Cancer Immunology

Expression of neolacto-series glycosphingolipids by tumors impairs the function of low-affinity immune receptor-ligand pairs.

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The transcriptional signature of neolacto-series glycosphingolipid (nsGSL) expression highly associates with patient survival in a number of cancers, such as glioma. We recently identified that nsGSLs on such tumor cells negatively affect immune cell activation *in vitro* (Jongsma et al., Immunity 2020). However, the mechanism underlying this immune suppression is unknown.

We discovered in a flow cytometry approach with barcoded cell lines that nsGSLs sterically shield several, but not all, immune cell surface receptors. In depth analyses of shielded receptor properties revealed that they have significantly shorter extracellular domains compared to non-shielded receptors, which may relate to the limited extracellular length of nsGSLs. Secondly, using genome editing and pharmacological inhibitors, we found that negatively charged sialic acids of nsGSLs likely interact with positively charged amino acids of shielded proteins. This interaction inhibited antibody binding to surface receptors, which was highly dependent on affinity as we established with a well-characterized antibody panel against CD147. Consequently, low-affinity interactions of the central immune receptors HLA class I and CD47 with their ligands LIR-1, KIR2DL2 (HLA class I), and SIRP-α (CD47) were largely impaired by nsGSLs.

Overall our data strongly indicate that expression of nsGSLs by tumor cells prevents productive communication towards immune cells through charge-based shielding of short receptors from their low affinity ligands. Because the GSL synthesis pathway is safely targeted in lysosomal storage diseases, our data warrant investigations on the efficacy of GSL synthesis inhibition to treat patients with nsGSL-rich tumors.