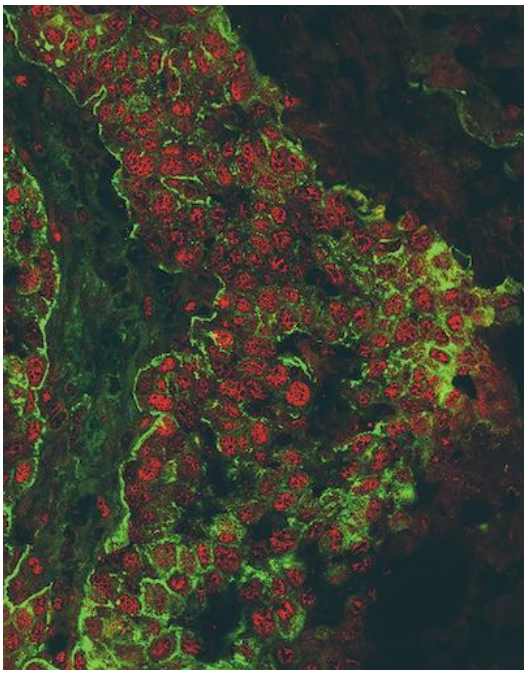
YAP says SRC it to me

April 18, 2016

A Neves



Immunofluorescence staining of squamous cell carcinoma tumor isolated from conditional knockout α-catenin mice with anti-integrin β4 (green) and anti-YAP1 (red) antibodies. The staining shows mislocalization of integrin β4 and activation of YAP1 in these tumors.

Image provided by Dr. Valeri Vasioukhin.

Most human cancers such as breast, colon and skin cancers are carcinomas, meaning that they originate in epithelial cells. Epithelial cells line our body surfaces, including our skin, and thus are major constituents of our organs. Protein complexes known as adherens junctions (AJs) play an important role in the organization of epithelial cells in tissues. AJs not only keep epithelial cells together, but also play critical roles in cell-cell signaling during both normal development and cancer. αE-catenin, a key component of AJs, is frequently inactivated in human skin squamous cell carcinomas (SCC), and it was shown to be a *bona fide* tumor suppressor using mouse models. Previous studies from Dr. Valeri Vasioukhin's Laboratory (Human Biology Division) identified the transcriptional co-activator and oncogene YAP1 as being essential for both hyperproliferation and loss of contact inhibition observed in mouse keratinocytes (skin cells) that lacked αE-catenin (αE-catenin-/-). However, it remains unclear mechanistically how αE-catenin is linked to YAP1 activity. In the current Fred Hutch study published in *Genes & Development*, Dr. Vasioukhin's Lab uncovered that the first known human oncogene and tyrosine kinase SRC, phosphorylates YAP1 in its transcription activation domain, and that this phosphorylation is important for YAP1's transcriptional and oncogenic activity.

The authors began by extending their previous short interfering RNA screen, which revealed that in addition to *Yap1*, *Itgb4* and *Src* were also required for hyperproliferation of αE-catenin-/- keratinocytes. *Itgb4* and *Src* genes encode β4 integrin and the oncoprotein SRC, respectively. The researchers found that β4 integrin drives hyperactivation of SRC which is necessary for hyperproliferation of αE-catenin-/- keratinocytes. Importantly, SRC was found to promote nuclear localization and transcriptional activity of YAP1 independent of the Hippo pathway, the major known regulator of YAP1 nuclear accumulation and activity. The investigators showed strong cooperation between SRC and YAP1 in malignant transformation. Using phospho-specific antibodies and an *in vitro* kinase assay, the scientists demonstrated that SRC directly phosphorylates YAP1 at three tyrosine residues (Y341, Y357, Y394). YAP1 protein replacement experiments utilizing either wild-type of phosphorylation site mutant YAP1 revealed critical role of SRC-mediated phosphorylation for both YAP1- and SRC-mediated cellular transformation. Finally, the researchers leveraged a SCC mouse model to demonstrate the potential utility of using an inhibitor of SRC-family kinases, dasatinib, for the treatment of SCC tumors that do not express αE-catenin.

In summary, this study revealed a previously unknown link between an oncogenic tyrosine kinase, SRC, and the key effector of the Hippo pathway, YAP1 that warrants further preclinical studies of dasatibib in αE-catenin-deficient SCCs. Said Dr. Vasioukhin "Oncogenic tyrosine kinases play an important role in human cancer. It is well known that they primarily impact PI3K and MAPK pathways. Our studies revealed a direct connection between oncogenic tyrosine kinase signaling and the effector of Hippo pathway YAP1. We found that YAP1 is directly phosphorylated at three sites by activated SRC family kinases and this phosphorylation results in YAP1 activation and malignant transformation. We propose that in addition to PI3K/MAPK, YAP1 phosphorylation and activation is another critical downstream pathway required for malignant transformation by oncogenic tyrosine kinases".

Li P, Silvis MR, Honaker Y, Lien WH, Arron ST, Vasioukhin V. 2016. αE-catenin inhibits a Src-YAP1 oncogenic module that couples tyrosine kinases and the effector of Hippo signaling pathway. *Genes and Development*. 30(7): 798-811.

Funding for this work was provided by the National Institutes of Health.