

免疫检查点PD-1/PD-L1阻断剂耐药机制的研究进展

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Title: Research progress on resistance mechanism of immune checkpoint PD-1/PD-L1 blockade agents

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摘要: 免疫检查点蛋白通过复杂机制抑制抗肿瘤免疫,进而介导恶性肿瘤的“免疫逃逸”。2018年诺贝尔生理学或医学奖的两位得主发现了抑制上述机制的癌症疗法,为人类抗肿瘤治疗带来曙光。近年来,针对程序性死亡受体-1(PD-1)/程序性死亡受体配体-1(PD-L1)的免疫检查点阻断治疗在多种恶性肿瘤中取得较好疗效,将肿瘤免疫治疗推向新的里程碑。然而继之出现的耐药问题,限制了其临床应用,成为这一领域新的难题。本文就PD-1/PD-L1阻断剂耐药现象及相关机制作一综述。

Abstract: Immune checkpoint proteins inhibit anti-tumor immunity through complex mechanisms, which in turn mediates the "immune escape" of malignant tumors. Two winners of the 2018 Nobel Prize in Physiology or Medicine have discovered cancer therapies that inhibit these mechanisms, bringing dawn to human anti-cancer treatment. In recent years, immune checkpoints blockade therapy for programmed death receptor-1 (PD-1)/programmed death receptor ligand-1 (PD-L1) has achieved good results in a variety of malignant tumors, pushing tumor immunotherapy to a new milestone. However, the emergence of drug resistance restricts its clinical application and poses new challenges to this field. In this article, we reviewed the drug resistance phenomenon and related mechanisms of PD-1/PD-L1 blockers.

参考文献/REFERENCES

- [1] Rotte A,D' Orazi G,Bhandaru M.Nobel committee honors tumor immunologists [J].Journal of Experimental & Clinical Cancer Research,2018,37(1):262.
- [2] Shi T,Ma Y,Yu L,et al.Cancer immunotherapy:A focus on the regulation of immune checkpoints [J].International Journal of Molecular Sciences,2018,19(5):1389.
- [3] Zhang L,Wang J,Wei F,et al.Profiling the dynamic expression of checkpoint molecules on cytokine-induced killer cells from non-small-cell lung cancer patients [J].Oncotarget,2016,7(28):43604.
- [4] Jenkins RW,Barbie DA,Flaherty KT.Mechanisms of resistance to immune checkpoint inhibitors [J].British Journal of Cancer,2018,118(1):9-16.
- [5] Markham A,Duggan S.Cemiplimab:First global approval [J].Drugs,2018,78(17):1841-1846.
- [6] Jia L,Zhang Q,Zhang R.PD-1/PD-L1 pathway blockade works as an effective and practical therapy for cancer immunotherapy [J].Cancer Biology & Medicine,2018,15(2):116-123.
- [7] Xu-Monette ZY,Mingzhi Z,Jianyong L,et al.PD-1/PD-L1 blockade:Have we found the key to unleash the antitumor immune response [J]?Frontiers in Immunology,2017(8):1597.
- [8] Zhu X,Lang J.Soluble PD-1 and PD-L1:Predictive and prognostic significance in cancer [J].Oncotarget,2017,8(57):97671-97682.
- [9] Quigley M,Pereyra F,Nilsson B,et al.Transcriptional analysis of HIV-specific CD8+ T cells shows that PD-1 inhibits T cell function by upregulating BATF [J].Nature Medicine,2010,16(10):1147-1151.
- [10] Zou W,Wolchok JD,Chen L.PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy:Mechanisms,response biomarkers, and combinations [J].Science Translational Medicine,2016,8(328):328rv4.

