Editorial Commentary

The way towards tailored treatment for metastatic renal cancer patients in the *omics* era: are we getting a "transcriptomic compass"?

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A transcriptome is a collection of all the gene readouts that are present in a cell. The instructions contained in the DNA of each single cell are transcribed into RNA, and the collection of the gene readouts for such transcription, the transcripts, constitute the transcriptome. Considering that the RNA sequence mirrors the sequence of the DNA from which it was transcribed, the transcriptome narrowly mirrors the genome, allowing to determine when and where each gene is turned on or off in the cell. Nevertheless, the concept of a single cell is only virtual. The transcriptome, as we can obtain it from a tissue analysis, is unavoidably constituted by the pool of all the gene readouts from a variety of cells, that for most tumors, far from being actually monoclonal, can be highly affected by heterogeneity. In the case of renal cell carcinoma (RCC), the illusion of clonal dominance is even more deceptive. Eminent authors found that more than 70% of driver mutations that are heterogeneous between tumor regions in RCC appear clonally dominant within individual regions (1). The presence of subclonal driver events may subtend undesirable clinical events in advanced RCC, such as the acquisition of resistance to targeted therapies (2,3). The regional isolation of tumor clades, together with parallel evolution of tumor subclones, raises questions about the reliability of the transcriptomic analysis: have they been obtained from representative samples? How optimally sample the mass to achieve the true transcriptomic map of the tumor? How reliably interpret the results?

Sometimes, the answer comes from the clinics. In the chaos of the *omics* in the current landscape of cancer diagnosis and prognostication, an upcoming issue is represented by the achievement of an excess of molecular data without clear clinical impact. Despite the dramatic increase of knowledge in the field of the molecular characterization of RCC, a plethora of translational studies have failed in linking the bench to the bedside, reporting weak or no correlation between the *omics* results and the clinical outcome of patients (4-8). Finally, on the threshold of the immunotherapeutic revolution, the first clinically meaningful evidence in favor of *omics* data begins to emerge in chorus, both from "old studies" with tyrosine kinase inhibitors (TKIs) and from new trials with immune checkpoint inhibitors (CKIs) (9-11).

In the elegant article recently published by Hakimi and coauthors in *Cancer Discovery*, the first insight for a possible transcriptomic approach to the treatment choice take place in the mind of the clinical oncologist, acquiring even more consistency in the light of the analogous results with the predictive transcriptomic maps obtained by McDermott *et al.* in an immunotherapeutic setting (10,11).

Within the COMPARZ trial population, Hakimi presented the largest molecular analysis of TKI-treated metastatic clear cell RCC (ccRCC) patients, describing the identification of genomic and transcriptional determinants of treatment response (9). The expression microarray data from 409 patients, enrolled in this non-inferiority study comparing pazopanib to sunitinib in the first-line treatment of metastatic RCC (mRCC), were analyzed identifying four biologically distinct clusters based on the 1,500 most variable genes. Overall survival (OS) and progression-free survival (PFS) curves where obtained according to the genomic cluster, demonstrating a significant association, with the worst OS for cluster 4 when compared to each other cluster [1, 2 and 3] individually or considered together (HR =2.09, 95% CI: 1.47–2.97) and the worst PFS for cluster 4 as compared to the others (HR =1.54, 95% CI: 1.13–2.09). Interestingly, they found that patients in the International Metastatic RCC Database Consortium (IMDC) poor-risk group were enriched with cluster 4 (χ^2 test P=0.017). Finally, the transcriptomic signatures of angiogenesis and immune associated genes in the tumors have been characterized, and the distribution of the RNA signature molecular subtypes was demonstrated to be significantly different between the four clusters (Kruskall-Wallis test), where cluster 3 had the highest angiogenesis gene expression levels (Angio^{high}) and cluster 1 had the lowest (Angio^{low}).

Far from describing merely mechanistical relationships, the authors clearly show that a high angiogenesis gene expression is associated with improved outcome to TKI therapy. Among the entire COMPARZ cohort, higher angiogenesis gene expression levels (Angio^{high}) were associated with improved objective response rate (ORR). Moreover, Angio^{high} group (relative to the median angiogenesis score) demonstrated improved OS (HR =0.68; 95% CI: 0.52–0.90) and PFS (HR =0.68, 95% CI: 0.53–0.88) when compared to the low angiogenesis gene expression (Angio^{low}) group. This was not confirmed for patients from cluster 4, suggesting that angiogenesis program alone cannot explain the poor outcome of the group, and that this group may be driven by the immune system suppression more than by the angiogenesis. A further demonstration in support of this concept is represented by the identification, in cluster 4, of the highest immune score, a marker of total immune infiltration, and of high percentage of PD-L1 positivity on tumor cells. Such elements suggest that cluster 4 is characterized by an immune infiltrated and suppressed tumor microenvironment (TME), with higher proportions of PD-L1 positive macrophages compared to other clusters. This finding is even more interesting outside of the population analyzed herein: indeed, we remind that cluster 4 is enriched in the IMDC poor-risk group, possibly justifying the better outcome of such subgroup of patients to immunotherapy combinations compared to sunitinib (12).

