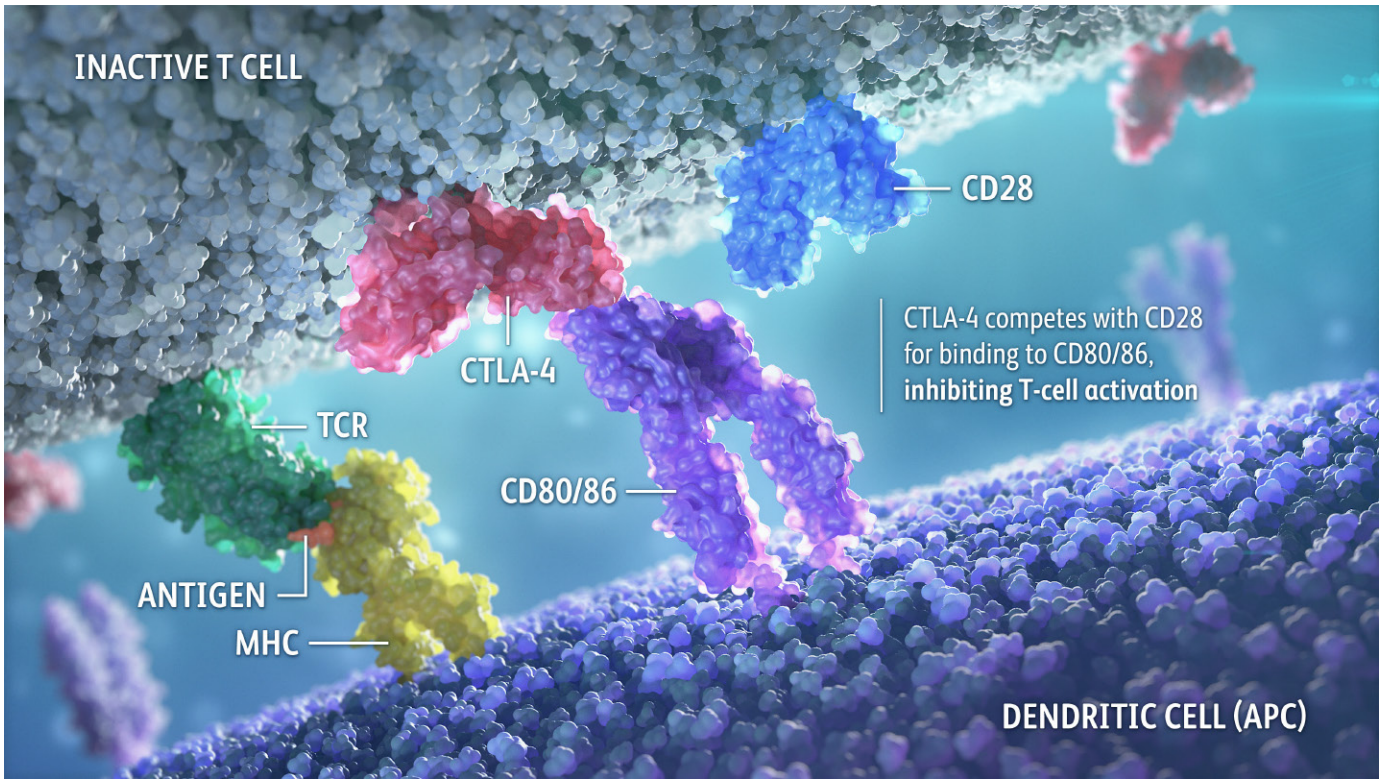
CTLA-4: negatively regulates long-term immune responses

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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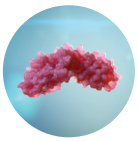

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Acronyms

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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