Editorial

Role of fibroblast growth factor receptor in sunitinib-resistant renal cell carcinoma

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In renal cell carcinoma (RCC), surgical therapy remains to be the only curative approach for patients with localised kidney tumor, with recurrence rates as high as 40% in high risk patients. As well, even though there are now many approved therapies for metastatic RCC (mRCC), resistance eventually develops and is fatal for metastatic patients. Tyrosine kinase inhibitors (TKIs) that target the VEGF pathway are considered first-line therapy for clear cell RCC, the most common type of RCC. Sunitinib, and less commonly pazopanib, are TKIs that prevent tumor induced angiogenesis and delays progression in mRCC. However, most patients on sunitinib develop resistance after a median time of 10–14 months and still mechanisms of TKI resistance is unclear (1).

Tran and colleagues have raised a few very important questions regarding sunitinib resistance development in RCC. In this study, they have used three state-of-the-art experimental models for angiogenesis to elucidate possible mechanisms and probable drug targets behind development of resistance to this antiangiogenic agent. They have shown that paracrine signalling between RCC and mural cells (endothelial cells and fibroblasts) is different in sunitinib-sensitive compared to sunitinib-resistant phenotypes. The authors have also shown increased endothelial cell (EC) proliferation and survival in a sunitinib-resistant model compared to -sensitive RCC. Interestingly, ERK activation (Phosphorylation of mitogen activated protein kinase, MAPK or ERK at T183/Y185) in ECs was blocked with sunitinib when co-cultured with sunitinib-sensitive RCC but not with resistant RCC. This proved that other growth factors might be secreted by sunitinib-resistant RCC that renders EC insensitive to sunitinib.

Previous study by Welti *et al.* showed that fibroblast growth factor-2 (FGF2) is the most potent mediator of EC resistance to sunitinib from a panel of growth factors (2). Further in-depth study by Tran and colleagues indicated that FGF2 could be responsible for restoring ERK activation in the presence of sunitinib. The group showed that FGF2 treatment also increased EC proliferation and survival, which could be neutralised by addition of antibody against FGF2. However, a correlation between FGF2 secretion and its receptor activation (phosphorylation of FGFR and its surrogate marker FRS2) was not found. The authors then took an innovative approach and used fibroblasts in the experimental model; fibroblasts treated with the condition media (CM) from sunitinib-resistant RCC showed substantial phosphorylation of FRS2 compared to sunitinib-sensitive RCC. Despite these convincing results, aberrant expression of FGFs and other related growth factors was observed in primary RCC cells. These seemingly paradoxical results are a clear indication towards the complexity of RCC and drug resistance development. However, the results show that FGF/FGFR mediated paracrine signalling to EC and fibroblasts by RCC may be central in sunitinib-resistance development. They have also shown that addition of Dovitinib and PD173074, small molecular inhibitors of FGF receptor signalling, could overcome the resistance in RCC.

It is noteworthy to highlight that the three different experimental models used by Tran and colleagues attempt

to mimic the "natural" tumor environment. In one model, they have isolated primary RCC from 65 patient tumors and established 27 primary cultures, including from patients with sunitinib resistance. These primary cells, both sunitinib sensitive and resistant RCC, were co-cultured with EC and fibroblasts to closely simulate the natural angiogenic environment. Furthermore, tumor graft treatment in mice (PDX) and chicken chorioallantoic membrane implantation (CAM) were used as angiogenic models. The authors from current study have extensive experience with human RCC tumor graft in mice. They have previously established a tumorgraft platform in their lab that retains human RCC histology, gene expression, DNA alternations, mutations and treatment responses of the patient (3). Hence, their PDX model attempts to mimic the natural angiogenic environment. CAM is another highly recognised angiogenic model where fertilised chicken embryos after 72h of incubation are used for grafting. During 4–5 days, somatic mesoderm of the chorion fuses with splanchnic mesoderm of the allantois forming a highly vascularised membrane. This serves as a platform to study tumour related angiogenesis. Moreover, CAM is ideal to study tumor angiogenesis as the host immune system is underdeveloped that supports efficient grafting. However, caution must be exercised in interpreting CAM data as it is a non-mammalian, embryonic angiogenesis model. Other angiogenic models are also available, namely corneal micropocket, mesentery, sponge/matrix implant, disk assay, matrigel plug and zebrafish (4). Among others, CAM and PDX are the most reliable and inexpensive models for investigating angiogenesis. As tumor development depends on the ability of RCC to support angiogenesis, antiangiogenic agents like sunitinib play a crucial role in tumor regression. Consequently, sunitinib is the first-line therapy for metastatic RCC patients.

The mechanisms proposed by Tram and colleagues further emphasize the contribution of tumor microenvironment in developing resistance. Compared to non-malignant tissue, tumor stroma has altered vasculature, extracellular matrix structure and stromal cell composition. Interestingly, increased number of fibroblasts may correlate with drug resistance development (5). Another study showed the association of increased FGF2 in prostate cancer tumor progression and metastasis. This group used metastatic prostate cancer mice model (TRAMP mice) crossed with FGF2 knockout mice ($FGF2^{-/-}$) to established the prominence of FGF2 in tumor progression. In this mice model, deletion of even one FGF2 allele increased survival, decreased metastasis and progression (6). Recently, importance of FGF2 and its aberrant signaling in pathogenesis of different types of cancer is being increasingly appreciated. Therefore, the mechanism elucidated by the authors involving fibroblast and FGF2 in conferring sunitinib resistance in RCC has important implications for advanced RCC patients.

The current study successfully portrays the complexity of tumor microenvironment and its importance in drug resistance development. The authors have also used commercially available FGF2/FGFR1 inhibitors (dovitinib and PD173074) to illustrate the importance of FGF2/FGFR1 inhibition in metastatic RCC. However, there are few caveats to this current study: (I) correlation between increased EC survival and proliferation with FGF2 without FGFR1 or FRS1 phosphorylation in unexplained; (II) no direct connection between FGFs secretion and sunitinib resistance development was found; and (III) the effect of dovitinib in Phase III clinical trial as a third-line therapy in metastatic RCC was comparable to sorafenib. However, the different cell types involved in the models used, e.g., mouse stoma versus human tumors, may explain these disparities. A further in-depth study involving human stroma is required to substantiate the importance of FGF2/FGFR1 signaling in sunitinib resistant metastatic RCC.

In conclusion, the results from this study provide more pieces to the complex puzzle of sunitinib resistance in metastatic RCC.

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Footnote

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