Does the tail wag the dog? How the structure of a protein's "tail" affects its function

Many proteins are attached to cell membranes by a glyco-lipid "tail" known as a glycosylphosphatidylinositol (GPI) anchor. It is becoming apparent that differences in the composition of these GPIs have profound influences upon protein structure, trafficking and function. Our recent study examined the effects of GPI structure upon the cellular prion protein (PrP^{C}). This protein is of interest as it can be converted into an alternatively folded, disease-associated isoform (PrP^{Sc}) commonly called a prion. Accumulations of PrP^{Sc} within the brain are associated with neurodegeneration and the clinical symptoms of prion diseases such as scrapie in sheep and Creutzfeldt-Jakob disease in humans. Our recent paper examined the effects of sialic acid, a rare modification of GPIs, upon the properties of PrP^{C}.

Our study reported 3 major observations;-

1) Desialylated PrP^{C} is not converted to PrP^{Sc}.
2) Desialylated PrP^{C} inhibits the conversion of PrP^{C} to PrP^{Sc}.
3) Desialylated PrP^{C} behaves differently from PrP^{C} with regards to its effects on membrane composition and cell signalling.

The obvious question; why do the effects of PrP^{C} and desialylated PrP^{C} differ so greatly? was explored. The first clue was the observation that PrP^{C} and desialylated PrP^{C} were targeted to different domains within the cell membrane. The membrane surrounding GPI-anchored proteins is composed of specific phospholipids, glycolipids and cholesterol that constitute a "raft". The composition of this raft is dependent upon interactions between the glycans on the GPI and membrane lipids. A change in the GPI, such as the loss of sialic acid, affects the composition of the surrounding membrane raft and has consequences for protein trafficking and function. Significantly higher concentrations of gangliosides and cholesterol associated with desialylated PrP^{C} compared with PrP^{C} and desialylated PrP^{C} and PrP^{C} trafficked differently within neurons.

PrP^{Sc} is thought to bind to PrP^{C} and convert it into PrP^{Sc} in a process that occurs within membrane rafts. The composition and function of these rafts is dynamic and controlled by an "induced fit" model. Since the composition of rafts is affected by the structure of GPIs then the raft surrounding a complex between PrP^{Sc} and PrP^{C} would be expected to differ from the raft surrounding PrP^{Sc} and desialylated PrP^{C}. We hypothesised that the binding of desialylated PrP^{C} to PrP^{Sc} changed the composition of local rafts so that they are unfavourable for the conversion of PrP^{C} to PrP^{Sc}. The clustering of GPIs containing sialic acid activated cytoplasmic phospholipase A_2 ($cPLA_2$) an enzyme that promotes PrP^{Sc} formation. In the presence of desialylated PrP^{C}, activation of $cPLA_2$ is reduced as it dissociates from PrP^{Sc}-containing rafts. Thus, the binding of desialylated PrP^{C} to PrP^{Sc} affects the composition of the underlying raft so that it no longer captures and activates $cPLA_2$.

In conclusion we show that sialic acid contained within the GPI “tail” affects the properties of PrP^{C}, altering the surrounding raft, the trafficking of PrP^{C} and PrP^{C}-induced cell signalling. Critically the presence of desialylated PrP^{C} reduced the activation of $cPLA_2$ and PrP^{Sc} formation. We propose that sialic acid on the GPI attached to PrP^{C} affects the membrane targeting and cell signalling that is conducive to its conversion to PrP^{Sc}. Consequently, therapeutics that block the incorporation of sialic acid into GPI anchors could prove useful in the treatment of prion diseases.

Publication

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