于T细胞非霍奇金淋巴瘤与胃癌,其中TAMs的PD-1高表达被确立为独立预后不良因素^[44,45]。多项研究共同提示,PD-1在TAMs中的过表达是多种恶性肿瘤的共性特征,其表达强度与疾病恶性程度密切相关。

功能上,PD-1⁺TAMs表现出显著的M2型促肿瘤表型,其特征包括CD206与CD11c高表达、主要组织相容性复合体II类分子低表达等^[43](图2c)。PD-1信号促进巨噬细胞向M2型极化,该现象在结直肠

癌、非小细胞肺癌、皮肤T细胞淋巴瘤和胶质母细胞瘤等多种肿瘤中均得到验证^[43]。机制上,PD-1通过激活JAK2-STAT3信号通路干扰IFN- γ 信号转导,增强M2型极化,并显著抑制TAMs对肿瘤细胞的吞噬功能,从而促进肿瘤发展^[46]。此外,PD-1⁺TAMs在骨肉瘤中亦显示吞噬功能缺陷,进而加速肿瘤转移^[47]。这些结果表明,PD-1⁺TAMs通过抑制吞噬活性、调控极化状态及分泌免疫抑制因子,成为驱动肿瘤免疫逃逸的关键因素。临床前研究表明,PD-1/PD-L1阻断可恢复TAMs的吞噬功能,抑制肿瘤生长并延长荷瘤小鼠生存期^[43]。在T细胞非霍奇金淋巴瘤中,PD-1⁺TAMs通过抑制M1型极化及促进IL-10分泌,协同促进免疫抑制^[44]。临床数据进一步证实,胃癌组织中PD-1⁺TAMs的浸润水平与患者总体生存率负相关,提示其可作为潜在的预后标志物^[45,48]。

除TME影响外,代谢因素亦参与调控TAMs中PD-1表达。肥胖相关分子(如IFN- γ 、瘦素和胰岛素)通过mTORC1与糖酵解通路诱导TAMs表达PD-1,进而抑制其吞噬与抗原呈递功能;而PD-1阻断可逆转该效应,提升TAMs的糖酵解水平与T细胞激活能力^[49]。这一机制部分解释了肥胖人群肿瘤风险升高的原因,也提示PD-1抑制剂在肥胖相关肿瘤中的潜在治疗价值。综上所述,PD-1通过促进TAMs向M2型极化、抑制其吞噬功能及参与代谢调控,在塑造免疫抑制微环境中发挥重要作用,成为肿瘤免疫治疗中的重要调控靶点。

3.3 PD-1在自然杀伤细胞中的功能

自然杀伤细胞(NK细胞)是先天免疫系统的关键效应细胞,在肿瘤免疫监视中发挥核心作用,能够直接杀伤肿瘤细胞及病原体感染细胞^[50]。生理状态下,健康个体NK细胞通常不表达PD-1^[51];然而,在多种恶性肿瘤中,NK细胞表面PD-1的异常表达已被广泛报道。临床研究显示,PD-1⁺NK细胞在多发骨髓瘤、肾细胞癌、卡波西肉瘤、肝细胞癌、食管鳞状细胞癌、结直肠癌、卵巢癌、非小细胞肺癌及霍奇金淋巴瘤等患者的TME及外周血中显著富集^[52]。尤其在食管癌、肝癌与非小细胞肺癌患者中,肿瘤浸润NK细胞的PD-1表达水平与疾病进展及不良预后显著正相关^[53]。

