c-Abl forces YAP to switch sides

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Abbreviations: c-Abl, Abelson murine leukemia viral oncogene; IL-2, interleukin 2; LATS, large tumor suppressor; Runx, Runx-related transcription factor; PPARγ2, peroxisome proliferator-activator receptor gamma 2; TEAD, transcriptional enhancer activator domain; TK, tyrosine kinase; YAP, YES-associated protein.

Cancer research has been significantly accelerated by viewing cancer as a functional collision between 2 dichotomous sets of genes: oncogenes and tumor suppressors. Signaling pathways turn oncogenes and tumor suppressors on and off to dictate cell fate decisions. We contend that signaling also dictates opposing behaviors of a given effector.

Based on a number of criteria, certain genes are categorized as oncogenes whereas the genes that oppose their function are regarded as tumor suppressors. This categorization is of enormous value in investigating the molecular basis of cell fate determination. By and large, these genes are components or targets of cellular signaling pathways that transmit bimodal on and off instructions. The extent to which this perception is correct forms the basis of our recent study. We investigated the crosstalk between the DNA damage response pathway and the Hippo pathway and revealed that a proto-oncoprotein switched to behave as a tumor suppressor. Our finding therefore violates the on/off instruction rules by including a third option of opposing antipodal switching.

The transcriptional coactivator YES-associated protein (YAP) enters the nucleus by default to target specific genes. YAP has been implicated as an oncogene in conjunction with the transcriptional enhancer activator domain (TEAD) family of transcription factors in human cancers, where it activates proliferative and antiapoptotic target genes. The activity of YAP is blunted by blocking its nuclear entry through the Hippo pathway, which is important in regulating cell contact inhibition, organ size control, and cancer development. Under conditions of cell–cell contact, upstream elements of the Hippo pathway transmit signals through the kinase large tumor suppressor (Lats), which phosphorylates YAP on serine residues resulting in YAP cytoplasmic sequestration, downregulation of its nuclear target genes, and compromised oncogenic potential.

A twist was introduced into this coherent picture when it was recognized that YAP is also a coactivator of proapoptotic genes. In response to DNA damage, YAP targets p73, a member of the tumor suppressor p53 family, to induce proapoptotic gene expression and initiate a cellular death axis. The non-receptor tyrosine kinase Abelson murine leukemia viral oncogene (c-Abl) is activated under conditions of DNA damage and phosphorylates tyrosine residues on both p73 and YAP. Tyrosine phosphorylated YAP promotes the death axis at 2 levels: by enhancing the p73-mediated death axis and by supporting p73 accumulation. Moreover, when c-Abl is activated in response to DNA damage, the tyrosine-phosphorylated YAP still binds TEAD but is unable to induce the survival axis. This process completely abrogates YAP oncogenic activity. Thus, as modified YAP also induces the death axis via p73, activated c-Abl switches YAP from being an oncogene to becoming a tumor suppressor (Fig. 1). These findings exemplify a newly emerging principle in signaling: not only turning on and off, but also dictating an opposing function.
At first it may appear odd that a cell would use the same protein as an onco-
genome and as a tumor suppressor. What could be the advantage of one effector
controlling 2 opposing tasks? Recent studies revealed that IL-2 exhibits paradoxical
behavior in the determination of T-cell homeostasis. 

By applying a mathematical
model, it was demonstrated that a single
secreted molecule makes the homeostasis
more robust against perturbations. In our
system, YAP tyrosine phosphorylation
simultaneously inhibits the survival axis
while inducing the death axis. This
ensures rapid and coherent adoption of
the new desired state.

The Hippo pathway turns YAP effector
activity on and off whereas the DNA
damage response switches YAP activity to
the opposing task. A key question is how
YAP ‘knows’ what to do when receiving 2
schizophrenic instructions. We hypothe-
sized that one instruction must be domi-
nant over the other. We found that when
the Hippo pathway is active, namely
under cell–cell contact conditions, the
DNA damage response is inactivated.
This is accomplished by a double lock
mechanism; on one hand the Hippo
kinase Lats neutralizes YAP via its seques-
trization in the cytoplasm, while on the
other hand it inhibits c-Abl kinase.

The next question is why the Hippo
pathway is dominant over the DNA dam-
age response. The Hippo pathway
model is important to reach rapid homeo-

ostasis, provided that the involved pathways
are hierarchically designed.

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