



HIF2-Plk1, An Oncogenic Pathway in Clear Cell Renal Cell Carcinoma

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Description

The majority of Clear cell Renal Cell Carcinoma (CcRCC) patients carries inactivation of the Von Hippel-Lindau (VHL) gene leading to genetic stabilization of Hypoxia-Inducible Factor alpha (HIF α). The HIF pathway drives tumor development and progression in the VHL-inactivated CcRCC. HIF transcriptionally targets over 100 genes (1) and the loss of VHL function induces constitutive HIF-1 α /2 α expression that markedly up regulated their target genes, including VEGF. Consequently, CcRCC are hyper-vascularized tumors.

Tyrosine Kinase Inhibitors (TKI) primarily targeting VEGF Receptors (VEGFRs) such as sunitinib, were the first-line therapies for the treatment of metastatic CcRCC during the last decade (2). In addition to its anti-angiogenic effects on endothelial cells, sunitinib directly targets tumor cells to inhibit their proliferation, migration, and survival (3,4). CcRCC patients receiving sunitinib ineluctably develop resistance through a genetic adaptation of tumor cells leading to their survival in the presence of the drug.

Our study (5) demonstrated that sunitinib-resistant CcRCC cells exhibit higher Polo-like kinase 1 (Plk1) expression. This result suggests that Plk1 induction is part of a genetic program associated with resistance to sunitinib. Plk1 is a serine/threonine kinase which acts during cell cycle progression (6) and involved in tumor progression.

Before our study, the molecular mechanisms linking Plk1 expression and tumor hypoxia were unknown.

In the context of CcRCC, the inactivation of VHL leads to HIF chronic stabilization and to the up regulation of the transcription of target genes independently of the oxygen concentration.

We showed that hypoxia-dependent up regulation of Plk1 relies on HIF-2 but not HIF1-dependent increased transcription, and on mutation of SETD2 in human CcRCC. Hence, our results are consistent with the tumor suppressor role of HIF-1 α whereas HIF-2 α is considered as an oncogene in CcRCC (7).

Metastatic CcRCC patients relapse despite inhibition of angiogenesis (with first-line treatment VEGFR-TKI like sunitinib) and immune checkpoint inhibitors (with second-line treatment anti-PD-1 like nivolumab). Predictive markers of efficacy of the current treatments and new therapeutic targets are urgently needed for patients in therapeutic impasses. Thus, Plk1 blockade represents an attractive and alternative therapeutic solution.

We provided compelling evidence showing that sunitinib resistant CcRCC cells are highly sensitive to Plk1 inhibition. Targeting Plk1 inhibited tumor and endothelial cell proliferation in mice models. Therefore, the therapeutic efficacy of Plk1 inhibitors also relies on the inhibition of angiogenesis, a key phenomenon in CcRCC. We showed also that aggressive CcRCC cells metastasized in zebra fishes' tails without genetic modification beforehand and Plk1 inhibition prevented this metastatic spreading. This exciting finding warrants clinical validation.

Moreover, we demonstrated that Plk1 is a driver of tumor growth orchestrated by the HIF-2 oncogenic pathway in CcRCC. Indeed, Plk1 is linked to a shorter survival in both non-metastatic and metastatic patients. It is a prognostic factor independent of the clinical prognostic IMDC score. Hence, a biological marker independent of clinical parameters provides an added value for the management of patients.

The new gold-standards for metastatic CcRCC patients in the first-line are TKI, immunotherapy (anti-PD1+anti-CTLA4) (8) or a combination of both therapies (9,10).

Based on gene expression, methylation status, mutation profile, cytogenetic anomalies, and immune cell infiltration, 4 subtypes of CcRCC patients (CcRCC1-4) have been determined (11,12). The CcRCC2&3-tumors often express proangiogenic genes and have a good prognostic under TKI therapy. CcRCC4-tumors exhibit an immune-inflamed phenotype, but an exhausted immune system. The CcRCC1-tumors belong to an immune-cold phenotype almost without lymphocyte infiltration (11,12). Both CcRCC1&4 have a bad prognosis under TKI therapy. Therefore, the CcRCC2&3-tumors are eligible for TKI therapy and the CcRCC4-tumors are potential good responders to immunotherapy (BIONIKK clinical trial, NCT02960906) (13). In contrast, CcRCC1-tumors fail to respond to either therapy.

Tumors of the CcRCC1 subtype strongly express Plk1. High Plk1 mRNA levels correlated with a poor response to immunotherapy (14).

Moreover, by transcriptomic analyses of CcRCC made by Braund et al. (15) from the clinical trials Checkmate 010 and 025, we showed that high Plk1 mRNA levels are predictive marker of a bad response to nivolumab as a second-line treatment (Figure 1A) while Plk1 expression did not impact the response to everolimus (mTOR inhibitor) as a second line treatment (Figure 1B).

The following monogram appears decisional for the therapeutic strategy for patients of the different subgroups:

- CcRCC2&3 subtypes (low PDL1 and Plk1 expression) are eligible for TKI,
- CcRCC4 subtype (high PDL1 and Plk1 expression) are eligible for immunotherapy,
- CcRCC1 subtype (low PDL1 expression but strong Plk1 expression) are eligible for treatment with Plk1 inhibitors.