功能上,PD-1在活化NK细胞中高表达,其与肿瘤细胞表面PD-L1结合后可抑制NK细胞脱颗粒(如

穿孔素与颗粒酶B释放)及其细胞毒性功能,从而削弱对肿瘤细胞的清除能力,促进免疫逃逸^[12](图2d)。在非小细胞肺癌患者中,肿瘤内PD-1⁺NK细胞相较于PD-1⁻NK细胞及外周血NK细胞表现出明显功能耗竭,表现为IFN- γ 、TNF- α 分泌减少,穿孔素与颗粒酶B释放受限,细胞毒性下降及凋亡敏感性增加^[54]。该PD-1依赖性功能耗竭机制在食管癌、肝癌及结直肠癌等消化道肿瘤中已被证实,PD-1/PD-L1信号通过抑制PI3K/AKT通路,削弱NK细胞的活化与抗肿瘤免疫功能^[53]。此外,PD-1还可通过跨细胞膜转移机制调控NK细胞功能。在白血病小鼠模型中,NK细胞与CD8⁺T细胞在吞噬肿瘤细胞过程中,经由信号淋巴细胞激活分子(SLAM)受体介导,可直接从白血病细胞获取PD-1,进而抑制NK细胞功能^[55]。该现象在克隆性浆细胞疾病患者临床样本中亦得到验证^[55]。PD-1/PD-L1阻断治疗可有效逆转NK细胞功能抑制。在慢性淋巴细胞白血病中,PD-1⁺NK细胞功能存在明显缺陷,而阻断PD-1信号可部分恢复其细胞毒性^[56]。临床前及临床研究进一步表明,抗PD-1/PD-L1单抗不仅能激活T细胞免疫应答,也可直接增强NK细胞的杀伤能力^[57]。该效应在人类白细胞抗原I类分子低表达或缺失的肿瘤(如经典霍奇金淋巴瘤)中尤为重要,提示NK细胞介导的固有免疫在免疫治疗中可能具有独立于T细胞的关键作用^[58]。综上,PD-1在NK细胞中的诱导性表达及其功能调控机制的明确,深化了对其在先天免疫与肿瘤免疫逃逸中作用的认知,也为基于NK细胞的免疫治疗策略提供了理论依据。

3.4 肿瘤微环境中不同免疫细胞PD-1信号的交互影响

在TME中,PD-1信号并非孤立作用于某一免疫细胞亚群,而是构成一个多细胞协同参与的复杂调控网络,共同调节适应性免疫与固有免疫应答。T细胞表面PD-1与PD-L1结合后,除直接抑制T细胞功能、促进其耗竭外^[12,18],亦通过改变细胞因子分泌谱(如IFN- γ 、IL-2等),间接影响巨噬细胞的极化方向与NK细胞的活化状态。例如,T细胞功能受抑导致IFN- γ 分泌减少,进而阻碍巨噬细胞向抗肿瘤M1表型极化,并削弱NK细胞的细胞毒性^[44,49]。同时,PD-1⁺TAMs通过分泌IL-10等抑制性细胞因子,进一步加剧T细胞耗竭并抑制NK细胞功能^[44],形成促进免疫逃逸的正反馈回路^[49]。此外,NK细胞功能下

降不仅削弱其对肿瘤细胞的直接杀伤作用,也降低其对T细胞的辅助激活能力,从而进一步加强TME中的免疫抑制状态^[53,57]。综上所述,PD-1信号通过多种免疫细胞间的交互作用,在TME中构建了一个协同促进肿瘤免疫逃逸的抑制性网络。深入解析该网络的组成与动态调控机制,对于发展能够整体重塑免疫微环境的PD-1靶向联合治疗策略具有重要指导意义。

4 PD-1在肿瘤细胞中的功能

传统观点认为,PD-1主要表达于T细胞,并通过与PD-L1结合抑制T细胞介导的抗肿瘤免疫反应^[2]。然而,近年来研究显示,PD-1也可在多种肿瘤细胞中固有表达,包括结直肠癌^[59]、甲状腺癌^[60]、胶质母细胞瘤^[61]、非小细胞肺癌干细胞样细胞群^[62]等。这一发现提示,PD-1/PD-L1轴除调控抗肿瘤免疫外,还可能直接参与肿瘤细胞内在信号转导。

肿瘤细胞固有PD-1的功能具有明显的肿瘤类型依赖性和信号通路依赖性。在多数报道中,肿瘤细胞PD-1表现出促癌作用。首先,PD-1可参与维持肿瘤干细胞特性。例如,在非小细胞肺癌肿瘤干细胞样亚群中,PD-1表达显著升高,并可通过激活mTOR信号、促进核糖体蛋白S6磷酸化,增强蛋白质合成、自我更新和细胞增殖^[62]。除维持干细胞样特征外,肿瘤细胞PD-1还可促进肿瘤细胞增殖、存活、迁移和转移。在Merkel细胞癌中,PD-1通过mTOR-mtROS通路增强肿瘤增殖^[5];在胶质母细胞瘤中,部分肿瘤细胞共表达PD-1与脑肿瘤起始细胞标志物,PD-1可通过招募SHP-2并激活NF-κB通路,促进肿瘤细胞增殖和自我更新^[61];在甲状腺癌中,PD-1过

