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Commentary

SH3BGRL2, a new downregulated tumor suppressor in clear cell renal cell carcinomas

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In this article of *EBioMedicine*, Bo Peng and colleagues show that the loss of SH3BGRL2, a novel tumor suppressor gene, activated Hippo / TEAD1 / Twist1 signaling pathway and promote aggressiveness of clear cell renal cell carcinomas (ccRCC) [1].

This suggests that poorly studied SH3BGR family, and more precisely SH3BGRL2, can have an important role in aggressiveness and metastasis development in ccRCC. The authors clearly demonstrate that the loss of expression of SH3BGRL2 in ccRCC induce cell proliferation, migration, invasion as well as tumor growth and metastasis. These phenomena are due to an increase of epithelial-mesenchymal transition (EMT). The loss of SH3BGRL2 induce (i) increase of LATS1/2 expression leading to YAP phosphorylation, activation and its translocation in nucleus, (ii) activated YAP in the nucleus bind its co-transcriptional factor TEAD and (iii) TEAD directly bind Twist promoter to favor its expression and induce EMT. Moreover, SH3GRL2 appears as a new independent prognostic factor for the disease-free survival (DFS, appearance metastasis) in ccRCC.

To understand the importance of the finding for clinical practice, it is important to know that the majority of ccRCC patients are diagnosed when the disease is non-metastatic. The primary tumor is removed by surgery. Nevertheless, 40% of patients will develop metastases. The time to onset of these metastases can vary from a few months to several years. It is important to note that, at the present time, there is no clinical data or biomarker to accurately determine which patients will develop rapid metastatic disease, actually incurable. Numerous clinical studies are testing adjuvant treatments in ccRCC (i.e. after the surgery of the primary tumor and before the appearance of metastatic disease). However, the results of phase III randomized clinical trials have been contradictory. ASSURE and ATLAS trials, enrolled patients with nonmetastatic RCC who receive anti-angiogenic treatment (sunitinib / sorafenib or axitinib respectively) or placebo, found no difference in DFS between groups [2]. It was the S-TRAC trial that was the first to show a significant improvement in DFS with patients treated with sunitinib (DFS of 6.8 v 5.6 years) [3]. Immune checkpoint inhibition has also assessed as potential adjuvant agents [2]. In view of the results of these trials, adjuvant therapy with ITK seems to be favorable for a particular patient subgroup, and biomarkers allowing to classify these patients at high risk of metastatic relapse are necessary. The loss of expression of SH3BGRL2 could be part of a set of markers predicting tumor aggressiveness of the primary tumor and the appearance of metastases.

The physiological and pathophysiological role of the SH3BGR family (SH3 domain binding glutamate-rich) and more particularly SH3BGRL2 (SH3 Domain Binding Glutamate Rich Protein Like 2) remains largely unknown. The SH3BGR family consists of four members: SH3BGR, SH3BGRL, SH3BGRL2 and SH3BGRL3. These small proteins contain a thioredoxin-like fold, SH3 binding domain, and glutamate-rich domain. While the loss of expression of SH3BRL2 is already described in esophageal squamous cell carcinoma and ovarian cancer, Bo Peng and colleagues are the first to dissect the molecular and functional consequences of this loss of expression in ccRCC. Moreover, the authors demonstrate for the first time a new target of largely study YAP pathway: TEAD binds directly the promotor of twist1 to induce its transcription and promotes EMT [1].

What do we know about other members of the SH3BGRL2 family? In Kaposi's Sarcoma, the loss of SH3BGR is due to expression of miR-K6-3p and induces cell migration and angiogenesis [4]. SH3BGRL acts as a tumor suppressor in lung and colorectal cancers and in Acute Myeloid Leukemia [5]. Nerveless, when SH3BGRL is mutated (R76C), it binds and activates SRC and promotes metastasis [6]. In ccRCC, this mutation is not found. In bladder cancer, high expression of SH3BGRL3 is related to lower survival rate. Interaction of SH3BGRL3 with EGFR activates AKT signaling pathway and promotes tumor growth and aggressiveness [7]. SH3BGR, SH3BGRL and SH3BGRL2 seem to be a suppressor tumor while SH3BGRL3 seems to be an oncogene.

Several questions remain unanswered:

- Do SH3BGR, SH3BGRL and SH3BGRL2 have the same functions and regulation? And what are the differences for SH3BGRL3?
- How SH3BGRL2 are downregulated in the ccRCC? Is it by methylation or regulation by microRNA?
- What are the signaling pathways induced by the loss of SH3BGRL2 expression and leading to the overexpression LATS1/2 and activation of YAP pathway?

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- Finally, could the loss of expression of SH3BGRL2 and the activation of the pro-tumor signaling pathway Hippo / TEAD / twist1 be generalizable to other cancers?

In conclusion, Peng et al. paved the way to understand the role and function of SH3BGRL2, proposing it as a tumor suppressor inhibiting Hippo / TEAD / twist1 signaling pathway. SH3BGRL2 could be a new prognostic marker in ccRCC. Nevertheless, new prospective studies need to be conducted in order to integrate SH3BGRL2 as a prognostic marker in clinical practice.

Declaration of competing interest

The author declares no conflict of interest.

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