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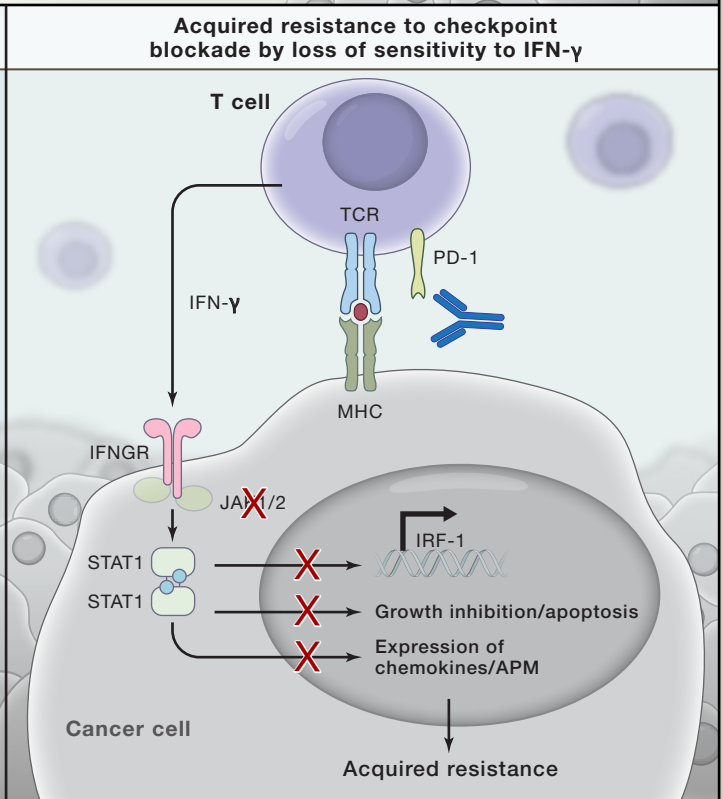
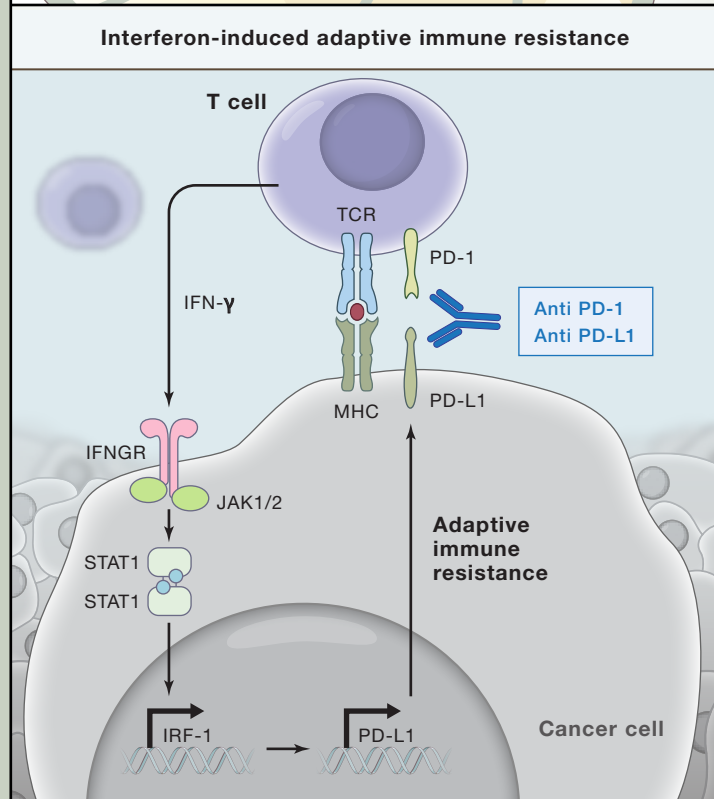
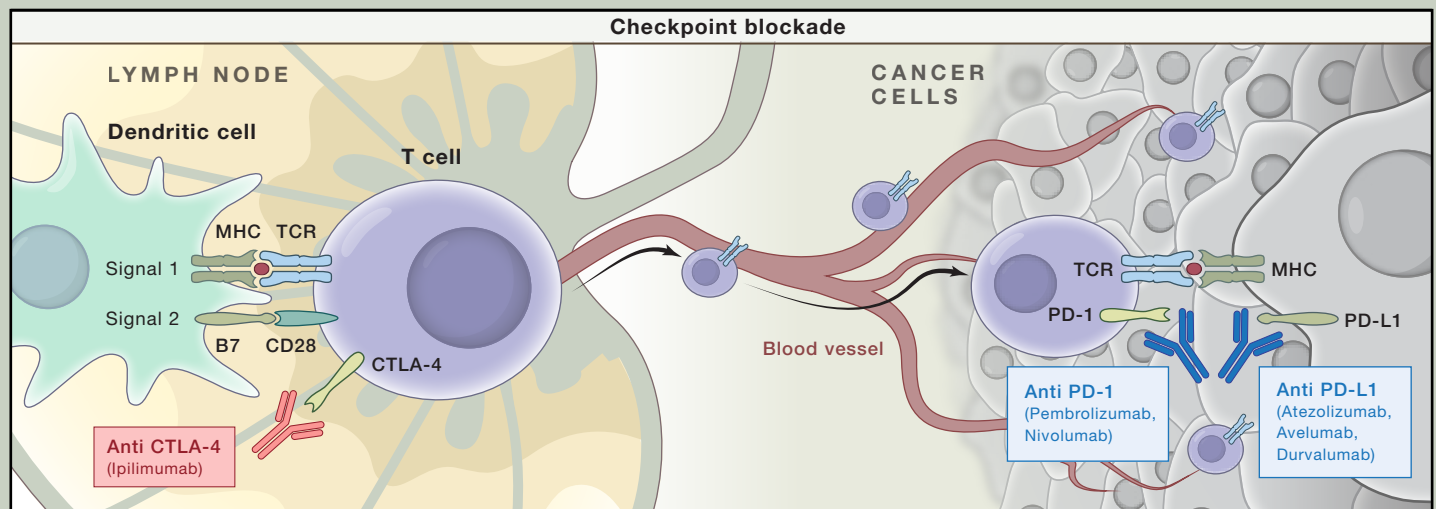
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SnapShot: Immune Checkpoint Inhibitors Cancer Cell

