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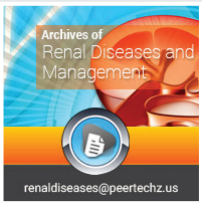

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Mini Review

Clinical implications of epigenetics in Renal Cell Carcinoma

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Abstract

Renal Cell Carcinoma (RCC), is the 9th most common cancer in the United States. The major classifications of RCC include clear cell (ccRCC), papillary (pRCC) and chromophobe (chRCC). Treatment for the localized disease includes resection or ablation with curative intent, or surveillance if these procedures are not feasible. Unfortunately, about one-third of patients will present with metastatic disease at the time of diagnosis and there are currently no reliable biomarkers to guide clinical decision-making. There is growing evidence that epigenetics plays a role in kidney cancer tumorigenesis and aggressiveness and new strategies for biomarker development are emerging. For example, DNA methylation patterns may be useful in distinguishing different types of RCCs and for distinguishing malignant kidney neoplasms from benign tumors. Epigenetic changes in RCC have also been associated with poorer response to treatment and have the potential to be novel drug targets in the treatment of mRCC. Here we discuss the epigenetics of RCC and the corresponding clinical implications.

Abbreviations

RCC: Renal cell carcinoma; mRCC: metastatic RCC; pRCC: papillary RCC; chRCC: chromophobe RCC

Introduction

Renal Cell Carcinoma (RCC), is now the 9th most common cancer in the United States [1,2]. For reasons that are unclear, men are more likely to be diagnosed with RCC than women [1,3]. The most common types of RCC are clear cell RCC (ccRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC). Clear cell is by far the most common histologic subtype occurring in about 70% of all cases. The other subtypes occur infrequently including carcinomas that do not fit into any diagnostic subtype and are thereby labeled unclassified [4]. African Americans are more likely to be diagnosed with non-clear cell RCCs such as papillary, chromophobe, medullary, and collecting duct subtypes [1,5].

Though more than a dozen targeted agents have become available since 2005 for the treatment of high-risk localized resected RCC and metastatic RCC, there is still no FDA-approved screening test [1,6]. Clinically, patients are usually asymptomatic with the diagnosis typically being made as the result of an incidental finding on an MRI, CT, or ultrasound [1]. Roughly 10% of patients present "classically" with the triad of hematuria, flank pain, and a palpable mass. Patients may also experience symptoms associated with hypercalcemia, Cushing Syndrome, left-sided varicocele, and hypertension [1].

Most patients present with localized disease and can be managed surgically with a partial or radical nephrectomy. For others, ablation or active surveillance may be appropriate [4]. However, about one-third of patients treated surgically with the intent to cure will develop local or metastatic disease recurrence [2]. Since roughly a third of patients will have metastatic RCC (mRCC) at the time of diagnosis, approximately half of all patients who are diagnosed with RCC will require systemic therapy. Unfortunately, systemic therapy is rarely associated with cure and side effects are common with overall survival (OS) of less than 5 years for 80% of patients with recurrent or metastatic disease [4].

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In recent years, the treatment of mRCC has transitioned from the use of high-dose interleukin-2 and interferon-α cytokine therapy to the use of Vascular Endothelial Growth Factor (VEGF) receptor inhibitors, mammalian target of rapamycin inhibitors (mTOR) and immune checkpoint inhibitors with significant improvements in OS [2]. However, primary or acquired drug resistance remains a vexing clinical problem. As such, there is a pressing need for novel diagnostic and therapeutic targets. New possibilities are emerging from the study of epigenetics in kidney cancer.

Epigenetics and kidney cancer

Epigenetics is the study of inheritable changes in gene expression that occur without modifications of the primary DNA sequence [7,8]. DNA methylation is the most well-studied type of epigenetic change that occurs in areas where dinucleotides of cytosine and guanine are linked by a phosphate group in a repeated sequence [8]. These dinucleotides are not evenly spaced throughout the genome, but instead are clustered together into "CpG islands" [8]. When CpG islands are methylated in promoter regions, transcription of the corresponding gene is silenced. Conversely, gene expression may resume after demethylation [8]. Silencing of tumor suppressor genes by DNA methylation predisposes patients to the development of many forms of human cancer [9,10].

