Abstract

A key prerequisite for a deeper understanding of biological processes at molecular level is a detailed description of the three-dimensional structure of interaction partners and their complexes. We adopted the IFN-γ complex as our model system. Even though IFN-γ is one of the key modulators of the immunity response, which has been studied intensively for more than 60 years, the structure of the accessory receptor chain and the understanding of the IFN-γ complex is still lacking. In this work we firstly discussed the binary system between IFN-γ and its high affinity receptor R1 which is structurally known. Using a new innovative methodology we focused on the modulation of the affinity between IFN-γ and its receptor R1. Our approach was based on the modulation of protein – protein stability by mutating cavities in the proteins´ structure and increasing the affinity about seven-fold. Secondly, we crystallized and solved the structure of the IFN-γ receptor 2, the accessory receptor molecule. Our analysis of variable residues on the surface of the structures of type II family receptors, to which receptor 2 belongs, revealed the putative binding site for IFN-γ. In the third part of our work, we crystallized IFN-γ from olive flounder *Paralichthys olivaceus* and solved its structure at 2.3 Å resolution (PDB code 6f1e). This structure differs from the other IFN-γ structures and indicates how the fish IFN-γ diverged while preserving the overall fold. We resolved a co-evolutionary aspect between IFN-γ and its high affinity receptor by using bioinformatics and biophysical experiments. Finally, we integrated our results obtained by different techniques and postulated the topology of the IFN-γ ternary complex based on our structure of IFN-γR2, SAXS data, and mutational scanning.