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Akt-ing up on SRPK1 – Oncogene or Tumor Suppressor?

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In this issue of Molecular Cell, Wang et al. report that the splicing kinase SRPK1 can function as both an oncogene and tumor suppressor by modulating the activation state of the protein kinase Akt. This is shown to be mediated by the ability of SRPK1 to bind to the Akt phosphatase PHLPP1.

The paradigm that signaling proteins can function exclusively as oncogenes or tumor suppressors in human cancer has been challenged by studies that have demonstrated that pro- and anti-tumorigenic functions can be ascribed to the same protein, depending on the context. This is particularly evident in hepatocellular carcinoma (HCC) where both inactivation as well as overexpression of molecules such as Met, NF-κB and β-catenin can promote cancer (Feng, 2012). Understanding whether a signaling protein functions as an oncogene or tumor suppressor in different settings is of critical importance. One of the most frequently deregulated pathways in cancer is the PI 3-K and Akt signaling axis, and numerous inhibitors targeting enzymes in this pathway are in clinical development (Engelman, 2009). Activation of Akt by PI 3-kinase requires binding of PIP3 to the pleckstrin homology domain of Akt, leading to a conformational change that exposes two phosphorylation sites in the catalytic domain. The phosphoinositide-dependent kinase-1 (PDK1) phosphorylates Akt at Thr308, whereas the mammalian target of rapamycin complex 2 (mTORC2) phosphorylates Ser473. Catalytically active Akt then phosphorylates a plethora of substrates that transduce secondary signal relay (Manning and Cantley, 2007). Hyperactivation of Akt has been causally linked to multiple phenotypes associated with tumorigenesis. Oncogenic somatic mutations in *PIK3CA*, loss of heterozygosity of the tumor suppressor *PTEN* and receptor tyrosine kinase amplification are examples of genetics lesions that promote Akt activation. Genetic inactivation of the serine/threonine phosphatases PHLPP1 and PHLPP2 is also associated with hyperactivation of Akt, due to constitutive Ser473 phosphorylation (Newton and Trotman, 2014).

Recent studies have provided a link between Akt signaling and RNA processing. For example, Akt1 and Akt3 have been shown to phosphorylate IWS1, a component of the RNA polymerase II complex (Sanidas et al., 2014). A similar link has been established with the

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observation that Akt can bind and modulate the activity of SR protein-specific kinases (SRPK) (Zhou et al., 2012). SR proteins are a family of splicing factors that modulate numerous functions beyond splicing control, including transcription and translation of RNA. A previous study demonstrated that SRPK1 can bind to activated Akt, an event that stimulates autophosphorylation and nuclear translocation of SRPK1, which in turn phosphorylates SR and regulates splicing (Zhou et al., 2012). In this mechanism, Akt signaling can directly influence RNA splicing through SRPK and SR protein function. Wang *et al.* extend these findings to show that in addition to modulating splicing, SRPK1 can also function to integrate growth factor signaling in the Akt pathway to modulate tumorigenesis (Wang et al., 2014). Surprisingly, they find that inactivation of SRPK1 in knockout mice is embryonic lethal and also significantly suppresses SR protein phosphorylation. The notion that SRPK1 may function as a tumor suppressor is highlighted by the finding that SRPK1$^{-/-}$ null immortalized MEFs display increased tumor development in mouse xenografts. This is indicative of a tumor suppressor-like activity for SRPK1, consistent with the finding that SRPK1 expression is undetectable in a number of human colon cancers. Paradoxically, distinct specimens collected from colon cancer patients actually reveal SRPK1 overexpression, also consistent with published reports of increased SRPK1 expression in breast, colon and pancreatic carcinoma (Hayes et al., 2007). Overexpression of SRPK1 would be more indicative of an oncogenic function for this protein. Since amplification and mutation/loss of heterozygosity of SRPK1 are relatively infrequent events in most human cancers, including colorectal carcinoma (Cancer Genome Atlas, 2012), epigenetic events are likely responsible for the inactivation and over-expression of SRPK1 reported in these studies.

