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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, Runt-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 proproliferative 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.[1] 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.[2,3] Tyrosine phosphorylated YAP promotes the death axis at 2 levels: by enhancing the p73-mediated death axis and by supporting p73 accumulation. Moreover, when coactivating the Runt-related transcription factor (Runx), YAP regulates the expression of Itch, the p73 E3 ligase. Upon tyrosine phosphorylation by c-Abl, YAP escapes Runx association and hence supports p73 accumulation.[4] c-Abl thus switches YAP behavior from activating the E3 ligase that induces p73 degradation to coactivating the accumulated p73. This regulatory module exemplifies the capacity of c-Abl to switch YAP behavior to promote the opposing function.

A similar behavior was discovered at the level of targeting the TEAD transcription factor. The nuclear YAP–TEAD complex controls the survival axis by inducing transcription of a set of genes involved in 2 major activities: supporting cell proliferation on one hand and inhibiting apoptosis on the other hand. These two YAP-regulated activities give rise to a net increase in the cell population. However, 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.[5] 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.

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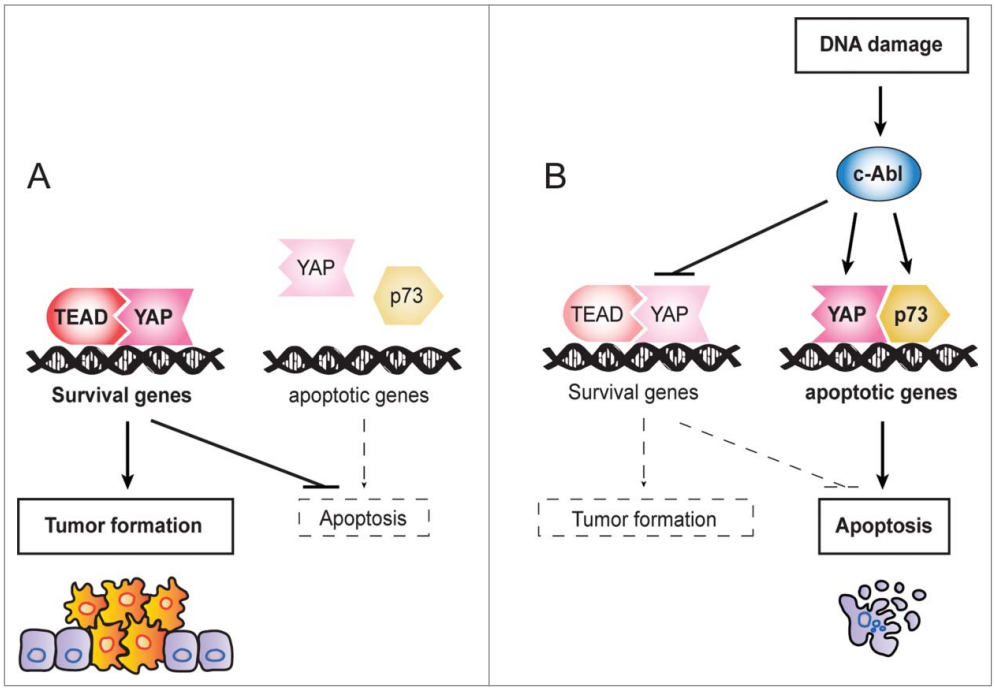

Fig. 1. YAP is switched from oncogene to tumor suppressor function through phosphorylation by c-Abl. (**A**) When the Hippo pathway is inactive, as in proliferating cells, YES-associated protein (YAP) coactivates the transcriptional enhancer activator domain (TEAD) transcription factor to express survival genes involved in the suppression of apoptosis. Activation of this survival axis may potentially contribute to tumor formation. (**B**) Under DNA damage conditions, Abelson murine leukemia viral oncogene (c-Abl) is activated and phosphorylates p73 and YAP. These modifications lead to YAP-p73 induced transcription of proapoptotic genes and activation of a death axis. Simultaneously, phosphorylation of YAP by c-Abl inhibits its potential to coactivate TEAD, resulting in blunting of the expression of antiapoptotic genes and promotion of apoptosis.

At first it may appear odd that a cell would use the same protein as an oncogene 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[6]. 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 hypothesized that one instruction must be dominant 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 sequestration in the cytoplasm, while on the other hand it inhibits c-Abl kinase activity.[7]

The next question is why the Hippo pathway is dominant over the DNA damage response. The Hippo pathway is functional at the level of on/off in a reversible manner. YAP enters and exits the nucleus based on received instructions and does not reach a fixed irreversible status. In contrast, c-Abl is involved in irreversible nuclear processes, such as inducing the death axis activity of YAP. Recently, we found that c-Abl promotes adipocyte differentiation, another irreversible process, by phosphorylation of the key adipogenic transcription factor peroxisome proliferator-activator receptor gamma 2 (PPARγ2) and its subsequent stabilization and activation.[8] It is therefore somewhat intuitive that the reversible processes would be dominant over the irreversible ones.

In summary, we attribute signaling to not only the capacity to turn downstream effectors on and off, but also the ability to impose an opposing task on a given effector. The interplay between the Hippo pathway and the DNA damage response nicely exemplifies this principle. In addition, we think that this model is important to reach rapid homeostasis, provided that the involved pathways are hierarchically designed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed

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