Evaluating the Molecular and Clinical Significance of CRH-Stress Regulators in Colorectal Cancer Pathophysiology Via Persistent IL-6/Stat3 Signaling.

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Abstract:

Chronic stress may contribute to colorectal cancer (CRC) development by perpetuating inflammatory responses. Here, we investigated the distribution of key stress regulators, specifically the Corticotropin-Releasing-Hormone (CRH)-family of neuropeptides and receptors, in CRC and their role in promoting tumor growth and oncogenic EMT.

Expression of CRH-family members was analyzed in CRC cell lines and tissues. Cell proliferation, migration and invasion were assesed in parental and CRHR2-overexpressing (CRHR2+) CRC cell lines after Ucn2 and/or IL-6 stimulation. CRHR2/Ucn2-targeted effects on tumor growth and EMT were also validated in SW620-xenograft mouse models.

CRC tissues and cell lines exhibited decreased CRHR2 and elevated Ucn2 levels compared to their normal counterparts. Ectopic CRHR2 activation by Ucn2 in CRC-CRHR2+ cells inhibited their proliferation, migration, invasion, colony formation and the expression of inflammation markers by suppressing IL-6/Stat3 signaling. Similarly, in vivo SW620-CRHR2+ xenografts demonstrated reduced tumor growth and expression of EMT-inducers. In CRC patients, CRHR2low expression was positively correlated with EMT phenotypes, higher risk for distant metastases and poorer clinical outcomes.

Overall, CRHR2 downregulation in CRC supports tumor growth and spread by sustaining chronic inflammation and persistent Stat3 activation. Consequently, stress-modified CRHR2 levels may serve as a signature with putative preventive, prognostic and therapeutic significance in colorectal malignancies.