表达与肿瘤分期和淋巴结转移相关,并可通过调控SHP2/Ras/MAPK通路促进细胞增殖与迁移^[60]。在三阴性乳腺癌中,肿瘤细胞PD-1被认为是YB-1的下游效应分子,可促进肿瘤生长和转移^[63]。在肝细胞癌中,PD-1与eIF4E及S6相互作用,激活mTORC1通路,促进肿瘤细胞存活与增殖^[64]。在黑色素瘤中,PD-1通过调控S6磷酸化驱动肿瘤生长,其敲除可显著抑制体内成瘤能力^[65]。此外,在胰腺导管腺癌中,PD-1能够以肝细胞生长因子依赖的方式激活MET信号,诱导上皮-间质转化,从而促进肿瘤进展;这一作用可在免疫缺陷背景下观察到,提示其具有免疫非依赖性的肿瘤细胞内在效应^[66]。

然而,肿瘤细胞PD-1并非普遍发挥促癌作用。在结直肠癌中,PD-1表达与较低病理T分期相关,其激活可抑制ERK1/2和p38磷酸化,从而阻滞细胞周期并抑制增殖^[59]。在部分非小细胞肺癌模型中,PD-1亦可通过抑制AKT和ERK1/2信号发挥抑癌作用,PD-1阻断反而可能增强肿瘤细胞存活和化疗耐受性^[67]。

因此,肿瘤细胞固有PD-1的生物学效应取决于肿瘤类型、细胞状态及下游信号网络(表1)。未来在评估PD-1/PD-L1靶向治疗时,应同时考虑免疫细胞PD-1和肿瘤细胞固有PD-1的表达与功能,以实现更精准的患者分层和治疗策略优化。

5 PD-1靶向治疗的研究进展

5.1 PD-1单抗的临床应用与耐药机制

针对PD-1/PD-L1轴的免疫检查点抑制剂(ICIs)通过阻断免疫检查点,重新激活T细胞介导的抗肿瘤免疫,增强免疫监视及肿瘤抑制作用,已在临床广泛

表1 PD-1在肿瘤中的功能概述
Table1 Overview of PD-1 function in tumors

癌种类型	PD-1角色	作用	参考文献
非小细胞肺癌	促癌	在肿瘤干细胞(CSCs)亚群中通过激活mTOR通路促进S6磷酸化,维持CSCs干性及自我更新	[62]
	抑癌	通过抑制AKT/ERK1/2信号阻滞细胞周期	[67]
甲状腺癌	促癌	通过去磷酸化SHP2-Tyr32激活Ras/MAPK,促增殖迁移	[60]
胶质母细胞瘤	促癌	在脑肿瘤起始细胞中通过SHP-2/NF-κB促进增殖和自我更新	[61]
三阴性乳腺癌	促癌	显著促进肿瘤生长和转移,YB-1是关键效应因子	[63]
Merkel细胞癌	促癌	激活mTOR-mtROS通路,促进肿瘤增殖	[5]
肝细胞癌	促癌	与eIF4E及S6相互作用促进其磷酸化,激活mTORC1通路,增强增殖和存活	[64]
黑色素瘤	促癌	通过调控S6磷酸化诱导肿瘤生长	[65]
胰腺导管癌	促癌	通过HGF依赖方式激活MET,诱导EMT并促进肿瘤进展	[66]
结直肠癌	抑癌	PubTbl cell与低pT分期相关;降低ERK1/2和P38磷酸化水平,抑制增殖	[59]

