SIGNALLING

BETting on YAP–TAZ

> high lethality in mice was rescued by expressing a mutated form of TAZ-4SA

The transcriptional regulators YAP and TAZ are activated in many human tumours and promote tumour growth. Zanconato, Battilana et al. recently showed that the concerted action of YAP and TAZ is required for the recruitment of the general co-activator bromodomain-containing protein 4 (BRD4) to enhancer elements, thereby maintaining high transcriptional rates for continuous cell growth in cancer models. On the other hand, Hagenbeek et al. demonstrated that YAP and TAZ have non-redundant functions in liver cancer, with YAP driving tumorigenesis in liver and TAZ promoting liver inflammation.

Zanconato, Battilana et al., who published their results in *Nature Medicine*, investigated the machinery mediating transcriptional addiction in cancer cells. In transcriptionally highly active triple-negative breast cancer (TNBC) MDA-MB-231 cells, the activation of essential genes for cell growth was YAP–TAZ-dependent. Hypothesizing that chromatin regulators are key components in this complex to maintain high transcription rates, the researchers performed chromatin immunoprecipitation combined with mass spectrometry and identified BRD4 as a chromatin interaction partner of YAP and TAZ. This interaction was sensitive to the bromodomain and extraterminal domain (BET) inhibitor JQ1, which abolished the expression of YAP–TAZ target genes. Enhancers occupied by YAP–TAZ were more sensitive to JQ1, enriched for BRD4 and displayed super-enhancer-like characteristics. In addition, the intrinsic acetyltransferase activity of BRD4 was required for YAP–TAZ function and, vice versa, YAP–TAZ was required for H3K122 acetylation to occur in target regions, thereby promoting transcription. In line with this, growth of YAP–TAZ-dependent TNBC-like tumours or liver tumours in mice was abolished by treatment with BET inhibitors.

Hagenbeek et al., who published their results in *Science Signaling*, analysed the differential effects of hyperactivated YAP or TAZ expression in a mouse model of liver cancer. Here, NRasV12 is co-expressed with the hyperactive YAP or TAZ and a Sleeping Beauty (SB) transposase through hydrodynamic tail vein (HTV) injection of the DNA constructs. When hyperactivated YAP, in which all large tumour suppressor (LATS) kinase phosphosites were mutated from serine to alanine (YAP-5SA), was co-expressed, this was sufficient to drive tumorigenesis. When hyperactivated TAZ, in which all LATS kinase phosphosites were mutated from serine to alanine (TAZ-4SA), was co-expressed, all mice in this treatment group died within 1 week, whereas control mice were unaffected. The high lethality of these mice was associated with enlarged livers, and with morphological and molecular features of inflammation in the livers, including increased infiltration of myeloid cells and increased levels of circulating pro-inflammatory cytokines, specifically CCL2. The high lethality in mice was rescued by expressing a mutated form of TAZ-4SA that cannot interact with the transcription factor TEAD. Importantly, when the dose of hyperactivated TAZ was reduced by expression of a single phosphosite mutant (TAZ-S89A), tumorigenesis was increased whereas lethality of mice was reduced compared with mice that expressed only NRasV12. However, this limited activity of TAZ was still sufficient to promote increased secretion of inflammatory cytokines, and tumour growth in these mice was reduced by inhibition of TAZ–TEAD interaction. Finally, the gene expression profiles in liver cancer cell lines derived from YAP or TAZ-driven tumours reflected the distinct observations in vivo: genes induced in YAP-transformed cells clustered distinctly from genes induced in TAZ-transformed cells, with pro-inflammatory genes more strongly expressed in TAZ-transformed cells.

Overall, the dependence of YAP–TAZ on BRD4 in regulating transcription opens up an attractive therapeutic opportunity, and inhibition of TAZ transcriptional activity might also present a new opportunity to reduce inflammation.

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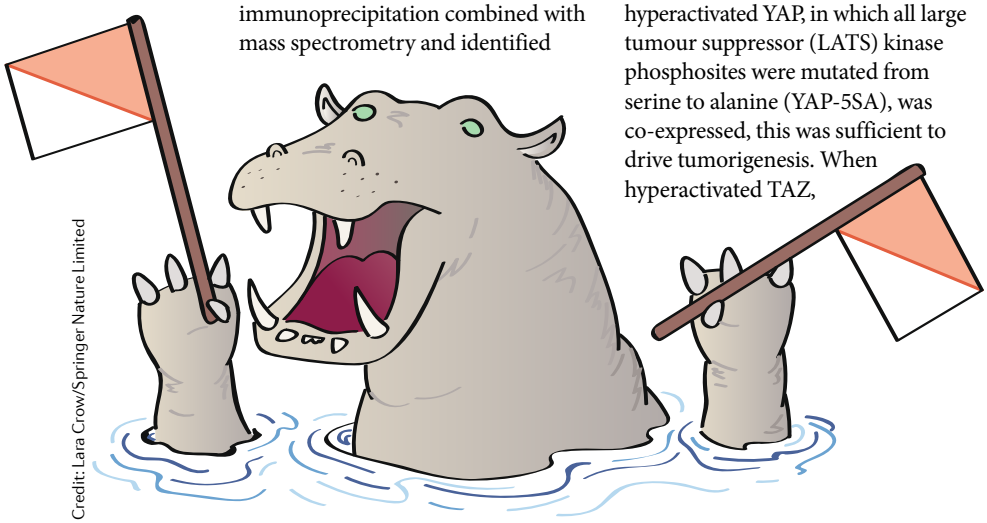

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ORIGINAL ARTICLES Hagenbeek, T. J. et al. The Hippo pathway effector TAZ induces TEAD-dependent liver inflammation and tumors. *Sci. Signal.* https://doi.org/10.1126/scisignal.aaj1757 (2018) | Zanconato, F. & Battilana, G. et al. Transcriptional addiction in cancer cells is mediated by YAP/TAZ through BRD4. *Nat. Med.* https://doi.org/10.1038/s41591-018-0158-8 (2018)