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Clinically approved checkpoint inhibitors

Agent	Mechanism of action	Approved for
Ipilimumab (Yervoy)	mAb targeting CTLA-4	Metastatic melanoma
Pembrolizumab (Keytruda)	mAb targeting PD-1	Metastatic melanoma, non-small-cell lung cancer, head and neck squamous cell cancer, classical Hodgkin's lymphoma
Nivolumab (Opdivo)	mAb targeting PD-1	Metastatic melanoma, non-small-cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, urothelial carcinoma
Atezolizumab (Tecentriq)	mAb targeting PD-L1	Non-small-cell lung cancer, bladder cancer
Avelumab (Bavencio)	mAb targeting PD-L1	Urothelial carcinoma, Merkel cell carcinoma
Durvalumab (Imfinzi)	mAb targeting PD-L1	Urothelial carcinoma

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Checkpoint Blockade: Main Concepts

Checkpoint blockade therapies induce major responses by releasing the inhibitory mechanisms that control T-cell-mediated immunity. Immune checkpoints refer to the set of inhibitory pathways that immune cells possess in order to regulate and control the durability of the immune response while maintaining self-tolerance. Among the different immune checkpoint receptors, antibodies blocking two of them have been approved by the FDA for clinical use: cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand PD-L1. CTLA-4 is expressed by T cells and controls T cell activation during early stages in the lymph nodes. CTLA-4 competes with the co-stimulatory receptor CD28 for the binding to ligands CD80 (B7.1) and CD86 (B7.2). Upon engagement of major histocompatibility complexes (MHCs) with T cell receptors (TCRs) (signal 1), CD28 binds to CD80/86 (signal 2) to expand TCR signaling and T cell activation. This process also triggers the surface expression of CTLA-4, which was previously located in intracellular vesicles in the naive T cell. CTLA-4 presents higher affinity for the CD80/86 ligands than CD28. Therefore, CTLA-4 outcompetes CD28 in the binding of these ligands and, by doing so, prevents and controls further proliferation of the initial T cell response. On the other hand, PD-1 is expressed on activated T cells, B lymphocytes, and natural killer cells and constitutes a main mechanism of tumor immune resistance in peripheral tissues. PD-1 contains a tyrosine-based inhibitory motif (ITIM) together with an immune-receptor tyrosine-based switch motif (ITSM), which is phosphorylated upon binding with the B7 family of ligands PD-L1 (B7-H1 or CD274) or PD-L2 (B7-DC or CD273). Ligand engagement leads to the recruitment of SH2 domains containing tyrosine phosphatase 2 (SHP-2), resulting in the suppression of T cell proliferation and response. The blockade of PD-1 receptor or its ligand PD-L1 with antibodies enhances pre-existent antitumor immune activity, providing patients with major and durable immune responses against the tumor.

