Peripherin and retinopathies

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The research interests of this group are concerned with the structure and function of integral membrane proteins with particular emphasis on G-protein coupled receptors, ion channels, the vacuolar H^+-ATPase and lipocalins/receptors. Previous reports have been concerned with G-protein coupled receptors and the vacuolar H^+-ATPase. Here, we report on a project dealing with a new subject - peripherin.

Peripherin/rds is an integral membrane glycoprotein found in the rim regions of vertebrate photoreceptor cell discs. Natural mutations of the encoding gene result in degenerative retinal disorders, such as retinitis pigmentosa. The retinal degeneration slow (rds) phenotype, observed in mice, is considered to be an appropriate model for peripherin/rds-mediated retinities pigmentosa. Associated abnormalities in the outer segment of photoreceptor cells have implicated peripherin/rds in some aspect of disc morphology, yet it remains unclear whether such morphological effects are the cause or the result of this condition. Recently, we obtained the first direct evidence to support a role foe peripherin/rds in maintaining the flattened vesicle morphology characteristic of photoreceptor outer segments. *In vitro* expression yields a 36-kDa immunoreactive species, which is inserted into membranes and undergoes N-glycosylation, inter- and intramolecular disulphide bonding, and dimerisation. Electron microscopy reveals that periopherin/rds flattens microsomal vesicles (Fig 1).

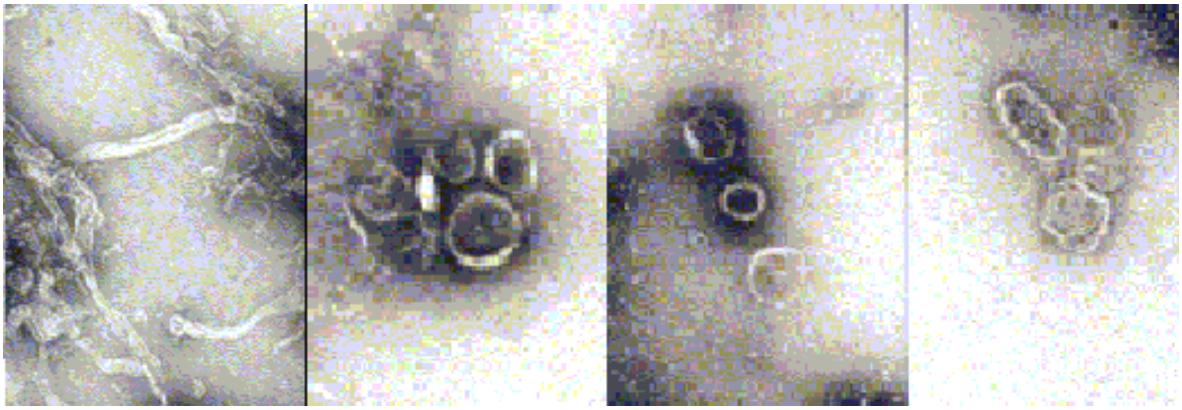

Figure 1.
Peripherin/*rds* under non-reducing conditions

RP Induced Mutations
C118S C165Y P216L

This effect appears to be dependent on disulphide bond formation but not N-glycosylation. The inability of several pathogenic peripherin/rds mutants to flatten membrane vesicles implicates such mutations as the primary cause of the retinal degeneration observed in retinitis pigmentosa.

Using the *in vitro* expression glycosylation system, we were also able to determine the topography of the protein in the bilayer, the region responsible for subunit interaction and the structural change which gives rise to one form of retinitis pigmentosa.

The discovery of the role of peripherin and the effect of natural mutations open up an approach to treatment which involves the use of small drug molecules rather than gene therapy.

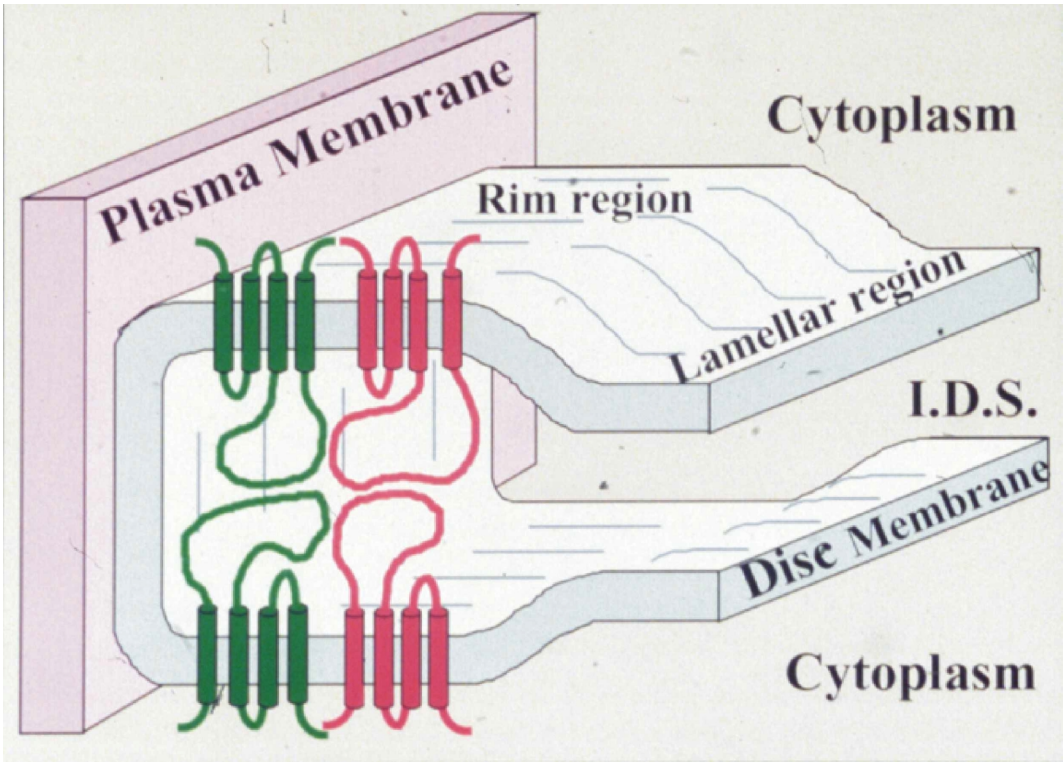

Figure 2 - Proposed Function

References

Wrigley, J.D.J., Ahmed, T., Nevett, C.L. & Findlay, J.B.C. (2000) Peripherin/*rds* influences membrane vesicle morphology. *J Biol Chem* , **275**, 13191-13194.

Wrigley, J.D.J., Nevett, C.L. & Findlay, J.B.C. (2002) Topological analysis of peripherin/*rds* and abnormal glycosylation of the pathogenic P216L mutation. Submitted

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