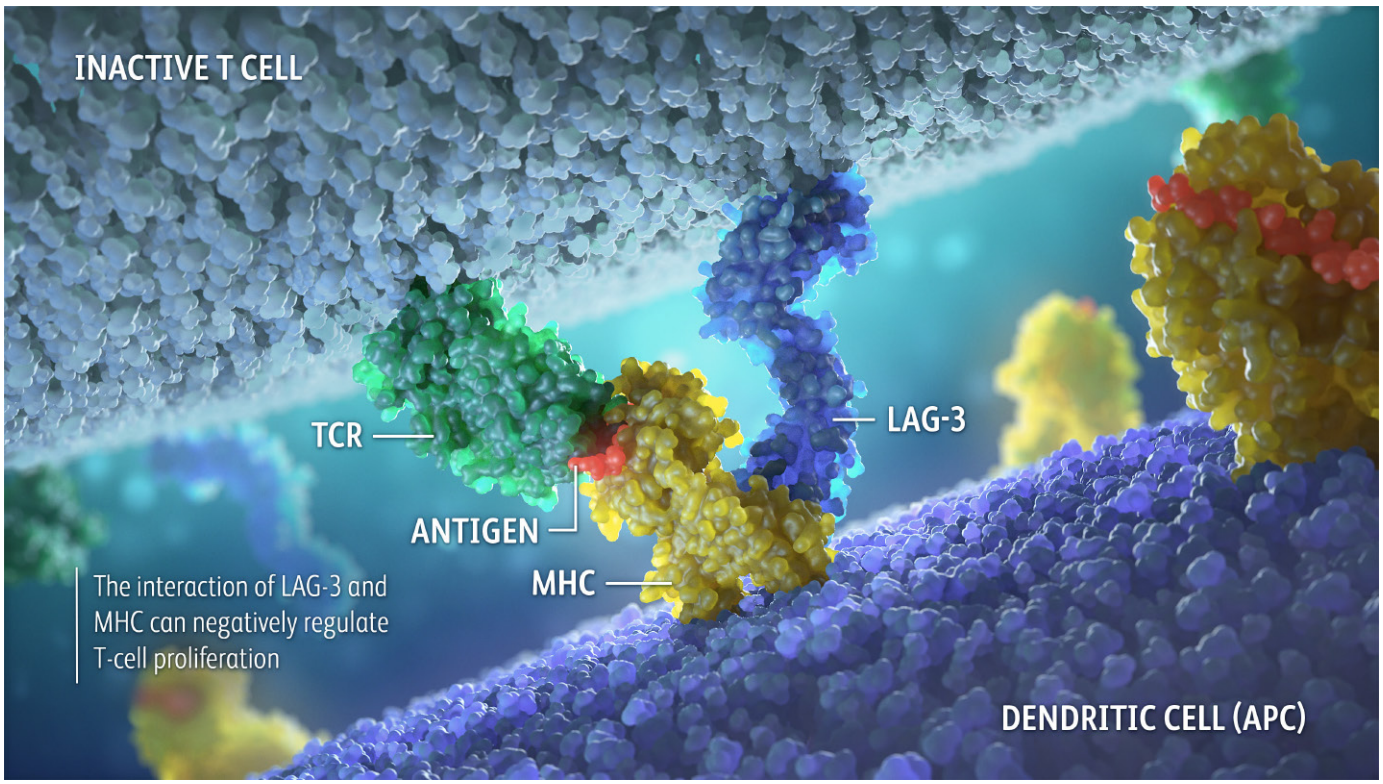
LAG-3: impairs T-cell function and can mark exhausted T cells

Role in normal cell

Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor expressed on the surface of both activated cytotoxic T cells and regulatory T cells (Tregs).[1-3] MHC, which presents antigens to T cells, is one of the ligands for LAG-3.[1-4]



Role in cancer cell

Similar to the expression and function of PD-1, repeated exposure to tumor antigen causes an increase in the presence and activity of LAG-3, leading to T-cell exhaustion.[5,6] T cells co-expressing both LAG-3 and PD-1 may show an even greater degree of exhaustion compared with those expressing LAG-3 alone.[7]

Preclinical evidence

Research is ongoing to understand how dual inhibition of LAG-3 and other checkpoint pathways may synergistically increase T-cell antitumor activity compared with the inhibition of either pathway alone.

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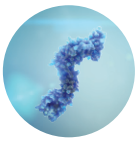

LAG-3: impairs T-cell function and can mark exhausted T cells

Acronyms

APC=antigen-presenting cell; MHC=major histocompatibility complex; PD-1=programmed death receptor-1; TCR=T-cell receptor.

