CTLA4

CTLA4 or CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), also known as CD152 (cluster of differentiation 152), is a protein receptor.

CTLA4, a negative regulator typically expressed on the surface of T lymphocytes,

Functioning as an immune checkpoint, downregulates immune responses. CTLA4 is constitutively expressed in regulatory T cells but only upregulated in conventional T cells after activation - a phenomenon that is particularly notable in cancers.

It acts as an “off” switch when bound to CD80 or CD86 on the surface of antigen-presenting cells.

The CTLA-4 protein is encoded by the Ctla4 gene in mice and the CTLA4 gene in humans.

It is targeted by immunotherapy in patients with an ever-expanding spectrum of cancers. Characterizing the expression of CTLA4 in the pituitary gland could provide additional rationale for using immune checkpoint inhibitors in pituitary adenoma patients who do not respond to conventional treatments. Sabini et al. assessed the expression of CTLA4 mRNA and protein in a panel of 157 human pituitary glands, 45 collected at autopsy and 112 at surgery. These specimens included 50 normal glands and 107 adenomas: 41 non-secreting, 25 PRL-, 24 ACTH-, 11 GH-, 2 TSH-, 1 FSH-secreting, and 3 atypical. Specimens were stained for CTLA4 and adenohypophyseal hormones using RNAscope in situ hybridization, immunohistochemistry, and RNAscope Multiplex Fluorescent Assay. CTLA4 mRNA was detectable in most normal pituitary glands (48 of 50, 96%) but varied in expression, with a histological score (H-score) ranging from 0.6 to 20. The variation did not depend upon the patient's gender and age, and was not significantly by the archival storage time. CTLA4 expression was higher (p= 0.022) in pituitary adenomas than normal glands, with the greatest levels seen in PRL- and GH-secreting adenomas (p= 0.009 and 0.023 versus normal, respectively). Eight of 25 (32%) prolactinomas and 3 of 11 (27%) GH-adenomas had an H-score greater than 20, while no differences were seen for the other types. These novel data highlight the expression of an immune checkpoint such as CTLA4 on pituitary endocrine cells, a finding that could be exploited for therapeutical applications [1)]

With the advent of cancer immunotherapy, there has been a major improvement in patients' quality of life and survival. The growth of cancer immunotherapy has dramatically changed our understanding of the basics of cancer biology and has altered the standards of care (surgery, radiotherapy, and chemotherapy) for patients. Cancer immunotherapy has generated significant excitement with the success of chimeric antigen receptor (CAR) T cell therapy in particular. Clinical results using CAR-T for hematological malignancies have led to the approval of four CD19-targeted and one B-cell maturation antigen (BCMA)-targeted cell therapy products by the US Food and Drug Administration (FDA). Also, immune checkpoint inhibitors such as antibodies against Programmed Cell Death-1 (PD-1), Programmed Cell Death Ligand-1 (PD-L1), and Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) have shown promising therapeutic outcomes and long-lasting clinical effect in several tumor types and patients who are refractory to other treatments. Despite these promising results, the success of cancer immunotherapy in solid tumors have been limited due to several barriers, which include immunosuppressive tumor microenvironment (TME), inefficient trafficking, and

heterogeneity of tumor antigens. This is further compounded by the high intra-tumoral pressure of solid tumors, which presents an additional challenge to successfully delivering treatments to solid tumors [2].

1)
Sabini E, Khan A, Caturegli P. Cytotoxic T lymphocyte-associated protein-4 (CTLA4) is overexpressed in a subset of prolactin- and growth hormone-secreting pituitary adenomas. Endocr Relat Cancer. 2023 Oct 1:ERC-23-0196. doi: 10.1530/ERC-23-0196. Epub ahead of print. PMID: 37870923.
2)
Guha P, Heatherton KR, O'Connell KP, Alexander IS, Katz SC. Assessing the Future of Solid Tumor Immunotherapy. Biomedicines. 2022 Mar 11;10(3):655. doi: 10.3390/biomedicines10030655. PMID: 35327456; PMCID: PMC8945484.