EBioMedicine 56 (2020) 102823

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Taking a SPOP at renal cell carcinoma – unraveling a novel pathway for Tumor progression in clear cell RCC

Hiren V. Patel[a], Sai K. Doppalapudi[a], Eric A. Singer[a,*]

[a] Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ 08902, United States

ARTICLE INFO

Article History:
Received 19 May 2020
Accepted 19 May 2020
Available online xxx

Renal cell carcinoma (RCC) accounts for 90% of kidney cancer cases, with the clear cell subtype (ccRCC) being the most common. Approximately 30% of patients initially present with metastatic RCC (mRCC) and about one-third of patients who undergo surgical extirpation have recurrence with distant metastases [1]. Therefore, developing novel strategies to identify tumors with a high risk of progression, recurrence, and treatment failure are paramount for reducing the mortality and morbidity of RCC. Initially, systemic therapy strategies focused on targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways, but the development of checkpoint inhibitor-based immunotherapies, alone and in combination, have proven to be critical in the management of mRCC [1].

In this article of *EBioMedicine*, Wang et al. elucidate a mechanism by which a protein in the ubiquitination pathway promotes RCC tumorigenesis [2]. Speckle-type POZ protein (SPOP) is a nucleoprotein that is uncharacteristically overexpressed in the cytoplasm of ccRCC and facilitates the degradation of Large Tumor Suppressor (LATS1) via phosphorylation and ubiquitination. This promotes cell proliferation and invasion by negatively regulating LATS1, an important cell cycle regulator. Overexpression of SPOP in a ccRCC xenograft mouse model corroborated these findings and immunohistochemistry of clinical samples demonstrated that SPOP overexpression was associated with LATS1 down-regulation within the cytoplasm. This suggests that SPOP serves as an oncogene in ccRCC and may represent a novel therapeutic target and biomarker for aggressive disease.

RCC provides a unique challenge for biomarker and therapy development. While ccRCC is present in the majority of cases, non-clear cell histology comprises approximately 25% of RCC cases, and tumor aggressiveness can vary significantly by histologic subtype [3]. Therefore, an ideal biomarker that provides objective, quantifiable endpoints for predicting distinct outcomes such as the risk of tumor progression, therapeutic response, or cancer-specific survival would be of great interest to clinicians and patients. Potential biomarkers for ccRCC have been identified primarily through retrospective analyses of archival specimens from past clinical trials and prospective biomarker-driven trials are currently underway [4]. Available biomarkers for RCC primarily act to predict response to therapy. For instance, a study which examined tissues from patients who subsequently underwent VEGF directed systemic targeted therapy found that those tumors with mutations in *KDM5C, PBRM1*, and *VHL* were more likely to respond to anti-VEGF therapy [5]. Similarly, mutations of *mTOR, TSC1*, and *TSC2* were associated with better responses to the mTOR inhibitor everolimus [6]. Interestingly, PD-1 and PD-L1 expression, primary targets for immunotherapies, have shown mixed results as effective biomarkers. While a dearth of biomarkers for RCC are present, identification of biomarkers that can predict RCC progression or treatment failure remains elusive [7]. SPOP may serve as a unique biomarker for determining risk of disease progression or likelihood of treatment efficacy given the overexpression and improper localization of SPOP.

SPOP overexpression in ccRCC has made it an attractive target for novel drug discovery efforts [8]. Inhibitors that target SPOP may also enhance diagnostics using sensitive imaging modalities, such as positron emission tomography or single-photon emission computerized tomography, that can determine tumor burden [8,9]. Combining advanced imaging methods with blood, urine, or tissue biomarkers may aid in identifying a subset of tumors that have an increased likelihood of growth and metastasis, which is of particular importance for patients electing active surveillance [3,10]. Unfortunately, current clinical trials have shown that tracer uptake demonstrates significant heterogeneity amongst patients with other locally advanced and metastatic cancers such as non-small cell lung cancer, bladder cancer, and triple negative breast cancer [9]. Nonetheless, tracers developed for SPOP may have the potential to improve the ability of current imaging techniques to assess tumor burden and growth during post-surgical surveillance or while receiving systemic therapy.

The role of SPOP in downregulating the tumor suppressor, LATS1, illustrates a novel pathway that can aid in developing biomarkers to diagnose aggressive disease, provide prognostic information, and

E-mail address: eric.singer@rutgers.edu (E.A. Singer).

https://doi.org/10.1016/j.ebiom.2020.102823

predict treatment success; thereby allowing for individualized, personalized oncologic care [3]. Work is still needed to fully understand how inhibition of SPOP can be utilized in the clinical setting for therapeutic and prognostic purposes, but the findings described by Wang et al. demonstrate several applications that may be important for the management of advanced and metastatic ccRCC.

Declaration of Interest

Authors have nothing to declare.

Funding

This work is supported by a grant from the National Cancer Institute (P30CA072720). EAS receives research support from Astellas/Medivation. These funding sources had no role in writing of the commentary.

Authors' contribution

Literature search: Patel, Doppalapudi, Singer
Writing manuscript: Patel, Doppalapudi
Critical revisions: Patel, Doppalapudi, Singer

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