REVIEW

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Renal carcinogenesis – insights into signaling pathways

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Abstract

Renal cancer represents about 3% of all human malignancies, 96% of cases being sporadic forms and only 4% hereditary. Research in renal tumor pathogenesis is currently oriented on the genetic and proteins framework of the renal cell carcinoma, with the aim to translate the level of knowledge on tumor subtypes from histological to molecular issues, simultaneously with the deciphering of the manner in which the signaling pathways intervene in the pathogenic mechanism. Alterations identified in proto-oncogenes and tumor suppressor genes lead to abnormal and deficient transmission of signal in the signaling pathways, and initiate the carcinogenesis mechanism by increased proliferation of tumor cells. Although it seems obvious that the classic sequence of carcinogenesis is respected at the renal site, unfortunately, the manner in which signaling pathways are involved, in the specific context of renal tumors, is not extensively investigated. This paper assembles recent data in the mainstream regarding the dialogue opened between the molecules in Wnt/β-catenin, PI3K/AKT/mTOR, and HGF/cMET signaling pathways. The review is also justified by the fact that these molecules may represent potential prognosis markers and/or therapeutic targets.

Keywords: renal tumors, carcinogenesis, signaling pathways, Wnt/β-catenin, PI3K/AKT, HGF/c-MET.

Hallmarks in renal cell carcinoma

Renal cell carcinoma (RCC) represents almost 3% of the malignant tumors in the adult and seems to be the most aggressive type of genitourinary cancer, and it is resistant to chemo- and radiotherapy [1]. The sporadic forms predominate, accounting for 96–97% and only 3–4% are hereditary [1, 2]. RCC has an extremely variable global incidence and mortality, because of the intervention of demographic, environmental and genetic factors [3]. Usually, RCC is asymptomatic until it reaches advanced stages, fact that influences prognosis; thus, survival at five years is >90% for stage I, and 20–30% for stage IV [4].

Originating in renal tubular structures, RCC displays strong heterogeneity, with multiple morphological subtypes: clear cell RCC (80%), papillary RCC (10–15%), chromophobe RCC (5%), collecting duct RCC (1%), and unclassified forms (2%) [2, 5].

Renal carcinogenesis involves the intervention of numerous signaling pathways. Multiple research reports bring solid evidence for the implication of Wnt/β-catenin, PI3K/AKT/mTOR (phosphatidylinositol 3-kinases/protein kinase B/mammalian target of rapamycin), HGF/c-Met (hepatocyte growth factor/c-mesenchymal epithelial transition factor), and MAPK (mitogen-activated protein kinase) pathways, by alterations in one or more components of their structure [2, 6].

This paper assembles recent data in the mainstream regarding renal carcinogenesis, the information being focused on the dialogue opened between the molecules in Wnt/β-catenin, PI3K/AKT/mTOR, and HGF/cMET signaling pathways, which result in the modification or alteration in transduction of intercellular signals.

Hereditary *versus* sporadic RCC – from genes and proteins towards a novel classification

Molecular disturbances identified mainly in hereditary renal tumors are multiple. For example, gene abnormalities such as VHL (von Hippel–Lindau), FHIT (fragile histidine triad protein), FLCN (folliculin), TSC (tuberous sclerosis complex), and SDHB (succinate dehydrogenase B) are associated to clear cell RCC; MET, FH (fumarate hydratase), FLCN, HPT-JT (hyperparathyroidism-jaw tumor syndrome), FPTC-PRN (familial papillary thyroid and renal cancer syndrome) or SDHB lead to the occurrence of papillary RCC, BHD/FLCN (Birt–Hogg–Dubé) and SDHB induce the development of chromophobe RCC, while FLCN, SDHB and FO (familial oncocytoma) determine the appearance of oncocytoma [6]. There are opinions according to which RCC is a metabolic disease, because several of these genes (for instance VHL, MET, FH, FLCN, SDHB, and TSC) seem to be involved in metabolic pathways linked to the metabolism of O_2, Fe, ATP or of other nutrients [7, 8].

There is a relative overlap in the gene expression of hereditary and sporadic renal carcinoma. Consequently, it is not clearly established if we may or may not speak about a pathogenic mechanism identical for hereditary and sporadic forms, respectively. For a similar mechanism plead the expression of VHL gene, as the presence of germline mutations of VHL gene is ascertained in 100% of the cases of hereditary clear cell RCC [4, 9, 10], as well as the evidence which proves that in two-thirds of sporadic clear cell RCC cases, VHL gene is inactivated by point mutations, deletions or hypermethylations of gene promoters [2, 9, 11]. An opposite example is provided by

a special histological type of hereditary papillary RCC, generally related to an activating point mutation in the tyrosine kinase domain of c-MET proto-oncogene – but this mutation is present only in 5–13% sporadic papillary RCC [2, 12].

Moreover, another histological type of hereditary papillary RCC is associated with an inactivating mutation of FH gene [2, 13], without evidences for the relationship of this event with the sporadic forms [14]. Nevertheless, mutations in BHD tumor suppressor gene are usually revealed in patients with chromophobe RCC developed within the context of the Birt–Hogg–Dubé hereditary syndrome [2, 15], while they are absent or extremely rarely present in sporadic chromophobe RCC.

