不同抗肿瘤治疗方式对PD-L1表达的影响及相关机制

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摘要：程序性死亡受体-1/配体-L1(PD-1/PD-L1)抑制剂作为免疫治疗的新型药物，常与放化疗、靶向治疗等联合应用到各种恶性肿瘤的治疗中，目前认为PD-L1表达率可预测PD-L1抑制剂疗效。而不同的抗肿瘤治疗会对PD-L1的表达产生不同的影响，因此明确不同抗肿瘤治疗方式对PD-L1表达水平的影响以及相关机制显得十分重要。本文总结了不同抗肿瘤治疗方式对PD-L1表达的影响以及其发生机制，指出了肿瘤患者在接受免疫治疗前以及治疗期间，需行二次甚至多次活检来明确肿瘤组织的PD-L1表达情况，以协助临床医师判断是否可以施行联合免疫治疗，帮助患者有更好的生存获益。

关键词：PD-1/PD-L1；放化疗；靶向治疗；免疫治疗

The effect of different anti-tumor treatments on the expression of PD-L1 and related mechanisms

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Abstract: In recent years, programmed death receptor-1/ligand-L1 (PD-L1) inhibitors are often used in combination with radiotherapy, chemotherapy, and targeted therapy in the treatment of various malignant tumors. It is currently believed that the expression rate of PD-L1 can predict PD-L1 efficacy of L1 inhibitor. This paper reviewed many domestic and foreign studies on the effects and mechanisms of different anti-tumor treatments on PD-L1 expression and found that there are differences in the effects of different treatment options on PD-L1 expression and the mechanisms involved. It is pointed out that before and during treatment, tumor patients need to undergo two or even multiple biopsies to confirm the expression of PD-L1 in tumor tissues, so as to assist clinicians in determining whether to combine immunotherapy, so that patients can have better survival benefits.

Key Words: PD-1/PD-L1; radiotherapy and chemotherapy; targeted therapy; immunotherapy

在传统手术治疗、放化疗、靶向治疗不理想的背景下，免疫治疗成为新的抗肿瘤治疗方式，其核心在于激活肿瘤患者自身免疫细胞对肿瘤细胞的杀伤能力，抑制肿瘤免疫逃逸的发生，以延长肿瘤患者生存期。其中，研究最为广泛的是免疫检查点抑制剂，如程序性死亡受体-1 (programmed cell death protein-1，PD-1)及其配体(programmed cell death protein-ligand 1，PD-L1)抑

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制剂目前已应用到肺癌、黑色素瘤、乳腺癌等的临床治疗中，并取得一定的疗效。但同时在临床应用中发现，相较于联合治疗，许多肿瘤患者对单用PD-1/PD-L1抑制剂的响应率并不高[1]，这使免疫联合治疗成为新的治疗手段。目前关于预测PD-1/PD-L1抑制剂疗效的生物标志物并未统一，其疗效可能与PD-L1表达率、肿瘤淋巴细胞浸润程度、高突变负荷、错配修复等相关[2]，其中临床上常以PD-L1表达率作为预测疗效的潜在指标，并认为PD-L1高表达的患者有更好的生存获益[3]。本文对放化疗、靶向治疗、抗血管生成治疗等不同抗肿瘤治疗方式对PD-L1表达影响及相关机制研究结果展开综述，期望能为临床上更好的应用免疫治疗提供参考。

1 PD-1/PD-L1的结构及表达

PD-1是一种抑制性受体，属于CD28家族成员，是由268个氨基酸残基组成的Ⅰ型跨膜蛋白。PD-1结构包括胞外免疫球蛋白可变区样结构域、跨膜区以及胞内区。其中，胞内区包括C端和N端氨基酸残基，含有2个独立的磷酸化作用位点，分别为免疫受体酪氨酸抑制基序和免疫受体酪氨酸转换基序。PD-1在T细胞、B细胞、单核细胞和树突状细胞等细胞中均有表达。

目前，已被证实的PD-1配体有两个：PD-L1和PD-L2，其中PD-L1是主要配体。PD-L1是B7家族中一个负性T细胞共刺激分子，主要表达于成熟的$CD4^+$ T细胞、 $CD8^+$ T细胞、单核细胞、巨噬细胞等造血细胞以及一些非造血细胞表面。

