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Meeting Report

Cancer Research

The Hippo Tumor Suppressor Network: From Organ Size Control to Stem Cells and Cancer

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The third meeting on the Hippo pathway was held as a Keystone Symposia Conference last May in Monterrey, California. Over the past several years, the Hippo tumor suppressor pathway has emerged as a complex signaling network that has significant implications for our understanding of the molecular mechanisms of cancer, development, and stem cell biology (reviewed in refs. 1–3). The main effectors of this pathway, Yes-associated protein (YAP) and Transcriptional coactivator with PDZ-binding motif (TAZ), are transcriptional coactivators that act as regulators of stem cell homeostasis and potent oncogenes. Abnormal expression of Hippo pathway components, in particular YAP and TAZ, is often observed in human cancer, and mice with mutations that activate YAP and TAZ or that directly overexpress YAP develop cancer in a variety of tissues. Therefore, the Hippo pathway has become an attractive target for the development of anticancer drugs. However, many questions about the Hippo pathway are still unanswered and several paradoxes about the function of the pathway have emerged in recent years. For example, does YAP act as an oncogene or a tumor suppressor, and what are the mechanisms that regulate the activity of the pathway? A flurry of new discoveries was presented at this year's Hippo meeting, which reflected on all aspects of the Hippo pathway, from signal transduction mechanisms to cancer research and regeneration. Thus, the meeting witnessed the fast progress in this field, which is due, in large part, to an active dialog between *Drosophila* geneticists, mammalian signalers, and cancer and developmental biologists.

Although many upstream components of the Hippo pathway have been identified in recent years, mechanisms of signal transduction and how different inputs are integrated into the pathway have been poorly understood. Substantial progress has been made in this area in the past 2 years and several researchers presented new findings of signal transduction mechanisms. Kun-Liang Guan (University of California, San Diego, La Jolla, CA) presented the first keynote lecture and showed that the Hippo pathway is acutely regulated by G-protein–coupled receptor signaling. Activation of G12/13-coupled receptors, such as stimulation by lysophosphatidic acid, results in LATS kinase inactivation and YAP/TAZ activation in a manner independent of the MST1/2 kinases. In contrast, stimulation of Gs-coupled receptors, such as by epinephrine, activates LATS kinase activity and inhibits YAP (4). He showed that Gs-coupled receptors act through cyclic AMP (cAMP) via protein kinase A and Rho GTPases to stimulate LATS kinase activity and YAP phosphorylation (5). Joseph Avruch (Massachusetts General Hospital, Boston, MA) presented the second keynote lecture. Using gene-targeted mouse models, he showed that MST1/2 act as robust tumor suppressors in the liver and colon (6, 7). He also showed that the MST1/2 substrate and cofactor for LATS/nuclear Dbf-2-related (NDR) kinases, MOB1, regulates the DOCK-C family of Rac1/Cdc42 guanine nucleotide exchange factors (GEF; and perhaps other targets), independently of and in parallel to the NDR-family kinases. Interestingly, although MST1 is reversibly activated in T cells, once activated in liver, it is converted to a constitutively active form by proteolytic cleavage. In addition, he showed that YAP protein abundance is controlled at the level of transcription, in part by the ETS transcription factor GA-binding protein (GABP; ref. 8), as well as by phosphorylation-directed ubiquitination and degradation. The presented work was an ongoing collaboration between his group, Dawang Zhou (Xiamen University, Xiamen, Fujian, China) and Nabeel Bardeesy (Massachusetts General Hospital, Boston, MA) for studies in the liver. Nic Tapon (Cancer Research UK, London, United Kingdom) presented his laboratory's efforts to identify new regulators of Hippo signaling using cell-based RNA interference screens in *Drosophila*. Using a Warts/LATS activity reporter based on the Split-TEV protein–protein interaction detection system, they identified the salt-inducible kinases Sik2/3 as potential nutritional/hormonal inputs in Hippo signaling (9). More recent work was aimed at identifying ubiquitin ligases involved in regulating stability of the Hippo scaffold partner Salvador.

