Cholesterol: the eyes have it

Cell membranes are a complex mosaic of lipids and proteins. The membrane phospholipids are arranged in a bilayer with their polar heads interacting with the surrounding water and their hydrocarbon tails forming a hydrophobic core. Membrane proteins are embedded in the bilayer or are associated with the bilayer surface. The precise properties of the membrane bilayer depend upon the properties of the lipids and the proteins that compose it. An essential component of most animal cells is cholesterol, which is involved in an array of cell functions. The mechanism of its action involves both its ability to alter membrane lipid bilayer properties and to directly interact with membrane proteins. The review summarized here focuses on cholesterol modulation of the activation of rhodopsin, the light sensitive protein embedded in the disk and the plasma membranes of the retinal rod outer segment (ROS) (Fig. 1). Rhodopsin is of particular interest because it is the archetype of the large family of G-protein coupled receptors, which are responsible for cellular response to a wide array of signals.

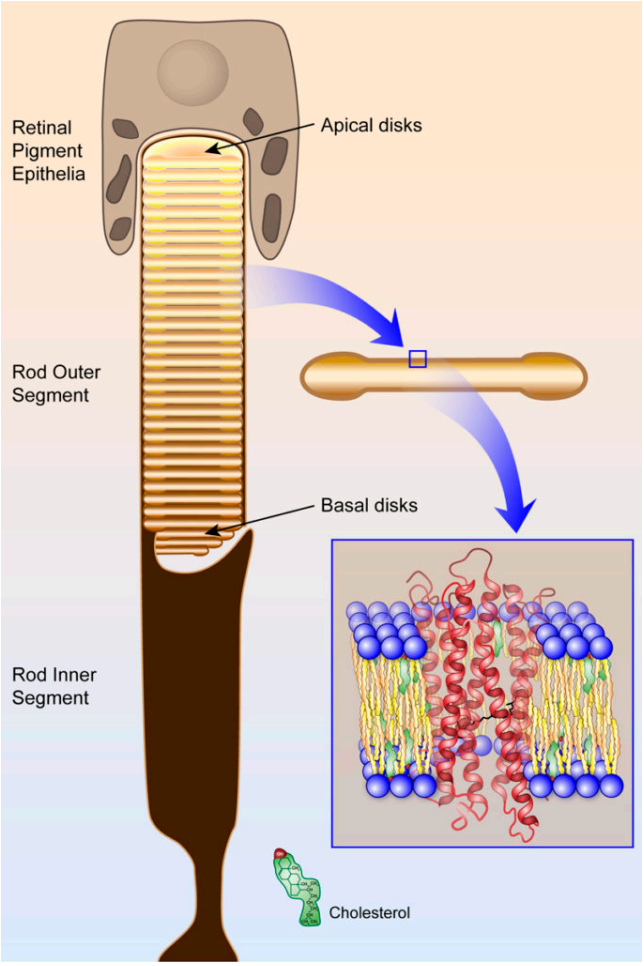

Fig. 1. The Rod Outer Segment. The decrease of disk membrane cholesterol and increase in the phospholipid unsaturation as disks are apically displaced is indicated by the dark to light gradient.

Rhodopsin is shown embedded in the membrane bilayer.

The cells responsible for light perception are in the retinal layer, located at the back of the eye. The cone cells are responsible for color vision and are preferentially found in the central region of the retina. The rod cells are preferentially found in the peripheral region. While rod cells are exquisitely sensitive to low levels of light they provide only black and white vision.

The ROS consists of a stack of flattened disk membrane vesicles surrounded by a plasma membrane (Fig. 1). Light impinging upon the disk membrane induces a conformational change in the rhodopsin structure. This critical shape change allows a G protein, transducin to bind and become activated, thus triggering a cascade that culminates in the visual response.

The disk membranes are synthesized at the base of the ROS and are displaced over the next several days to the apical tip. The lipid composition of disks is modified during this transit. The studies reviewed show that the cholesterol composition of the ROS plasma membrane and newly synthesized disks is approximately 30%. As the disks are displaced, the cholesterol in the disks drops to less than 10%. This drop in cholesterol is accompanied by an increase in the unsaturation of the hydrocarbon region of bilayer lipids.

This lipid modification is important because the ability of rhodopsin to undergo a light stimulated conformational change is sensitive to the properties of the lipid bilayer. That is, if the bilayer properties restrict conformational change, the activation of the visual cascade will be inhibited. Cholesterol renders the bilayer hydrocarbon core more resistant to accommodating conformational changes in rhodopsin. The decrease in cholesterol and increase of unsaturated lipids of the bilayer generates a milieu in which rhodopsin can readily undergo the appropriate light stimulated conformational change. Experiments in both plasma membrane and disk membranes have shown that cholesterol inhibits light activation of rhodopsin. This is further supported by investigations using rhodopsin reconstituted into well-defined lipid bilayers. There is also compelling evidence that cholesterol binds directly to rhodopsin. However, the role of bound cholesterol in rhodopsin function or stability is unclear.

If the cholesterol composition of the ROS deviates from the normal composition, degenerative disease and other visual defects may result. Royal College of Surgeons rats provide a model of degenerative disease. These rats exhibit an abnormal cholesterol distribution among the disks and plasma membrane. In the human disease, Smith-Lemli-Opitz (SLOS) syndrome there is a decreased ability to synthesize cholesterol. It is clear that cholesterol plays a complex role in the maintenance of photoreceptor structure and function.

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