It is well documented that mutations of the VHL tumor suppressor gene are implicated in ccRCC carcinogenesis [11]. However, the sole loss of the VHL tumor suppressor gene does not appear to be sufficient to induce ccRCC. There is a long latency of disease progression in patients who harbor the mutation and deficiency of VHL in rats is not associated with the development of ccRCC [4]. Nevertheless, loss of function by mutation or silencing of the VHL gene is implicated in up to 90% of ccRCC cases in humans [12]. Herman and colleagues found that 88% of the tumors they studied (26 cell lines) showed inactivation of the VHL gene due to methylation of CpG islands [13].

The VHL gene encodes an E3 ubiquitin ligase that ubiquitinates hypoxia-inducible factor (HIF) HIF-1α and HIF-2α which results in their rapid degradation by proteasomes [4]. In 2020 Nam, et al. described a potential role for DNA methylation in the regulation of HIF target genes such as adrenomedullin (ADM) and TNF alpha-induced protein 6 (TNFAIP6) in ccRCC tumor tissue. These investigators found a correlation between hypomethylation of several HIF target genes and increased expression of these genes in metastatic tumor tissue [14]. Taken as a whole, epigenetic regulation appears to play a role in the modulation of VHL signaling at multiple levels within the pathway including HIF-mediated regulation of carcinogenesis, cell cycle progression, and angiogenesis [3,14].

Clinical utility of epigenetics and RCC

Given that ccRCC is so heavily associated with loss or inactivation of VHL, the Cancer Genome Atlas (TCGA) chose ccRCC as the first kidney cancer to study and publish which solidified the importance of VHL and other genes in ccRCC [14,15]. The TCGA characterized 289 genes that were shown to be methylated in ccRCC tumors [16]. Rickets, et al. also used TCGA data to demonstrate a correlation between hypermethylation of CDKN2A and poor survival in ccRCC, pRCC, and chRCC [17]. In a study from Japan, Sato, et al. found a correlation between hypermethylation of BAP1 (a tumor suppressor gene that encodes a deubiquitinating enzyme regulating key cellular pathways) and worse OS in primary ccRCC [18].

In an intriguing study of tissue from the National Cancer Institute Cooperative Human Tissue Network and cell lines, Nam and colleagues compared metastatic RCC to primary RCC and normal renal tissue. They found that expression of estrogen-receptor-related-γ (ERR-γ), the gene product of the estrogen receptor-related gamma gene (ESRRG) was decreased in primary ccRCC and even more so in metastatic disease [14]. They were also able to demonstrate more prominent changes in hypermethylation of metastatic tumors when compared to the primary neoplasms. In addition, decreased expression of ESRRG gene correlated with decreased survival suggestive of a more aggressive phenotype [14]. These investigators also reported DNA methylation of metabolic and transporter genes.

In another key study by Wei, et al. investigators compared the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score to a five CpG classifier risk stratification model they developed based on DNA methylation patterns [19,20]. These investigators utilized genome-wide CpG methylation profiling of ccRCC to identify clinically relevant CpG sites in five genes: PITX1, FOXE3, TWF2, EHBP1L1, and RIN1 [19]. A methodology based on these five CpG sites was devised to accurately stratify patients into high- and low-risk groups within each of the five SSIGN risk categories. In other words, DNA methylation status was able to distinguish favorable and unfavorable subgroups in every SSIGN risk group. In this international study, the findings were reproducible across multiple centers regardless of country, race, or clinical center [19].

A Korean study performed by Kang, et al. also attempted to use DNA methylation patterns in primary neoplasms to better predict outcomes in patients with ccRCC [21]. They found that promoter hypermethylation of ZNF278, DDP6, and FAM155A was associated with an aggressive tumor phenotype that was associated with early distant metastasis. Multivariate analysis showed that methylation of these genes alone or in combination was an independent predictor of distant metastasis.

In a study from China of ccRCC cell lines and tumor tissues, Liu, et al. found that GPX3 methylation could serve as a prognostic biomarker for early metastasis and poor clinical outcomes [22]. These investigators found that 77.1% of primary ccRCC tumors (n = 210) had aberrant methylation of GPX3 which was associated with high tumor nuclear grade. GPX3 encodes for glutathione peroxidase 3 which scavenges reactive oxygen species [22]. These investigators concluded that the failure of GPX3 expression may compromise cellular antioxidant systems and predispose cells to tumorigenesis. Since GPX3 hypermethylation can be detected in urine, serum, and blood samples, it may prove to be a clinically relevant biomarker in the future [22].

