Biallelic *TSC2* Mutations in a Patient With Chromophobe Renal Cell Carcinoma Showing Extraordinary Response to Temsirolimus

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Abstract

mTOR inhibitors are used to treat renal cell carcinoma (RCC). Treatment response is variable and appears to correlate with genetic alterations that activate mTOR signaling. Recently, everolimus was suggested to be more effective than sunitinib in chromophobe RCC (chRCC), a tumor with frequent mTOR pathway defects. This report presents the genomic and functional characterization of a metastatic chRCC that showed complete response at metastatic sites and 80% reduction in primary tumor size upon temsirolimus treatment. After surgery, the patient remained disease-free for 8 years after temsirolimus therapy. Whole-exome sequencing (WES) revealed 2 somatic variants in *TSC2*, a critical negative regulator of mTOR: a splicing defect (c.5069-1G>C) and a novel missense variant [c.3200_3201delinsAA; p.(V1067E)]. In vitro functional assessment demonstrated that the V1067E substitution disrupted *TSC2* function. Immunohistochemistry in the tumor tissues revealed increased phosphorylated S6 ribosomal protein, indicating mTOR pathway activation. In conclusion, WES revealed *TSC2* inactivation as the likely mechanism for this extraordinary response to temsirolimus. These findings support high efficacy of mTOR inhibitors in a subset of patients with chRCC and propose sequencing of mTOR pathway genes to help guide therapy.

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Chromophobe renal cell carcinoma (chRCC) is the third most frequent kidney cancer histologic subtype, accounting for approximately 5% of all RCC cases. At diagnosis, chRCC is generally confined to the kidney but can metastasize. At advanced stages, clinical options are limited, and the median overall survival for patients with chRCC treated with targeted drugs ranges between 25 and 32 months.^{1–3} The rapamycin analogs everolimus and temsirolimus are effective anticancer drugs that inhibit mTOR complex 1 (TORC1) signaling.^{4–6} The mTOR pathway is frequently activated in

cancer through activating mutations in the *MTOR* gene or inactivation of the mTOR-negative regulators *TSC1* and *TSC2*.^{7,8} In RCC, approximately 10% of clear cell and 5% of papillary and chromophobe subtypes have mutations in *MTOR*, *TSC1*, or *TSC2*.^{9–11} In addition, inactivation of *PTEN* is frequent in chRCC. Altogether, genomic targeting of the mTOR pathway occurs in 23% of chRCC cases,^{11,12} suggesting sensitivity of this RCC subtype to mTOR inhibitors. A recent phase II randomized trial in patients with non-clear cell RCC found that everolimus was associated with a longer me-

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dian progression-free survival (PFS) than sunitinib for chRCC¹³; however, the number of cases included was low, stressing the need for additional studies.

Extraordinary responses to mTOR inhibitors have rarely been described in patients with cancer. These responses include a patient with metastatic bladder cancer who experienced a complete response to everolimus for >2 years,¹⁴ a patient with platinum- and taxane-refractory urothelial carcinoma treated with pazopanib/everolimus who experienced a complete radiologic response for >14 months,¹⁵ and a patient with metastatic anaplastic thyroid cancer with a sustained 18-month response to everolimus.¹⁶ In all of these patients, either *TSC1*/*TSC2*-inactivating or *MTOR*-activating mutations were identified. In metastatic chRCC, cases with partial response (PR) to mTOR inhibitors have been described,^{2,17–22} and in clear cell RCC an overrepresentation of *MTOR*, *TSC1*, and *TSC2* mutations in patients with a PR to rapalogs was found.^{23,24} Further studies determining the impact of mutational events on the response to mTOR inhibitors are required.

In this study, we performed a genomic and functional characterization of a metastatic chRCC with an extraordinary response to temsirolimus. Complete remission of the metastatic lesions and an >80% reduction in the size of the primary tumor occurred on temsirolimus treatment, and the patient remained disease-free for >8 years. The mechanism underlying the extraordinary response to temsirolimus was identified by whole-exome sequencing (WES), in vitro functional assessment, and immunohistochemistry.

