REVIEW ARTICLE

CONTENTS

Comparative analysis of the roles of PBRM1 and SETD2 genes in the pathogenesis and progression of renal cell carcinoma: An analytical review

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ABSTRACT

Clear cell renal cell carcinoma (ccRCC) is characterized by frequent mutations in chromatin-modifying genes, notably PBRM1 and SETD2, which play critical roles in tumorigenesis and disease progression. These mutations affect chromatin remodeling and histone methylation, influencing cellular functions such as tumor suppression, genomic integrity, and cell cycleregulation. Despite their prevalence, the distinct biological impacts and clinical implications of PBRM1 and SETD2 mutations remain incompletely understood. This review aims to elucidate the functional similarities and differences between PBRM1 and SETD2 mutations in ccRCC, investigate their roles in tumor progression and metastasis, and assess the potential clinical and therapeutic implications of these genetic alterations in the context of precision oncology. A comprehensive literature review was conducted, analyzing genomic, transcriptomic, and clinical data from ccRCC cohorts. Functional studies of PBRM1 and SETD2 mutations were examined alongside gene set enrichment analyses (GSEA), histopathologic observations, and molecular profiling of primary and metastatic tumor sites. Recent advances in therapeutic strategies targeting these mutations were also reviewed. PBRM1 mutations occur early in ccRCC development, altering chromatin accessibility and acting as tumor co-initiators, while SETD2 mutations arise later, exacerbating genomic instability and promoting metastasis. Both genes share tumor suppressor functions but differ in their genetic interactions and pathways. Co-mutation of PBRM1 and SETD2 correlates with increased tumor aggressiveness, poor prognosis, and higher metastatic potential. Emerging therapeutic approaches, including targeted molecular therapies and immunotherapies, show promise in addressing these mutation-driven pathways. PBRM1 and SETD2 mutations critically influence the molecular pathogenesis and clinical outcomes of ccRCC. Understanding their distinct and cooperative roles can enhance molecular profiling and guide personalized treatment strategies. Further research is warranted to develop targeted therapies that exploit the vulnerabilities associated with these chromatin-modifying gene mutations, ultimately improving prognosis and therapeutic response in ccRCC patients.

KEY WORDS: renal cell carcinoma, kidney cancer, surgical intervention, genetic syndrome

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INTRODUCTION

Renal Cell Carcinoma (RCC) is the most common type of kidney cancer. Each year, approximately 270,000 individuals are diagnosed worldwide with RCC, while over 116,000 deaths are attributed annually to this disease, making it the 14th leading cause of cancer-related deaths [1]. RCC is a cancer of kidney tubular cells and frequently progresses asymptomatically. The symptoms that are suggestive of RCC always appear at a time when the disease is already advanced and has a poor prognosis [2]. Despite surgical intervention, 20-30% of patients will have a relapse or develop metastases within five years, while treatment of metastatic RCC is mainly palliative and ineffective. Due to the unique heterogeneity of RCC, discovering effective therapy is particularly challenging. Advanced RCC represents the genetic syndrome associated with a number of gene mutations whose products are involved in general cellular processes [3]. Although CCRC and paRCC are closely related by genetic and histological features, the gene mutations responsible for the tumor genesis of these tumours have completely distinct sets. The loss of different chromatin regulators is the main carcinogenic event leading to different RCC histotypes [4]. Clear cell RCC (ccRCC) is caused by the inactivation of the VHL gene and at least one out of three genes coding for chromatin regulators: BAP1, PBRM1, and SETD2. A significant reduction of the disease-free interval between the primary tumour resection and the onset of tumour metastatization was observed in patients with a mutation in one of the VHL, BAP1, PBRM1, or SETD2 genes [5]. CCRC is usually diagnosed too late to be salvaged. Consequently, it is necessary to deepen the molecular background of ccRCC to reduce the number of deaths caused by kidney cancer [6]. BAP1, PBRM1, and SETD2 are important chromatin regulators whose products

are often damaged in ccRCC [7]. Nearly 350 mutations are known in the BAP1 gene, while more than 700 and 500 variations are known in the PBRM1 and SETD2 genes respectively [5]. A thorough experimental examination of the effect of these changes is particularly burdensome. Bioinformatics tools were used to predict the effects of all known mutations within BAP1, PBRM1, and SETD2 genes [8].