应用^[68]。作为ICIs的核心代表,PD-1单克隆抗体在多种恶性肿瘤中展现出差异化的疗效格局(表2)。在经典型霍奇金淋巴瘤中,Nivolumab与Pembrolizumab的客观缓解率(ORR)高达87%^[69],耐药较为罕见^[70],多与9p24.1/PD-L1基因缺失或JAK2/STAT通路突变相关^[71],超进展(HPD)发生率低于1%^[72]。在微卫星高度不稳定/错配修复缺陷(MSI-H/dMMR)转移性结直肠癌中,KEYNOTE-177 III期研究显示,一线Pembrolizumab治疗的ORR为43.8%,中位无进展生存期为16.5个月,显著优于化疗,该研究确立了其在MSI-H/dMMR结直肠癌一线治疗中的地位^[73]。其耐药机制可能与肿瘤突变负荷(TMB)降低、人类白细胞抗原I类分子表达缺失及抗原递呈障碍有关^[74],HPD发生率低于2%^[75]。在晚期黑色素瘤(KEYNOTE-006试验)中,Pembrolizumab单药治疗的ORR为33.7%^[76],耐药多与IFN- γ 信号通路突变(如JAK1/2缺失)相关,HPD发生率约为5%^[77]。对于PD-L1高表达($\geq 50\%$)的非小细胞肺癌,KEYNOTE-024研究中Pembrolizumab组ORR为46.1%,5年总生存率达31.9%,显著优于化疗^[78]。耐药常由EGFR/ALK驱动基因突变或STK11/LKB1缺失引起^[79],HPD风险升高至13.8%^[80]。在胃癌中,ATTRACTION-02研究表明亚洲人群ORR为11.2%^[81],弥漫型胃癌因低TMB、MHC-I缺失、Wnt/ β -catenin通路激活及癌相关成纤维细胞间质屏障形成“冷肿瘤”微环境而导致耐药^[82],HPD发生率为10.7%^[83]。在肝细胞癌(CheckMate 040试验)中Nivolumab治疗的ORR为20%^[84],其耐药机制涉及PKC α /ZFP64/CSF1信号轴激活,促使巨噬细胞向M2

型极化并抑制T细胞功能^[85],HPD风险为12.7%^[86]。在三阴性乳腺癌(KEYNOTE-086 Cohort B)中,CPS ≥ 10 患者接受Pembrolizumab治疗的ORR为21.4%^[87],耐药机制涵盖抗原呈递下调、免疫抑制微环境形成、替代检查点(TIM-3/LAG-3/TIGIT)激活、MAPK/PI3K/WNT等促癌通路异常活化及T细胞耗竭等多重因素^[88]。综上所述,PD-1单抗在不同恶性肿瘤中的疗效存在明显异质性,该差异与肿瘤分子特征及肿瘤微环境密切相关。耐药机制主要包括抗原呈递缺陷、抑制性微环境形成、替代性免疫检查点激活以及致癌信号通路异常等多个层面。深入揭示PD-1单抗耐药机制,将为克服耐药、开发新型联合治疗策略提供重要理论基础。

5.2 联合策略与新型药物的研究进展

PD-1抗体联合治疗在多种肿瘤类型中展现出显著临床进展。在广泛期小细胞肺癌的二线治疗中,一项II期研究报道,替雷利珠单抗联合安罗替尼及伊立替康方案的ORR达50%,中位无进展生存期(PFS)为7.1个月,中位总生存期(OS)为7.5个月,并在脑转移及免疫检查点抑制剂耐药人群中仍具抗肿瘤活性^[89]。LAG-3抑制剂与PD-1抗体的联合应用亦显示出协同增效作用。例如,Eftilagimod alpha联合帕博利珠单抗及化疗用于非小细胞肺癌一线治疗,ORR达60.8%,中位OS延长至32.9个月^[90]。Relatlimab与纳武利尤单抗联合方案目前已获准用于晚期黑色素瘤的一线治疗^[91]。在新辅助治疗方面,纳武利尤单抗联合瑞拉利单抗用于可切除非小细胞肺癌,主要病理缓解率(MPR)达30%,且未增加手术难度或影响手术实施^[91]。此外,PD-1抗体联合

表2 PD-1靶向治疗概述
Table 2 Overview of PD-1 targeted therapy

癌种类型	ORR(%)	HPD发生率(%)	耐药机制	参考文献
经典型霍奇金淋巴瘤	87.0	<1.0	多与9p24.1/PD-L1基因缺失或JAK2/STAT通路突变相关	[68-72]
微卫星高度不稳定/错配修复缺陷转移性结直肠癌	43.8	<2.0	肿瘤突变负荷(TMB)降低、HLA-I类分子表达缺失以及抗原递呈障碍	[73-75]
黑色素瘤	33.7	5.0	IFN- γ 信号通路突变(如JAK1/2缺失)	[76,77]
非小细胞肺癌	46.1	13.8	EGFR/ALK驱动基因或STK11/LKB1缺失	[78-80]
胃癌	11.2	10.7	低TMB、MHC-I缺失、Wnt/ β -catenin通路激活及癌相关成纤维细胞间质屏障形成“冷肿瘤”微环境	[81-83]
肝细胞癌	20	12.7	激活PKC α /ZFP64/CSF1信号轴,招募并促使巨噬细胞极化为免疫抑制性的M2型	[84-86]
三阴性乳腺癌	21.4		肿瘤通过下调抗原呈递、塑造免疫抑制微环境、代偿性激活TIM-3/LAG-3/TIGIT等替代检查点、异常激活MAPK/PI3K/WNT等促癌信号通路以及诱导T细胞耗竭	[87,88]

