Glycosylphosphatidylinositols: More than just an anchor?

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Glycosylphosphatidylinositol anchors are more than just a cell membrane attachment. The role of sialic acid on the glycosylphosphatidylinositol (GPI) anchor has been investigated, particularly in the context of prion disease formation. Our recent paper demonstrated that desialylated PrP C inhibited PrP Sc formation. Aggregated PrP Sc creates a signaling platform in the cell membrane incorporating and activating cytoplasmic phospholipase A2 (cPLA2), an enzyme that regulates PrP C trafficking and hence PrP Sc formation. The presence of desialylated PrP C caused the dissociation of cPLA2 from PrP-containing platforms, reduced the activation of cPLA2 and inhibited PrP Sc production. We concluded that sialic acid contained within the GPI attached to PrP C modulates local membrane microenvironments that are important in PrP-mediated cell signaling and PrP Sc formation.

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cholesterol; glycosylphosphatidylinositol; phospholipase A2; sialic acid

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after cholesterol depletion, whereas PrPC redistributed to the normal cell membrane, and that desialylated PrPC had a demonstrably longer half-life than PrPC in neurons. We speculated that if sialic acid contained within the GPI competes with gangliosides for sialic acid-binding proteins, then the removal of sialic acid would allow the incorporation of more gangliosides into PrPSc-containing rafts. Gangliosides help sequester cholesterol that increases membrane rigidity and stabilize lipid rafts. Therefore, the increased concentrations of gangliosides surrounding desialylated PrPC would explain the observed increased cholesterol concentration in lipid rafts surrounding desialylated PrPC. This hypothesis is compatible with reports that the concentrations of gangliosides in lipid rafts affects the expression of PrPC.

When neurons from transgenic mice in which the PrP protein had been deleted (Prnp(0(0)) neurons) were pulsed with PrPSc, we found that PrPC was converted to PrPSc, but desialylated PrPC was not. Perhaps of greater interest were observations that in wildtype neurons and neuronal cell lines the presence of desialylated PrPSc significantly reduced the conversion of PrPC to PrPSc. While most potential therapeutics for prion diseases are targeted at the protein component of PrP, our work highlights the importance of the underlying cell membrane. Since the composition and hence the function of lipid rafts is controlled by an “induced fit” model we hypothesized that the binding of desialylated PrPC to PrPSc modified the lipid rafts involved in PrPSc formation. Because the composition of lipid rafts is affected by the glycan composition of GPIs we expected that the lipid rafts surrounding PrPSc:PrPC complexes would differ from that of lipid rafts surrounding complexes of PrPSc:desialylated PrPC. We proposed that the binding of desialylated PrPC to PrPSc changes the composition of the lipid rafts so that it inhibits the conversion of PrPC to PrPSc.

The coalescence of outer membrane lipid raft proteins affects the composition of the cytoplasmic leaflet and its association with signaling molecules. The clustering of sialic acid-containing GPIs attached to PrP proteins activates cPLA2, an enzyme that promotes PrPSc formation. This occurs naturally as a consequence of PrPSc self-aggregation, and cPLA2 is concentrated within PrPSc-containing lipid rafts. The binding of desialylated PrPC to PrPSc changed the underlying membrane so that it no longer captured and activated cPLA2. This reduced the activation of cPLA2 by existing PrPSc and hindered the conversion of PrPC to PrPSc. It is noteworthy that desialylated PrPC is surrounded by more gangliosides than PrPC, which is consistent with reports that gangliosides inhibit the activation of cPLA2.

We concluded that sialic acid in the GPI anchors affects the properties of PrPC, altering the surrounding membrane; PrP-induced cell signaling and the trafficking of PrPC. Critically desialylated PrPC reduced the activation of cPLA2 and PrPSc formation in prion-infected cells. We propose that sialic acid on the GPI anchor attached to PrPC affects its precise membrane targeting and the subsequent cell signaling that is conducive to its conversion to PrPSc.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**References**


