Title: Epithelial stromal interaction 1 (EPSTI1) is an epithelial modulator of chemotherapy response in colorectal cancer

Authors:
Erdogan Pekcan Erkan, Emmi Hämäläinen, Julia Kolikova, Kornelia Kuc, Kalle Ojala, Meiju Kukkonen, Ismail Hermelo, Selja Koskensalo, Timo Tarvainen, Alli Leppä, Ilona Keränen, Carola Haapamäki, Essi Karjalainen, Monika Carpelan-Holmström, Laura Renkonen-Sinisalo, Laura Koskenvuo, Pauli Puolakkainen, Jukka-Pekka Mecklin, Elina Virolainen, iCAN, Matti Nykter, Lauri A. Aaltonen, Anna Lepistö, Ari Ristimäki, Toni T. Seppälä

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Abstract
Epithelial cell–intrinsic mechanisms that shape chemotherapy response in colorectal cancer (CRC) remain poorly understood due to confounding signals from the tumor microenvironment. Using genomic, transcriptomic, and drug response profiling of patient-derived tumor organoids (PDTOs), we found that elevated interferon-stimulated gene (ISG)-driven JAK–STAT activity correlated with reduced sensitivity to standard chemotherapies. Reanalysis of public single-cell RNA sequencing datasets from rectal tumors before and after neoadjuvant therapy showed that persistent epithelial ISG expression was associated with incomplete pathological response, identifying *EPSTI1* as a putative regulator of chemotherapy response. Analysis of deconvoluted bulk RNA-seq from matched normal colon, primary tumors, and liver metastases revealed *EPSTI1* upregulation in primary tumors compared with normal tissue, with heterogeneous expression across metastases, suggesting divergent regulation during disease progression. Functional assays demonstrated that *EPSTI1* knockdown impaired CRC cell viability and increased chemosensitivity, whereas overexpression partially restored resistance. Collectively, these findings establish *EPSTI1* as a previously unrecognized epithelial determinant of chemotherapy response in CRC and highlight the therapeutic potential of targeting epithelial ISG pathways to improve treatment outcomes.