

HYALURONAN–PLASMA MEMBRANE DIRECT INTERACTION MODULATES SURFACE DYNAMICS

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Glycosaminoglycans are the most abundant compounds of the glycocalyx, a highly charged layer of biological macromolecules attached to a cell membrane. This layer functions as a barrier between a cell and its surroundings, meaning that any molecule entering or leaving a cell permeates through it [1]. Glycosaminoglycans in the glycocalyx can be either free, *e.g.* hyaluronan, or covalently bound to glycocalyx proteins, such as heparan sulphate, chondroitin sulphate, and dermatan sulphate. In both cases, glycosaminoglycans are long negatively charged sugar polymers often located close to the plasma membrane surface, and therefore, they could potentially interact with one another. Very little is known about the nature of this interaction and its biological relevance. Experimental data suggest that heparan sulphate prefers to be displaced away from a membrane, while chondroitin sulphate prefers direct contacts with a membrane, though the grounds for such statement can be debated [2]. Still, this view is consistent with an observation that the syndecan-4 attachment sites for glycosaminoglycans that are close to the transmembrane domain are often populated with chondroitin sulphate instead of the usual heparan sulphate [3]. Also experimental data suggest that hyaluronan loosely interacts with membranes [4].

Hyaluronan is a non-branched polymer constituted by the repetition of a $[-(\beta\text{-}4)\text{ D-glucuronic acid } - (\beta\text{-}3)\text{ N-acetyl-D-glucosamine } -]$ dimer. It is also known as the megadalton molecule as its length can reach several micrometers. We believe that due to this formidable span, if a significant although transient interaction with the membrane can be found, hyaluronan can be the key compound of an exoskeleton. In this context, it could work like the cytoskeleton helping to compartmentalize and confine the motion of the membrane bound molecules, *e.g.* membrane-proteins, in the extracellular side of plasma membrane. In this work we have analyzed in detail the hyaluronan membrane interaction using all atom molecular dynamics simulation. Our experiments show that the hyaluronan membrane interaction is highly dependent on the nature of the underlying membrane and the ionic strength of the surrounding solution. In general the interaction per dimer is slightly below $K_B T$. However, in our simulations long polymers show a persistent but reversible attachment to the membranes. When bonded we see that hyaluronan does not modify significantly the dynamics of the simulated membrane as whole. However, the dynamics in the proximity of the interaction area is clearly modified. Taking into account the already crowded nature of the plasma membrane, this extra interaction could play a significant role, promoting flows of lipids along the hyaluronan chain when in contact with the membrane. Finally, we have observed that hyaluronan may induce exclusion of cholesterol under the contact area (local phase separation) changing the underlying lipid dynamics.

References

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