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GLYCOSWITCH — A NOVEL SIGNALING CIRCUIT TO CONTROL ENDOCYTOSIS

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Glycosphingolipids (GSLs) are present at the plasma membrane of mammalian cells. Their molecular mechanisms of function remain in many cases poorly understood. We have previously established a model according to which oligomeric lectins of pathogenic (Shiga and cholera toxins, polyomaviruses) or endogenous origins (galectins) use GSLs to drive the biogenesis of tubular endocytic pits from which clathrin-independent endocytic carriers are generated. This model was termed GlycoLipid-Lectin (GL-Lect) driven endosytosis. We have now built a nanoscale force sensor that allows to study how the specific molecular geometry of Shiga toxin-GSL complexes favors their membrane-mediated clustering leading to GL-Lect driven endosytosis. Furthermore, we have discovered a N-glycan based mechanism by which the endogenous galectin-3 is converted specifically on bent-closed inactive α5β1 integrin from its monomeric state in solution to an oligomeric state that gains the capacity to interact with GSLs and to drive endocytic uptake of the integrin [1]. This process is regulated by growth factor signaling through the reversible removal of sialic acid from cargo proteins such as the integrins, which reveals that the glycan makeup of glycoproteins at the cell surface is not as static as it is typically perceived [2]. We have termed this the GlycoSwitch. We are now exploring the structural, molecular, and pathophysiological aspects of the GlycoSwitch, including epithelial-mesenchymal plasticity in normal and tumoral breast tissue.

References

1. Shafaq-Zadah M et al. Nat Commun 16: 9461, 2025
2. MacDonald E et al. Nat Cell Biol 27: 449-463, 2025