AIM

This review aims to elucidate the functional similarities and differences between PBRM1 and SETD2 mutations in ccRCC, investigate their roles in tumor progression and metastasis, and assess the potential clinical and therapeutic implications of these genetic alterations in the context of precision oncology.

MATERIALS AND METHODS

A comprehensive literature review was conducted, analyzing genomic, transcriptomic, and clinical data from ccRCC cohorts. Functional studies of PBRM1 and SETD2 mutations were examined alongside gene set enrichment analyses (GSEA), histopathologic observations, and molecular profiling of primary and metastatic tumor sites. Recent advances in therapeutic strategies targeting these mutations were also reviewed.

REVIEW AND DISUSSION

DEFINITION AND CLASSIFICATION OF RENAL CELL CARCINOMA

Renal Cell Carcinoma (RCC) is not a single disease, but several histologically defined cancers with different genetic drivers, clinical courses, and therapeutic responses [1]. The prevalence of RCC is rising worldwide. To grasp advances in the pathogenesis and clinical progression of RCC, it is crucial to understand its taxonomy. According to the histopathological and molecular levels, RCC can be classified into many subtypes, of which clear cell RCC accounts for the majority of cases, followed by papillary RCC and chromophobe RCC. Each RCC subtype has unique histological features, although some subtypes share an overlapping microscopic morphology. To improve the diagnostic consistency and assist the selection of modern targeted therapy, numerous criteria have been established to define RCC at the histopathological level. Epidemiological studies suggest that different RCC subtypes exhibit distinct genetic alterations, aggressiveness, and prognosis [9]. Therefore, it is necessary to develop a subtype-specific biomarker and identify therapeutic vulnerabilities based on the genetic hallmarks of each RCC subtype. For example, PBRM1 mutations are predominant in patients with ccRCC and are considered as an independent worse prognostic hallmark [10].

EPIDEMIOLOGY AND RISK FACTORS

Renal Cell Carcinoma (RCC) accounts for about 80-90% of kidney cancers and is the sixth most common cancer in men and the tenth in women. In the United States, it was estimated that 73,820 new cases of RCC would be diagnosed in 2019, and there were 14,770 estimated deaths [11]. The incidence rate of RCC varies globally and is rapidly rising in more developed regions. The overall 5-year survival for kidney and renal cancers is 73%. In more developed regions, the 5-year survival is 65%. RCC is about twice as common in males as in females after adjusting for age. The highest incidence rate of RCC is in North America (12 per 100,000) and the lowest is in South Central Asia (4 per 100,000). Some side-by-country comparisons include the following: Age-standardized mortality rates in Japan have been decreasing 4.9% per year, whereas rates in Spain have been increasing 1.8% per year. The mean age-adjusted incidence rate over the past years has increased fairly steadily worldwide, but at different rates in more versus less developed regions [12]. RCC is cystic, which enables it to often grow to a relatively large size before causing symptoms. Indeed, while localized disease is usually asymptomatic, metastatic disease presents more often with the classic symptoms. RCC has subtypes based on cell histology. Different histologic types of RCCs have distinct cytogenetic abnormalities and demonstrate various susceptibilities to environmental carcinogens. Clear cell RCC (ccRCC) is the most common histologic subtype of RCC and is significantly associated with striking chromosomal loss on the short arm of chromosome 3. Analysis of the central TCGA cohort revealed frequent, previously unreported, hemizygous loss of 9p in von Hippel-Lindau (VHL) wild-type papillary RCC [13]. Likewise, the frequency of 9p loss was significantly elevated in wild-type TCGA ccRCCs. The 15 suppressor gene commonly mutated in this setting, demonstrating 9p hemizygous loss, for which silencing significantly increased proliferation, was PBRM1 [14].

GENETIC ALTERATIONS IN RENAL CELL CARCINOMA

1 in 63 individuals will develop Renal Cell Carcinoma (RCC). It is clear that both tumors and normal tissues accumulate multiple mutations and genomic alterations.