Interferon-Induced Adaptive Immune Resistance

Interferons play a major role in mediating antitumor responses, and they constitute the basis of adaptive immune resistance through PD-1:PD-L1 interactions. There are three main types of IFNs: (1) type I, which includes IFN- α and IFN- β , (2) type II IFN- γ , and (3) type III IFN- λ . All three types of IFNs involve similar mechanisms of action. Binding to its specific receptor activates the associated Janus kinases (JAKs) and results in the recruitment of signal transducers and activators of transcription (STATs). Signal transduction is then completed by translocation of the activated STATs to the nucleus, where they bind to specific elements of target promoters to amplify and regulate the expression of critical mediators of the immune response involved in cell proliferation, apoptosis, antigen-processing machinery, or migration. However, interferons might also lead to the expression of genes that are involved in immunosuppression, such as PD-L1 or indoleamine-2,3-dioxygenase (IDO), which can be induced in response to both type I and type II IFNs. Although PD-L1 could also be constitutively expressed by activation of different oncogenic pathways, interferon-induced PD-L1 expression seems to be a major mechanism whereby cancer cells evade T cell attack. In short, antigen-specific T cells release IFN- γ upon activation through their TCR upon recognition of cognate antigen presented by MHCs. Consequent engagement to IFNGR1 and IFNGR2 on tumor cells leads to JAK1 and JAK2 activation, resulting in STAT1 and STAT3 recruitment and phosphorylation. The complex is then translocated to the nucleus, where it binds to the gamma-activated sequence, resulting in interferon regulatory factor 1 (IRF1) activation. IRF1 induces PD-L1 expression, which is predominant at the invasive tumor margins where initial T cell/cancer cell interaction occurs, and blocks the antitumor response of the pre-existing T cells. This process, termed adaptive immune resistance, allows cancer cells to evade the immune response by expressing molecules, in this case PD-L1, that inhibit the initial T cell attack. PD-1 blockade therapies induce responses by inhibiting the adaptive immune resistance.

Acquired Resistance to Checkpoint Blockade by Loss of Sensitivity to IFN- γ

Mutations or epigenetic silencing of mediators of the IFN- γ /IFNGR/JAK/STAT/IRF1 axis would result in the loss of sensitivity to the IFN- γ pathway. In addition to PD-L1 upregulation, IFN- γ exhibits a potent anti-proliferative effect on cancer cells together with an increase in the expression of T-cell-attracting chemokines and antigen-presenting machinery (APM) components. Given the scenario in which PD-1/PD-L1 engagement is already being blocked, continued exposure of cancer cells to T-cell-released IFN- γ induces a selective pressure that promotes the selection of cancer cells that have acquired defects in the IFN- γ pathway. Here, insensitivity to IFN- γ functions as an immune-evasion mechanism that allows cancer cells to overcome the IFN- γ -mediated growth arrest, T cell attraction, and increased antigen-presenting machinery expression.

REFERENCES

- García-Díaz, A., Shin, D.S., Moreno, B.H., Saco, J., Escuin-Ordinas, H., Rodríguez, G.A., Zaretsky, J.M., Sun, L., Hugo, W., Wang, X., et al. (2017). *Cell Rep.* **19**, 1189–1201.
- Pardoll, D.M. (2012). *Nat. Rev. Cancer* **12**, 252–264.
- Parker, B.S., Rautela, J., and Hertzog, P.J. (2016). *Nat. Rev. Cancer* **16**, 131–144.
- Platanias, L.C. (2005). *Nat. Rev. Immunol.* **5**, 375–386.
- Sharma, P., Hu-Lieskovan, S., Wargo, J.A., and Ribas, A. (2017). *Cell* **168**, 707–723.
- Shin, D.S., Zaretsky, J.M., Escuin-Ordinas, H., García-Díaz, A., Hu-Lieskovan, S., Kalbasi, A., Grasso, C.S., Hugo, W., Sandoval, S., Torrejon, D.Y., et al. (2017). *Cancer Discov.* **7**, 188–201.
- Tumeh, P.C., Harview, C.L., Yearley, J.H., Shintaku, I.P., Taylor, E.J.M., Robert, L., Chmielowski, B., Spasic, M., Henry, G., Ciobanu, V., et al. (2014). *Nature* **515**, 568–571.
- Walker, L.S.K., and Sansom, D.M. (2011). *Nat. Rev. Immunol.* **11**, 852–863.
- Zaretsky, J.M., García-Díaz, A., Shin, D.S., Escuin-Ordinas, H., Hugo, W., Hu-Lieskovan, S., Torrejon, D.Y., Abril-Rodriguez, G., Sandoval, S., Barthly, L., et al. (2016). *N. Engl. J. Med.* **375**, 819–829.
- Zou, W., Wolchok, J.D., and Chen, L. (2016). *Sci. Transl. Med.* **8**, 328rv4.