Healthy competition

The phenomenon of cell competition, whereby less fit cells within epithelial tissues are eliminated by their fitter neighbours, was first identified in *Drosophila* and has since been proposed as a mechanism utilized by both cancer cells and host cells in mammalian systems to influence tumour progression. While investigating whether the surrounding environment could be involved in determining how successfully a tumour establishes itself within a tissue and then grows, Moya et al. uncovered a non-cell autonomous, tumour suppressive mechanism of competition driven by the Hippo pathway effectors YAP and TAZ in peritumoural hepatocytes that limits liver cancer in mice.

The transcriptional co-activators YAP and TAZ are overexpressed and hyperactivated in many human cancers and as a result are traditionally viewed as having a tumour-promoting function. Might they also be involved in suppressing the onset of tumorigenesis in normal epithelial cells? To answer this question, the researchers used a mouse model of cholangiocarcinoma induced by hydrodynamic tail vein injection (HDTV) of plasmids expressing activated forms of Notch and AKT to generate intrahepatic seeding. Macroscopic tumours appeared in the liver after 6 to 7 weeks with tumour cells characterized by high levels of YAP and TAZ. Interestingly, while hepatocytes in normal mouse livers expressed negligible amounts of YAP, hepatocytes surrounding tumours showed YAP accumulation. Importantly, the YAP present within these peritumoural hepatocytes was active as determined by profiling the expression of YAP and TAZ target genes from purified hepatocytes of normal and tumour-bearing livers.

Next, to determine whether active YAP-expressing hepatocytes might restrain the growth of liver tumours, *Yap* was deleted, along with its redundant homologue *Taz*, specifically in hepatocytes and not

in tumour cells. Once tumours had been allowed to form in these mice, *Yap* and *Taz* were then conditionally knocked out, which accelerated tumour growth owing to increased tumour cell proliferation. Performing the opposite experiment, wherein YAP and TAZ were hyperactivated in peritumoural hepatocytes by conditionally deleting the upstream negative regulators LATS1 and LATS2, was sufficient to dramatically decrease tumour burden by >70% of the volume seen in control mice. Validating this finding, transgenic mice conditionally overexpressing a constitutively active version of human YAP exclusively in hepatocytes were induced to form tumours. This approach similarly resulted in tumour elimination.

As elevated YAP levels were able to trigger hepatocyte proliferation and liver overgrowth, it could be reasoned that excessive peritumoural hepatocyte proliferation alone was the mechanism driving the observed tumour regression. To exclude this possibility, the authors elicited hepatocyte overproliferation by concurrently expressing oncogenic *Braf^{V600E}* and deleting *Pten* in peritumoural hepatocytes. Under these conditions, tumour growth was not modified, implying that activation of YAP and TAZ in peritumoural hepatocytes imparts a tumour suppressive effect.

TUNEL staining, which labels fragmented DNA generated during cell death, was detected in tumour cells enclosed by hepatocytes either overexpressing active YAP or conditionally knocked out for LATS1 and LATS2, indicating that the mode of tumour cell elimination might be through a type of programmed cell death. In line with this finding, a reduction in levels of the anti-apoptotic BCL-2 protein in regressing tumours compared with tumours from control mice was noted; a phenotype that could be reversed by conditional overexpression of BCL-2 in tumour cells.

Credit: Lara Crow/Springer Nature Limited

In cell competition, it is the relative level and not the absolute level of a molecular pathway that determines which cells will become winners or losers. Thus, the authors set out to evaluate how competing signals from YAP and TAZ in tumour cells might influence their relative fitness against the surrounding activity of the liver parenchyma. Once macroscopic tumours had been established, conditional deletion of *Yap* and *Taz* from tumour cells led to a decreased tumour load. This phenotype could be counteracted by concurrent deletion of *Yap* and *Taz* from both tumour cells and peritumoural hepatocytes, demonstrating that tumour cell survival is reliant on YAP and TAZ when tumour cells are growing in the presence of wild-type hepatocytes.

Lastly, to show that tumour suppressive competition was not limited to mouse models of cholangiocarcinoma, hepatocellular carcinoma was induced in mice by HDTV of plasmids co-expressing oncogenic *Myc* and *Nras^{G12V}*. When these mice also overexpressed active YAP in hepatocytes, tumour growth was suppressed. Similarly, YAP activation in peritumoural hepatocytes following HDTV of *Nras^{Q61K-/-}*; *Ink4a^{-/-}* mouse melanoma cells to mimic melanoma metastasis to the liver was capable of reducing metastatic load by 98%.

With the inhibition of YAP and TAZ now being actively pursued as a cancer therapy, recognition of a role for these effectors in containing tumour growth suggests a change in research strategy might be warranted.

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“a non-cell autonomous, tumour suppressive mechanism of competition driven by the Hippo pathway effectors

ORIGINAL ARTICLE Moya, I. M. et al. Peritumoral activation of the Hippo pathway effectors YAP and TAZ suppresses liver cancer in mice. *Science* **366**, 1029–1034 (2019)