1. B7 and CD28 family immunoglobulins structure-function analysis

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B7 and CD28 protein families are critical co-signaling molecules in T-cell response. Structure and sequences analysis has shown highly structural similarity and conserved functional motifs among each family. Computational approaches were applied to determine the additional members of human B7/CD28 inhibitory pathways.

T lymphocytes play a major role in the immune response [1]. Manipulation of co-signaling molecules provides possibilities for the development of new therapeutics to treat autoimmune diseases, transplantation rejection and tumor or viral infections. B7 and CD28 protein families are critical co-signaling molecules in T-cell response. It has been implied experimentally that more family members of human B7/CD28 inhibitory pathways exist and should be discovered in order to elucidate the mechanism and improve the therapeutic applications. Structure and sequences analysis has shown that each family members share high structural similarity and conserved functional motifs. Computational biological approaches were used to determine the additional members of human B7 and CD28 families. By searching Ensembl database, all annotated sequences of B7 and CD28 families were collected respectively for all species (referred by family sequences in below). Their common domain structure of immunoglobulin V-set was determined by PFam [2].

The crystal structure (PDB code: 1I85) provides template for further structural analysis. SuperFamily [3] database searching collected proteins sequences containing PDB structure-known immunoglobulin (Ig) domains of all species, and human Ig domain-containing peptide sequences (referred by hIg sequences in below). The specific multiple sequence alignments of Ig domains adjusted to the distinctive subgroups of B7 and CD28 sequences were performed with SuperFamily, ClustalW [4] and T-Coffee[5].
The program Correl (developed in Sander's group) was then applied to determine the conserved residues among the B7 and CD28 families sequences, using entropy based clustering of multiple sequence alignments and PAM family of scoring matrices [6]. Clustering analysis was applied to the obtained multiple sequences alignments of family sequences and hIg sequences to determine sequence neighborhoods around B7 and CD28 family members. A phylogenetic tree is then constructed based. The sequence similarity thresholds were optimized through literature and Ensembl/InterPro [7] databases searching. The sequences without functional annotation were proposed as potential members of B7 and CD28 families.

References:
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