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Evaluating the therapeutic potential of a novel ADAM10 modulator in colorectal cancer

The ADAM10 metalloproteinase contributes to colorectal cancer tumorigenesis, predominantly through the activation of critical oncogenic pathways, including Notch and EGFR. This enzyme uniquely exhibits two conformations: an open, active state and a closed, inhibited state. Significantly, the active conformation, associated with elevated proteolytic activity, is prevalently observed in colorectal cancer cells. Our research investigates a novel human monoclonal antibody designed to selectively bind the active conformation of ADAM10, targeting its substrate-binding cysteine-rich domain.

Methodology: We assessed the anti-tumoral effects of this antibody in vitro through cell viability assays and signaling pathway analyses. We examined the antibody's efficacy across various colorectal cancer cell lines, including COLO205, SW620, and DLD-1, as well as CRC KrasG12D; Apc+/-; Trp53-/- (KAP) organoids. Additionally, we conducted in vivo studies using COLO205 and DLD-1 xenograft models, along with in vitro assays to evaluate anti-invasive properties in the SW620 metastatic cell line.

Results: Our data shows that the antibody can inhibit the activation of the Notch signaling pathway in COLO205 and SW620 cell lines, as well as in KAP organoids. In the DLD-1 cell line, which is characterized by active EGFR signaling but lacks active Notch signaling, the antibody effectively blocks EGFR phosphorylation. These molecular interactions correlate with reduction in cell viability across the tested cell lines. In vivo assessments reveal that the antibody substantially attenuates tumor growth in xenograft models. Additionally, it significantly decreases cell invasion in SW620 cells, indicating potential anti-metastatic properties.

Conclusion: This study highlights the therapeutic potential of targeting the active conformation of ADAM10 in colorectal cancer. The demonstrated efficacy of this novel antibody in diminishing tumor viability and interfering with major oncogenic pathways, comb