Structure and Function of an Inflammatory Cytokine, Interleukin-2 and its Implications in Drug Design

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Introduction:

Interleukin-2 (IL-2), an inflammatory cytokine, is an essential regulator for cellular functioning. The IL-2 ligand-receptor complex dictates various immuno-regulatory/stimulatory reactions involving complex cellular signaling processes. Using computer simulations based on available crystal structures, we report the temporally variant structural aspects of the IL-2 ligand-receptor interfaces. The intended goal of this effort is to generate simulated results that could potentially aid the designs of novel structure-based therapeutics.

Methods

- JINK is used as structural representatives of wt IL-2.
- IL-2Rα receptor bound IL-2, dimeric 1Z92.
- Tetramer unit of 2BS1 system, for which the IL-2 bound IL-2α, β, and common γ receptor are used for the MD simulation.
- Nanoscale Molecular Dynamics (NAMD) and Visual Molecular Dynamics (VMD) programs have been used.

Results and Discussion

- Structure of the IL-2 and IL-2R
  - JINK the wild type (wt) apo IL-2, is a homo dimer (Figure 3A).
  - Mutation induced free energy changes (ΔG) for the wt IL-2 protein were determined. In most cases, the ΔAG value, is positive indicating overall stabilizing effect (Figure 3B).
  - 1Z92 is the hetero-dimeric structure of IL-2 bound IL-2Rα (Fig. 3C).
  - 2BS1 is a hetero-tetrameric complex of IL-2 bound IL-2Rαβγ (Fig. 3D).

- Clinical Implication of IL-2/IL-2R Signaling in Disease propagation and design of targeted IL-2 or IL-2R therapeutics for various treatments
  - Interruption of the IL-2/JAK and JAK/STAT signaling pathways by using selective IL-2 and JAK inhibitors have been linked to widespread implications in next generation drug development.
  - Several IL-2 and IL-2R based therapies are in their clinical phases: anti-IL-2 Daclizumab® (Dac, Biogen.Inc and AbbVie), chimeric mAb Basiliximab® (Novartis Inc.), recombinant IL-2 Aldesleukin® (Novartis Inc.).

- Summary and Outlook
  - These results in combination with published data provide a overall framework to identify the ligand-receptor interfaces of the protein complexes, and also help to assess their stabilities with time [1].
  - This in turn could be utilized for designing more stable protein variants, or targeted therapeutic agents.

Reference