Fortunately, the latest technologies have addressed whole-exome and next generation sequencing [15]. As for the other tissues, more than 1.5 × 1010 of the bases exposed to UV or of the bases wandering in electrons, are changed every day. The early-stage detection, classification of the cancer and prediction of drug responses are typically based on the examination of a layout of a tissue obtained from a patient by biopsy. Uncovering of key genetic alterations could pave a way to identify potential biomarkers, useful for early detection and prediction of the cancer. Nevertheless, what is more crucial is the revelation of mechanism of the cancer development, so that tailored therapy may be proposed. The advancement in next-generation sequencing methods offers the detailed exploration of cancer's genetic complexities for the different tissues [2]. A shift to the molecular view of the disease had encouraged whole-genome, whole-exome and targeted next-generation sequencing to analyze the genetic changes in Renal Cell Carcinoma. Vaccine therapy was found to decelerate Renal Cell Carcinoma progress. Vaccination against mutant PBRM1 can prevent Renal Cell Carcinoma growth, including the out-of-frame switch peptide. RCC is a highly drug-resistant and recalcitrant disease of the kidney. The prevalence among men reaches 2% and among woman 1%; more than 100,000 individuals die of it [16].

OVERVIEW OF KEY GENES INVOLVED IN RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is the leading cause of mortality among all urological cancers. Overall survival at 5 years for patients with advanced RCC is less than 10% [17]. Recent genomic analysis has revealed the landscape of genetic alterations in RCC that appear to involve genes mutated at low frequency. The three genes most commonly mutated in clear cell RCC (ccRCC, accounting for over 75% of cases) are VHL, PBRM1, and SETD2 [16]. The Products of these genes are part of the nuclear protein ubiquitin-ligase module or epigenetic complex involved in chromatin remodeling, transcriptional regulation of targeted genes, and cell cycle control. The frequent, and often mutual, mutation of these genes in ccRCC suggests the existence of a complex network portraying the oncogenic nature of this cancer type, and provides the opportunity for a comprehensive study to clarify better ways of intervention for ccRCC patients. The involvement of interactions of these tumor-associated genes is supported by recent papers suggesting a novel aspect of PBRM1 biology implicating the PBRM1 interaction with H3K27me3 marking in the control of transcript level [18]. The relevance of those interactions in RCC carcinogenesis is broadened here, providing evidence of the involvement of PBRM1 and SETD2 in ccRCC-stromal cell communication, and their reciprocal participation in crosstalk between ccRCC cells and fibroblasts. Independent results obtained on PBRM1 silencing in ccRCC cell lines, and co-culturing IHH and HEK 293T cells confirm that CD70, TNFSF13 and IL1RL1 genes are up-regulated or down-regulated, respectively, in response to PBRM1 loss. Furthermore, evidence of mutually exclusive mutation of PBRM1 and SETD2 in RCC patients provides more information to that reported in the existing literature, and is suggestive of its involvement in common RCC carcinogenic pathways [18, 19].

PBRM1 GENE

Via its Gln-rich domain, the PBRM1 gene encodes tumor suppressive proteins with significant roles in chromatin regulation and gene expression [20]. This gene was the most under-reconstructed in PCC, indicating that it is a rare gene that is frequently mutated or epigenetically altered in most types of cancer. In ccRCC, it is the second-most changed gene among 124 cases [21]. Moreover, the transformation of PBRM1 is the dominant genetic and epigenetic change in mutations, deep deletion, DNA methylation and the processes of histone modification in all types of changes in ccRCC [22]. To explore the mechanism of PBRM1 transformation in ccRCC, we note that PBRM1 prefers to interact with DNA-binding or chromatin-remodeling proteins and those with PAAR; the PAAR domain is closer to the transformation profile of PBRM1; discuss and argue the mechanism of PBRM1 transformation in ccRCC. This research suggests that mutations in PBRM1 are correlated with genomic stability, which has been considered a cause of cancer in previous observations. But at the individual gene level, mutations of PBRM1 alone did not result in the occurrence of ccRCC or other cancers. Analyzing data from a variety of tumor forms and observing that the proliferation of tumors in which PBRM1 is transformed is slower than in tumors without transformation. Comparing the effects of altered PBRM1 on OS and DFS in a diversity of cancers, it is found that PBRM1 has a significantly greater effect on both OS and DFS specifically in ccRCC [8].

