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GAG–CCL2 Disruption as a Therapeutic Strategy to Reverse Immune Evasion and Enhance Cancer Immunity

Tumor-associated glycosaminoglycans (GAGs) critically shape the immune landscape by sequestering chemokines such as CCL2, thereby orchestrating the recruitment and polarization of immunosuppressive myeloid cells. However, the therapeutic potential of disrupting GAG-chemokine interactions in solid tumors remains unexplored. Here, we demonstrate that elevated expression of GAG biosynthesis genes and CCL2 in head and neck cancer is linked to poor prognosis, marked immunosuppression, angiogenesis, and epithelial-mesenchymal transition. We evaluated the potential of MMIb, a CCL2 fragment containing a GAG-binding domain, in reprogramming the tumor microenvironment to reverse myeloid-mediated immunosuppression and enhance anti-tumor immunity. *In vitro*, MMIb prevents the immunosuppressive polarization of macrophages in the presence of tumor-derived factors and GAGs. In murine tumor models, MMIb treatment reduces tumor growth, diminishes infiltration by myeloid cells, and attenuates angiogenic and EMT signatures. Proteomic profiling and flow cytometry reveal that MMIb reprograms myeloid cells toward an immunostimulatory phenotype, enhances antigen presentation, and augments interferon signaling, resulting in improved T cell activation and reduced exhaustion. Notably, MMIb is effective both as a preventive and therapeutic intervention in established disease. *Ex vivo*, MMIb limits monocyte migration and suppressive polarization in human tumor explants. These findings establish GAG-CCL2 interactions as a central axis of immune evasion and tumor progression, and identify selective disruption of this pathway as a strategy to reprogram the tumor microenvironment and potentiate anti-tumor immunity. Our work highlights the translational potential of targeting GAG-chemokine interactions for cancer therapy, with broad implications for overcoming immune escape in tumors characterized by high GAG and CCL2 expression.

Research type

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