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INTERACTION OF THE IFN-IFNAR1 COMPLEX WITH RIBONUCLEOTIDES AND D-MANNITOL: PROSPECTS FOR THE DEVELOPMENT OF NEXT-GENERATION INTERFERON-BASED THERAPEUTICS

Aim. To elucidate the molecular mechanisms underlying the interaction of the IFN α -2b-IFNAR1 complex with ribonucleotides and D-mannitol to inform the development of next-generation interferon-based drugs. **Methods.** Fluorescence quenching experiments were performed using a Jasco FP-8200 spectrofluorimeter. Binding affinities (K_d) were calculated using the Stern-Volmer, Scatchard, Klotz, and Hill models. Molecular docking was performed with AutoDock Vina using AlphaFold-derived structures. **Results.** Free ribonucleotides (AMP, UMP and total oligoribonucleotide mix (ORNs)) showed the highest affinity for the heterodimeric IFN-IFNAR1 complex, with dissociation constants in the submicromolar range (K_d 0.14–0.56 μ M). The highest affinity was observed for AMP in the complex with D-mannitol (K_d = 0.14 μ M according to the Hill model). Converting ribonucleotides from the free acid to the disodium form led to a significant (3–10-fold) decrease in affinity. D-mannitol exhibited a clear, selective positive effect: it significantly enhanced the binding of AMP, UMP and ORNs, reducing K_d to up to 30% of the initial value, and this effect was most pronounced in the functional heterodimeric IFN-IFNAR1 complex. For isolated proteins (IFN α -2b and IFNAR1), the modulatory effect of mannitol was much weaker. Molecular docking confirmed the experimental data and revealed that GMP+D-mannitol forms the most stable complex with the IFN-IFNAR1 heterodimer (ΔG_{dock} = –9.4 kcal/mol). Analysis of intermolecular contacts revealed an extensive network of hydrogen bonds and the participation of D-mannitol as a “bridging” modulator that stabilises the conformation of the binding site. We found significant differences in the GMP+D-mannitol binding profiles between individual proteins and their complex, indicating allosteric effects in the formation of a functional receptor heterodimer. **Conclusions.** The data demonstrate that free ribonucleotides and their D-mannitol complexes can serve as effective low-molecular-weight modulators of the interferon system. These findings provide a foundation for the development of next-generation interferon therapeutics with improved stability, enhanced receptor affinity, and potentially superior therapeutic efficacy. **Grants.** IMBG Simons Foundation Grant for Ukrainian institutions № SFI-PD-Ukraine-00017453.

Keywords: interferon α -2b, IFNAR1, ribonucleotides, D-mannitol, allosteric modulation, fluorescence spectroscopy, molecular docking, next-generation therapeutics.

REFERENCES

1. Tkachuk Z. Multiantivirus Compound, Composition and Method for Treatment of Virus Diseases. U.S. Patent 20,120,232,129. 2013.
2. Lakowicz JR. Principles of Fluorescence Spectroscopy. 3rd ed. Springer; 2006.
3. Ajay, Murcko MA. Computational methods to predict binding free energy in ligand-receptor complexes. *J Med Chem.* 1995;38(26):4953–67.

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