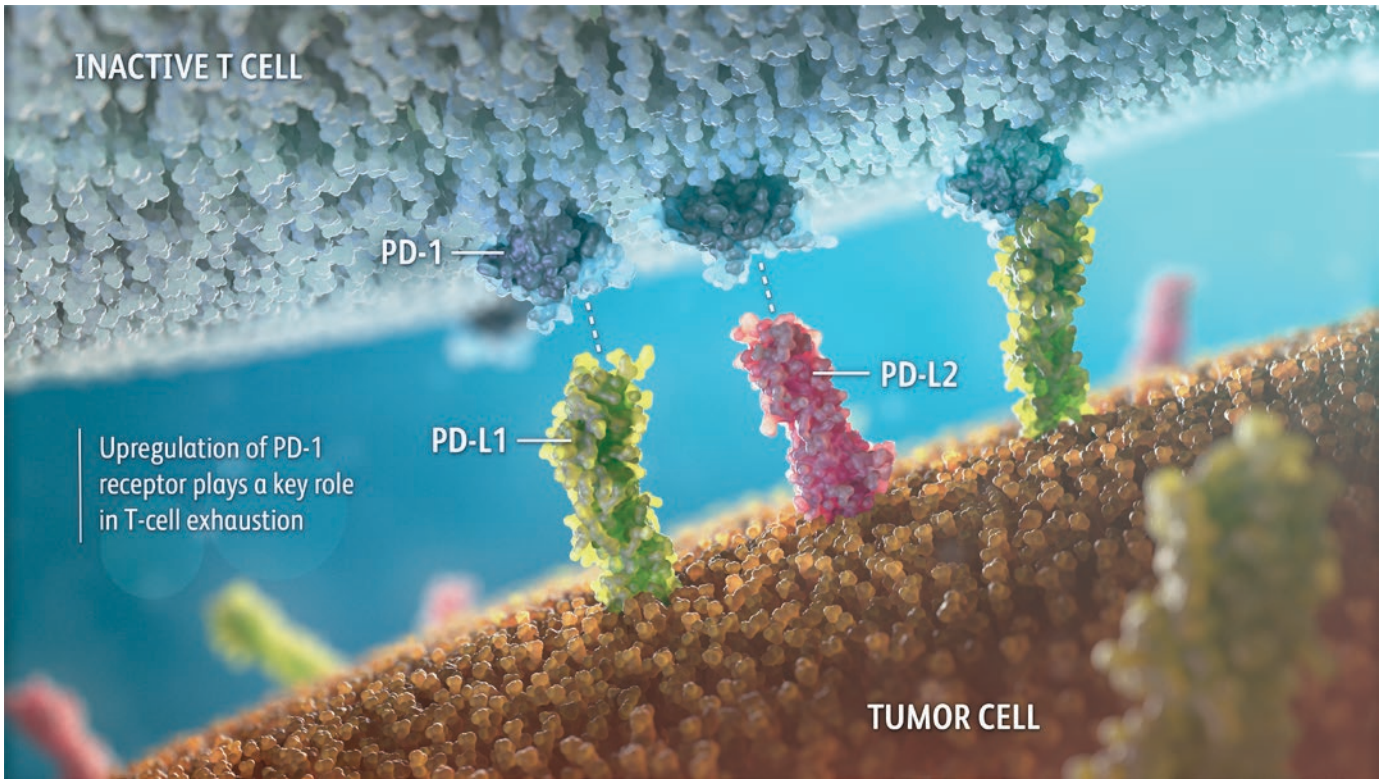
PD-1: induces T-cell exhaustion and drives immune escape

Role in normal cell

Programmed death receptor-1 (PD-1) is an immune checkpoint receptor on cytotoxic T cells with two ligands, PD-L1 and PD-L2.[1-3] Upregulation of PD-1 and its ligands may play a key role in T-cell exhaustion and in preventing autoimmunity.[3-5]



Role in cancer cell

In cancer, PD-L1 and PD-L2 expressed on the surface of multiple solid tumors and hematologic malignancies promote T-cell exhaustion, suggesting a role for PD-L1 and PD-L2 in tumor immune evasion.[1-3,6-13] As uncontrolled PD-1 signaling multiplies over time, exhausted T cells become increasingly disabled and lose essential functions.[3,6,7,14]

Preclinical evidence

Preclinical studies suggest that PD-1 blockade reinvigorates exhausted T cells and restores their cytotoxic immune function.[15] Inhibiting both PD-1 ligands (PD-L1 and PD-L2) may be more effective at reversing T-cell exhaustion than inhibiting PD-L1 alone.[16]

Acronyms

PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; PD-L2=programmed death ligand 2.

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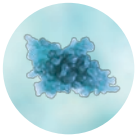

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References

1. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*. 2000;192(7):1027-1034.
2. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol*. 2001;2(3):261-268.
3. Ahmadzadeh M, Johnson LA, Heemskerk B, et al. Tumor antigen–specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood*. 2009;114(8):1537-1544.
4. Barber DL, Wherry EJ, Masopust D, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature*. 2006;439(7077):682-687.
5. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science*. 2001;291(5502):319-322.
6. Catakovic K, Klieser E, Neureiter D, Geisberger R. T cell exhaustion: from pathophysiological basics to tumor immunotherapy. *Cell Commun Signal*. 2017;15(1):1.
7. Peng W, Liu C, Xu C, et al. PD-1 blockade enhances T-cell migration to tumors by elevating IFN-γ inducible chemokines. *Cancer Res*. 2012;72(20):5209-5218.
8. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti–PD-1 therapy. *Clin Cancer Res*. 2014;20(19):5064-5074.
9. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res*. 2007;13(7):2151-2157.
10. Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clin Cancer Res*. 2005;11(8):2947-2953.
11. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A*. 2007;104(9):3360-3365.
12. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-3377.
13. Jung HI, Jeong D, Ji S, et al. Overexpression of PD-L1 and PD-L2 is associated with poor prognosis in patients with hepatocellular carcinoma. *Cancer Res Treat*. 2017;49(1):246-254.
14. Lee J, Ahn E, Kissick HT, Ahmed R. Reinvigorating exhausted T cells by blockade of the PD-1 pathway. *For Immunopathol Dis Therap*. 2015;6(1-2):7-17.
15. Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res*. 2013;19(5):1021-1034.
16. Hobo W, Maas F, Adisty N, et al. siRNA silencing of PD-L1 and PD-L2 on dendritic cells augments expansion and function of minor histocompatibility antigen–specific CD8+ T cells. *Blood*. 2010;116(22):4501-4511.

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