CANCER

mTOR inhibition curbs colorectal cancer

Mutations in the gene that encodes APC (adenomatous polyposis coli) are common in colorectal cancer — they are responsible for familial adenomatous polyposis (FAP) and also have a key role in the majority of cases of sporadic disease. APC regulates the WNT signalling pathway, thereby affecting various cellular processes, but the precise molecular mechanisms that mediate the effects of APC inactivation on tumorigenesis remain unclear. Now, writing in *Nature*, Sansom and colleagues have identified a key role for mammalian target of rapamycin (mTOR) signalling in APC-deficient colorectal cancer. Inhibition of mTOR effectively suppressed intestinal tumorigenesis and increased survival in mouse cancer models.


S.Harris/NPG

Previous studies have suggested that the serine/threonine kinase mTOR — a known mediator of growth and proliferation, particularly as part of the mTOR complex 1 (mTORC1) — may be important in intestinal tumorigenesis. Therefore, Sansom and colleagues set out to investigate the role of mTOR signalling in APC-deficient colorectal cancer.

First, the authors noted that *Apc* deletion in mice increased mTORC1 effector phosphorylation, and treatment of mice with the mTOR inhibitor rapamycin specifically blocked phosphorylation of the mTORC1 effector, ribosomal protein S6. Rapamycin also blocked intestinal regeneration following exposure of mice to γ-irradiation, demonstrating a requirement for mTOR signalling in this process. Importantly, rapamycin did not affect apoptosis or proliferation in the normal intestine.

To further investigate the role of mTOR signalling, the authors deleted raptor (encoded by *Rptor*; an essential component of mTORC1) in the intestinal epithelium of mice. Raptor proved to be essential for the proliferative phenotype that was observed during intestinal regeneration or after *Apc* deletion. Loss of raptor had no effect on mitosis or apoptosis and did not affect normal gut homeostasis.

Next, they assessed the potential of inhibiting mTOR as a putative anticancer strategy. In mice, 30 days of rapamycin treatment, initiated 10 days after *Apc* deletion, effectively suppressed tumour development. Rapamycin was also effective in mice with established adenomas — 30 days of treatment eliminated clinical symptoms, caused significant tumour regression and increased survival compared with control mice.

The authors then examined the mechanism of mTORC1 requirement after APC loss. Given that mTORC1 is known to regulate protein synthesis and translational control, they assessed changes in translational activity following *Apc* deletion. *In vitro* and *in vivo* studies that measured polysomal distribution and ribosomal run-off rates indicated that *Apc* deletion increased the rate of translational elongation. Furthermore, in mice, cycloheximide (an inhibitor of elongation) reduced proliferation that was associated with *Apc* deletion to a level similar to that seen with rapamycin.

Analysis of multiple knockout and knock-in allele mouse models revealed that the effects of APC loss on translational elongation were mediated by increased activity of eukaryotic elongation factor 2 (eEF2), due to S6 kinase-mediated inhibition of eEF2 kinase, which is required for increased intestinal proliferation. Such increased translational elongation increased levels of the cell-cycle regulating protein, cyclin D3.

These findings suggest that targeting mTOR and translational control may represent a potential strategy for early-stage treatment and prevention of colorectal cancer.

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