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Other forms of epigenetic regulation that appear to be relevant in kidney cancer include modification of the histone proteins H3kK4me2 and H3k18Ac which have been linked to worse prognosis [23] and modifications of H3 via acetylation that has been inversely correlated with tumor progression, staging, and Fuhrman grade [24].

MicroRNAs (miRNAs) are small non-coding RNAs that can operate as both tumor suppressors and oncogenes due to their ability to regulate proliferation and cell cycle progression [7,25]. Epigenetic regulation of miRNA expression also appears to have prognostic significance in RCC [7]. Heavy methylation of miR-9-1 and miR-9-3 has been linked to decreased OS in RCC. Heavy methylation of miR-9-3 has also been associated with an increased risk of recurrence [26]. Though DNA methylation status was not specifically assessed, downregulation of miR1-141 and miR-200b was associated with a 99% sensitivity and 100% specificity for distinguishing chRCC from oncocytoma (a benign renal neoplasm) on ex vivo fine needle aspiration [25].

Epigenetic regulation of gene expression may also involve long noncoding RNAs (lncRNAs) such as HOX transcript antisense intergenic RNA (HOTAIR) and DNA methylation-deregulated and RNA m6A reader cooperating (DMDRMR) [27-29]. HOTAIR has been proposed as an oncogene in that it upregulates a histone demethylase, KDM6B, that targets the SNAI1 gene which has been implicated in epithelial mesenchymal transition (EMT) [28]. DMDRMR facilitates tumor growth and metastasis by binding to insulin-like growth factor 2 mRNA binding protein which stabilizes the cell cycle kinase CDK4 [29].

Finally, cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) is a highly sensitive assay capable of detecting early-stage malignant neoplasms of the kidney. In a genome-wide cfDNA methylation analysis that included patients with early-stage RCC, cfMeDIP-seq achieved an area under the receiver operating characteristic (AUROC) curve of approximately 0.9 for detecting and classifying RCC patients from patients with other tumor types and healthy controls [6].

Epigenetics and drug resistance in RCC

The current preferred treatment regimen in advanced ccRCC includes a dual therapy composed of an immune checkpoint inhibitor (ICI) such as pembrolizumab, ipilimumab, or nivolumab, paired with a tyrosine kinase inhibitor (TKI) such as axitinib, cabozantinib, or lenvatinib, per the National Comprehensive Cancer Network (NCCN) guidelines. For favorable risk advanced ccRCC first line combinations include axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab [30-32]. It is important to note that these combinations are the same for unfavorable and poor risk ccRCC except for the addition of ipilimumab + nivolumab and monotherapy of cabozantinib (as a category 2a recommendation) [33,34]. The optimum therapy for non-clear cell RCC has yet to be established.

Expression of VEGF and Platelet-Derived Growth Factor (PDGF) are upregulated in RCC [35]. This upregulation is the target of TKIs when treating for mRCC [35]. TKIs, which include sunitinib, pazopanib, axitinib, lenvatinib, sorafenib, and cabozanitinib, are proposed to exert their effect in RCC through antagonism of the tyrosine kinase receptors for VEGF and PDGF leading to a decrease in tumor angiogenesis [35]. However, despite targeted therapy, 20-30% of patients on TKIs are drug resistant and most of these patients experience disease progression in less than 3 months [35]. Among patients on sunitinib only 20-30% of patients will initially respond and almost all responders develop resistance in 2 years [36]. There have been several proposed mechanisms associated with resistance to TKI in RCC which include lysosomal sequestration, signaling pathway activation, and epigenetic modifications that promote EMT [37,38].

A study performed in China looked at DNA methylation and sunitinib resistance in advanced ccRCC patients. These investigators found that hypomethylation in the glutaminyl peptide-cyclotransferase (QPCT) promoter region showed a poorer response to sunitinib therapy [39]. Dubrowinskaja, et al. also investigated epigenetic changes in RCC patients and response to anti- VEGF therapies, sunitinib, sorafenib, bevacizumab, and axitinib. This team of investigators found that hypermethylation of neurofilament heavy polypeptide (NEFH) demonstrated a shorter OS for patients and hypermethylation of NEFH was associated a 91% sensitivity at detecting therapy failure [40]. Hypermethylation of cystatin 6 (CST6) and ladinin 1 (LAD1) has been linked to shorter OS and progress free survival (PFS) in patients with advanced RCC while being treated with sunitinib, sorafenib, axitinib, and bevacizumab [41]. These finding suggest that DNA methylation patterns may also be useful for selecting the best treatment options of patients with mRCC.