2 PD-1/PD-L1信号通路

PD-1/PD-L1作为一对负性共协调刺激分子，共同组成PD-1/PD-L1信号通路，对T细胞的活化及免疫应答的调控起重要作用。一方面通过激活PD-1/PD-L1通路，可诱导和维持自我免疫耐受，对防止组织产生过度炎性反应及自身免疫性疾病的发生有积极作用[4]。另一方面肿瘤细胞表面的PD-L1通过与肿瘤浸润淋巴细胞(tumor infiltrating lymphocytes，TIL)表面的PD-1结合，抑制TIL活性，诱导其凋亡，从而促进抑制性肿瘤微环境的形成，帮助实现肿瘤免疫逃逸[5]。因此，有相关研究认为，PD-1/PD-L1通路可能是实现肿瘤免疫逃逸的关键。近年来，PD-1/PD-L1抑制剂成功为对抗人类癌症，特别是实体肿瘤提供了一个重大突破，已经成为肿瘤免疫治疗领域的一大热点。

3 不同抗肿瘤治疗方式对PD-L1表达的影响

3.1 放射治疗可通过破坏肿瘤细胞以及肿瘤微环境诱导肿瘤细胞PD-L1表达上调

放射治疗是一种利用放射线治疗肿瘤的局部治疗方法，单独放射治疗无法产生持久的抗肿瘤反应，因此临床上常将其用于联合治疗。研究发现，放疗可以通过改变肿瘤的免疫原性[6]以及肿瘤微环境[7]，诱导PD-L1表达增加。多项研究报道，经放疗后的肿瘤组织PD-L1表达上调[8-10]，相关机制如下。(1)破坏DNA结构。研究发现，放疗可破坏DNA双链结构，进而激活相关信号通路来诱导肿瘤细胞PD-L1表达[11,12]。(2)释放炎症因子，如IFN-γ、IL-2等。放疗可造成局部组织炎症反应，诱导淋巴细胞产生的IFN-γ增加，IFN-γ作为PD-L1表达的强刺激因子，起到促进PD-L1表达上调的作用[13]。(3)影响信号通路。放疗通过影响PI3K/AKT[14]、JAK/STAT[8-15]等重要信号通路诱导肿瘤细胞PD-L1表达上调。(4)影响驱动基因状态。有研究发现，EGFR突变阳性的食管癌患者经过放射治疗后，肿瘤细胞PD-L1表达上调，其机制可能与EGFR磷酸化状态相关[16]。综上，放射治疗可诱导肿瘤细胞表面PD-L1表达上调，增加PD-L1抑制剂疗效。此外，多项临床研究均对放疗联合免疫治疗给予了不错的评价[17,18]，目前更多研究着重探索两者在治疗上的循序、剂量等关系。而更大型、更广泛的临床研究也正在进行中，其结果值得期待[19]。

3.2 不同的化学治疗方案对肿瘤细胞PD-L1表达影响存在差异

化疗作为肿瘤三大传统治疗方法之一，通过抑制癌细胞增殖和诱导癌细胞凋亡起到杀灭肿瘤细胞的目的。研究表明，化疗药物具有免疫调节作用[20]，目前认为化疗药物可通过促进炎症因子释放以及影响信号通路等途径调控肿瘤细胞PD-L1表达。铂类药物[21]、培美曲塞[22]、紫杉醇[23]等化疗常用药物可通过促进IFN-γ的释放进而上调PD-

L1在肿瘤细胞的表达。其中铂类药物[24]、紫杉醇[25]还可通过影响MARK等信号通路上调PD-L1表达。但也有研究报告，铂类药物对PD-L1表达无影响甚至呈下调作用[26,27]，该差异可能与铂类药物浓度相关[28]。同时培美曲塞/西地那非在肺癌的治疗中起到下调PD-L1表达的作用[29]。此外，还有具有特殊作用的化疗药物，比如吉西他滨，作为去甲基化药物，通过DNA去甲基化作用，诱导血液系统疾病、结肠癌肿瘤细胞的PD-L1表达增加。据报道，蒽环类药物对肿瘤细胞PD-L1表达有特殊的核迁移现象[30]，可通过降低癌细胞表面PD-L1表达进而上调PD-L1在核内的表达。目前虽暂没有证据表明化疗联合PD-L1抑制剂治疗会增加总体毒性的发生率以及严重程度[31]，但化疗药物种类众多，且临床上往往多药联合或联合其他抗肿瘤治疗，使预判PD-L1表达变化变得十分困难，因此在肿瘤患者化疗联合免疫治疗时，有必要建议患者再次或多次行组织活检来明确肿瘤细胞的PD-L1表达水平，从而帮助临床医师判断疗效。

