ACTIVATION OF THE HIPPO PATHWAY IS REQUIRED FOR ANOIKIS

Limitation of organ size by the Hippo tumor suppressor pathway maintains tissue homeostasis and prevents uncontrolled cell growth. The Hippo pathway kinases LATS1/2 phosphorylate the oncoprotein YAP, preventing its nuclear translocation and target gene activation. The upstream regulatory mechanisms of Hippo pathway kinase activation remain poorly understood, although previous reports have shown that high cell density and cell–cell contact promote Hippo pathway activation and subsequent YAP inhibition. Zhao and colleagues demonstrate that cell detachment also rapidly activates the Hippo pathway, leading to YAP phosphorylation and cytoplasmic sequestration that could be reversed with cell reattachment. Additionally, the use of cytoskeleton-disrupting agents revealed that loss of actin cytoskeleton integrity specifically promoted YAP phosphorylation and inhibition in a LATS1/2-dependent manner. In normal cells, cell detachment from the extracellular matrix induces a specific type of cell death called anoikis that is subverted in cancer cells to allow survival in the bloodstream during metastasis. The authors therefore hypothesized that YAP inhibition by LATS1/2 would activate anoikis in response to cell detachment. Indeed, ectopic expression of wild-type YAP or knockdown of LATS1/2 reduced anoikis in noncancerous mammary epithelial cells grown in suspension or ultra-low attachment by more than 50%, and ectopic expression of a nonphosphorylatable YAP mutant blocked anoikis completely. The authors provide additional evidence that decreased anoikis due to aberrations in the Hippo pathway promotes metastasis through their observation that LATS1/2 expression was significantly downregulated in metastatic prostate cancers compared with benign adjacent prostate tissue or localized primary prostate cancers. Collectively, these data suggest that targeted inhibition of YAP might be a useful approach for inducing anoikis and preventing metastasis in cancers with Hippo pathway abnormalities.


Retinoblastoma

Major finding: SYK is upregulated by nongenetic mechanisms in retinoblastoma.

Concept: Epigenetic deregulation of cancer pathways may be important in genomically stable tumors.

Impact: Small-molecule SYK inhibitors may be considered for retinoblastoma therapy.

EPIGENETIC ACTIVATION OF SYK IS A KEY FEATURE OF RETINOBLASTOMA

The underlying mechanism of retinoblastoma formation following RBU biallelic inactivation remains poorly understood. Zhang and colleagues sought to identify cooperating genetic alterations that drive retinoblastoma progression by performing whole-genome sequencing on 4 primary human retinoblastoma samples and matched normal tissue. Strikingly, the retinoblastomas had hardly any structural variations and an extremely low mutation rate. The exons of the few genes affected by missense mutations were sequenced in an additional 42 retinoblastomas, and only BCOR was found to be recurrently mutated in 6 samples. These findings were surprising given previous in vitro studies implicating the retinoblastoma protein (RB) in maintenance of genomic stability, and instead suggested that retinoblastomas were genomically stable and required few genetic lesions to develop other than biallelic RBU loss. To determine the extent to which epigenetic changes contribute to retinoblastoma progression in the absence of genomic instability, the authors compared histone modifications, DNA methylation, and gene expression in primary retinoblastomas and normal retinas. Interestingly, the spleen tyrosine kinase (SYK), which has no known function in the developing eye and is not expressed in retinal cells, was strongly upregulated and marked by activating histone modifications. Immunohistochemical analysis of a larger cohort of retinoblastomas showed extremely strong SYK staining in all of 82 tumor samples. Retinoblastoma cells were specifically sensitive to SYK inhibition in vitro, and conjunctival administration of the small-molecule SYK inhibitor BAY 61-3606 improved outcome in an orthotopic retinoblastoma xenograft model. Together, these integrative analyses suggest that epigenetic changes are important in retinoblastoma etiology and identify SYK as a promising therapeutic target.