Despite ICI therapy regimen for advanced RCC there is no published research on epigenetic changes related to drug resistance to ICI in RCC at this time. However, this provides a potential frontier for further research to help alleviate drug resistance in metastatic patients.

Novel epigenetic targets for the treatment of RCC

Epigenetics have been shown to play a role in the development of RCC, progression of RCC, and resistance to TKI therapy in RCC. These epigenetic alternations provide opportunities for the discovery of new targets for drugs to combat RCC. Currently there are seven FDA agents that target 3 epigenetic classes, DNA Methyltransferases inhibitors (DNMTi), Histone Deacetylase inhibitors (HDACi) and EZH2 inhibitors [42]. Currently a number of trials investigate the use of an HDACi and TKI to reverse acquired resistance and re-sensitization of tumors to TKI therapy [35]. There was a phase I study that evaluated safety, tolerability, and preliminary efficacy of a HDACi, vorinostat, plus sorafenib in patients with RCC and non-small cell lung cancer [43]. However, this trial showed poor tolerance and no confirmed response [43]. Another study paired vorinostat with pazopanib in advanced solid tumor, including RCC, and that combination achieved

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stable disease for at least 6 months or partial response in 19% of all patients with a median OS of 8.8 months [44]. Vorinostat has also been paired with bevacizumab in a multicenter, single-arm phase I/II clinical trial [45]. This trial had 33 patients with metastatic or unresectable ccRCC. With the dual therapy patients achieved 5.7 months of median PFS and 13.9-month median OS [45]. Toxicity was a significant problem in these initial studies.

Currently there is limited information on pairing novel epigenetic targeting drugs with ICI therapy in advanced RCC disease. There are three clinical trials underway examining the use to Vorinostat with Pembrolizumab (NCT02619253), Entinostat with Atezolizumab plus Bevacizumab (NCT03024437) and Entinostat with Novolumab plus Ipilimumab (NCT03552380). The results of these trials are yet to be published but could yield promising results for more targeted therapies.

Conclusion

Epigenetic studies are revealing new strategies for developing diagnostic and prognostic biomarkers for kidney cancer as well as strategies for developing novel therapeutic agents. Downstream targets of VHL signaling pathways such as HIF target genes may represent viable therapeutic targets based on selective demethylation. Investigation into DNA methylation of RCC has elucidated multiple genes that are associated with more aggressive RCC phenotypes (Table 1). DNA methylation status may also be useful for distinguishing benign from malignant renal neoplasms and aggressive from indolent disease. In addition, hypermethylation of particular gene promoters have shown to be predictor of poorer outcomes of patients on TKI treatment (Table 2). The study of other epigenetic mechanisms such as the regulation of gene expression by histones, miRNAs and lncRNAs will likely yield clinically meaningful opportunities to find viable biomarkers, better predict patient prognosis, and address the thorny problem of drug resistance.

Table 1: Selected hypermethylated genes linked with more aggressive phenotypes of RCC and their corresponding function.

Gene	Function	Citation
PITXI	Immune Response Network	Wei JH 19
FOXE3	Transcription factor	Wei JH 19
TWF2	Cancer cell proliferation	Wei JH 19
EHBP1L1	Cytoskeleton organization	Wei JH 19
RIN1	EMT	Wei JH 19
GPX3	Anti-oxidant system	Liu 21
CDKN2A	Cell cycle regulator	Rickets 16
BAP1	Deubiquitinating enzyme	Soto 18
ZNF278	Transcription repressor	Kang 21
DDP6	Regulator of voltage gated potassium channels	Kang 21
FAM155A	Unknown	Kang 21
ESSRG	Regulator of mitochondrial metabolism	Nam 14

Table 2: Selected genes associated with poor response to particular Tyrosine Kinase Inhibitor treatment.

Gene	Therapeutic Agents	Citation
QPCT	Sunitinib	Zhao 34
NEFH	Sunitinib, sorafenib bevacizumab, axitnib	Dubrowinskaja 35
CST6	Sunitinib, sorafenib bevacizumab, axitnib	Peters 36
LAD1	Sunitinib, sorafenib bevacizumab, axitnib	Peters 36

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