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Anti-Tumour Treatment

New molecular targets in non clear renal cell carcinoma: An overview of ongoing clinical trials

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ABSTRACT

Non-clear cell renal cell carcinomas (nccRCCs) are a heterogeneous group of tumors, characterized by different histological features, molecular alterations, clinical outcomes, and responses to treatment. According to the 2004 WHO classification, 50 different histotypes were recognized. In 2013, five new distinct epithelial tumors and three provisional entities have been added to this classification, relying on morphology, immunohistochemistry, cytogenetics, and molecular pathology advances.

Targeted therapies against VEGF and mTOR pathways have become the cornerstones of the treatment for clear cell RCC, dramatically revolutionizing the patients' prognosis. Interestingly, other than mTOR and VEGF pathways, tumor proliferation of some nccRCC histotypes seems to depend on alternative signaling pathways, as demonstrated by the close correlation between papillary RCC and activation of the HGF/MET axis. Currently, several strategies are under evaluation in patients with nccRCC. These approaches include TKIs and mTOR inhibitors, MET-pathway antagonists and immunotherapy. The aim of this review is to analyze the rationale for the use of TKIs and mTOR inhibitors as treatment options for nccRCC and to describe the future therapeutic perspectives for these patients.

Introduction

Kidney cancer is a heterogeneous aggregate of several malignant subtypes, differing in histological features, genetic abnormalities, and clinical course. Renal cell carcinoma (RCC), tumor arising from epithelial cell of proximal convoluted tubule, represents the vast majority (approximately 85%) of kidney cancer [1]. RCC is generally divided into two major groups: clear cell RCC (ccRCC), which accounts for 70–85% of the epithelial tumors of the kidney, and non-clear cell renal cell carcinoma (nccRCC), a mixture of tumors of differing morphology, immunohistochemistry, genetics, and clinical behavior, which encompasses the remaining 15–30% of RCC. The 2004 WHO classification identifies papillary RCC (pRCC, 10–15% of RCC), chromophobe RCC (chRCC, 4–5%), collecting duct carcinoma and renal medullary carcinoma, mucinous tubular and spindle cell carcinoma, and Xp11.2 translocation carcinoma, as the main nccRCC subtypes. Moreover, RCCs are defined as unclassified when lacking the characteristics of distinct subtypes, or if showing mixed histological features or extreme sarcomatoid differentiation preventing a clear subtyping [2]. Based on advances in knowledge of basic morphology, immunohistochemistry, cytogenetics, and molecular pathology, the International Society of Urological Pathology (ISUP) has recently introduced five new distinct renal epithelial tumors: tubulocystic RCC, acquired cystic disease-associated RCC, clear cell (tubulo) papillary RCC, the microphthalmia transcription factor (MiT)-family translocation RCCs [in particular t(6;11) RCC], and hereditary leiomyomatosis

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Table 1
Renal cell carcinoma (RCC) histotypes and novel entities.

Histotypes
- Clear renal cell carcinoma
- Multilocular clear cell renal cell neoplasm of low malignant potential
- Papillary renal cell carcinoma
- Chromophobe renal cell carcinoma
- Hybrid oncocytic chromophobe renal cell carcinoma
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- MIT family translocation renal cell carcinoma
- Xp11 translocation renal cell carcinoma
- t(6;11) renal cell carcinoma
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma
- Acquired cystic disease-associated renal cel carcinoma
- Clear cell papillary (tubulopapillary) renal cell carcinoma
- Hereditary leiomyomatosis-associated renal cell carcinoma
- Renal cell carcinoma, unclassifies

New renal histotypes
- Tubulocystic RCC
- Acquired cystic disease-associated RCC
- Clear cell (tubulo) papillary RCC
- Microphthalmia transcription factor (MiT)-family translocation RCCs
- Hereditary leiomyomatosis RCC syndrome-associated RCC

Emerging or provisional entities
- Thyroid-like follicular RCC
- Succinate dehydrogenase B deficiency-associated RCC
- ALK translocation RCC

syndrome-associated RCC (Table 1, Figs. 1 and 2). Moreover three rare carcinomas have been defined as emerging or provisional new entities: thyroid-like follicular RCC; succinate dehydrogenase B deficiency-associated RCC; and ALK translocation RCC [3] (Fig. 2). Although the ISUP Vancouver classification contemplates RCC prognostic factors (tumor necrosis, sarcomatoid/rhabdoid differentiation), grading, staging, and molecular characteristics, a direct clinical significance of each histological subtype still lacks.

