Modelling of human adiponectin trimer and its complex with ADIPOR1 receptor: possible therapeutic targets in the treatment of obesity-related insulin resistance

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Motivation

It has been clearly demonstrated that human adipose tissue express and secretes biologically active polypeptides, which act at both local (autocrine/paracrine) and systemic (endocrine) level. Many of the so-called adipokines regulate the energy balance, glucose, and lipids and contribute to diseases associated with obesity like the insulin resistance, cardiovascular diseases, and so on. Recently the hormonal role of the adiponectin in the obesity-related insulin resistance has been emphasized because its plasma levels in presence of visceral adiposity have been found markedly reduced in contrast to the dramatic increase of other adipokines. The physiological role of adiponectin is mediated by two receptors (ADIPOR1 and ADIPOR2) but the downstream signaling pathways responsible for the metabolic effects are poorly known. For these reasons the adiponectin and its receptors can be considered as very tempting targets for possible therapeutic interventions.

Methods

The three-dimensional model of the three human adiponectin chains was performed by a comparative modelling strategy using MODELLER9v5 program and evaluated in terms of the stereochemical, structural packing and energetic quality. Modeling of the human adiponectin receptor 1 (ADIPOR1) was obtained using an integrated protocol based on the methods of fold-recognition and comparative modeling. The ADIPOQ/ADIPOR1 and Osmotin/ADIPOR1 complexes were modeled using docking programs and analyzed to identify the amino acids at the interface, putative H-bonds and salt-bridges.

Results

We have modelled the three-dimensional structure of the adiponectin trimer and its ADIPOR1 receptor, and, successively, of their complex. The residues involved in the complex formation were carefully evaluated in order to know the molecular basis of this interaction as well as the physico-chemical features of these residues. Moreover, the complex between ADIPOR1 and the osmotin, being a small vegetable protein and having a fold similarity to adiponectin, was modelled and the

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interaction residues in this complex were evaluated. On the basis of these results an osmotin peptide was selected and its interaction with ADIPOR1 was modelled. Amazingly, our data show that the osmotin peptide is firmly positioned in the same area of receptor with which both the adiponectin and the osmotin interact. Therefore, it can be used to design a drug miming the adiponectin action. Furthermore, the possible health role of osmotin, as component of a human diet reach in fruit and vegetables, can be hypothesized.

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