PCSK9 three-dimensional reconstruction by homology modelling and new LDL receptor interaction regions

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Abstract

Dyslipidemias are a group of functional disease caused by any alteration in lipid metabolism, resulting modifications in plasma of lipoproteins. The most important lipoprotein related with high risk to develop atherosclerosis is low-density lipoproteins, that is treated mainly by statins, the first-choice pharmacological therapy, a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR). In this way, proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that cleaves low-density lipoprotein (LDL) receptor and therefore it controls cholesterol homeostasis. Some specific mutations cause gain-in-fuction of PCSK9, which result in increased cholesterol levels in blood. In this way, the PCSK9 has been used as a target to develop cholesterol lowering terapies. This work aimed to build a tridimensional model of Proprotein convertase subtilisin/kexin type 9 (PCSK9) protein to study the interaction regions with the LDL receptor, an important molecule in cholesterol homeostasis. The PCSK9 3D structure (Proprotein convertase subtilisin/kexin type 9) were constructed by homology modelling method. In this way, was used the crystallized structure deposited in Protein Data Bank (PDB: 2P4E) to identify the catalytic site regions of interest, between disorganized or conserved regions of PCSK9. The global alignment was validated by Z-score and Ramachandran graphics. In the 3D model of PCSK9, it was possible to identify regions had not been elucidated in the crystallographic structure (Figure 1). The regions reconstructed by the homology modeling method are mainly found in the PCSK9 catalytic domain (in yellow), where interactions with the LDL receptor occur. The C-terminal domain (in green) is responsible for the structural stability of PCSK9. The pre-domain (in red) is the self-cleaved region by PCSK9 itself and is not part of the tertiary structure that interacts with the LDL receptor. In the catalytic domain, amino acids (Asp168, Glu169, Tyr170, Gln171, Pro172, Pro173 and Asp174) that are not found in the PDB:2P4E crystallographic structure can be observed, possibly due to the limitation of the crystallography method in predicting very labile regions. The Ramachandram graph presented 0.1% (Gly68) of amino acids outliers, demonstrating robustness of the constructed model. Three-dimensional reconstruction makes it possible to understand the structure of PCSK9 and to identify new regions of interaction with the LDL receptor that may be important for the development of new drugs.

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