In the Hakimi's work, differently from what happened in the study by McDermott *et al.* (11), there was no significant difference in angiogenesis gene expression among IMDC risk groups. Nevertheless, the poor risk IMDC group was enriched with Angio$^{low/high}$-Macrophage^{high} trascriptomic elements. Overall, patients in the Angio^{low}-Macrophage^{high} group demonstrated the worst outcomes compared to the Angio^{high}-Macrophage^{low} group, which had the best survival outcomes in terms of OS and PFS. These results are consistent with those by McDermott *et al.*, possibly assuming different predictive value according to the considered systemic therapy. In fact, despite Hakimi *et al.* did not have a control group, being treated patients with TKI in each treatment arm, a possible predictive value seems to emerge from the IMmotion 150 and 151 trials, finally enticing the possibility to use transcriptomics to predict treatment benefit (10,11).

Most importantly, the authors finally demonstrate that the molecular variables are not only useful per se for prognostication of benefit in TKI-treated ccRCC patients, but also allowed to integrate clinical models to predict clinical benefit with higher reliability. Indeed, incorporating transcriptomic and genomic profiles with IMDC clinical variables, the c-index for OS increased from 0.63 to 0.69 and for PFS from 0.60 to 0.65, improving the predictive ability of molecular variables alone.

In the IMmotion 150 phase II study, a similar transcriptome map of angiogenesis and immune-associated genes was achieved in mRCC tumors, and it was used to perform interesting subgroup analysis according to systemic therapy (11). RNAseq gene expression data shows response signatures of clinical relevance. First, sunitinib demonstrated improved PFS in Angio^{high} subset *vs.* Angio^{low} subset (HR =0.31, 95% CI: 0.18–0.55), but this element was not relevant in the experimental arms with atezolizumab (anti-PD-L1) alone or atezolizumab plus bevacizumab (anti-VEGF). On the other hand, atezolizumab plus bevacizumab demonstrated improved PFS *vs.* sunitinib in the Angio^{low} subset (HR =0.58, 95% CI: 0.35–0.98), and improved PFS in T-effector^{high} subset *vs.* T-effector^{low} subset (HR =0.50, 95% CI: 0.30–0.86). Moreover, this

therapeutic combination demonstrated improved PFS *vs.* sunitinib in the T-effector^{high} subset. The authors finally interestingly identified a further differentiation within the T-effector^{high} signature basing on myeloid inflammation (^{low} or ^{high}) and demonstrated that the addition of bevacizumab with atezolizumab can be associated with improved benefit in T-effector^{high}/Myeloid Inflammation^{high} subgroup. The map was confirmed and validated in the IMmotion 151 trial, once again supporting the evidence that the relative expression of Angiogenesis and T-effector signatures allows to identify differential PFS benefits for atezolizumab plus bevacizumab *vs.* sunitinib. Also in this study, sunitinib showed improved PFS in Angio^{high} *vs.* Angio^{low} subsets (HR =0.59, 95% CI: 0.47–0.75). On the other hand, Atezolizumab plus bevacizumab improved PFS *vs.* sunitinib in T effector^{high} and in Angio^{low} tumors (respectively, HR =0.76, 95% CI: 0.59–0.99 and HR =0.68, 95% CI: 0.52–0.88) (11).

Moreover, the transcriptomic analysis of the IMmotion 151 study finally demonstrated that certain clinical or pathological features are subtended by typical *omics* pattern, allowing to uncover that the angiogenesis gene signature is highly represented in MSKCC favorable risk group of patients (74%), whilst T-effector^{high} signature can be found irrespective of the clinical risk group (36% in favorable risk and 43% in intermediate/poor risk group), but it seems to be more represented in sarcomatoid tumors (54%), which contrariwise have mostly an Angio^{low} signature.

The IMDC score, until yesterday confined solely for prognostication (12), is currently used as an unexpected predictive tool for treatment choice, grossly discriminating mRCC patients more likely to benefit from TKI from those needing immunotherapy combination. In this light, the recently evidenced correlation of such clinical models with transcriptome could motivate their reliability.

In spite of the innovational insights offered by Hakimi and coauthors, and considering that TKI monotherapy is going to become a niche in the currently rich first-line treatment landscape for mRCC patients, their results would deserve validation in more recent settings, such as the one providing the combination of TKI and CKI as first-line therapy (13,14). Despite the consistency and the complementarity between transcriptomics results and their impact on TKI and CKI treatments, the reproducibility of the same findings for different TKIs or in the case of TKI-CKI combinations is not obvious, since the authors themselves found that the predictors differed by the type of TKI received (9). Future studies should specifically explore these transcriptomic profiles within the context of the new available treatment options, such as the combination of axitinib and CKI (pembrolizumab or avelumab).

As the matter of fact, thanks to such recent data, after previous disappointments with the genomics (currently consolidated for the management of other malignancies), the transcriptomics have opened its glimmer in mRCC clinical practice, offering new insights for the smart planning of future *omics*-guided translational trials.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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