Pisa, October 2011

The TSH receptor on Red Blood Cells

The short movie was produced to illustrate a new finding, by our colleagues at the Institute of Clinical Physiology of the CNR here in Pisa, published in 2009 (Silvana Balzan, Renata Del Carratore, Giuseppina Nicolini, Francesca Forini, Valter Lubrano, Marcella Simili, Pier Alberto Benedetti and Giorgio Iervasi. TSH induces co-localization of TSH receptor and Na/K-ATPase in human erythrocytes. Cell Biochem Funct 2009; 27: 259–263).

This short movie is honored by a music composed by Oscar winning musician Nicola Piovani, and is accompanied by the voice of actor Ugo Morosi (in Italian and English) that explains some of the details shown in the images.

It shows Thyrotropin (also called Thyroid Stimulating Hormone, TSH) flowing in the blood stream and binding to the TSH receptor on the surface of red blood cells. After binding, the dimeric receptor splits into two subunits each of which can leave the lipid raft to associate with other proteins of the cellular surface.

Biological and technical details

The first scene shows the isolated hormone, flowing freely in the medium. TSH is a dimeric protein, composed of two subunits: a specific beta part, and a common alpha subunit, which is also found in other hormones of the same family. Together, they form a small glycoprotein, which we have modelled by homology on the basis of the crystal structure of the Follicle-stimulating hormone (pdb entry 1xwd). TSH bears 3 oligosaccharide chains, which can be recognized as the most mobile appendices on the surface, and is represented with a very rough, hydrophilic surface.

The TSH receptor, a G protein coupled receptor, is composed of an extracellular part (most of what we can see in the movie), which was modelled using data of the crystal structure (pdb file 3g04), and of a transmembrane and homodimerization domain. The transmembrane part is invisible from the outer side, yet it is important for the correct placement of the monomers: we have obtained inspiration for the placement using the file pdb 1n3m, which describes a different protein whose transmembrane domain share some features with the TSH receptor.

The membrane of the red blood cell is populated by a number of different proteins: it is possible to see the transferrin receptor (pdb 1de4 CF chains), the Glucose transporter (glut-1, pdb file 1suk), Glycophorin A (pdb file 1afo), Beta2 adrenergic receptor (pdb file, 3nya), ICAM 4 (pdb file 3bn3), p47 (pdb file 1pwb, C chain), the trimeric RH factor (the Human Rhesus glycoprotein RHAG trimer, pdb 3hd6), EMMPRIN (3b5h), the anion exchanger Band 3 (based on model 2a65-a), Aquaporin (1fqy) and the Na/K pump (2zxe, 3kdp e 3a3y).
Also the extracellular space is filled with numerous proteins, among which we have included albumin (pdb 3jry), and the immunoglobulin G (1igt).

The movement of the TSH receptor, that switches between a closed and an open conformation, is based on a skeleton system, placed with care according to the domain subdivision of the protein. The OS chains are always more mobile that the aminoacid component, and can be recognized.

Finally we follow the TSH receptor dimer separating into its two subunits, one of which is seen associating with the Na/K pump.

Only at the end we can recognize that the membrane belongs to a red blood cell, when the camera zooms out and the entire blood flow is followed in a small vase.

All video material has been realized using Blender and BioBlender

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