Commentary

SH3BGL2, a new downregulated tumor suppressor in clear cell renal cell carcinomas

Maeva Dufies

Centre Scientifique de Monaco, Biomedical Department, Principality of Monaco, Monaco

ARTICLE INFO

Article History:
Received 13 January 2020
Accepted 13 January 2020
Available online xxx

In this article of EBioMedicine, Bo Peng and colleagues show that the loss of SH3BGL2, 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 SH3BGL2, can have an important role in aggressiveness and metastasis development in ccRCC. The authors clearly demonstrate that the loss of expression of SH3BGL2 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 SH3BGL2 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, SH3BGL2 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 (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 SH3BGL2 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 SH3BGL2 (SH3 Domain Binding Glutamate Rich Protein Like 2) remains largely unknown. The SH3BGR family consists of four members: SH3BGR, SH3BGLR, SH3BGL2 and SH3BGL3. These small proteins contain a thioredoxin-like fold, SH3 binding domain, and glutamate-rich domain. While the loss of expression of SH3BGL2 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 promoter of twist1 to induce its transcription and promotes EMT [1].

What do we know about other members of the SH3BGL2 family? In Kaposi’s Sarcoma, the loss of SH3BGR is due to expression of miR-K6-3p and induces cell migration and angiogenesis [4]. SH3BGL acts as a tumor suppressor in lung and colorectal cancers and in Acute Myeloid Leukemia [5]. Nevertheless, when SH3BGL 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 SH3BGL3 is related to lower survival rate. Interaction of SH3BGL3 with EGFR activates AKT signaling pathway and promotes tumor growth and aggressiveness [7]. SH3BGR, SH3BGLR and SH3BGL2 seem to be a suppressor tumor while SH3BGL3 seems to be an oncogene.

Several questions remain unanswered:

- Do SH3BGR, SH3BGLR and SH3BGL2 have the same functions and regulation? And what are the differences for SH3BGL3?
- How SH3BGL2 are downregulated in the ccRCC? Is it by methylation or regulation by microRNA?
- What are the signaling pathways induced by the loss of SH3BGL2 expression and leading to the overexpression LATS1/2 and activation of YAP pathway?
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.

Acknowledgments

The author is supported by the Government of the Principality of Monaco.

References

[1] Yin L, Li W, Xu A, Shi H, Wang K, Yang H, et al. SH3BGRL2 inhibits growth and metastasis in clear cell renal cell carcinoma via activating hippo/TEAD1-Twist1 pathway. EBioMedicine 2020;51:102596. doi: 10.1016/j.ebiom.2019.12.005.
[2] Riedy DC, Buller DM, Ristau BT. The current state of adjuvant therapy following surgery for high-risk renal cell carcinoma. Eur Urol Focus 2019;5:935–8. doi: 10.1016/j.euf.2019.03.020.
[3] Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 2016;375:2246–54. doi: 10.1056/NEJMoa1611406.
[4] Li W, Yan Q, Ding X, Shen C, Hu M, Zhu Y, et al. The SH3BGR/STAT3 pathway regulates cell migration and angiogenesis induced by a gammaherpesvirus microRNA. PLoS Pathog 2016;12:e1005605. doi: 10.1371/journal.ppat.1005605.
[5] Xu L, Zhang M, Li H, Guan W, Liu B, Liu F, et al. SH3BGRL as a novel prognostic biomarker is down-regulated in acute myeloid leukemia. Leuk Lymphoma 2018;59:918–30. doi: 10.1080/10428194.2017.1344843.
[6] Wang H, Liu B, Al-Aidaroos AQO, Shi H, Li L, Guo K, et al. Dual-faced SH3BGRL: oncogenic in mice, tumor suppressive in humans. Oncogene 2016;35:3303–13. doi: 10.1038/onc.2015.391.
[7] Chiang C-Y, Pan C-C, Chang H-Y, Lai M-D, Tsai T-S, Tsai Y-S, et al. SH3BGR3 protein as a potential prognostic biomarker for urothelial carcinoma: a novel binding partner of epidermal growth factor receptor. Clin Cancer Res 2015;21:5601–11. doi: 10.1158/1078-0432.CCR-14-3308.