Supplementary to the research oriented on the genetic profile of RCC, studies based on microarray technologies state that modifications specific to renal carcinogenesis are built, regardless of histological form and sporadic or hereditary status, on the existence of a unique transcriptome (that include all RNA molecules and other non-coding RNA transcribed in a population of cells) variable with external environmental conditions [4].

Signaling pathways

Research in renal tumor pathogenesis is currently oriented on the genetic and proteins framework of the RCC, with the aim to translate the level of knowledge on tumor subtypes from histological to molecular issues, simultaneously with the deciphering of the manner in which the signaling pathways intervene in the pathogenic mechanism [1, 4, 16]. Alterations identified in proto-oncogenes and tumor suppressor genes lead to abnormal and deficient transmission of signal in the signaling pathways, and initiate the carcinogenesis mechanism by increased proliferation of tumor cells.

Wnt/β-catenin pathway

Activation of Wnt signaling pathway regulates various cell processes such as proliferation, migration, differentiation, motility and survival [17]. Consequently, overexpression of signals by various mutations sets in motion the carcinogenesis, including the renal one [2, 17, 18]. When Wnt pathway is activated, Wnt proteins link to specific receptors on cell surface and mediate intracellular signals [17]. There are two types of Wnt signaling pathways described [18]. The canonical pathway, involved more clearly in carcinogenesis is β-catenin-dependent, with an extremely important involvement of specific ligands. Non-canonical pathway, less studied in carcinogenesis is a β-catenin-independent pathway, and causes modifications in cell polarity and motility.

Wnt signaling [2, 18] is initiated after the binding of Wnt ligand to a Frizzled receptor complex. The process is mediated by Dishevelled protein, which inhibits the phosphorylation of β-catenin by GSK3β (glycogen synthase kinase 3β), with result in its cytoplasmic accumulation [18]. Later on, nuclear translocation of β-catenin is produced, where it forms a complex with transcription factors from the LEF-TCF (lymphoid enhancer-binding factor 1-T cell specific transcription factor 7) family, that activates the transcription of target genes such as D1 and L1 cyclin, and Nr-CAM, with the stimulation of neoplastic transformation and/or tumor progression [18]. Thus, β-catenin, responsible for cadherin-mediated cell-to-cell adhesion, has a crucial role in Wnt signaling [2].

When the Wnt pathway is not activated, the absence of Wnt signals triggers the phosphorylation of β-catenin by a multi-protein complex comprising CK1 (casein kinase 1), GSK3β, APC (adenomatous polyposis coli protein), and axin [2, 18]. Within this complex, β-catenin is recognized by the B-TrCP (B-transducing repeat containing protein) component of the E3 ubiquitin ligase complex, which also includes Skp1 and Cul1, and is degraded by the 26S proteasome complex [2, 18].

Although the number of papers focused on the investigation of Wnt pathway in renal carcinogenesis is small, the reported results are relevant. There is evidence that in RCC the Wnt pathway intervenes in the development of the disease by changing apoptosis [19]. The β-catenin translocated into the nucleus activates the oncogene MYC, present in some clear cell RCC and papillary RCC [20, 21]. Moreover, it appears that the activation of Wnt pathway, which leads to the mediation of tumor cell proliferation, implies the simultaneous activation of mTOR pathway, by inhibition of GSK3β [18]. Frizzled receptors in Wnt pathway display in renal carcinogenesis an altered expression [18, 22]. The increased expression of Fzd5 and Fzd8 was proven in RCC, as compared to normal renal tissue, as well as the correlation of Fzd5 with nuclear expression of D1 cyclin in approximately 30% of clear cell RCC [22].

Other molecules involved in the operation of Wnt pathway are VHL and HIF [18, 23]. Interaction between VHL and HIF1α [24] regulates the expression of numerous genes (Glut1, TGF, erythropoietin, VEGF, and PDGF), and promotes the institution of an advantageous microenvironment for angiogenesis and an increase in cellular proliferation [18]. On the other hand, loss of pVHL leads to combined de-repression of HIF–β-catenin with repercussions on Wnt/β-catenin pathway [25]. HIF-2α, as well as HIF-1α, interacts with the β-catenin/TCF complex, which facilitates genic transcription, with development of tumor cells presenting co-activated HIF-2α and β-catenin [26]. The interaction HIF-2α–β-catenin is opposed to HIF1-α on β-catenin and, consequently, on the proliferation of tumor cell, which suggests that disturbances in HIF-1α/HIF-2α ratio may cause cell proliferation when hypoxia coexists with Wnt stimulation [26]. Moreover, loss of VHL leads to activation of oncogenic signaling pathway β-catenin/HGF and, consequently, through β-catenin, the Wnt pathway becomes involved in renal carcinogenesis [27].