- [11] Beaver JA,Hazarika M,Mulkey F,et al.Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression:a US Food and Drug Administration pooled analysis [J] .*The Lancet Oncology*,2018,19(2):229-239.
- [12] Lim SY,Rizos H.Immune cell profiling in the age of immune checkpoint inhibitors:implications for biomarker discovery and understanding of resistance mechanisms [J] .*Mammalian Genome*,2018(7669):1-13.
- [13] Patel SA,Minn AJ.Combination cancer therapy with immune checkpoint blockade:Mechanisms and strategies [J] .*Immunity*,2018,48(3):417.
- [14] Nowicki TS,Hu-Lieskovian S,Ribas A.Mechanisms of resistance to PD-1 and PD-L1 blockade [J] .*The Cancer Journal*,2018,24(1):47-53.
- [15] Wang Q,Wu X.Primary and acquired resistance to PD-1/PD-L1 blockade in cancer treatment [J] .*International Immunopharmacology*,2017(46):210-219.
- [16] Li N,Qin J,Lan L,et al.PTEN inhibits macrophage polarization from M1 to M2 through CCL2 and VEGF-A reduction and NHERF-1 synergism [J] .*Cancer Biology & Therapy*,2015,16(2):297-306.
- [17] Skoulidis F,Goldberg ME,Greenawalt DM,et al.STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma [J] .*Cancer Discovery*,2018:CD-18-0099.
- [18] Ramos RN,Piaggio E,Romano E.Mechanisms of resistance to immune checkpoint antibodies [J] .*Handbook of Experimental Pharmacology*,2017(2017):1-20.
- [19] Sun C,Mezzadra R,Schumacher TN.Regulation and function of the PD-L1 checkpoint [J] .*Immunity*,2018,48(3):434.
- [20] Sharma P,Hulieskovian S,Wargo J,et al.Primary,adaptive, and acquired resistance to cancer immunotherapy [J] .*Cell*,2017,168(4):707-723.
- [21] Bai J,Gao Z,Li X,et al.Regulation of PD-1/PD-L1 pathway and resistance to PD-1/PD-L1 blockade [J] .*Oncotarget*,2017,8(66):110693.
- [22] Henau OD,Rausch M,Winkler D,et al.Overcoming resistance to checkpoint blockade therapy by targeting PI3Ky in myeloid cells [J] .*Nature*,2016,539(7629):443.
- [23] Koyama S,Akbay EA,Li YY,et al.Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints [J] .*Nature Communications*,2016(7):10501.
- [24] O'Donnell JS,Long GV,Scolyer RA,et al.Resistance to PD1/PDL1 checkpoint inhibition [J] .*Cancer Treatment Reviews*,2017(52):71-81.
- [25] Deepak M,Dipti V,Smyth MJ.Overcoming acquired PD-1/PD-L1 resistance with CD38 blockade [J] .*Cancer Discovery*,2018,8(9):1066-1068.
- [26] Chen L,Diao L,Yang Y,et al.CD38-mediated immunosuppression as a mechanism of tumor cell escape from PD-1/PD-L1 blockade [J] .*Cancer Discovery*,2018,8(9):1156-1175.
- [27] Lin H,Wei S,Hurt EM,et al.Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression [J] .*Journal of Clinical Investigation*,2018,128(2):805.
- [28] Tong M,Wang J,He W,et al.Predictive biomarkers for tumor immune checkpoint blockade [J] .*Cancer Management and Research*,2018(10):4501.
- [29] Yi M,Jiao D,Xu H,et al.Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors [J] .*Molecular Cancer*,2018,17(1):129.
- [30] Karamouzis MV,Papavassiliou AG.Combination of checkpoint inhibitors with other agents as a strategy to improve anti-cancer effect-A glimpse to the future [J] .*Expert Opinion on Investigational Drugs*,2018(2018):569-572.
- [31] Borghaei H,Langer CJ,Gadgeel S,et al.24-month overall survival from KEYNOTE-021 cohort G:Pemetrexed and carboplatin with or without pembrolizumab as first-Line therapy for advanced nonsquamous non-small cell lung cancer [J] .*Journal of Thoracic Oncology*,2018,14 (1) : 124-129.
- [32] Hongshu S,Ningxia M,Ying W,et al.Anti-PD-1/PD-L1 therapy for non-small-cell lung cancer:Toward personalized medicine and combination strategies [J] .*Journal of Immunology Research*,2018(2018):1-17.

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