Lung cancer is the most common cancer worldwide and the leading cause of cancer-related mortality. Despite significant advances towards understanding its causal mechanisms, the morbidity and mortality rates of lung cancer remain high, due to cancer recurrence and metastasis (1). Therefore, identifying effective strategies for screening and detecting early-stage lung cancers is important for improving the long-term survival of patients. Tumour biomarkers play a critical role in early tumour diagnosis, monitoring high-risk populations, judging the severity of diseases, formulating individual therapy, evaluating treatment and prognosis, and investigating the course of the disease (2). Tumour biomarkers represent a promising tool for developing effective strategies for early diagnosis, detection of recurrence, and monitoring of cancer progression.

Cancer progression and development are multi-stage and multi-gene processes, which are widely attributed to dysfunctions in cellular signalling pathways. The Hippo pathway is an emerging tumour suppressor pathway that regulates cancer cell proliferation, apoptosis, metastasis, and stemness maintenance (3). An increasing number of studies are suggesting that the Hippo pathway regulates a series of biological functions in cancers through cross-talk with other signalling pathways, including the Wnt pathway. Recent studies have demonstrated that the Hippo pathway interacts with the Wnt pathway to modulate cancer development and progression (4,5). However, very few studies have focused on the interplay of the Hippo and Wnt pathways in lung cancer development.

In a recently published study, Han et al. (6) had demonstrated that WWC3, a member of the WWC family that also includes the highly similar proteins WWC1 and WWC2, is poorly expressed in lung cancer tissues; they also showed that its expression is associated with the TNM stage and the survival of the patients. They verified the functional expression of WWC3 in vivo and in vitro by knocking it down or overexpressing it, and concluded that WWC3 could inhibit the proliferation and invasion of lung cancer cells. Furthermore, they found that the regulatory mechanism might involve two aspects. First, the WW domain and ADDV domain of WWC3 interacts with the PY motif and PDZ domain of Dishevelled 2 (Dvl2) and reduces the nuclear translocation of β-catenin, thus inhibiting the activation of the Wnt pathway. The second aspect is that Dvl2 competes with WWC3 and occupies its WW-binding domain to suppress the interaction between large tumour suppressor 1 (LATS1) and WWC3, which decreases the phosphorylation of LATS1 and increases the nuclear transport of the Hippo pathway effector, yes-associated protein (YAP), thus attenuating the Hippo pathway. Taken together, these findings indicated that WWC3 could act as a bridge linking the Hippo and Wnt pathways to regulate the development and progression of lung cancer. Thus, WWC3 may be a novel molecular target for treating lung cancer.

In summary, Han et al. clearly established the regulatory network between the WWC3, Hippo, and Wnt pathways in lung cancer development. Evidence from different studies has
shown that the chemoresistance of lung cancer is associated with dysfunctions of signalling pathways such as the Hippo (7) and Wnt pathways (8). In this study, we speculated that WWC3 could act not only as a clinical biomarker for patients with lung cancer, but also as a therapeutic target for regulating the Wnt and Hippo pathways, thus enhancing the clinical benefits of chemotherapy. Today, small-molecule therapeutics is the main strategy for personalised treatment of advanced cancer (9). Thanks to advances in pharmaceutical chemistry and protein structural biology, an increasing number of small-molecule modulators are being manufactured and used in clinical trials. However, because of the complexity of the human body, converting scientific research into clinical application is a long and time-consuming affair. Therefore, achieving a greater understanding of the clinical roles and molecular mechanisms behind important lung cancer-associated genes (such as WWC3) will be crucial for developing small-molecule modulators or antibody-based drugs for treating lung cancer. With all these efforts, targeted therapy may become a promising therapeutic strategy for treating lung cancer in the near future.

Acknowledgements

Funding: This work was supported by the National Natural Science Foundation of China (81472694), China 111 Project (111-2-12), and the student innovation project of Central South University (2017zzts010).

Footnote

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

References


Cite this article as: Ou C, Li X, Li G, Ma J. WWC3: the bridge linking Hippo and Wnt pathways in lung cancer. J Thorac Dis 2017;9(8):2315-2316. doi: 10.21037/jtd.2017.08.35