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SnapShot: Immune Checkpoint Inhibitors

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Check point blockade

Cancer cell

Interferon-induced adaptive immune resistance

Adaptive immune resistance

Clinically approved checkpoint inhibitors

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