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Multilayered molecular profiling supported the monoclonal origin of metastatic renal cell

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Primary renal carcinomas have significant intratumoral heterogeneity and are composed of multiple distinct subclones. However, whether metastatic renal tumors also have startling intratumoral heterogeneity or whether development of metastatic renal carcinomas is due to early dissemination or late diagnosis remain largely unknown. To decipher the evolution of metastatic renal cancer, we analyzed the multilayered molecular profiles of the primary renal tumor, local invasion of the vena cava and distant metastasis to the brain from the same patient by whole-genome sequencing, whole-exome sequencing, DNA methylome profiling and transcriptome sequencing. We found that the metastatic renal tumor had a significantly low degree of heterogeneity than the primary tumor and was likely to be resulted from recent clonal expansion of a rare, advantageous subclone. Consequently, the expression of some key pathways that are targeted by clinically available drugs showed distinct patterns between the primary and metastatic tumors. From the genetic distances between different tumor subclones, we estimated that the progeny subclone giving rise to distant metastasis took over half a decade to acquire the full potential of metastasis since the birth of the subclone that evolved into local invasion of vena cava. Our evidence supported that the metastatic renal cancer was likely to be of monoclonal origin and demonstrated that distant metastasis may occur late during renal carcinoma progression. Thus, there was a broad window for early detection of circulating tumor cells and future targeted treatments for patients with metastatic renal cancer should rely on the molecular profiles of metastases.

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