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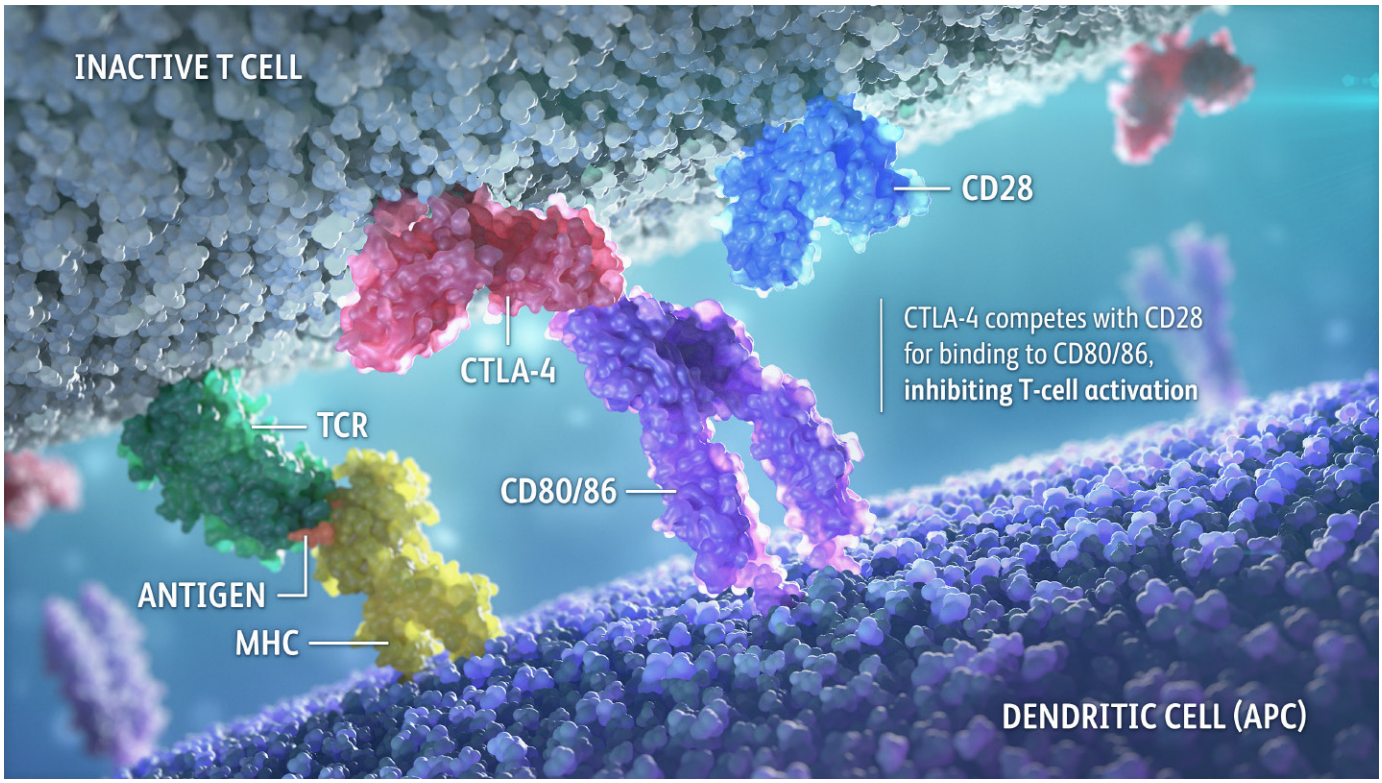
CTLA-4: negatively regulates long-term immune responses

Role in normal cell

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is an immune checkpoint receptor expressed on the surface of activated T cells and Tregs.[1-3]

- Binding of CTLA-4 on cytotoxic T cells to CD80/86 on APCs inhibits T-cell activation[4]
- Continuous expression of CTLA-4 on Tregs is critical for their suppressive activity[2,5]



Role in cancer cell

Tumor cells utilize the CTLA-4 pathway to suppress initiation of an immune response, decreasing T-cell activation and ability to proliferate into memory T cells.[6,7]

Preclinical evidence

Preclinical data demonstrate that treatment with antibodies specific for CTLA-4 can restore an immune response through increased activation, accumulation, function, and survival of T cells and memory T cells as well as the depletion of Tregs.[6,8,9]

Optimizing CTLA-4 blockade

Novel approaches to enhance either the degree or specificity of immune activation with CTLA-4 blockade are under investigation.[10,11]

