

Adrenergic signaling induces a pro-tumorigenic B cell state in colorectal cancer

TT1-02

M.S. Thijssen^{I,III}, S.S. Schonkeren^I, L. Coolkens^I, Y. Zou^I, L. Temmeman^I, J. de Vaan^I, M. Idris^I, J. Vrancken^{II}, K. Wouters^I, N. Vaes^I, M.J. Gijbels^I, S. Scardellato^{III}, E. Wijnands^I, W. van de Wetering^{IV}, F. Verhaegen^V, L.J. Dubois^{IV}, E. Biessen^I, C. Lopez Iglesias^{IV}, K.M. Smits^I, A. Bardelli^{III}, S. Casola^{III}, W. Boesmans^I, V. Melotte^I

^IDepartment of Pathology, Maastricht University Medical Center+, Maastricht, Netherlands, ^{II}Hasselt University, BIOMED Research Institute, Hasselt 3500, Belgium, Hasselt, Belgium, ^{III}IFOM ETS - The AIRC Institute of Molecular Oncology, Via Adamello 16, Milano, Italy, ^{IV}Maastricht University, Maastricht, Netherlands, ^VDepartment of Radiation Oncology (MAASTRO Lab), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, Netherlands

The importance of neuron-tumor crosstalk has gained increasing attention, yet its influence on the cellular and molecular landscape of colorectal cancer (CRC) remains largely unexplored. Here, we show that colonic innervation shapes the tumor immune microenvironment in a murine model of colitis-associated CRC. Although neuronal density does not affect tumor number, size, or overall burden, transcriptomic profiling of cells isolated from the tumor of hypo-innervated mice revealed extensive differential gene expression, including genes involved in immunoglobulin (Ig) signaling and the cancer-relevant hallmark ‘avoiding immune destruction’. Flow cytometry analysis of leukocyte populations demonstrated a significant reduction of B cells in the cancerous colon of hypo-innervated mice, notably a decrease in germinal center B cells and an altered class-switching profile, characterized by reduced IgA and increased IgD expression. Fluorescence and transmission electron microscopy showed that colonic B cells are primarily localized in the submucosa near neuronal processes containing varicose release sites, suggesting direct neuron-B cell interactions. Functional assays revealed that adrenergic stimulation of B cells promotes their proliferation and maturation, enhances IL-10 secretion, and alters immunoglobulin profiles. Strikingly, the transcriptome of epinephrine-treated B cells closely mirrors that of plasma cells from human CRC tissues, and the transcriptomic signature of these epinephrine-stimulated B cells associates with poorer patient survival. Together, these findings uncover an adrenergic neuron - B cell axis in CRC, providing evidence for direct neuroimmune interactions that affect B cell maturation and may influence tumor progression and therapeutic responses.