3.3 靶向治疗可通过干预驱动基因状态或信号通路调控肿瘤细胞PD-L1表达

随着EGFR、ALK、BRAF等驱动基因的不断确认，抗肿瘤治疗进入了精准医疗时代，针对其靶点的药物也成功应用于临床抗肿瘤治疗中，并获得了不错的疗效。

3.3.1 通过干预驱动基因状态下调PD-L1表达

据报道，靶向基因突变状态与PD-L1表达水平相关，认为抑制驱动基因可下调PD-L1在肿瘤细胞中的表达。目前已有研究显示，表皮生长因子受体(epidermal growth factor receptor，EGFR)基因突变状态与PD-L1表达存在一定的联系[32]，表皮生长因子受体酪氨酸激酶抑制剂可通过抑制EGFR去磷酸化下调PD-L1表达[33,34]。间变性淋巴瘤激酶(anaplastic lymphoma kinase，ALK)作为肺癌的驱动基因，ALK抑制剂可下调PD-L1在*ALK*基因突变阳性肿瘤中的表达。BRD4作为溴结构域和超末端家族蛋白家族(bromodomain and extra terminal domain，BET)成员之一，目前有研究认为，*BRD4*的过度扩增与乳腺癌发病密切相关，BET抑制剂可抑制其扩增，起到下调PD-L1表达的作用[35,36]。*Myc*作为较早发现的一组癌基因，同样也发现，BET抑制剂可通过抑制*Myc*扩增从而降低PD-L1的表达[37]。但也有研究发现，*EGFR*突变的非小细胞肺癌患者经酪氨酸激酶抑制剂治疗后PD-L1的表达水平反而增加[38]。

3.3.2 通过影响MAPK、PI3K-AKT-mTOR信号通路调控PD-L1表达

PD-L1表达还受到多种信号通路影响，其中以MAPK信号通路、PI3K-AKT-mTOR信号通路为研究热点。MAPK信号通路由RAS-RAF-MEK-ERK等蛋白激酶组成。多项研究证实阻碍该通路可下调PD-L1在肿瘤细胞的表达。*KRAS*突变阳性的肺腺癌可通过ERK途径诱导PD-L1表达上调，KRAS抑制剂可通过抑制该途径下调PD-L1表达[39]。BRAF是MAPK信号通路的最强激活剂，约一半黑色素瘤患者中可发现*BRAF*突变，BRAF抑制剂通过调节STAT1、c-JUN/AP1活性降低肿瘤细胞PD-L1表达[40]。MEK-ERK位于MAPK信号通路下游，EMK抑制剂可单独应用或与BRAF、 KRAS抑制剂联合应用增强抗肿瘤效果[41]。PI3K-AKT-mTOR作为另一重要信号通路，抑制该通路同样可降低PD-L1在肿瘤细胞中的表达[42]。癌基因*PTEN*作为该通路的负性调节因子，有研究发现，该基因的缺失可导致胶质瘤[43]和乳腺癌[44]细胞中PD-L1表达增强。目前，临床上针对驱动基因阳性患者首选靶向治疗，其原因可能与驱动基因阳性患者往往肿瘤细胞的PD-L1表达程度低、淋巴细胞浸润程度低，以及酪氨酸激酶抑制剂对PD-L1表达具有抑制作用有关，使驱动基因阳性患者难以从靶向治疗联合免疫治疗中获益。但目前有研究表明，“靶向+免疫+化疗+抗血管生成药物”的四联方案较“靶向+化疗+抗血管生成药物”的三联方案，肿瘤患者的疾病无进展期以及总生存期明显延长[45]。此外，对于罕见突变的患者，免疫治疗可能也是较好的选择[46]。因此，并非所有的驱动基因阳性患者均不适宜行免疫治疗，需要综合考虑肿瘤细胞PD-L1表达水平、基因突变状态、肿瘤微环境等因素，实现真正的精准医疗。