Wang et al propose that Akt and PHLPP are responsible for determining the fate of SRPK1 as an oncogene or tumor suppressor (Wang et al., 2014). Specifically, they show that inactivation of SRPK1 leads to hyperactivation of Akt by attenuating the recruitment of PHLPP1, thus maintaining a hyperphosphorylated Akt species at pSer473. Surprisingly, phosphorylation of key substrates of Akt in SRPK1$^{-/-}$ MEFs in response to EGF is significantly attenuated. Thus the specific mechanism(s) by which hyperactivated Akt mediated tumorigenesis in the context of SRPK1 deficiency remain to be determined. To test the model that overexpression of SRPK1 also facilitates tumorigenesis through Akt/PHLPP1, overexpression of SRPK1 was engineered and this also results in a marked induction of Akt phosphorylation. The authors propose that the decreased association of Akt with PHLPP1 is due to an increased association of PHLPP1 with SRPK1. This translates into enhanced anchorage-independent cell growth that is reversed by an Akt inhibitor. Whether this is sufficient to translate into true oncogenesis *in vivo* remains to be determined, but illustrates the concept that SRPK1 can function as both an oncogene as well as a tumor suppressor depending on the context. The precise nature of this context remains to be explored.

This work opens many questions as to the nature of the mechanisms by which SRPKs can mediate tumorigenesis dependent on their splicing effects, or by modulating signaling pathways such as Akt. It is noteworthy that PHLPPs have also been shown to modulate ERK signaling (Li et al., 2014), whereas minimal effects on ERK phosphorylation are observed

upon SRPK1 inactivation. Similarly, the PHLPP1 and PHLPP2 isoforms show specificity towards Akt1, Akt2 and Akt3 (Brognard et al., 2007), but whether this specificity is maintained in the context of SRPK1 inactivation or overexpression is not known. Regardless, this new study reinforces the emerging concept that molecules such as SRPK1 can function as both oncogenes and tumor suppressors in the context of inactivation and overexpression. The challenge remains to explore the specific mechanism that account for both activities in human tumors, which will be particularly important for cancer therapeutics.

References

Brognard J, Sierecki E, Gao T, Newton AC. Molecular cell. 2007; 25:917–931. [PubMed: 17386267]

Cancer Genome Atlas N. Nature. 2012; 490:61–70. [PubMed: 23000897]

Engelman JA. Nat Rev Cancer. 2009; 9:550–562. [PubMed: 19629070]

Feng GS. Cancer cell. 2012; 21:150–154. [PubMed: 22340589]

Hayes GM, Carrigan PE, Miller LJ. Cancer research. 2007; 67:2072–2080. [PubMed: 17332336]

Li X, Stevens PD, Liu J, Yang H, Wang W, Wang C, Zeng Z, Schmidt MD, Yang M, Lee EY, et al. Gastroenterology. 201410.1053/j.gastro.2014.02.003

Manning BD, Cantley LC. Cell. 2007; 129:1261–1274. [PubMed: 17604717]

Newton AC, Trotman LC. Annual review of pharmacology and toxicology. 2014; 54:537–558.

Sanidas I, Polytarchou C, Hatziapostolou M, Ezell SA, Kottakis F, Hu L, Guo A, Xie J, Comb MJ, Iliopoulos D, et al. Molecular cell. 2014; 53:577–590. [PubMed: 24462114]

Wang P, Zhou Z, Hu A, Ponte de Albuquerque C, Zhou Y, Hong L, Sierecki E, Ajiro M, Kruhlak M, Harris C, et al. Molecular cell. 2014

Zhou Z, Qiu J, Liu W, Zhou Y, Plocinik RM, Li H, Hu Q, Ghosh G, Adams JA, Rosenfeld MG, et al. Molecular cell. 2012; 47:422–433. [PubMed: 22727668]