Case Report

A 34-year-old woman presented with a large mass (>10 cm) in her right kidney that was histologically identified as an chRCC with eosinophilic features (Figure 1A). Imaging detected retroperitoneal adenopathies and metastatic lesions in her femur and lungs (N>5), and the patient was classified as having a poor prognosis according to Memorial Sloan Kettering Cancer Center criteria. Weekly treatment with 25 mg of temsirolimus was started in June 2008, and 4 months later a >50% reduction in renal tumor size and calcification of the femoral lesion were seen. At 6 months, progressive reduction of the renal and ganglionic lesions was observed, and at 8 months, metastatic lesions were no longer detectable in the

lungs and retroperitoneal adenopathies were reduced; by 15 months, the renal tumor volume had decreased by 80% (Figure 1B,C). [Supplemental eFigure 1](#) shows response in the metastatic lesions (available with this article at JNCCN.org).

In December 2009, a right nephrectomy was performed. Pathologic studies confirmed a renal carcinoma, pT1b. The patient was disease-free and continued temsirolimus until September 2011, when

Figure 1. Histologic findings and CT scans. (A) Hematoxylin-eosin staining of the chromophobe renal cell carcinoma in a biopsy pretreatment (original magnification x20). (B) Axial CT scans of the abdomen showing a 10.5-cm mass in the right kidney and retroperitoneal adenopathies (arrows), and (C) a 2-cm renal lesion after temsirolimus treatment.

treatment was suspended and she started clinical follow-up. During these 39 months, the patient did not experience any grade 2–4 toxicities, only some grade 1 fatigue that did not require specific treatment; thus, the drug administration schedule remained unchanged throughout treatment. Twenty months after stopping temsirolimus treatment, a CT scan revealed a 13-mm retroperitoneal adenopathy that in subsequent months grew to 15.5 mm. A retroperitoneal lymphadenectomy performed in October 2013 revealed an unclassifiable renal metastasis of 22 mm, with areas of rhabdoid transformation and capsular rupture in one lymph node, and monitoring of the patient continued. In December 2016, the patient complained of pain affecting the right hip. A bone scan and a nuclear magnetic resonance (NMR) could not prove active disease, but a biopsy of the right femur demonstrated infiltration by the renal tumor. After interdisciplinary discussion, temsirolimus treatment was recommended. After one dose, the pain disappeared. The patient is currently receiving temsirolimus at 25 mg per week, again experiencing clinical response with no pain and no toxicity reported since temsirolimus initiation.

WES was performed on DNA isolated from the primary tumor, the lymph node metastatic lesion after disease recurrence (formalin-fixed paraffin-embedded tissues), and the patient's peripheral blood (see supplemental eAppendix 1 for a detailed description of the study methodologies). The depth of coverage obtained was 102x, 116x, and 90x (for primary tumor, metastasis, and blood, respectively). Somatic variants, those detected in the tumor DNA but not in the germline DNA, were determined. A total of 401 somatic single nucleotide variants (SNVs)/small insertions or deletions (indels) leading to nonsynonymous or loss-of-function (LOF) variants were identified in the primary tumor (supplemental eTable 1). Among mTOR pathway genes, we found 2 mutations in *TSC2*, a critical negative regulator of TORC1, which were validated by Sanger sequencing. One was an LOF mutation that disrupted a canonical splice site (c.5069-1G>C), and the other was a novel missense variant [c. 3200_3201delinsAA, p.(V1067E); Figure 2].

To assess the effect of the novel p.(V1067E) variant on *TSC2* activity, in vitro functional assessment was performed in 3H9 (*TSC2* $-/-$ HEK 293T) cells (Figure 3). In brief, cells expressing the *TSC2*-p.

Figure 2. Mutations in *TSC2* in chromophobe renal cell carcinoma revealed by whole-exome sequencing (WES). WES of the primary tumor tissue after temsirolimus treatment and of the retroperitoneal metastasis revealed 2 somatic *TSC2* mutations in both tumors. Representative genome images from the Integrative Genomics Viewer (Broad Institute) of the *TSC2* (NM_000548.3) mutations, along with the number of reads for the reference and variant alleles: (A) c.3200_3201delinsAA, p.(V1067E) (exon 28) and (B) c.5069-1G>C (intron 39).

