Uncovering the Structural and Functional Information on CTLA-4 (Cytotoxic T-lymphocyte protein 4)

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CTLA-4 – an overview

Preview

Nowadays, a large number of people seem to suffer from common diseases that affect them daily such as diabetes, celiac or in some cases lupus. So, have you ever wondered how our immune system can differentiate between our own cells and external invaders? The answer lies within the complex arrangement of signaling particles and receptors that organize immune responses, which leads us to our chosen protein CTLA-4. CTLA-4 performs a major role when it comes to our immune system. Without this protein, friend and foe are no longer distinguished by our defense mechanism. In fact, the CTLA-4 protein unlocked the full potential of cancer immunotherapy. So, whenever you recover from a disease or whenever your wounds heal, keep in mind that CTLA-4 paved the immune system's response.

CTLA-4 (Cytotoxic T-lymphocyte protein 4)

The protein CTLA-4 is the cytotoxic T-lymphocyte protein 4, also known as Cytotoxic T-lymphocyte-associated antigen 4, or by its antigen name CD152 (cluster of differentiation152).

Evidence of existence

The evidence exists at protein level. To elaborate, the existence of this protein can be expressed and characterized in multiple species, including humans and mice. CTLA-4 protein has been detected by various methods, for example, Western blotting, immunohistochemistry, and flow cytometry. Several experiences were conducted to study the function and determine the existence of the CTLA-4 protein. In 1996, After identifying CTLA-4's presence on human T-cells using monoclonal antibodies, researchers analyzed the genetic variations of CTLA-4 in a large number of patients. The results showed that specific genetic variations in the CTLA-4 gene were associated with a higher risk of experiencing autoimmune diseases. Thus, supporting the crucial function of CTLA-4 in immune control. Additionally, experimental studies were also conducted on mice. Scientists used antibodies to identify its expression in various mouse tissues. Similarly to the human CTLA-4, the protein was found on activated T-cells, as well as in the spleen, lymph nodes, and peripheral blood in mice.

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Isoforms of CTLA-4

Alternate splicing gives rise to 5 isoforms of CTLA-4: P16410-1, which is the canonical form, P16410-2, P16410-3, P16410-4, and P16410-5.

Isoform 2 of Cytotoxic T-lymphocyte protein 4 (P16410-2), also known as ss-CTLA-4 is composed of 56 amino acids with a mass of 6,560 Da. Compared to the canonical isoform which is composed of 223 amino acids, this product is missing the 38-204 amino acids. According to the CTLA-4's genomic organization, the removal of exons encoding the transmembrane and extracellular domains generates the ssCTLA-4 mRNA. However, the splicing process and the importance of these isoform's expression is still unknown.

CTLA-4 involvement in biological processes

The primary role of CTLA-4 is to maintain the body's immune system and preserve its homeostasis. CTLA-4 is mainly found in activated T-cells which it regulates, and it is usually accompanied by the stimulatory co-receptor CD28. This protein binds to 2 ligands which are CD80/B7-1 and CD86/B7.2, which help it achieve its task. However, some antibodies, like Ipilimumab, bind to the receptor of cytotoxic T-lymphocytic protein and inhibits its function, which can be used as a treatment for certain diseases.

Function of CTLA-4

The CTLA4 protein is an inhibitory receptor acting as a major negative regulator of T-cells, a protein found on T lymphocytes that helps keep the body's immune responses in check. When CTLA-4 is bound to another protein called B7, it helps keep T cells from killing other cells, including cancer cells. CTLA-4 mediates immunosuppression by indirectly diminishing signaling through the co-stimulatory receptor CD28. Although both receptors bind CD80 and CD86, CTLA-4 does so with much higher affinity, effectively out-competing CD28. In addition to regulating the activity of T-cells, CTLA-4 maintains their number which helps build immune tolerance and avoid autoimmunity.

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Diseases associated with CTLA-4

Several publications have supported the association between CTLA-4 variants and several diseases, namely systematic lupus erythematosus (SLE), Graves disease, type 1 diabetes mellitus 12 (T1D12), insulin-dependent diabetes mellitus (IDDM), Celiac disease 3 (CELIAC3) and Immune dysregulation with autoimmunity, immunodeficiency, and lymphoproliferation (IDAIL).

The association of the CTLA4 gene with autoimmune disease can be explained by the gene's key role in T lymphocyte proliferating response. Several polymorphisms are known to alter this protein's function: a microsatellite in the 30 untranslated region (3'UTR) and a single nucleotide polymorphism (SNP) involving a A to G transition at position 49 of exon 1.

Protein 3D structure

The protein CTLA-4 does have an experimental 3D structure. This protein's entry in the protein data bank (PDB) is 1l8L/ 1l85. The 3D structure represents the extracellular domain structure of the protein which is crucial for ligand-binding and determining the protein's function, especially in the immune system.

Figure 1: CTLA-4's 3D structure

However, the 3D structure does not cover the entire protein length, it is only part of it. The X-Ray structure covers mostly the residues between 36 and 161. The entire length of the protein is 223 amino acids.

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Sequence alignment of the CTLA-4 protein in different species

Figure 2: Sequence alignment of the CTLA-4 protein in humans, mice, and rabbits, according to Uniprot's alignment tool. This figure highlights the sequences of high and low conservation between the 3 proteins as well as the sequence that codes for the domain of CTLA-4_HUMAN.

According to Figure 2, the highest similarity between the 3 sequences is found at the end, from 183 to 223 amino acids.

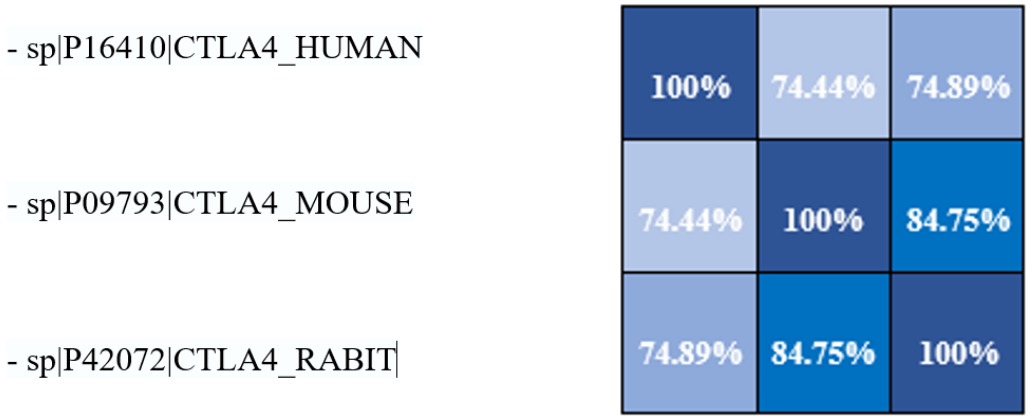

Figure 3: Percent Identity Matrix of CTLA-4 in humans, mice, and rabbits according to UniProt Alignment tool.

CTLA-4 can be also found in many other species like mice and rabbits. After choosing the 2 proteins from these 2 species, by aligning their CTLA-4 protein sequences with the human CTLA-4 protein sequence, a percentage of sequence identity is shared between the 3 proteins more precisely: 74.44 % sequence identity between the human and mouse CTLA-4 protein, 84.75 % sequence identity between the human and the rabbit CTLA-4 protein and finally 74.89 % sequence identity between the mouse and the rabbit CTLA-4 protein.

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