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Exploring the interaction between mammalian extracellular vesicles and Siglecs

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Extracellular vesicles (EVs) participate in intercellular communication in health and disease. However, the molecular interactions between EVs and cells, which facilitate cell-cell communication, are yet to be fully uncovered. The surface of EVs is decorated with glycans, including glycoproteins, glycosaminoglycans, and glycolipids. EVs have a distinct glycan signature that differs from their parent cell membrane, suggesting that EV glycosylation may selected in order to facilitate this cell-cell communication. As mammalian cells express lectins that can recognize and differentially respond to glycosylation patterns, they are well positioned to serve as a mechanism by which EVs act.

Within the immune system, EVs have been shown to promote immunological tolerance towards 'self'. We hypothesize that sialic acid-binding Ig-like lectins (Siglecs), which bind sialylated glycans and act as a 'brake' on immune cells, serve as a molecule mechanism linking EVs and immunological tolerance. A procedure to isolate EVs from cultured cells or blood was optimized and found to reliably yield EVs in the 50-200 nm range. Fluorescent labeling of isolated EVs has enabled interactions with Siglecs to be studied in two flow-cytometry-based assays: (1) a microbead assay wherein a soluble Siglec is immobilized and (2) cultured cells uniquely overexpressing a single Siglec. Using these assays, several novel Siglec-EV interactions have observed with Siglec-2 (CD22) and Siglec-6. Interactions with Siglecs are of particular interest because our lab has recently discovered that Siglec-6 can bind glycolipids (Schmidt, *manuscript in preparation*). Indeed, we find that enzymatic treatment of EVs with Endoglycoceramidase (EGCase), an enzyme capable of removing the carbohydrate from glycolipids, reduces the binding of EVs to Siglec-6, suggesting that binding of EVs to hSiglec-6 is glycolipid-mediated.

Given the relevance of both CD22 and Siglec-6 cells, we are now focusing on testing whether these Siglec-EV interactions relate to B cell tolerance. Progress towards understanding the role of these Siglecs in tolerance to EVs will be presented. Taken together, our preliminary data suggest that the ability of EVs to interact with Siglecs may be more broad than previously anticipated.