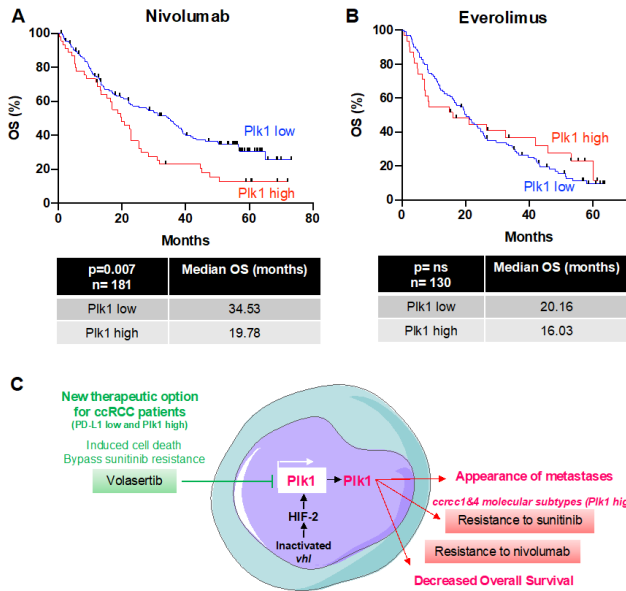


Figure 1: A and B, The levels of Plk1 mRNA in tumors from metastatic CcRCC patients treated with nivolumab (anti-PD-1) or everolimus (mTOR inhibitor) in the second line correlated with OS. The third quartile of Plk1 expression was chosen as the cut-off value. The Kaplan-Meier method was used to produce survival curves and analyses of censored data were performed using Cox models. Statistical significance (p values) is indicated.

C. The summary diagram of our study describing the link between HIF-2-dependent stimulation of Plk1 gene transcription. In addition to its tumor promoting role, Plk1 drives resistance to TKI and probably to anti-PD-1 and appears as a key target for a subgroup of metastatic CcRCC patients in therapeutic impasses (5).

In brief, our study deciphered the phenomenon linking a physical driver of tumor aggressiveness (hypoxia, HIF-2) to a biological

determinant of tumor cell proliferation and angiogenesis (Plk1). The link between the two actors is HIF-2, which drives Plk1 gene transcription. In addition to its tumor promoting role, Plk1 drives resistance to TKI and appears as a key target for a subgroup of metastatic CcRCC patients in therapeutic impasses (Figure 1C).

References

1. Manalo DJ (2005) Transcriptional regulation of vascular endothelial cell responses to hypoxia by HIF-1. *Blood* 105: 659-669.
2. Eisen T(2012) Targeted therapies for renal cell carcinoma: Review of adverse event management strategies. *J Natl Cancer Inst* 104: 93-113.
3. Giuliano S (2015) Resistance to sunitinib in renal clear cell carcinoma results from sequestration in lysosomes and inhibition of the autophagy flux. *Autophagy* 11: 1891-1904.
4. Dufies M (2017) Sunitinib stimulates expression of VEGFC by tumor cells and promotes lymphangiogenesis in clear cell renal cell carcinomas. *Cancer Res.* 77: 1212-1226.
5. Dufies M (2021) Plk1, up regulated by HIF-2, mediates metastasis and drug resistance of clear cell renal cell carcinoma. *Commun Biol* 4: 166.
6. Liu Z, Sun Q, Wang X (2017) PLK1, A potential target for cancer therapy. *Trans Oncol* 10: 22-32.
7. Biswas S (2010) Effects of HIF-1alpha and HIF-2alpha on growth and metabolism of clearcell renal cell carcinoma 786-0 xenografts. *J Oncol.*
8. Motzer RJ (2018) Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 378, 1277-1290.
9. Motzer RJ (2019) Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 380: 1103-1115.
10. Rini BI (2019) Pembrolizumab plus axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 380: 1116-1127.
11. Beuselinck B (2015) Molecular Subtypes of Clear Cell Renal Cell Carcinoma Are Associated with Sunitinib Response in the Metastatic Setting. *Clin Cancer Res* 21: 1329-1339.
12. Verbiest A (2019) Clear cell renal cell carcinoma: Molecular characterization of imdc risk groups and sarcomatoid tumors. *Clinical Genitourinary Cancer* 17: e981-e994.
13. Epailard N (2020) BIONIKK: A phase 2 biomarker driven trial with nivolumab and ipilimumab or VEGFR Tyrosine Kinase Inhibitor(TKI) in naïve metastatic kidney cancer. *Bulletin du Cancer* 107: eS22-eS27.
14. Li M, Liu Z & Wang X (2018) Exploration of the combination of PLK1 inhibition with immunotherapy in cancer treatment. *Journal of Oncology* 1-13.
15. Braun D (2020) Interplay of somatic alterations and immune infiltration modulates response to PD-1 blockade in advanced clear cell renal cell carcinoma. *Nat Med* 26: 909-918.