Editorial

The large tumor suppressor family: friend or foe?

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General concept of Hippo

In the past few years, Hippo signaling cascade has been a hotspot for scientists who work in the area of cell biology, especially cancer cell biology (1-4). The core components of this pathway in mammalian cells consist of MST1/2 (STE20-like protein kinase 1), MAP4Ks (mitogen-activated protein kinase kinase kinase kinases) and LATS1/2 (the large tumor suppressor 1/2) (5). During the activation of this pathway, LATS1/2 is phosphorylated and activated by MST1/2 or MAP4K family, which directly induces the phosphorylation of YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif). YAP and TAZ lie in the center of Hippo, so their phosphorylation prevents themselves from translocation into the nucleus and therefore stops conveying signals to the downstream (6).

Accordingly, both silencing of MST1/2 (7) and over activation of YAP (8) are capable of promoting abnormally large organ size, respectively, which clearly illustrates a suppressor function of Hippo for carcinogenesis. After YAP successfully enters into the nucleus and binds with its transcriptional factors, the proliferative signals are delivered, which subsequently promotes expression of growth-related genes including CTGF (connective tissue growth factor), c-Myc and Cyr61 (Cysteine-rich angiogenic inducer 61). These downstream targets of Hippo directly induce cell proliferation and eventually tumor initiation under pathological circumstances.

In spite of the fact that numerous papers in the past have well identified the role of Hippo as a controlling mechanism that limits the proliferation of cells in case the organs overgrow (1,3,9), there are still scientists who have successfully proved that active Hippo leads to tumorigenesis (3,9-11). The reason for this controversy is mainly due to the dual function of this cascade within different contexts, and it is even more complicated when it comes to immune responses. We should investigate more about the interaction between carcinogenesis and anti-cancer immunity of host for there is still a large gap in this area. Clearly, Toshiro *et al.* have well demonstrated this bifunctional pathway as well as the regulatory mechanisms underneath (12). Indeed, LATS1/2 exerts the tumor suppressive role *in vitro*, which is in line with former results. On the other hand, interestingly, its deletion *in vivo* activates host anti-cancer responses, which therefore keeps suppressing carcinogenesis just as if LATS1/2 is still alive. This paper provides us a new landscape of how Hippo is involved in immunogenicity regulation. During the *in vivo* experiments, LATS1/2 dKO (double knockout) markedly inhibits tumor cell proliferation and metastasis. However, deletion of LATS1/2 in tumor cells leads to the secretion of nucleic-acid-rich EVs (extracellular vesicles). These vesicles activate TLRs-MYD88/TRIF-IFN pathways of host and promote anti-cancer immunity, which finally helps the mice reduce tumor burden. In three different types of cancer cell lines (melanoma, squamous cell carcinoma and breast cancer), a series of immune responses are identified, meaning that based on some certain contexts, Hippo behaves contradictorily. Moreover, LATS1/2 might be proposed to

be a target for anti-cancer immunotherapy.

Bifunctional property of Hippo

As mentioned, an opinion of tumor suppressor Hippo has been wildly embraced by scientists, whereas only a few people believe that it facilitate cancer initiation and progression. In this issue of *Cell*, the authors have also looked into the role of LATS1/2 in various types of cancer, including breast cancer, skin cancer and squamous cell carcinoma. Among these 107 datasets, unsurprisingly, the results or at least the trends are not in accord with each other (12). Moreover, hypo-expression of YAP was found to be associated with poor outcomes (10,11). Under this circumstance, Toshiro *et al.* attribute this discrepancy to a context-dependent manner. Superficially, their results seem to support the point of view that fights against with what we generally accept.

In fact, they established a novel concept that LATS1/2 restrains both tumorigenesis and immunogenicity, the two crucial characterizations for LATS1/2 to keep human body balance. On one hand, LATS1/2 stops cells from abundantly proliferating through phosphorylating YAP, which makes YAP isolated in the cytoplasm, therefore proliferative signals are cut. On the other hand, LATS1/2 plays an important role in immunogenicity, another regulatory mechanism to control tissue homeostasis. Physiologically, during the process of development and regeneration, Hippo is off and the cells grow. With the inactivation of LATS1/2, cell proliferation is likely to be beyond control. These LATS1/2-silenced ectopic cells then trigger a strong immune response, which in turns terminates them and guard the healthy body. In a way, these two features of LATS1/2 serve the same purpose, homeostasis.

However, the cell lines used in this study are Hippo-independent, even though LATS1/2 dKO slightly increase their proliferation *in vitro*. Thus, during the *in vivo* experiment on immune-competent mice, the cytotoxic immune response activated by LATS1/2 silencing outweigh the growth benefits the cells gain from the LATS1/2 loss. This might partly explain the results of this paper.

