The RAS and YAP1 dance, who is leading?

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The Hippo-signaling effector YAP1 was recently found to compensate for oncogenic RAS in certain neoplasms, suggesting so far unanticipated molecular interplays between these major signaling routes. A new study in this issue of *The EMBO Journal* details KRAS-dependent control of YAP1 stability as well as positive feedback regulation via the RAS/YAP1/EGFR-ligand axis as novel molecular mechanisms that could become exploitable for therapeutic strategies.

See also: X Hong *et al* (November 2014)

Ras genes (H, N and KRAS) are the most frequently mutated oncogenes in human cancer, with KRAS having the highest incidence of mutations in adenocarcinomas of the lung, colon and pancreas (Pylayeva-Gupta *et al*, 2011). However, no specific therapies have been developed to directly target RAS and no effective therapies exist for RAS-driven cancers. Complex feedback loop mechanisms and toxicity have so far limited the clinical use of drugs targeting RAS downstream signaling effectors, like ERK and AKT (Chandarlapaty, 2012). YAP1 (Yes-associated protein 1) is a transcriptional co-activator, whose physiological activity is tightly regulated through the canonical and non-canonical Hippo pathway to drive context-dependent transcriptional programs that promote cell proliferation (Piccolo *et al*, 2013). Recent work has determined that YAP1 also plays an oncogenic role in multiple cancer types due to *YAP1* gene amplification or YAP1 protein stabilization and nuclear localization due to the deregulation of multiple core signaling pathways that influence cell polarity and the response to tropic cues (Piccolo *et al*, 2013).

Importantly, several groups have recently shown that YAP1 can functionally compensate

for the loss of oncogenic KRAS in several neoplasms (Kapoor *et al*, 2014; Shao *et al*, 2014). In particular, Kapoor *et al* showed that YAP1 is highly expressed in the quasi-mesenchymal subtype of human pancreatic cancers, which are cancers less dependent upon oncogenic KRAS for proliferation and survival. Furthermore, YAP1 also plays critical roles in tumor progression as its genetic ablation also prevents cancer progression in a murine model of pancreatic cancer driven by oncogenic *Kras* (Zhang *et al*, 2014). By providing an escape route for KRAS oncogene addiction, the YAP1 pathway emerges as an attractive therapeutic target in such tumors. However, the molecular mechanisms interconnecting RAS and YAP1 are poorly understood, limiting the development of such potential therapeutic strategies.

In this issue of *The EMBO Journal*, Hong *et al* (2014) propose a new mechanism to explain the role of YAP1 in RAS-mediated cellular transformation. In agreement with the aforementioned studies, Hong and colleagues confirm that YAP1 is required for efficient RAS-induced cellular transformation and tumor formations *in vivo* (Nguyen *et al*, 2014; Shao *et al*, 2014). They furthermore show that oncogenic RAS is able to stabilize endogenous YAP1 protein by downregulating the mRNA levels of the SOCS box proteins SOCS5 and 6, thereby preventing YAP1 ubiquitination. SOCS6 was shown to co-immunoprecipitate with and target YAP1 for ubiquitin-mediated degradation via the Cullin-RING-E3 ubiquitin complexes. The authors also show that SOCS6 can ubiquitinate LATS-insensitive YAP1 mutants to partially suppress the

Figure 1. Models of YAP1 in relation to RAS.

(A) Transient signaling. In the presence of wild-type RAS, YAP1 is transiently activated by different mechanisms one of which is through RAS-mediated downregulation of SOCS 5/6. (B) Constitutive signaling. In the presence of mutant RAS, YAP1 is upregulated by a constitutive active RAS. (C) Loss of mutant RAS selects for YAP1 signaling.

soft agar growth of RAS-transformed cells. Overall, these results led the authors to suggest that RAS might control YAP1 protein turnover through a Hippo-independent mechanism. Supporting the hypothesis of SOCS6-mediated degradation of YAP1, the authors report the inverse correlation between the expression of SOCS6 and that of a known YAP1 target gene, Amphiregulin (AREG). AREG is an epidermal growth factor receptor (EGFR) ligand that has been shown to promote YAP1-dependent proliferation and migration, but not EMT (Zhang et al, 2009). Consistent with this, the authors demonstrate that the genetic ablation of AREG by shRNAs significantly reduces YAP1-induced colony formation, thereby suggesting that the RAS/YAP1/AREG feedback loop is important for RAS-mediated transformation (Fig 1).

This new clue directly connecting RAS to YAP1 via controlling YAP1 protein stability strengthens prior reports and provides a fresh perspective on pathways that should now be investigated to determine the exact sequence of events leading to YAP1 elevation by oncogenic RAS. Such approaches should include efforts to clarify whether SOCS 5/6 is transcriptionally silenced by oncogenic RAS due to specific transcriptional repressors or rather due to more global chromatin modifiers, since epigenetic-altering drugs are now

being developed. Furthermore, whether the repression of SOCS5/6 is dominant over other pathways that are commonly dysregulated in RAS cancers and previously known to stabilize YAP1, such as dysregulated polarity pathways (Pagliarini & Xu, 2003), should also be systematically addressed in RAS-driven cancers. YAP1 represents a critical vulnerability in RAS mutant cells that may explain some of the pleiotropic effects of this master oncogene, and has the potential of causing its undoing.

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