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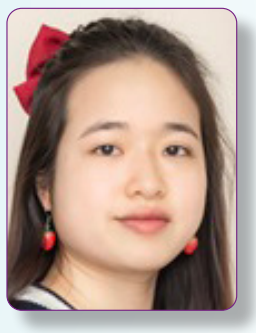

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communications biology

A feedforward loop between STAT1 and YAP1 stimulates lipid biosynthesis, accelerates tumor growth, and promotes chemotherapy resistance in mutant KRAS colorectal cancer

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Colorectal cancer (CRC) is a heterogeneous disease with various genetic mutations and metabolic alterations, including KRAS mutations, particularly in the CMS3 subtype. These mutations significantly alter cellular metabolism, especially lipid and sterol biosynthesis, influencing tumor growth and therapy resistance.

In tumorous conditions, STAT1, traditionally recognized for its anti-tumor role in immunology, exhibits pro-survival characteristics, though unclear mechanisms. Investigating STAT1 function in isogenic colorectal tumor cells with wild-type or mutant KRAS, we found that STAT1 specifically promotes tumor survival and proliferation with mutant KRAS.

Gene expression profiling revealed that STAT1 promotes the expression of sterol and lipid biosynthesis genes in these cells. This effect depends on STAT1 phosphorylation at S727, which upregulates SREBP1 and SREBP2 to drive de novo lipid production.

In mutant KRAS cells, STAT1 amplifies the mevalonate pathway, maintaining its S727 phosphorylation and establishing a positive feedback loop through the transcription factors YAP1 and TEAD4, further driving lipid biosynthesis and tumor growth. This STAT1-YAP1 axis promotes mutant KRAS tumor cells' resistance to mevalonate pathway inhibitors, which can be overcome by pharmacologically targeting the YAP1-TEAD interaction. Moreover, this axis contributes to the inherent resistance of mutant KRAS colon cancer cells to EGFR-targeted therapy.

Our study underscores the establishment of a feedforward loop between STAT1 and YAP1, driving the upregulation of lipogenic pathways and conferring resistance to mevalonate pathway and EGFR inhibitors in mutant KRAS cells. This intricate interplay reveals a potential target for therapeutic intervention in the context of mutant KRAS-associated cancers.

Together, these findings identify the STAT1-YAP1 pathway as a critical mediator of therapy resistance and a promising therapeutic target in mutant KRAS colorectal cancer.

https://www.nature.com/articles/s42003-025-08740-2