The Hippo pathway is known to be regulated by the neurofibromatosis type 2 (NF2) tumor suppressor protein (also known as Merlin), although the mechanisms underlying this have remained unclear. Filippo Giancotti (Memorial Sloan-Kettering Cancer Center, New York, NY) and colleagues previously reported that mammalian Merlin suppresses tumorigenesis by inhibiting the E3 ubiquitin ligase CRL4-DCAF1 in the nucleus (10). At the meeting, he presented evidence that CRL4-DCAF1 inhibits the output of the Hippo pathway by promoting ubiquitylation of LATS1 and 2. Genetic epistasis experiments indicated that this signaling connection sustains the oncogenicity of Merlin-deficient tumor cells. Jeffrey Schindler (Massachusetts Institute of Technology, Cambridge, MA) showed that the two major Merlin isoforms are able to

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suppress growth of mesothelioma cell lines and exert an inhibitory effect in YAP-driven transcription that occurs through the TEAD-family of transcription factors. Evidence was presented that at least some of this regulation occurs independently of the core Hippo pathway. In addition, the WW domains of YAP are not required for this regulation to occur when cells are confluent. Isabel Serrano (British Columbia Cancer Research Center, Vancouver, Canada) showed that integrin-linked kinase (ILK), which is overexpressed in a significant fraction of human tumors, silences the Hippo pathway by inhibiting the Merlin phosphatase MYPT1. They showed that all components of the pathway downstream of Merlin are inactivated in an ILK-dependent manner, and that genetic deletion, or pharmacologic inhibition of ILK *in vivo* leads to Hippo pathway reactivation and inhibition of tumor growth. Inhibiting ILK may thus provide a rational therapeutic approach for treating tumors in which the Hippo pathway is silenced.

Another input into the Hippo pathway that has emerged in recent years is the Angiomotin (Amot) family of adaptor proteins, which link the Crumbs complex and other polarity complexes at the plasma membrane to the Hippo pathway. Wanjin Hong (Institute of Molecular and Cell Biology, Proteos, Singapore) presented his current work on identifying Amot family members as novel substrates of Hippo pathway kinases. The N-terminal regions of AMOT, Angiomotin-like 1 (AMOTL1), and AMOTL2 contain an identical HvRslS consensus site for LATS1/2-mediated phosphorylation. Phosphospecific antibodies against AMOT and AMOTL2 validated the phosphorylation of this site. Analysis of mutants mimicking nonphosphorylated and phosphorylated forms suggests that LATS1/2-mediated phosphorylation likely serves to dissociate Amot proteins from actin filaments and cell junctions in dense cell cultures. Furthermore, the nonphospho and phospho forms of AMOT proteins may stimulate and inhibit cell proliferation, respectively. Hiroshi Sasaki (Kumamoto University, Kumamoto, Japan) showed that AMOT and AMOTL2 are essential for activation of the Hippo pathway and cell specification in preimplantation mouse embryos. In nonpolar inner cells, AMOT localizes to adherens junctions where cell–cell adhesion activates the Hippo pathway. In the outer cells, apical cell polarity complexes sequester AMOT away from basolateral adherens junctions, suppressing Hippo signaling. In adherens junctions, AMOT is phosphorylated by LATS, which inhibits AMOTs' interaction with F-actin. This mechanism establishes position-dependent differential Hippo signaling, thereby leading to differential cell fates (11). Jacob J. Adler (Indiana University School of Medicine, Indianapolis, IN) presented evidence that the ubiquitin ligase ITCH and YAP exist in a common complex mediated through the 130-kDa isoform of AMOT. This complex results in the inhibition of YAP-dependent transcription and cellular growth. This inhibition likely occurs via multiple mechanisms including stabilization of LATS1, stabilization of AMOT, and ubiquitination of YAP (12). Joe Kissil (Scripps Institute, La Jolla, CA) discussed the use of genetic approaches to dissect the functional consequences of AMOT–YAP interactions. AMOT is required for hepatic oval cell reactions and tumorigenesis in response to toxin-induced injury or *Nf2* loss in a liver-specific *Amot* knockout mouse. He also presented evidence that AMOT regulates YAP both in the cytoplasm and in the nucleus: in the cytoplasm, the AMOT-p130 isoform prevented the phosphorylation of YAP by blocking interaction with LATS1, and in the nucleus, AMOT-p130 associates with a YAP–TEAD transcriptional complex, where it regulates a subset of YAP target genes. These findings indicate that AMOT acts as a YAP cofactor, augmenting its activity as a transcriptional regulator and thereby facilitating tumorigenesis.

