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Keywords: transthyretin, amyloid, chemico-biological space.

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Structural basis for inhibition of interferon alpha signaling pathway and its therapeutic potential in SLE patients

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Increasing evidences suggest that the type I interferon (IFN) plays a critical role in the etiopathogenesis of systemic lupus erythematosus (SLE), which makes it a promising therapeutic target for the treatment of the disease. By screening a large size non-immune human antibody library, we have developed a human single-chain antibody (ScFv) AIFN α 1bScFv01 and corresponding whole antibody AIFN α 1bIgG01, that recognizes recombinant human interferon alpha1b (hIFN α 1b) with high specificity and high affinity. The IgG antibody can down-regulate the expression of *ISG15* and *IFIT-1* induced by either recombinant hIFN α 1b or naive IFN- α presented in SLE patient's sera. The crystal structure of AIFN α 1bScFv01-hIFN α 1b complex solved to 2.8 Å resolution reveals that both Pro26-Gln40 region in loop AB and Glu147-Arg150 region in helice E of hIFN α 1b contribute to binding with AIFN α 1bScFv01. Four residues of above two regions (Leu30, Asp32, Asp35 and Arg150) are critical for the formation of antigen-antibody complexes. AIFN α 1bScFv01 shares partial epitopes of IFN α 1b with its receptor IFNAR2. AIFN α 1bIgG01 has a much higher affinity for IFN α 1b than IFNAR2 ($K_D = 0.747$ nM versus 100 nM), making it unavailable for binding to IFNAR2 and preventing the activation of IFN- α -mediated signaling pathway. Thus, AIFN α 1bIgG01 exhibits its neutralizing activity through competition with IFNAR2 to bind with IFN- α . Our results highlight the potential use of the human antibody for modulating the activity of IFN- α in SLE.

Keywords: SLE, IFN α , ScFv antibody

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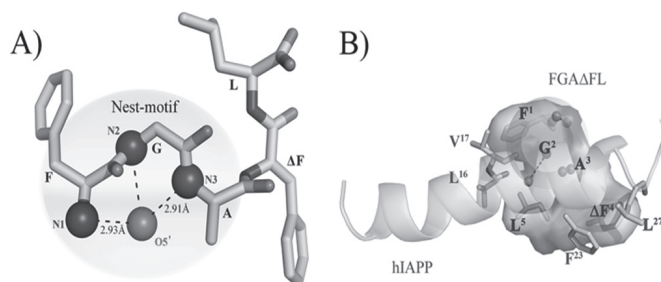
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Structure of peptide inhibitor of human islet amyloid polypeptide fibrillization

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Type-2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetes worldwide. Over 100 million people worldwide have T2DM, and the prevalence is increasing dramatically in both the developed and developing countries. Amyloid deposits have been observed in a vast majority of the T2DM patients and these are primarily on account of misfolding and aggregation into fibrils of human islet amyloid polypeptide (hIAPP), a 37 residue endocrine hormone secreted by pancreatic β -cells. It has been suggested that intermediates produced in the process of fibrillization are cytotoxic to insulin producing β -cells. Hence, the inhibition of misfolding/fibrillization of hIAPP could be a possible strategy to mitigate T2DM. The misfolding of hIAPP involves structural transition from its native state (coil and/or helical and/or transient helical conformation) to β -sheet conformation. We have targeted hIAPP fibrillization by designing short peptides containing the helix inducing α,β -dehydrophenylalanine (Δ Phe or Δ F) amino acid and the fibrillization inhibition was monitored by thioflavin-T assay and electron microscopy. We find that the short peptides inhibit fibrillization without any cytotoxic effect as tested on RIN4fm pancreatic cell line. Of these, the penta-peptide, FGA Δ FL is the most effective inhibitor of hIAPP fibrillization. We successfully crystallized the penta-peptide and solved its 3D structure at atomic resolution using direct methods. Molecular conformation of the peptide reveals the occurrence of a nest-motif (Fig. A) involving the stretch FGA in the penta-peptide and a type-I β -turn. To gain structural understanding and visualize the probable interactions of the hIAPP with FGA Δ FL, molecular docking studies were performed using AutoDock4. Here, we considered the penta-peptide as receptor and hIAPP₆₋₃₀ (PDB: 2KB8) as ligand. The best ligand pose was selected from the cluster with the highest occurrence and the lowest binding energy (-6.41 kcal/mol). The interactions stabilizing FGA Δ FL-hIAPP complex, are nest-motif interactions, hydrophobic interactions and aromatic interactions (Fig. B). We propose, on the basis of FGA Δ FL crystal structure and molecular docking, that the penta-peptide binds to the helical conformation of hIAPP which is considered as transient in nature and/or preferred in membranous environment. Here, the penta-peptide binds at the C-terminal of helical hIAPP₆₋₃₀, stabilizes the helical conformation and makes the transition from alpha to beta structure unfavourable, thereby curtailing the fibrillization process. Thus, the crystal structure of the penta-peptide inhibitor together with computational docking studies provides an atomic level picture of the possible mechanism by which the penta-peptide manifests its fibrillization inhibition activity. Further studies are underway in our laboratories to develop even more potent inhibitors of hIAPP fibrillization and the details will be presented.



Keywords: diabetes, amyloid, inhibitor

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Studies of nucleotide metabolism from blood fluke *Schistosoma mansoni*

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