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Designing of Long-Acting Agonists and Antagonists of Glycoproteins Using Gene Fusion and Site-Directed Mutagenesis

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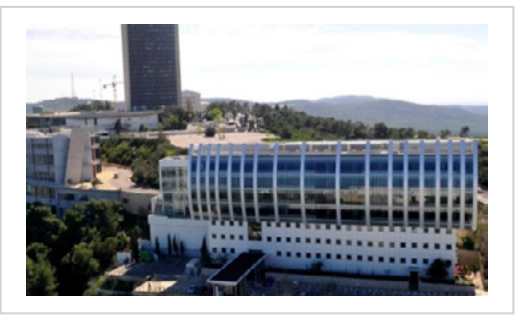
Abstract

Glycoprotein hormones (FSH, LH, hCG and TSH) are a family of heterodimeric proteins composed of two noncovalently linked subunits, α andβ. Oligosaccharides on the glycoprotein hormones have been implicated in several actions including the maintenance of intracellular stability, secretion, assembly, receptor binding, steroidogenesis and modulation of plasma half-life. Glycoproteins are used clinically in the treatment of many diseases. One major issue regarding the clinical use of many peptides is their short half-life due to the rapid clearance from the circulation. To overcome this problem, we used genetic engineering techniques that have been found successful for designing long acting hormones. The signal sequence of O-linked oligosaccharides was added to the coding sequence of human follitropin (FSH), erythropoietin (EPO) and Growth Hormone (GH). It was postulated that the O-linked oligosaccharides add flexibility, hydrophilicity and stability to the protein and it was suggested that O-linked oligosaccharides play an important role in preventing plasma clearance and thus increasing the half-life of the protein in circulation. Using this strategy, a long acting FSH (ELONVA) was approved by the European Commission (EC) for treatment of fertility since 2010. In addition, long acting GH (GENOTROPIN) was passed successfully clinical trials phase 3 and will be suggested for use once a week. Thus, designing long acting peptides will diminish the cost of these drugs and perhaps reduce the number of injections in the clinical protocols. On the other hand . On the other hand we found that deletion of N-linked oligosaccharides from hTSH and FSH subunits by site-directed mutagenesis resulted in a significant decrease in the bioactivity without affecting the binding affinity. Moreover, mutated variants of TSH and FSH compete with TSH-WT and FSH-WT in a dose dependent manner. Thus, these variant, behave as potential antagonists, which may offer novel therapeutic strategies in the treatment of human diseases. In conclusion, it was found that addition o-linked oligosaccharides or deletion of N-linked oligosaccharides could be interesting strategy for designing new analogs of glycoproteins.

Biography

Fuad Fares has completed his MSc and DSc studies at the Faculty of Medicine, Technion-Israel Institute of Technology, and postdoctoral studies at the Department of Molecular Biology and Pharmacology, School of Medicine, Washington University, St. Louis Missouri. He developed the Department of Molecular Genetics at Carmel Medical Center. He is associated professor at the Department of Human Biology, University of Haifa and head the Laboratory of Molecular Genetics. He has published more than 100 manuscripts in reputed journals and served as a member of the Israel Council for Higher Education last 15 years. He is the the founder of PROLOR Biotech company for “Designing long acting recombinant proteins” and CanCurX for “Identification of Natural products for treatment of cancer”.



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