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

Urmi Roy
Department of Chemistry and Biomolecular Science
Clarkson University, Potsdam, NY 13699
e-mail: urmi@clarkson.edu

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*.

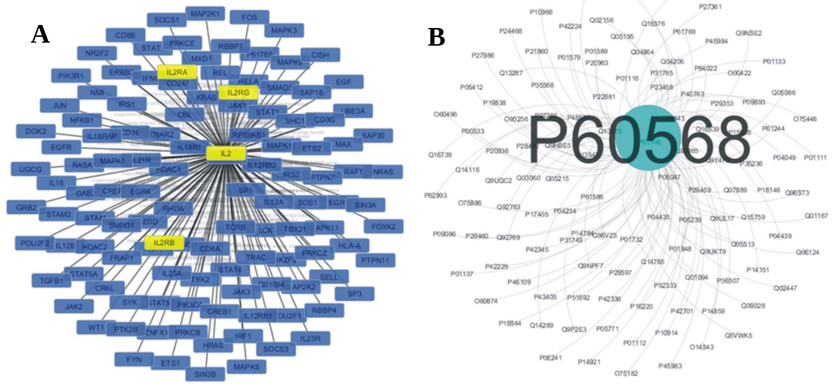

Fig. 1. **A**. Schematics of the IL-2/IL-2R signaling pathways. **B**. The workflow view of the IL-2/IL-2R network, based on the protein's UniProt accession id.

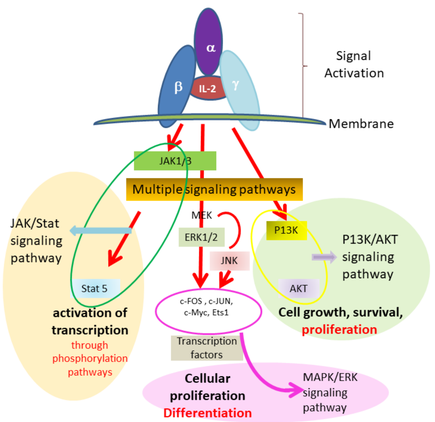

Fig. 2. Drawing illustrating the major signaling cascades of IL-2/IL-2R.

Methods

- **3INK** is used as structural representatives of of wt **IL-2**.
- **IL-2Rα** receptor bound **IL-2**, dimeric **1Z92**.
- tetrameric unit of **2B5I** 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

- **3INK** the wild type (wt) **apo IL-2**, is a homo dimer (Figure 3A).
- Mutation induced **free energy changes** (ΔΔG) for the wt IL-2 protein were determined. In most cases, the ΔΔG value, is **positive** indicating overall stabilizing effect (Figure 3B).
- **1Z92** is the hetero-dimeric structure of **IL-2** bound **IL-2Rα** (Fig. 3C).
- **2B5I** is a hetero-tetrameric complex of **IL-2** bound IL-2Rαβγ (Fig. 3D) .

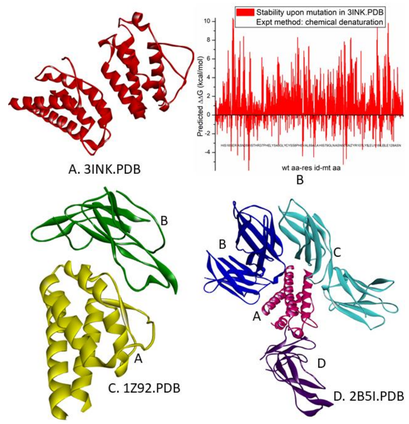

Figure 3. A. Ribbon diagram of wt IL-2. **B.** Mutation induced stability changes in wt IL-2. **C-D**. IL-2 bound receptor dimer and tetramer.

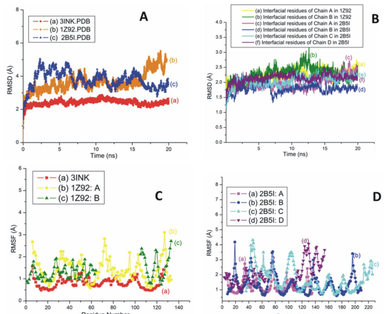

Fig. 4. A. RMSD plots for the wt IL-2 and ligand–bound IL-2R systems. **B**. RMSD plots of the interfacial residues in IL-2/IL-2R systems. **C-D**. Alpha carbon RMSF plots for the wt IL-2 and IL-2/IL-2R systems.

❑ Structural Analyses of the Individual Protein Chain and Protein Complex using Molecular Dynamics Simulation

- The **wt IL-2** exhibits the *lowest* RMSD variation (Fig. 4A).
- The **protein complexes** and the **interfacial residues** in the ligand–receptor system are overall stable as functions of time(Fig. 4B-D).
- **No** major *secondary structural variations* are observed in **wt IL-2** (Fig. 5).
- The tetrameric **2B5I** interfacial residues are *more stable* than the dimeric **1Z92** interfacial areas (Fig. 6).

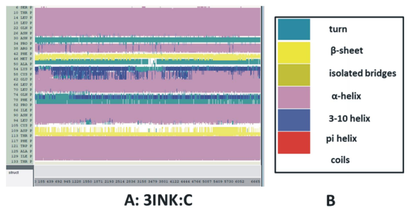

Figure 5. **A**. Time-series of secondary structure-changes in wt IL-2 ligand protein. **B**. The color-code explanation of protein's secondary structures.

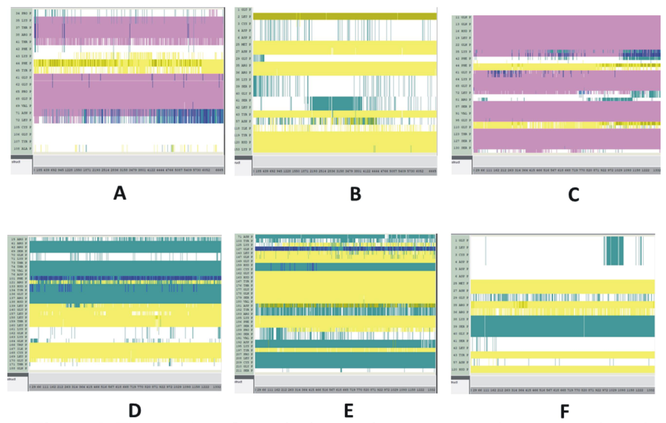

Figure 6. Time-series of proteins' secondary structure-changes at selected interfacial areas of IL-2/IL-2R. **A-B**. 1Z92. **C-F**. 2B5I.

❑ 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
[1] U. Roy, Structure and Function of an Inflammatory Cytokine, Interleukin-2, Analyzed using the Bioinformatic Approach, *The Protein Journal*, 1-12 (2019). DOI: 10.1007/s10930-019-09833-8, and references therein.