贝伐珠单抗在晚期肝细胞癌一线治疗中也显示出显著生存获益,尤其在乙肝高感染率、高肿瘤负荷的中国人群中疗效突出,为该类患者提供了新的治疗选择^[92]。现有临床证据表明,PD-1抗体与不同作用机制药物的联合策略可显著提升疗效,未来需进一步探索最佳联合模式及预测性生物标志物,以推动精准治疗的发展。

除了与传统作用机制药物的联合,新型双特异性抗体的开发为PD-1靶向治疗开辟了全新路径。Ivonescimab(AK112)作为全球首个靶向PD-1与VEGF-A的四价双特异性抗体,在早期临床研究中显示出潜在治疗价值^[93]。其I期研究结果显示,该药在整体人群中的ORR为25.5%,并在铂耐药卵巢癌、微卫星稳定/错配修复正常结直肠癌及PD-1耐药非小细胞肺癌等难治类型中表现出抗肿瘤活性^[93]。III期HARMONI-2研究进一步证实,在PD-L1阳性晚期非小细胞肺癌患者中,Ivonescimab一线单药治疗的中位PFS显著优于帕博利珠单抗(11.1个月 vs 5.8个月,HR=0.51)^[93]。该药物通过同时阻断PD-1与VEGF-A信号,协同重塑肿瘤免疫微环境,且安全性优于传统联合方案^[93]。未来研究拟拓展其在肝癌、子宫内膜癌等实体瘤中的应用,并探索与抗体药物偶联物(ADC)及TIGIT抑制剂的联合策略,具有成为新一代免疫治疗基准药物的潜力^[93]。无论是多种药物的联合应用还是双特异性抗体的设计,其核心思路均在于通过多靶点协同调控肿瘤微环境,以期克服耐药、扩大获益人群,这代表了肿瘤免疫治疗未来的主要发展方向。

6 结论与展望

PD-1作为关键的免疫检查点分子,在免疫调控、肿瘤发生与发展以及治疗抵抗中发挥核心作用。研究表明,PD-1不仅负向调控T细胞的活化与功能,还参与巨噬细胞、NK细胞等天然免疫细胞的功能调节。近年来,肿瘤细胞固有PD-1的发现进一步拓展了其生物学意义。该分子可通过激活mTOR-mtROS等信号通路,以非免疫方式直接参与肿瘤干性维持、增殖调控及凋亡进程,并在部分癌种中表现出促癌与抑癌的双重功能,为理解PD-1在肿瘤微环境(TME)中的多功能性提供了新视角。在临床治疗层面,PD-1/PD-L1抑制剂在多种恶性肿瘤中显示出差异化的疗效格局,从霍奇金淋巴瘤的高反应率

(ORR 87%)至胃癌(ORR 11.2%)、肝细胞癌(ORR 20%)等实体瘤中的有限疗效,反映出肿瘤异质性及TME的复杂影响。耐药机制涵盖抗原呈递缺陷、抑制性微环境形成、替代性免疫检查点激活以及致癌通路异常等多个层面,超进展(HPD)风险已成为临床实践中需关注的问题。为应对上述挑战,PD-1抗体与抗血管生成药物、LAG-3抑制剂或PD-1/VEGF双特异性抗体等联合策略逐渐成为研究热点,其通过协同调节免疫微环境、逆转T细胞耗竭及阻断代偿信号,展现出增强抗肿瘤免疫及克服耐药的潜力。

基于当前研究进展,靶向肿瘤细胞固有PD-1已成为新的干预方向。小分子抑制剂针对其下游信号通路在抑制肿瘤干性与增殖方面初显潜力;PD-1抗体联合小分子制剂或mTOR通路抑制剂等多模式策略,也正被探索用于协同调控肿瘤细胞与免疫微环境。未来研究应致力于系统解析肿瘤固有PD-1在不同癌种及细胞亚型中的信号网络,结合分子分型开发高特异性靶向治疗与联合方案,并建立相应的预测性生物标志物体系,从而推动肿瘤免疫治疗向更广谱、高效与精准的方向发展。

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