V1067E variant were compared with cells expressing wild-type *TSC2*, the pathogenic variants *TSC2*-p.R611Q and *TSC2*-F690Sfs*8, and cells not expressing *TSC2*. The ratio of T389-phosphorylated S6K and total S6K (T389/S6K ratio) was used to estimate TORC1 activity. As shown in Figure 3B, TORC1

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activity was clearly increased for V1067E compared with wild-type TSC2, and similar to that obtained for the pathogenic TSC2 mutations, indicating that V1067E disrupts TSC2 function. In addition, the amount of the TSC2-p.V1067E variant detected by immunoblotting was reduced compared with wild-type TSC2 (Figure 3C), suggesting that the V1067E substitution decreases TSC2 stability.

In addition to TSC2, 10 other genes implicated in cancer in Cancer Gene Census were also altered in the primary tumor (*ABL1*, *ATM*, *BCL11B*, *BRD3*, *CIC*, *ERCC2*, *FANCD2*, *FAT1*, *KAT6A*, and *SPEN*), but none of these variants affected genes in the mTOR pathway and they have not been previously described in tumors, according to COSMIC database. In the retroperitoneal lymph node metastasis that developed 2 years after temsirolimus treatment stopped, 25 somatic SNV/indels leading to nonsynonymous or LOF variants were identified (supplemental eTable 1). Of these, 15 were exclusive to the metastasis and 10 were shared with the primary tumor. The TSC2 mutations were among the shared variants. Regarding LOF variants present

in the metastasis, these affected *AHNAK*, *CNBD1*, *MNT*, *SH3BGR*, and *TSC2*.

Immunohistochemistry analysis revealed positive immunostaining for phosphorylated S6 ribosomal protein (phospho-S6), a downstream marker of TORC1 activity, in the tumors of the patient (Figure 4A,B), whereas it was absent in the normal kidney tissue surrounding the primary lesion (Figure 4C). These data provide further evidence of mTOR pathway activation in the tumor tissue. Regarding TSC2, low expression was detected in the tumors compared with other chRCC cases (supplemental eFigure 2), consistent with a biallelic inactivation of TSC2 in the tumor (splicing defect in one allele plus a missense mutation leading to a low stability protein in the other allele).

Discussion

A recent study suggested that treatment with everolimus might be more effective than sunitinib for chRCC.¹³ Although these results still need to be validated, this notion is supported by the high rates of PI3K-mTOR pathway activation in this histologic

Figure 3. Functional assessment of the TSC2-p.V1067E variant. 3H9 (TSC2 $-/-$ HEK 293T) cells were transfected with expression constructs encoding the indicated TSC2 variants. Cleared cell lysates were analyzed through immunoblotting and (A) the signals for TSC2, TSC1, total S6K (S6K) and T389-phosphorylated S6K (T389) were determined per variant (in triplicate), relative to the wild-type control (TSC2) in 2 independent experiments. The mean (B) T389/S6K ratio and (C) TSC2, (D) TSC1, and (E) S6K signals are shown for each variant. (F) The mean FLAG (peptide DYKDDDDK) signal is shown for the wild-type, p.F690fs, and p.V1067E FLAG-tagged TSC2 variants (F). In each case, the dotted line indicates the signal/ratio for the wild-type (TSC2 or FLAG-TSC2 = 1.0). Error bars represent the standard error of the mean. Amino acid changes are given according to TSC2 (cDNA reference transcript sequence NM_000548.3).

Figure 4. Immunohistochemical study of the tumors (all: original magnification x20). mTOR pathway activation was evaluated by performing immunohistochemical staining of phospho-S6 ribosomal protein (Ser235/236) antibody. Representative immunohistochemical images of the (A) primary tumor, (B) metastasis, and (C) normal kidney.

subtype, and suggests genetic screening as a valuable tool to make first-line therapeutic decisions. However, whether mutations in genes encoding mTOR pathway components can be used as biomarkers to predict high efficacy of mTOR inhibitor therapy is still unclear. This report identifies TSC2 deficiency as the mechanism most likely responsible for an ex-

traordinary response to temsirolimus in a patient with metastatic chRCC.

