Programmed cell death protein 1

Programmed cell death protein 1, also known as PD-1 and CD279 (cluster of differentiation 279), is a cell surface receptor that plays an important role in down-regulating the immune system and promoting self-tolerance by suppressing T cell inflammatory activity. PD-1 is an immune checkpoint and guards against autoimmunity through a dual mechanism of promoting apoptosis (programmed cell death) in antigen-specific T-cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (anti-inflammatory, suppressive T cells).

Through these mechanisms, PD-1 inhibits the immune system. This prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells.

PD-1 (Programmed Cell Death Protein 1): Normally, PD-1 is expressed on the surface of T cells, and when it binds to its ligand, PD-L1, which is often overexpressed on cancer cells, it inhibits T cell activity. PD-1 Inhibitors (e.g., Pembrolizumab, Nivolumab): These drugs block the interaction between PD-1 and PD-L1, unleashing the T cells to recognize and attack cancer cells.

Inhibitors to the checkpoint proteins cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are becoming widely used in cancer treatment.

A new class of drugs that block PD-1, the PD-1 inhibitors, activate the immune system to attack tumors and are therefore used with varying success to treat some types of cancer.

The PD-1 protein in humans is encoded by the PDCD1 gene.

PD-1 is a cell surface receptor that belongs to the immunoglobulin superfamily and is expressed on T cells and pro-B cells.

PD-1 binds two ligands, PD-L1 and PD-L2.

Autophagy could promote tumor growth in specific cancer types. Tumor intrinsic PD1 or PD-L1 could both increase autophagy through ATG13 interaction [1)].

Intravenous administration of programmed cell death protein 1 and CTLA-4 inhibitors have low activity in patients with Glioblastoma recurrence. In a phase, I clinical trial, intracerebral (IC) administration of ipilimumab (IPI) and nivolumab (NIVO) in combination with intravenous administration of NIVO was investigated.

Within 24 hours following the intravenous administration of a fixed-dose (10 mg) of NIVO, patients underwent a maximal safe resection, followed by injection of IPI (10 mg; cohort-1), or IPI (5 mg) plus

NIVO (10 mg; cohort-2) in the brain tissue lining the resection cavity. Intravenous administration of NIVO (10 mg) was repeated every 2 weeks (max. five administrations). Next-generation sequencing and RNA gene expression profiling was performed on resected tumor tissue.

Twenty-seven patients were enrolled (cohort-1: n=3; cohort-2: n=24). All patients underwent maximal safe resection and planned IC administrations and preoperative NIVO. Thirteen patients (cohort-1: n=3; cohort-2: n=10) received all five postoperative intravenous doses of NIVO. In cohort-2, 14 patients received a median of 3 (range 1-4) intravenous doses. Subacute postoperative neurological deterioration (n=2) was reversible on steroid treatment; no other central nervous system toxicity was observed. Immune-related adverse events were infrequent and mild. GB recurrence was diagnosed in 26 patients (median progression-free survival (PFS) is 11.7 weeks (range 2-152)); 21 patients have died due to progression. Median OS is 38 weeks (95% CI: 27 to 49) with a 6-month, 1-year, and 2-year OS-rate of, respectively, 74.1% (95% CI: 57 to 90), 40.7% (95% CI: 22 to 59), and 27% (95% CI: 9 to 44). OS compares favorably against a historical cohort (descriptive Log-Rank p>0.003). No significant difference was found with respect to PFS (descriptive Log-Rank test p>0.05). A higher tumor mRNA expression level of B7-H3 was associated with significantly worse survival (multivariate Cox logistic regression, p>0.029).

Conclusion: IC administration of NIVO and IPI following maximal safe resection of rGB was feasible, safe, and associated with encouraging OS [2)]

In a study, Bornschlegl et al. assessed the expression of PD-1 and CTLA-4 on 19 leucocyte populations in the peripheral blood of 74 cancer patients. A reference data set for PD-1 and CTLA-4 was established for 40 healthy volunteers to determine the normal expression patterns for these checkpoint proteins.

Unsupervised hierarchical clustering found four immune profiles shared across the solid tumor types, while chronic lymphocytic leukemia patients had an immune profile largely unique to them. Furthermore, we measured these leucocyte populations on an additional cohort of 16 cancer patients receiving the PD-1 inhibitor pembrolizumab in order to identify differences between responders and non-responders, as well as compared to healthy volunteers (n = 20). They observed that cancer patients had pre-treatment PD-1 and CTLA-4 expression on their leucocyte populations at different levels compared to healthy volunteers and identified two leucocyte populations positive for CTLA-4 that had not been previously described. We found higher levels of PD-1+ CD3+ CD4- CD8- cells in patients with progressive disease and have identified it as a potential biomarker of response, as well as identifying other significant differences in phenotypes between responders and non-responders.

Conclusion: These results are suggestive that categorization of patients based on immune profiles may differentiate responders from non-responders to immunotherapy for solid tumors. [3)].

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The success in lung cancer therapy with programmed death (PD)-1 blockade suggests that immune escape mechanisms contribute to lung tumor pathogenesis. We identified a correlation between EGF receptor (EGFR) pathway activation and a signature of immunosuppression manifested by upregulation of PD-1, PD-L1, CTL antigen-4 (CTLA-4), and multiple tumor-promoting inflammatory cytokines. We observed decreased CTLs and increased markers of T-cell exhaustion in mouse models of EGFR-driven lung cancer. PD-1 antibody blockade improved the survival of mice with EGFR-driven adenocarcinomas by enhancing effector T-cell function and lowering the levels of tumor-promoting cytokines. Expression of mutant EGFR in bronchial epithelial cells induced PD-L1, and PD-L1 expression was reduced by EGFR inhibitors in non-small cell lung cancer cell lines with activated EGFR. These data suggest that oncogenic EGFR signaling remodels the tumor microenvironment to trigger immune escape and mechanistically link treatment response to PD-1 inhibition.

Significance: We show that autochthonous EGFR-driven lung tumors inhibit antitumor immunity by activating the PD-1/PD-L1 pathway to suppress T-cell function and increase levels of proinflammatory cytokines. These findings indicate that EGFR functions as an oncogene through non-cell-autonomous mechanisms and raise the possibility that other oncogenes may drive immune escape. [4].

Local failures following radiation therapy are multifactorial, and the contributions of the tumor and the host are complex. Current models of tumor equilibrium suggest that a balance exists between cell birth and cell death due to insufficient angiogenesis, immune effects, or intrinsic cellular factors. Liang et al. investigated whether host immune responses contribute to radiation-induced tumor equilibrium in animal models. They report an essential role for immune cells and their cytokines in suppressing tumor cell regrowth in two experimental animal model systems. Depletion of T cells or neutralization of IFN-γ reversed radiation-induced equilibrium, leading to tumor regrowth. They also demonstrate that PD-L1 blockade augments T cell responses, leading to rejection of tumors in radiation-induced equilibrium. They identified an active interplay between tumor cells and immune cells that occurs in radiation-induced tumor equilibrium and suggest a potential role for disruption of the PD-L1/PD-1 axis in increasing local tumor control. [5]

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