- One recent approach aims to improve the specificity of CTLA-4 blockade by reducing antibody binding outside of the tumor microenvironment –To localize anti–CTLA-4 activity to the tumor, probody technology has been developed where the antibodies are masked with a peptide that is removed by enzymes that are active primarily in the TME[10-12]
- An alternative approach developed is the generation of a nonfucosylated (NF) form of anti–CTLA-4 antibodies that increases their affinity for FcγR, leading to enhanced Treg depletion by immune-mediated ADCC and increased effector T-cell activation[13,14]

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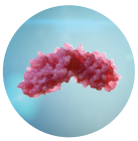

CTLA-4: negatively regulates long-term immune responses

Acronyms

ADCC=antibody-dependent cellular cytotoxicity; APC=antigen-presenting cell; FcγR=fragment crystallizable receptor gamma; MHC=major histocompatibility complex; TCR=T-cell receptor; TME=tumor microenvironment; Treg=regulatory T cell.

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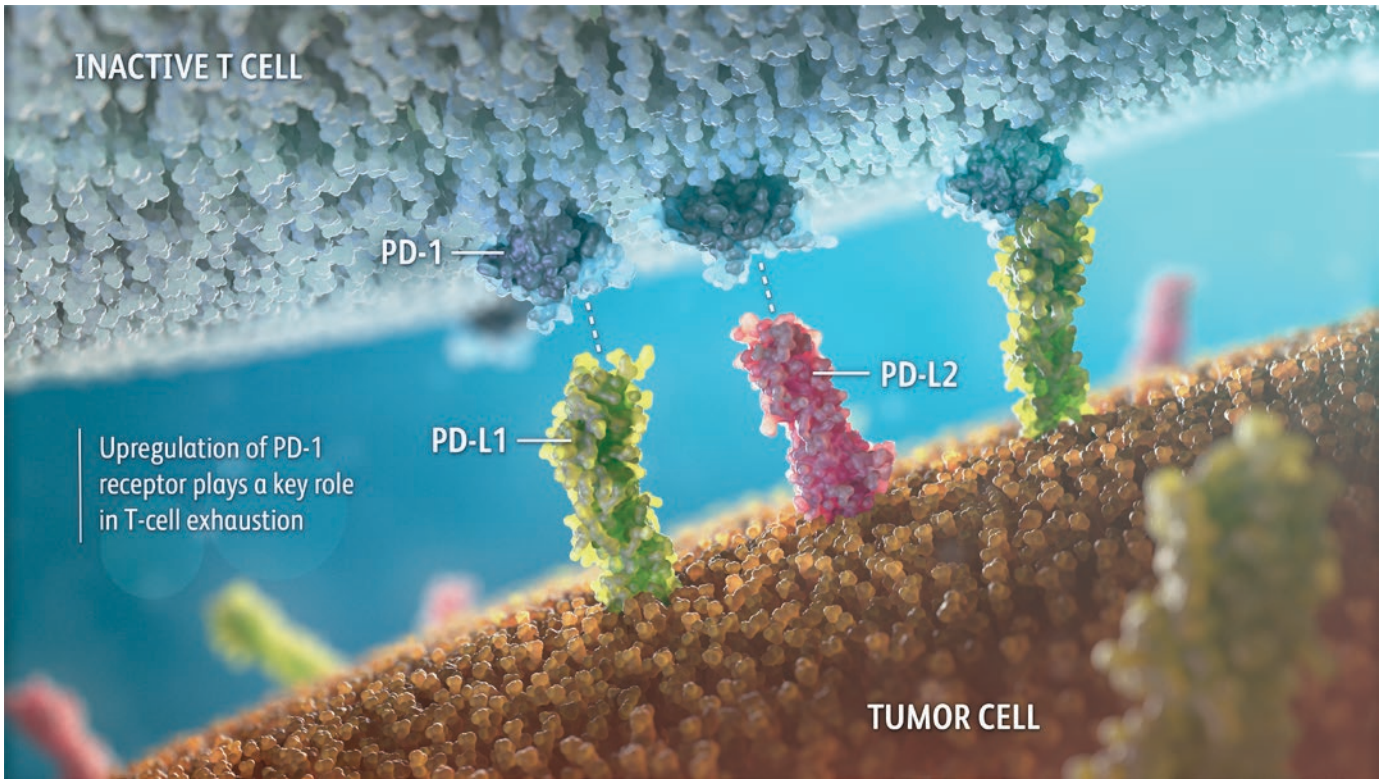
PD-1: induces T-cell exhaustion and drives immune escape

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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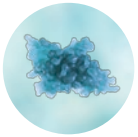

PD-1: induces T-cell exhaustion and drives immune escape

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