The optimum targeted therapy for chRCC is still not well-defined. Most trials for metastatic RCC are performed with clear cell tumors and include a limited number of chRCC cases.^{21,25–27} A recent randomized phase II trial in non-clear cell RCC comparing everolimus and sunitinib found heterogeneity of clinical benefit according to the RCC histologic subtype, with everolimus being associated with longer median PFS than sunitinib only in the chRCC subtype (n=16).¹³ In agreement, a phase II trial with everolimus suggested that patients with chRCC (n=8) seemed to have longer PFS than those with other non-clear cell RCC histologic subtypes.²⁷ However, another trial that included patients with chRCC (n=12) found that their overall survival was longer with sunitinib compared with everolimus,² although among the 3 PRs obtained with everolimus, 2 corresponded with chRCC, and targeted sequencing in 1 of these cases revealed a TSC2 mutation. In other studies, 2 of 9 patients with chRCC treated with mTOR inhibitors maintained treatment for >1 year,²⁶ and a patient with advanced chRCC experienced a 20-month clinical response to temsirolimus.²¹ Thus, although limited, increasing evidence seems to support sensitivity of chRCC to mTOR inhibitors.

The genomic landscape of 66 chRCCs was recently described by The Cancer Genome Atlas.¹¹ Mutations in *PTEN*, *MTOR*, and *TSC1/TSC2* were frequent (with 9, 2, and 4 mutated cases, respectively), indicating that the mTOR pathway is often affected in chRCC,¹¹ in line with previous immunohistochemistry studies.¹² Therefore, although data for chRCC are limited due to small sample sizes, clinical and genetic evidence suggests that mTOR inhibitors could be superior to VEGF pathway inhibitors for chRCC treatment, at least in a subset of patients. Unfortunately, cases directly linking mutational events to response to mTOR inhibitor therapy in chRCC are scarce.

This study identified 2 inactivating mutations in *TSC2* (c. 3200_3201delinsAA and c.5069-1G>C) in a patient with chRCC who experienced an extraordinary response to temsirolimus. These mutations have not been previously described in cancer, but can be classified as pathogenic: the c.5069-1G>C splice site variant because it was identified as a de novo germline mutation in an individual with TSC,²⁸ and the p.V1067E substitution based

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on functional in vitro assessment (Figure 3). Both TSC2 mutations were present in the primary tumor and in a lymph node metastasis removed 2 years after temsirolimus treatment was stopped, suggesting that this is an early driver event and that this lesion might also be sensitive to mTOR inhibitor therapy. None of the metastasis-specific mutations detected were linked to mTOR signaling. Consistent with the genetic and in vitro results, activation of the mTOR pathway was detected by immunohistochemistry in primary and metastatic tumor samples. Thus, our study links TSC2 deficiency with an extraordinary response to temsirolimus in chRCC.

The largest study performed to date investigating the association between mTOR pathway mutations and response to rapalogs, mainly in clear cell RCC, found a statistically significant association between mutations in genes encoding components of the mTOR pathway and improved rapalog response.²⁴ The type of mutation (different inactivating mutations in *TSC1/TSC2* or different functionally confirmed *MTOR*-activating mutations) did not seem to influence response^{15,23,24,29} and support the ongoing “basket” trials (ClinicalTrials.gov identifiers: NCT02201212 and NCT02352844). However, mutations in these genes were not detected in some patients who experienced response, whereas some patients with no response did have mutations.²⁴ These discrepancies have been suggested to reflect the moment in which the activation of the mTOR pathway occurred (eg, early vs late mutations).³⁰ Clear cell RCC and chRCC arise from different cell lineages and share few genomic features.^{11,31} In clear cell RCC, *VHL* inactivation is the driver event, followed by mutations in additional genes (eg, *PBRM1*, *SETD2*, *MTOR/TSC1/TSC2*), whereas in chRCC, *VHL* is unaffected and mutations in genes encoding mTOR pathway components seem to be the driver events. These differences between clear cell and chromophobe subtypes might be crucial for the

response to mTOR inhibitors. Thus, clear cell RCC results might not be applicable to chRCC and suggest that specific therapeutic strategies and biomarkers might be required for these different tumor subtypes.

Regarding the potential cost-effectiveness of genetic screening to identify patients with chRCC with mutations in the mTOR pathway, these mutations are relatively scarce in a rare disease. However, if an association between the mutations and the response to mTOR inhibitors can be clearly established, there is a good opportunity for applicability, supported by the decreasing sequencing costs and increasing costs associated with cancer treatment.

Conclusions

Although patients with chRCC have benefited from treatment with mTOR inhibitors, the mechanisms underlying these responses are still not well understood. This study directly linked *TSC2* inactivation to an extraordinary response to temsirolimus in chRCC. This result, together with evidence from previous studies, suggests that sequencing of mTOR pathway genes might be a valuable tool to guide therapy in chRCC.

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