Design and in silico Validation of a Novel Fc-fusion Protein for the Treatment of Myasthenia Gravis

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Myasthenia gravis (MG) is a debilitating autoimmune disease of the neuromuscular junction that affects over a million people and can cause life-threatening muscle weakness. As current treatments for MG, like most autoimmune diseases, result in non-specific and harmful immunosuppression, a method to target only the disease's source–autoantibodies and autoreactive immune cells–is needed. To tackle this issue, I designed a novel antigen-conjugated Fc-fusion protein for the selective depletion of autoantibodies and autoreactive cells for MG patients and evaluated the protein's properties and functionality in silico. The antigen, a commonly targeted part of the nicotinic acetylcholine receptor, was linked with a flexible linker to a modified version of the human IgG1 Fc. ProtParam found that the final heterodimeric protein has a molecular weight of 73.14737 kilodaltons with 423 residues in the first chain and 223 residues in the second chain. The 3D construct, which was generated with AlphaFold, was assessed with MolProbity Ramachandran analysis, which showed that 96.4% of residues were in favored regions, and ERRAT2, which gave the fusion construct an overall quality factor (OQF) of >80. A 50 ns MD simulation with GROMACS revealed relative stability with the RMSD only fluctuating +- 1 Angstrom after 25 ns. Cluspro docking simulations and subsequent PRODIGY binding affinity calculations indicate selective affinity of the antigen portion for MG autoantibody Fabs. The Fc-modifications increased binding affinity to Fc receptors IIa and IIIa. These analyses depict a functional protein suitable for downstream in vitro experimentation and a potentially exciting new treatment approach for MG and other autoimmune diseases (currently afflicting ~10% of the world's population).

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