A study on the dynamics and structure of the glycoprotein LDL Receptor Related Protein 1 (LRP1)

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Abstract

The brain is the most energy-expensive organ in humans consuming around 20% of the body metabolic resting rate. At the same time, the molecular balance that leads to biochemical reactions in the brain makes it extremely delicate to alterations from the outside environment, that is, the blood circulation. Evolution made our bodies to develop a special wall between neurons and the blood flux, the Blood-Brain Barrier BBB. Composed of endothelial cells that tightly wrap the capillaries, the BBB applies strict control over the molecules that enter and exit the brain. In this control, the membrane proteins called receptors, located in the BBB, play a fundamental role by binding to the molecular agents and activating the inwards/outwards transport mechanism. The present research aims to focus on the structure and function of a particular receptor, the low-density lipoprotein receptor-related protein 1, LRP1. LRP1 is composed of 4544 amino acids, around 1200 of which are involved in three long clusters (highlighted in red in Fig.1), believed to have an active role in ligand binding activity [1][2] and to activate a peculiar transport mechanism [3]. The interactions of the clusters with each other as well as with molecules activate the transport. Glycans, sugar chains connected to the backbone of LRP1, are another variable that enters the equation and that have been demonstrated to be of great importance for the correct protein function [4]. This investigation approaches the problem from a computational biophysical point of view, using the atomistic molecular dynamics MD implemented in Gromacs. The MD results, even if preliminary, allow us to speculate on the role of the glycans in flexible glycoproteins and on the structural characterization of LRP1 clusters as polymers. The dynamic and structural information extracted will then be joined in a coarse-grained model that will extend the study to n>1 LRP1 receptors, allowing us to observe collective transport mechanisms.

FIGURES

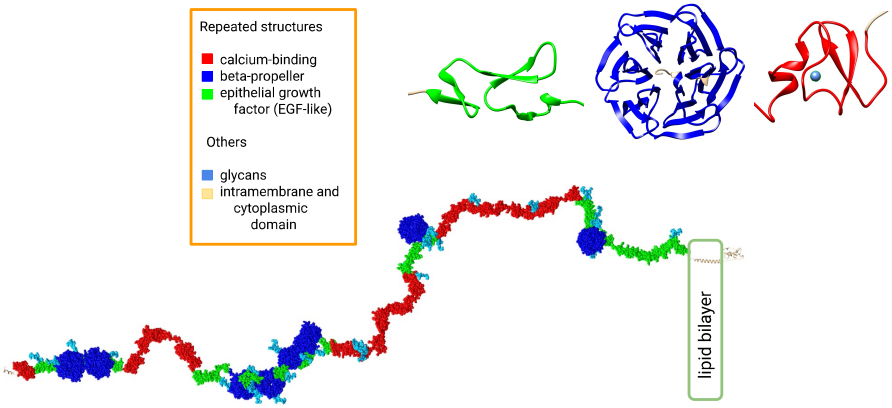

Figure 1: The LRP1 conformation shows the consecutive disposition of three units: the epithelial growth factor, the beta-propeller domain and the calcium-binding unit. 30 glycans are present all along the structure. The structure has been stretched for clarity.

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