Hippo and cancer immunogenicity

Researchers who focus on the crosstalk between Hippo pathway and inflammatory responses also support the idea proposed in this project (13,14). Under an immune-competent situation, cancer cells with LATS1/2 silenced automatically secrete EVs into their environment. These nucleic-acid-enriched vesicles are easily sensed by the immune system of the host, which leads to the activation of the TLRs-MYD88/TRIF pathway and the release of type I IFN (interferon), an important cytokine for robust immunity to fight against neoplasia. Similarly, quite a few studies, as well, indicated that there is an autonomous contribution of type I IFN for cancer cells themselves during chemotherapy (15,16). However, the authors observed a parallel level of type I IFN between LATS1/2-dKO cells and their negative controls. Furthermore, LATS1/2 deficiency is needed to activate TLRs-MYD88/TRIF pathway, and the LATS1/2-impaired-cancer-cell derived EVs are capable of stimulating dendritic cells. Together with a previous report (17), these results above point out that this increased type I IFN might predominantly come from immunocytes of the host instead of those LATS1/2-null cancer cells.

Even though some scientists have been working hard on the protein-protein interactome within Hippo in the past few years (18), there is still a large undiscovered realm in regards to EV biogenesis. Nevertheless, the study has provided some clues about the involvement of Hippo in the process of anti-cancer immunogenicity, which enlightens us on the regulatory mechanisms of EV biogenesis. YAP has been reported to regulate microRNA (miRNA) expression (19), while miRNA plays a role in mediating EVs (20). According to these findings, the reason for the enhanced immunogenicity regarding LATS1/2-dificient cells is possibly due to hyperactivation of YAP/TAZ. Additionally, TEAD family is indispensable for YAP to exert anti-tumor function (12), yet it is not necessary for TEADs to participate in YAP-related miRNA biogenesis (19). And LATS1/2 depletion does not alter the miRNA expression in EVs neither (12), which indicates that YAP-activated cancer inhibition requires TEAD-associated transcription rather than miRNA biogenesis. Intriguingly, proliferation inhibitory effect of the LATS1/2 impairment is more significant than that of YAP/TAZ abundance, which indicates that extra substrates are involved in the repression of immunoreaction. Multiple studies have identified some novel targets of LATS1/2 in spindle regulation (21,22). Given that dysploidy has various effects on cancer immunogenicity (23), this immune inhibition might be attributed to these targets of LATS1/2 in spindle orientation.

Hippo and immunotherapy

Illustrated by clinical evaluation, there is a great progress

in studying immune checkpoint inhibitors for anti-tumor immunotherapy (24). Yet, these promising results benefit only a fraction of patients who happen to bear specific mutations or some other genetic conditions that are targets of these inhibitors (25). Variant cancer types or even individuals may circumscribe the response that a patient reacts to this anti-tumor immunotherapy, which is exactly a factor to stimulate the development of individual medication. This study has comprehensively demonstrated an elevated host anti-cancer immunity and its tumoricidal potential activated by LATS1/2 deletion. Based upon these observations, LATS1/2, therefore, is proposed to serve as a novel target for cancer therapy. Complementarily, it is likely that enhanced immunogenicity of cancer cells help improve the efficacy of immune checkpoint inhibitors, which means that dual therapy of both checkpoint inhibitors and LATS1/2 inhibitors may offer a new therapeutic strategy for some certain type of cancer, particularly non-YAP-driven, with low immunogenicity. Furthermore, even though it is still a myth, somatic or germline mutations in core members of Hippo are rarely found in human neoplastic tissues (1,3), which makes LATS1/2-inhibiting agents effective in most cases.

Summary and future direction

In this study, the authors have clearly illustrated the dual functions of Hippo cascade under different circumstances. Deletion of LATS1/2, a key component of the pathway, leads to tumor growth *in vitro*, whereas LATS1/2-null cells secrete EVs, activating TLRs-MYD88/TRIF pathway and stimulating anti-tumor responses of an immune-competent host. Eventually, these neoplastic cells are eliminated. This study also suggests a role of LATS1/2 to be a therapeutic target for anti-cancer medication.

On the other hand, crosstalk between EV biogenesis, inflammatory responses and Hippo is quite complicated. Deep understanding regarding this area is urgently needed. Even though the results of this study seem promising, it has not been identified whether this intervention could serve patients effectively in the clinic. Further investigations delineating the translational potential of LATS1/2 inhibitors will be of benefit to the clinical implication in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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