3.4 抗血管生成药物可通过影响细胞因子以及STAT3表达调控肿瘤细胞的PD-L1表达

血管生成是肿瘤发生、发展和转移的必经过程，也是其重要的生物学标志之一。研究发现，

促血管生成因子的分泌使肿瘤血管异常生长，淋巴细胞难以浸润，形成肿瘤微环境。而抗血管生成药物能使肿瘤血管正常化，改变缺氧的微环境，提升组织血液灌注和淋巴细胞浸润，提高免疫治疗的疗效[47,48]。抗血管生成药物索拉菲尼、瑞戈非尼可通过促进IFN-γ分泌上调PD-L1的表达[49,50]，加强免疫治疗疗效。但研究还发现，贝伐单抗[51]以及舒尼替尼[52]等药物可通过抑制STAT3活化来下调PD-L1表达。转化生长因子-β (transforming growth factor-β，TGF-β)是一种具有高度特异性的促血管内皮细胞生长因子，用瑞戈非尼、乐伐替尼处理鼠源性肝癌细胞株发现，乐伐替尼组肝癌细胞株TGF-β1、PD-L1表达均上升，而瑞戈非尼组表达均下降，认为其机制是通过调控TGF-β1表达进而影响PD-L1表达[53]。虽然不同抗血管生成药物对PD-L1表达的影响并不一致，但由于肿瘤淋巴细胞浸润程度以及肿瘤微环境同样也是影响PD-L1抑制剂疗效的因素，并且国内外均有研究报告了抗血管药物联合免疫治疗能帮助肿瘤患者获得更好的生存期[54,55]。因此，抗血管生成药物联合PD-L1抑制剂治疗仍可作为肿瘤患者的治疗选择之一。

4 抗肿瘤治疗耐药与肿瘤细胞PD-L1表达水平的关系

在抗肿瘤治疗过程中，药物耐药的发生是不可避免的，正因如此，尽管不同的抗肿瘤药物不断面世，但肿瘤患者的生存期仍受限，关于耐药发生的机制也是肿瘤学研究的热点之一。研究发现，PD-L1表达上调与抗肿瘤治疗耐药的发生相关[56,57]，甚至可以作为预测肿瘤耐药的指标之一。据报道，在顺铂耐药的非小细胞肺癌临床样本中，PD-L1表达显著增加[58]，敲除*PD-L1*基因或降低其表达可使耐药的肿瘤细胞重新恢复对化疗的敏感性[59,60]。研究发现，PD-L1高表达可诱导非小细胞肺癌的吉非替尼原发性并易于获得耐药性[61]，可能与MET、EGFR-T790M表达上调相关[62,63]。此外，应用PD-L1抑制剂可诱导肿瘤细胞的PD-L1表达下降，进而影响PD-L1抑制剂疗效，产生免疫耐药[64]。有研究还发现，多重耐药肿瘤细胞系的PD-L1表达高于单耐药细胞系[65]。然而，经化疗后复发的多形性胶质母细胞瘤患者的PD-L1表达水平较初发者是降低的[66]。目前国内外尚缺乏关于PD-L1表达与肿瘤耐药发生的相关机制的进一步研究以及多种抗肿瘤治疗手段联合免疫治疗能否逆转耐药状态相关的临床研究。但根据上文文献综述，可推测，PD-L1抑制剂仍是放化疗、靶向治疗耐药后患者的一个治疗选择。

5 总结

随着PD-1/PD-L1抑制剂在肿瘤治疗研究中的不断进展，免疫治疗成为肿瘤患者新的治疗选择。目前的相关研究报道认为，肿瘤细胞PD-L1表达情况与PD-1/PD-L1免疫抑制剂治疗效果之间存在相关性。因此，了解不同抗肿瘤治疗对PD-L1表达的影响是有必要的。从上文综述的各项研究中，我们发现放射治疗可诱导肿瘤细胞PD-L1表达上调，而不同化疗方案和不同的靶向治疗则对肿瘤PD-L1表达影响存在差异，导致临床医生难以通过PD-L1表达率预判PD-1/PD-L1抑制剂的疗效。且大多数肿瘤患者往往采用放化疗或联合靶向治疗等综合治疗方案，并且治疗期间常伴随着耐药的发生，这使肿瘤细胞PD-L1的表达水平变得更加不可预测，因此需要对肿瘤组织进行两次甚至多次活检来明确其PD-L1表达情况，进而帮助临床医生判断是否需要联合免疫治疗，以使肿瘤患者有更好的生存获益。除了PD-L1表达率，PD-L1抑制剂疗效还受肿瘤淋巴细胞浸润程度、高突变负荷、免疫应答等多方面约束，使大多数患者难以从PD-L1抑制剂中受益，由上文可见，PD-L1表达受到多种信号通路以及细胞因子等因素调控，进而提出猜想，能否找到共同存在的机制并进行干预，来调控PD-L1表达，代替PD-L1抑制剂，同时又能不受肿瘤淋巴细胞浸润程度等因素制约。此外，肿瘤耐药发生与PD-L1表达水平及机制研究也值得进一步探索。目前，PD-L1抑制剂以联合用药方式为主，并且相应的临床研究也在进展中，但多种治疗手段联合的个体化、规范化的综合治疗方案仍有待商榷。我们相信随着对PD-L1表达及机制研究的不断进展，能让肿瘤患者得到更加有效、安全的治疗。

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