Furthermore, recent studies validate the role of other two proteins, Jade-1 (gene for apoptosis and differentiation in epithelia) and HIG2 (hypoxia-inducible protein-2). Jade-1, possibly a new E3 ubiquitin ligase, conducts the degradation of β-catenin [18, 28, 29]. Jade-1, overexpressed through the intervention of VHL, works as renal tumor suppressor gene. Hence, loss of pVHL

determines the decrease in levels of Jade-1, with the increase in β-catenin, elements which may trigger, by convergent action, renal carcinogenesis [18]. HIG2 binds to the extracellular domain of Fzd10 receptor and induces transcription of target genes for Wnt pathway, which grants it the role of inductor for cell proliferation, target for β-catenin/TCF4 complex and potential marker for RCC [30].

Another recent study concentrated on the direct relationship between Wnt pathway and renal carcinogenesis indicates the presence of homozygous deletions of CXXC4, a gene that codes Idax (inhibitor molecule of Wnt pathway) in severe forms of RCC [31]. Also, the role of IGFBP4 as activator of Wnt pathway has been proven, as well as the relationship between IGFBP4 overexpression and promotion of cell increase, motility and invasion in RCC, simultaneously with the overexpression of MT-MMP and M-CAM [18, 32].

PI3K/AKT pathway

PI3-K is a family of enzymes involved in the monitoring of cell increase, proliferation, motility, adhesion, survival, intracellular traffic, and angiogenesis [33].

Signaling *via* PI3-K pathway is initiated by interaction of specific ligands (EGF, IGF, and HGF) with membranar receptor tyrosine kinases (EGFR – epidermal growth factor receptor, c-kit, and INS-1 – insulin receptor 1) [2]. The interaction ligand – receptor determines the conversion of PIP2 (phosphatidylinositol 4,5-2P) into PIP3 (phosphatidylinositol 3,4,5-3P), which at its turn relays signals of increase and survival by recruiting AKT (protein kinase B) and PDK (phosphoinositide dependent-kinase) [2, 7]. Cytoplasmic AKT is activated in the cell membrane by phosphorylation at two independent positions through PDK1 and mTOR involvement [2, 7].

An important role in PI3K/AKT pathway is played by PTEN, a tumor suppressor gene that acts as a phosphatase that catalyzes the dephosphorylation of PIP3 into PIP2 and determines the inhibition of AKT [2, 34, 35]. PTEN inactivates the signaling cascade and regenerates PIP2. Normally, PTEN induces apoptosis when necessary [2, 35]. Mutations and deletions of PTEN occur when enzyme activity is inactivated, leading to uncontrolled cell proliferation [2].

At renal level, PI3K recruits cytoplasmic AKT from the membrane level. Once activated, AKT inhibits apoptosis by phosphorylation and inactivation of pro-apoptotic proteins: procaspase 9, BAD – member of bcl-2 family, ASK1 (apoptosis signal regulating kinase-1) [2, 36]. PI3K inhibits GSK-3β, which normally phosphorylates and induces degradation of cell cycle control proteins (D1 cyclin) and of transcription factors promoters of proliferation, as c-myc, β-catenin, c-Jun and Notch [2].

HGF/MET pathway

HGF and MET coupling determines phosphorylation of two tyrosine residues located at the C-terminal domain of MET, which will trigger the selection of several adapter proteins (Gab1, Grb2, SHC, STAT3, and PI3K), in addition to activation of Ras/MAPK and PI3K/AKT systems, thus supporting RCC proliferation and tumoral invasion [2, 37]. In parallel, phosphorylation of MET promotes phosphorylation of β-catenin and its separation from E-cadherin, followed by translocation of β-catenin in the nucleus and activation of transcriptional genes [2, 38].

The renal site comprises a considerable amount of HGF and urokinase – the activator of HGF. The relationship between the expression of HGF and its receptor c-MET, and hereditary [39–41] or sporadic papillary RCC is already ascertained [12, 41, 42].

Moreover, relatively recent evidence establish that in RCC the expression of VHL inhibits the signaling *via* β-catenin stimulated by HGF; consequently, the loss of VHL in RCC may activate signaling *via* HGF induced β-catenin [2, 27]. Starting from the sequence of these events which lead to initiation and progression of renal carcinogenesis, therapeutic strategies were developed applicable in RCC, with the aim to impede the activation of this pathway, by stopping the self-phosphorylation of c-MET, cutting off the HGF–c-MET coupling or the inactivation of activated c-MET [2, 41].

Final remarks

Although it seems obvious that the classic sequence of carcinogenesis is respected at the renal site, unfortunately, the manner in which signaling pathways are involved, in the specific context of renal tumors, is not extensively investigated. The molecules forming these pathways, considered main pillars in the pathogenic mechanism, have a complex behavior.

Like in a kaleidoscope where the image changes in relation to the angle of the perspective, these molecules are either overexpressed or underexpressed, through down-regulation and/or up-regulation, in similar or different conditions. This is the reason why their crossbred dialogue represents a real challenge for research in this domain, in the attempt to identify new prognosis markers and possible therapeutic targets oriented towards the renal site.

Therefore, this review, designed as a useful tool in understanding the operation of signaling pathways, opens for those interested new perspectives in the thoroughgoing study of the mechanism of renal carcinogenesis.

Conflict of interests

The authors declare that they have no conflict of interests.

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