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Abstract

Exosomes, also known as microvesicles (EMVs), are nano-sized membranous particles secreted from nearly all mammalian cell types. These nanoparticles play critical roles in many physiological processes including cell-cell signaling, immune activation and suppression, and are associated with disease states such as tumor progression. The biological functions of EMVs are highly dependent on their protein cargo, which can dictate pathogenicity. We hypothesized that N-linked glycosylation is a sorting signal for protein recruitment into EMVs and that association with glycosylated proteins might also drive recruitment of the tetraspannin CD81 into EMVs. To this end our grant objectives were: 1.) Determine whether recruitment to MVEx of glycosylated CD81 interaction partners (GIPs) is glycan-dependent. and 2) Examine whether association between GIPs and CD81 is necessary for CD81 recruitment to MVEx. In the course of this work, we identified specific glycosylated targets, including EWI-2, a glycosylated CD81 interacting partner, and demonstrated alteration of their recruitment to EMVs as a function of their glycosylation status upon pharmacological manipulation. Further, we showed that genetic manipulation of the glycosylation levels of EWI-2, directly impacted its recruitment as a function of N-linked glycan sites. Contrary to our hypothesis, no impact was observed on CD81 recruitment. Taken together, our data provides strong evidence that N-linked glycosylation directs glycoprotein sorting into EMVs and serves as a determinant of EMV cargo selection.