STRUCTURE AND FUNCTION OF PBRM1

The polybromo-1 protein, encoded by the PBRM1 gene, can structure a Transcriptional inhibits a repressor complex with SWI/SNF subunits and BCL7B inhibits transcription. Polybromo-1 is a nuclear protein pres-

ent in a wide range of human tissues and commonly expressed in neoplastic cells, which has potential value for the differential diagnosis of carcinoma and melanoma. This discovery of PBRM1 has enhanced the understanding of the broad and critical role of SWI/SNF gene misregulation in human cancer pathogenesis by providing the ability to directly study a near universal and extensive set of tumors related to the highly conserved SWI/SNF core ATPase machinery [23]. PBRM1 mutation is particularly common when ARID1A is silenced or mutated and demonstrates that ARID1A, PBRM1 or BRM suppresses or promotes melanocyte neoplasia and invasion in a BRAFV600E context-dependent manner with distinct kinetics. Hence, both BRCA1 and Polybromo-1 are independently necessary for the repair of DNA double-strand breaks [24]. Polybromo-1 is thought to have important functions in cell cycle regulation, gene transcription, and chromatin architecture [20]. Polybromo-1 (PBRM1) is a chromatin remodeling factor that belongs to the protein associated with the Brg/Brm and BRCA1 complex. BRCA1 is a tumor suppressor gene associated with breast and ovarian cancer, and its product has E3 ubiquitin-protein ligase that acts on histone H2A and regulates the repair of DNA double-strand breaks. PBRM1 is a DNA binding protein containing six BRCT domains, similar to BRCA1 with an ordinary 1,863 amino acids. BRCA1 and PBRM1 co-localize in the nucleus and exhibit similar expression patterns in various normal human tissues. It was found for the first time that BRCA1 interacts with PBRM1 through the third BRCT domain of BRCA1 and the sixth BRCT domain of PBRM1. BRCA1 is combined with PBRM1 during DNA replication and/or DNA repair after irradiation. The coexistence of these two proteins is thought to be necessary for the repair of DNA double-strand breaks, and RNA interference-mediated knockdown or gene mutation of BRCA1/PBRM1 will lead to increased sensitivity to ionizing radiation [25].

ROLE OF PBRM1 IN RENAL CELL CARCINOMA

There are many recent studies, much of them website-based, which have estimated the impacts of gene mutations on tumor initiation, progression, or the prognosis of disease. However, few studies have explicitly estimated the genetic roles of PBRM1 in a large tumor base in the pattern of transcriptome expression, immune cell infiltration, and disease prognosis. Epigenetic modifier genes are described as the second maximal transformative genes in many tumors following well-established tumor suppressor, oncogene, and DNA reparation genes. For instance; ATM, BAP1, BRCA2, CUX1, KMT2D, MGMT, and PBRM1 [20]. Therefore, in ccRCC, who has been reporting epidemiological and clinical aspects with estimates of specific metabolic patterns, many crucial the features of genetic and epigenetic alterations to PBRM1 as well as results of experiments related to anti-PD-1 immunotherapy for clear cell renal cell carcinoma [26]. Further attention is given to the genetic or epigenetic mutations that occur in PBRM1, which have formed as one of the two crucial genes correlated with chromatin regulation in the complete reinterpretation of ccRCC [18]. It is noted about the systems through which such changes lead to the appearance, mapping, shape, histone remodeling, and DNA methylation reconfiguration of tumor [27]. Directions also address the genetic condition and molecules separately or jointly transforming when the mutation of PBRM1 arises in different exon domain amino acids or amino-acid residues of introns. Indicates that effects include tumor endophytic reprogramming, skin alteration, tumor metabolic reconfiguration, and inhibition of T cell activity, genetic instability, and upregulation of noncanonical oncogene paths, such as JAK/Stat [28]. It is also noted that the epigenetic mechanics conduce to the reconfiguration of immune cells in the TME away from an anti-tumor phorotype [22]. Such the end Duarte shedding light on the mechanism's result in immunotherapy and may have the potential to help the further innovative treatment of RCC [29].