With the exception of the collecting duct carcinoma (which showed sensitivity to platinum-based chemotherapy), a historical resistance to cytotoxic treatments and cytokine-based immunotherapies characterizes metastatic RCCs [4,5]. Whilst the introduction of anti-angiogenic agents that block the vascular endothelial growth factor (VEGF) signaling pathway (sunitinib, sorafenib, pazopanib, axitinib and bevacizumab) or inhibit the mammalian target of rapamycin (mTOR) pathway (everolimus and temsirolimus) has completely changed the treatment of ccRCCs, very little evidence exists in the realm of nccRCCs. In fact, patients with nccRCC histologic subtypes were excluded or underrepresented in many clinical trials testing these targeted-therapies [6]. Therefore, the optimal therapeutic strategy for nccRCC has defaulted to being the same strategy for clear cell carcinomas; however, better treatments focused specifically for nccRCC are an area of unmet need (See Table 2).

This paper describes the main signaling pathways underlying non-clear cell nccRCC carcinogenesis, focusing on potential targets for current and future therapeutic approaches.

nccRCC histological subtypes

Papillary RCC

pRCC, the most frequent subtype of nccRCC – accounting for 10–15% of RCC – comprises a heterogeneous group of tumors with papillary architecture on histopathological evaluation. It originates from renal tubular epithelium and typically grows forming papillae supported by a fibrous–vascular axis containing foamy macrophage, cholesterinic necrosis and psammoma bodies. Necrosis and hemorrhage are frequently present. Tubulopapillary and solid-glomerulus architectures are also described. The possible coexistence of clear cells, as well as a sarcomatoid dedifferentiation, correlates with aggressive pathological features and poorer outcomes [7].

Among papillary tumors, two histological subtypes are described, according to histological patterns and cellular features, genetic alterations, and different prognosis. Type 1 papillary RCC contains basophilic cells with scanty cytoplasm organized in a single-line, exhibits regular, round nuclei, is often bilateral or multifocal, and may occur in the context of an autosomal dominant hereditary papillary RCC syndrome (HPRC) characterized by activating mutations of MET oncogene [8]. Type 1 pRCC tends to be

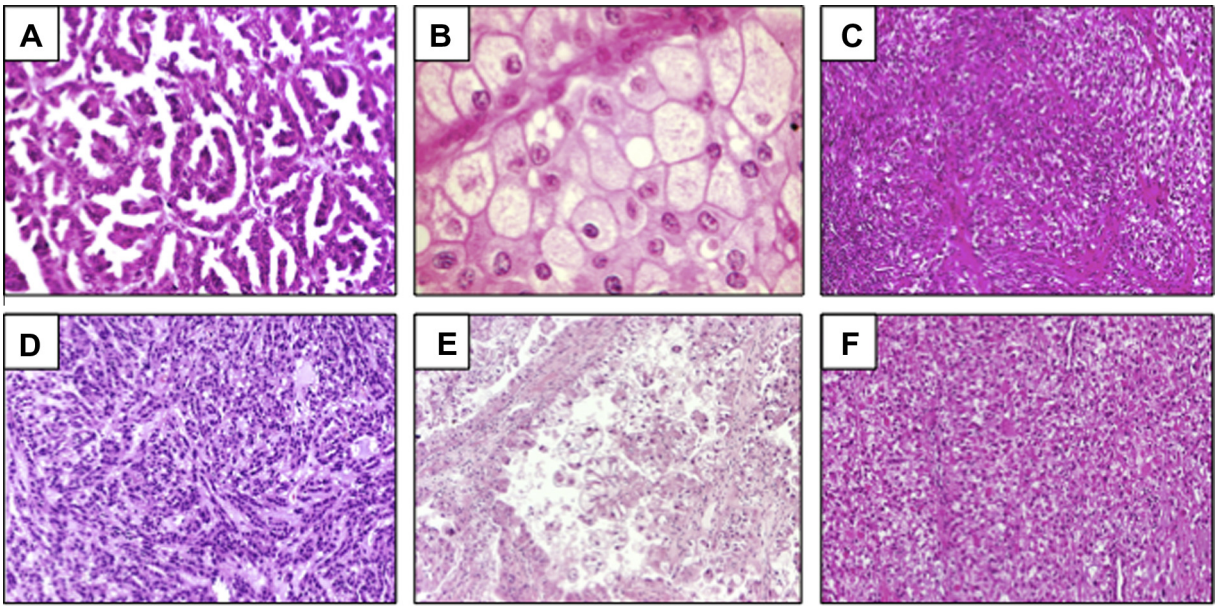

Fig. 1. Non-clear cell histologies. (A) Papillary renal cel carcinoma (type 1); (B) chromophobe renal cel carcinoma; (C) medullary renal cel carcinoma; (D) mucinous tubular and spindle cell carcinoma; (E) Xp11 translocation renal cell carcinoma; (F) unclassified renal cell carcinoma.