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TUMOUR IMMUNOLOGY

NLRC3 inhibits mTOR in colorectal cancer

NLRs (NOD-like receptors) are members of a large family of intracellular innate immune sensors that mediate numerous biological functions. Although most NLRs function as activators of innate immunity, NLR family CARD-containing 3 (NLRC3) has been described as a negative regulator of inflammatory signalling pathways. Reporting in *Nature*, Kanneganti and colleagues show that NLRC3 protects against the development of colorectal cancer through the inhibition of the PI3K–mTOR pathway.

The expression of NLRC3 is greatly reduced in the tumour tissue of patients with colorectal cancer compared with healthy tissue. To investigate the role of NLRC3 in tumorigenesis, the authors used an established model of colitis-associated colorectal cancer, which involves the injection of mice with azoxymethane followed by three rounds of dextran sulfate sodium treatment. At day 80 after injection of azoxymethane, the expression of *Nlrc3* was significantly reduced in the tumour tissue of wild-type mice compared with healthy colon tissue. Furthermore, *Nlrc3*$^{-/-}$ mice lost more body weight, suffered more severe shortening of and damage to the colon and developed significantly more colon tumours compared with wild-type mice.

Nlrc3$^{-/-}$ mice had increased levels of pro-inflammatory cytokines and chemokines and increased activation of immune signalling pathways in colon tissue at day 14 after azoxymethane treatment compared with control mice. Furthermore, the numbers of macrophages, neutrophils and natural killer cells in the colon of *Nlrc3*$^{-/-}$ mice were higher than in wild-type mice at day 14. Together, these data indicate that NLRC3 helps to protect against colitis-associated colorectal tumorigenesis.

Next, the authors found that mice lacking NLRC3 specifically in intestinal epithelial cells developed the highest number of tumours, followed by mice lacking NLRC3 in haematopoietic cells, whereas mice lacking NLRC3 in myeloid cells developed the same number of tumours as wild-type mice. The intestinal epithelial cells of *Nlrc3*$^{-/-}$ mice expressed significantly higher levels of proliferation markers, and colonic epithelial stem cells from *Nlrc3*$^{-/-}$ mice more readily developed into organoids in *ex vivo* cultures than did cells from wild-type mice. Thus, NLRC3 functions predominantly to suppress the hyperproliferation of enterocytes. These observations were confirmed in a spontaneous mouse model of colon cancer (*Apc*$^{Min/+}$ mice).

The increased cellular proliferation of epithelial cells and enhanced organoid formation in the absence of NLRC3 were associated with increased activation of the mechanistic target of rapamycin (mTOR) signalling pathway. The phosphorylation levels of the upstream signalling molecules phosphoinositide 3-kinase (PI3K), phosphoinositide-dependent protein kinase 1 (PDK1) and AKT, as well as of mTOR itself, were increased in the colon tissue of *Nlrc3*$^{-/-}$ mice compared with wild-type mice at day 14. Treatment of *Apc*$^{Min/+}$*Nlrc3*$^{-/-}$ mice with an inhibitor of the PI3K–AKT–mTOR pathway reduced the tumour burden to a level observed in control mice, which suggests that NLRC3 restricts enterocyte proliferation via the PI3K–mTOR pathway during colon tumorigenesis.

Finally, NLRC3 was found to directly interact with the p85 subunit of PI3K, suggesting that NLRC3 controls the mTOR pathway by disrupting the association between the PI3K p85 and p110α subunits and reducing the activation of p85.

This study identifies NLRC3 as an inhibitory sensor of the PI3K–AKT–mTOR signalling pathway that protects against tumorigenesis in colorectal cancer. Further investigation is needed to determine the mechanism by which NLRC3 is regulated.

Olive Leavy

> “NLRC3 functions … to suppress the hyperproliferation of enterocytes”

ORIGINAL ARTICLE Karki, R. *et al.* NLRC3 is an inhibitory sensor of PI3K–mTOR pathways in cancer. *Nature* http://dx.doi.org/10.1038/nature20597 (2016)