The Hippo pathway is unique in that many of its components contain WW domains. Indeed no other known signaling pathway is so rich in terms of the repeated occurrence of the WW module and PPxY-containing ligands (13). Marius Sudol (Geisinger Clinic, Danville, PA) updated us on the most recent developments in the study of the WW domain and its signaling complexes. He discussed unpublished data from a large proteomic screen with individual WW domains of YAP, proposing that although in most of the cases the phosphorylation of the signature tyrosine (Y) in PPxY-motif in cognate ligands of YAP WWs acts as a negative regulator of binding, for some of the ligands, including WBP2 protein for example, the PP-x-(phospho-Y) could positively regulate the binding. This finding has important ramifications and suggests potentially new cross-talk between signaling via tyrosine kinases and the Hippo pathway. In addition, he reported the generation of a new animal model for YAP. Mice with knockin (KI) mutant YAP lacking the PDZ-binding motif (YAP KI δC) were generated and are embryonic lethal as homozygotes. YAP KI δC heterozygotes are now being studied to reveal a potential role of YAP in the regulation of tight junctions.

The Hippo pathway does not act in isolation but interacts with other signaling pathways to regulate cellular behavior. Several researchers presented findings of cross-talk between the Hippo pathway and other pathways. Stefano Piccolo (University of Padua, Padua, Italy) presented evidence that TAZ protein stabilization could be a consequence of WNT signaling pathway activation, as TAZ is degraded by the same destruction and ubiquitin-ligase complex involved in β-catenin instability (14). As previously reported, YAP and TAZ are also regulated by extracellular matrix (ECM) stiffness, cell shape, and cytoskeletal tension (15, 16). When cells are cultured on stiff ECM, YAP and TAZ are in the nuclei and induce target gene expression, whereas they are inhibited and relocalized in the cytoplasm in cells cultured on a soft ECM. He showed that YAP and TAZ are active in cells with spread cell morphology similar to cells growing at low density on plastic dishes or seeded on large fibronectin islands, but YAP and TAZ are inactivated in small, roundish, unspread cells seeded on small islands. Bob Varelas (Boston University, Boston, MA) presented work examining the mechanisms by which YAP and TAZ direct TGF-β–mediated signals in cancer. Nuclear YAP/TAZ synergize with TGF-β–activated SMAD transcription factors to promote protumorigenic transcriptional events in breast cancer cells. Interestingly, they discovered that nuclear YAP/TAZ can also repress tumor suppressive transcriptional events by recruiting the NCoR/HDAC3 chromatin-remodeling complex to distinct gene promoters. Because TGF-β has both tumor suppressive and tumor-initiating activity, the presence of nuclear YAP or

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TAZ may provide a mechanism for how TGF-β–mediated signals are directed towards promoting aggressive cancer phenotypes. Cathie Pfleger (Mount Sinai School of Medicine, New York, NY) presented provocative data from a genetic screen aimed to elucidate the mechanisms of alcohol-mediated cancer in *Drosophila*. Using overgrowth models exposed to alcohol, she reported a genetic interaction between alcohol and Hippo signaling. Alcohol enhanced overgrowth from loss of the tumor suppressor components Expanded, Hippo, and the *Drosophila* LATS homolog Warts, but not from overexpression of Yorkie (Yki), the *Drosophila* YAP/TAZ homolog; alcohol also promoted Hippo signaling in both flies and mammalian cells, suggesting that Hippo signaling interactions with alcohol are conserved and may implicate Hippo signaling in alcohol-associated cancers. A model was presented that the Hippo tumor suppressor network is activated in response to dietary alcohol to prevent alcohol-mediated effects on developmental patterning and tissue growth.

The Hippo pathway regulates gene expression through complexes of YAP/TAZ with various DNA-binding transcription factors such as the TEAD family as their main interactors. Scalloped (Sd), the TEAD transcription factor in the fly, is a crucial partner for Yki and can genetically account for gain-of-function Yki phenotypes. However, how Yki regulates normal tissue growth remains a long-standing puzzle because Sd, unlike Yki, is dispensable for normal growth in most *Drosophila* tissues. D.J. Pan (Johns Hopkins University, Baltimore, MD) presented evidence that Sd functions as a default repressor and that Yki promotes normal tissue growth by relieving Sd-mediated repression. They further identified a Tondu-domain containing protein, Tgi, as a cofactor involved in Sd's default repressor function and showed that VGL4, the mammalian ortholog of Tgi, potently suppresses the YAP oncoprotein in transgenic mice (17). Yiting Qiao (Cancer Science Institute, Singapore, Singapore) discussed the connection between TEADs and RUNX3 (Runt-related transcription factor 3), a well-documented tumor suppressor, frequently inactivated in gastric and lung cancer. She presented data showing that RUNX3 can bind to TEADs, reduce their DNA-binding affinity, and diminish their transcriptional activity. Thus, RUNX3 is a novel negative regulator of TEADs and may play an important role in preventing oncogenic transformation caused by deregulated Hippo signaling.