SETD2 GENE

Recent advances in genomic studies reveal that the genetic landscape of Renal Cell Carcinoma (RCC) includes mutations in tumor-suppressor genes, prominently PBRM1, encoding ARID2[31]. PBRM1 is the second most altered gene in clear cell RCC (ccRCC) [31]. Another important gene, SETD2, which encodes a histone methyltransferase, also contributes to adverse clinical outcomes in ccRCC by repressing pathogenic LINE-1 [30]. In cases where SETD2 is mutated or downregulated, LINE-1 repression is homogeneously reactivated, showing a complementary functional enrichment compared to PBRM1 [31]. Reports detail the contributions of SETD2 mutations to ccRCC progression, indicating these mutations result in poorer outcomes [32]. SETD2, the fourth most frequently altered gene, plays a critical role in DNA damage repair. Its trimethylated H3K36 mark associates with open-chromatin linked to elongating RNA polymerase II. Loss of H3K36 trimethylation due to SETD2 functional loss correlates with inhibited repair of DNA double-stranded breaks and decreased survival [31]. Gene alterations in SETD2 show branched patterns in multi-regional samples of treated ccRCC [30]. Furthermore, several chemotherapy drugs are significant for

treating ccRCC with pathological SETD2 alterations and correlate with H3K36 depletion [31]. Results indicate that SETD2 gene alterations are linked to unfavorable clinical outcomes, underscoring its potential as a drug target and biomarker [31, 32].

STRUCTURE AND FUNCTION OF SETD2

SETD2 (SET domain containing 2) is a ubiquitously expressed SET domain-containing histone 3 lysine 36 trimethylase (H3K36me3) that interacts with elongating RNA pol II via the RNA pol II-associated factor complex (PAF1c), for the recruitment of H3K36me3 to transcribing gene bodies, being the principal mediator of H3K36me3 [32]. The functions for H3K36me3 include the regulation of Pol II and nucleosome density across exons, alternative splicing, and DNA repair. Biallelic inactivation in SETD2 is associated in clear cell renal cell carcinoma (ccRCC) with reduced survival and earlier time to recurrence [18]. SETD2 mutant tumors harbored global and tumor-specific alterations in bulk DNA methylation patterns. There is enrichment of bis-synchronous methylation events in tumors harboring mutations in genes of several pathways. Notably, mutual exclusivity of methylation events was observed in tumors with alternative mechanisms of pathway deregulation, suggesting a branched epigenetic evolution [33]. In SETD2 WT cells, hypomethylation-induced replication stress activates the DNA damage response (DDR). Recent findings have characterized an epigenetic determinism associated with reduced H3K36 tri-methylation, detected in ccRCC molecular subtypes and correlated with unfavorable outcomes, suggesting that SETD2 loss may not be restricted to VHL disease [18]. SETD2, ubiquitously expressed SET-containing methyltransferase, trimethylates lysine 36 of histone H3 (H3K36me3) along transcribed gene bodies encompassing in a wide-open chromatin structure. H3K36me3 enriches across exons and, due to histone-DNA contacts, induces higher nucleosome density. Decreasing nucleosome occupancy at exon boundaries increases nucleosome turnover, facilitating Pol II passage across splice sites to promote exon definition and splicing fidelity. By adopting decompacted nucleosomal arrays, tumor-specific mutations impair H3K36me3-mediated exon definition, decrease fidelity of co-transcriptional splicing, and increase the inclusion of unique exons. Additionally, ectopically methylated loci generated by mutant tumors exhibit genome-wide altered nucleosome positioning [34]. Collectively, these findings mechanistically define how SETD2 mutations dysregulate alternative splicing and actively utilize physiologic chromatin forces to directly impact splicing fidelity [35].

