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12P LECTIN GALACTOSIDE-BINDING SOLUBLE 3 BINDING PROTEIN (LGALS3BP) IS A CANCER-ASSOCIATED LIGAND FOR INHIBITORY SIGLECS

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Tumor cells subvert the control of the immune system by downregulation of their antigenicity and production of an immunosuppressive microenvironment including the upregulation and engagement of inhibitory receptors on immune cells. Therapeutic strategies have demonstrated that the immune system can be reactivated and control established cancers by blocking inhibitory receptors on immune cells such CTLA-4 and PD1. While such activation of the immune system is successful in some patients, many patients still show cancer progression after some time. Thus, the definition of new targetable immunomodulatory pathways is needed to improve the outcome in those patients. Recent evidence suggests that sialic acid dependent ligands on tumor cells can engage inhibitory sialic acid binding immunoglobulin-like lectins (Siglecs) on NK cells and cells of the myelomonocytic lineage and thereby facilitate evasion of immune-mediated killing. Moreover, the presence of a natural variant of Siglec-9 with reduced binding capacity to sialic acid dependent ligands in patients with non-small cell lung cancer improved the two year survival in a retrospective multivariate analysis. Here we identify a novel cancer-associated ligand for immuno-inhibitory Siglecs by affinity chromatography and subsequent proteomic analysis.
LectinGalactoside-Binding Soluble 3 Binding Protein (LGALS3BP) bound to various inhibitory Siglecs including Siglec-5, Siglec-9 and Siglec-10 with high affinity. LGALS3BP was previously found to be upregulated in various carcinomas such as breast, colorectal, prostate and lung cancer and linked to advanced stage and poor prognosis. The exact function during cancer progression, however, was not yet defined. Our findings provide a novel insight into how LGALS3BP could promote immune evasion by inhibiting immune cell activation through engagement of Siglecs and defines LGALS3BP-Siglec interactions as potential novel target to interfere with cancer progression and reactivate the immune system against carcinomas.

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