YAP is also known to interact with the p53 family of transcription factors and three talks discussed new findings in this area. Yael Aylon (Weizmann Institute, Rehovot, Israel) discussed her work on the cross-talk between LATS2 and the p53 pathway. Previously, they showed that the LATS2-p53 axis is critical for the maintenance of chromosome number, activation of p53 in response to oncogenic stress, and apoptosis of transformed polyploid cells (18). Currently, they are exploring the function of LATS2 in embryonic stem cell differentiation. They observed that LATS2 knockout embryonic stem cells are less able to maintain pluripotency and respond less effectively to differentiation triggers, compared with wild-type embryonic stem cells. Giovanni Blandino (Regina Elena Cancer Institute, Rome, Italy) showed data on the regulation of the functional axis ATM/YAP/PML/p53 by the WRN helicase, whose loss-of-function is associated with Werner syndrome. The YAP/PML complex is recruited onto p53 responsive elements and drives the transcription of senescence-associated genes. In addition, WRN depletion induces a senescence-associated secretory phenotype (SASP), consisting of proteins such as interleukin-8. Removal of YAP, PML, or p53 strengthens the SASP phenotype (19). Yosef Shaul (Weizmann Institute, Rehovot, Israel) reported that the Hippo pathway regulates cell fate decisions in response to DNA damage. At high cell density, when the Hippo pathway is active, DNA damage-induced apoptosis and the activation of the tyrosine kinase c-Abl were suppressed. Inhibition of c-Abl by LATS2 was mediated through LATS2 interaction with, and phosphorylation of c-Abl. Consequently, the c-Abl substrates involved in apoptosis induction, YAP and the tumor suppressor p73, were not activated (20). These findings explain a long-standing enigma of why densely plated cells are radio-resistant.

Helen McNeil (University of Toronto, Toronto, Canada) presented their studies of YAP function during mouse kidney development using a conditional knockout strategy that specifically inactivated YAP within the nephrogenic lineage. They found that YAP is essential for nephron induction and morphogenesis, surprisingly, in a manner independent of regulation of cell proliferation and apoptosis. YAP is known to respond to mechanical stresses in cultured cells downstream of the small GTPase Rho A and they found that inactivation of the Rho GTPase Cdc42 phenocopied loss of YAP and resulted in severe defects in nephrogenesis. Ablation of Cdc42 decreased nuclear localization of YAP, leading to a reduction of YAP-dependent gene expression. She proposed that YAP responds to Cdc42-dependent signals in nephron progenitor cells to activate a genetic program required to shape the functioning nephron (21). Bernhard Schermer (University of Cologne, Cologne, Germany) presented unpublished and recently published data on the role of Hippo signaling in the pathogenesis of cystic kidney diseases. He showed that several NPHP proteins negatively regulate the Hippo pathway, thereby activating YAP/TAZ transcriptional activity and promoting cell proliferation (22). Mutations of these NPHP genes cause a cystic-degenerative kidney disease with small-sized kidneys called Nephronophthsis (NPH). In contrast, he reported high levels of nuclear YAP in the cyst-lining epithelium of kidneys from an ADPKD (autosomal-dominant polycystic kidney disease) mouse model, confirming a previous study from Dorien Peters' laboratory (23). ADPKD is a frequent and highly proliferative cystic kidney disease with massively enlarged kidneys. Taken together, by balancing YAP and TAZ activity, the Hippo pathway might be critical for the maintenance of kidney architecture and function.

Finally, Joan Brugge (Harvard Medical School, Boston, MA) reported on data from Amy Bui in her laboratory describing the effects of loss-of-function of YAP during cytokinesis. YAP knockdown caused dramatic ectopic blebs and protrusions during cytokinesis associated with altered spindle orientation, mislocalization of central spindle proteins that regulate contractile activity, decreased Rho activation, and a low percentage of failed cytokinesis and

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micronuclei formation. Interestingly, they found that YAP is phosphorylated by cyclin-dependent kinase-1 (CDK-1) during mitosis and interacts with PATJ, which is also important for controlling the orientation of the mitotic spindle and membrane blebbing.

In closing, the meeting was unique in bringing together *Drosophila* geneticists, basic and clinical cancer researchers, and the stem cell research community. The meeting highlighted the rapid progress in the field but also emphasized the limited understanding that we still have about this pathway's regulation and function. We expect continued fast pace of the Hippo field and look forward to the next discoveries in this exciting time of Hippo pathway research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G. Halder, F. Camargo
Writing, review, and/or revision of the manuscript: G. Halder, F. Camargo

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