ROLE OF SETD2 IN RENAL CELL CARCINOMA

The findings and functions of PBRM1 and SETD2 genes on renal cell carcinoma, and the interrelation between PBRM1 deletions and SETD2 mutations propose a potential therapeutic approach, have attracted a great deal of attention and have been studied actively by various research groups [31]. The nature of the gene mutations that occur in PBRM1 and SETD2 is different: for PBRM1, the majority of gene alterations are deletions, some of which may be germline variations; and for SETD2, the majority are single nucleotide substitutions or insertions and deletions. Concerning how these gene alterations contribute to renal carcinogenesis, some studies report that mutations in PBRM1 or SETD2 have few, if any, effects on the expression of their target genes. Detailed examination of the TCGA database indeed showed that PBRM1 deletion mutations had no effect on the RNA expression of theoretically related genes [8, 26]. Similar results were found for PBRM1 deletions [36]. Rather than these expressions, alterations in PBRM1 and SETD2 mutations were found to be significantly correlated with the histological grade and stage of RCC [18]. This result was also found in studies using The Cancer Genome Atlas database [37] more than a half patients with high stage and grade in the ccRCC deletion group belong to group 1 or 2, respectively. Similarly, 70% of the carcinoma setting occur in individuals falling into group 1 or 2 [38]. Together, these data suggest that PBRM1 deletion and SETD2 mutations are likely to be tumor-promoting by enhancing tumor malignancy, and that the molecular pathways influenced by these mutations are not involved in cell proliferation [39]. According to them mutational analysis, the novel variant of SETD2 V882I was determined as loss-of-function [38]. In the single cell growth assay, RCC4 Setd2-/- V882I and pFLAG-SETD2 V882I did not exhibit significant effects on colony formation with or without the supplementation of doxycycline. In addition to no significant increase in H3K36me3 at 23% GC loci, fluctuation H3K36me3 expression was not shown by IF. On the other hands, the supplementation of doxycycline in this setting portrayed that H3K36me3 enrichment was significantly elevated to similar baseline wt levels just after 5 days [39]. These results suggest that not only R1621 and V1662, the loss of SETD2 activity by mutating the highly conserved motif in the bifurcated SET domain, also showed a loss of the H3K36me3 increase function during the last month, leading to accumulation of SETD2 substrate and genome instability [40]. Hadlots of H3K36me3 enrichment on GC notably failed to elevate cellular level of CDC9A in RCC4 Setd2-/- V882I, suggesting that optimal cell condition might be crucial for regulating SETD2 bioorthogonal activity.

Together, the above results demonstrate that successful analytical approach using the simple model used enabled the identification of potentially deleterious SETD2 mutations in RCC [18].

COMPARATIVE ANALYSIS OF PBRM1 AND SETD2 IN RENAL CELL CARCINOMA

There are now five major gene families known to be significantly mutated in ccRCC, with an overarching mutational frequency range of 2.3–8.5% and including mutations of tens to hundreds of genes. However, very little is known regarding the relationships between PBRM1 or SETD2 and the genes in the other families and how they synergize to create the ccRCC landscape [41]. Future studies are needed to reveal deep biological relationships between PBRM1 and SETD2 [18]. Upset plots represent the intersections between gene sets, with bar plots showing the individual set sizes. These plots illustrate that different potential biological consequences result from truncating mutations of PBRM1 and VHL, BAP1, and/or SETD2 in ccRCC, indicating distinct or complementary functional relationships among these genes [40]. Annotation, enrichment, and network analysis of the downstream genes of this unique set of ccRCC samples revealed that PBRM1Δ and VHLΔBAP1ΔSETD2Δ could play complementary roles in activating fibroblast growth factor signaling through dysregulation of the KLF5-GNA13-ERBB3-MAPK pathway [41]. Published data from patient ccRCC samples were retrieved [42]. Renal cell carcinoma (RCC) is the most lethal urological tract malignancy in adults, with clear cell RCC (ccRCC) accounting for 75–80% of cases [25]. The majority of sporadic cases are associated with inactivation of the von Hippel-Lindau (VHL) gene [43]. Besides VHL loss, ccRCC exhibits deregulation of multiple signaling pathways that promote angiogenesis and tumor growth [5]. Exome sequencing of ccRCC samples has identified several novel genes, with PBRM1 and SETD2 identified as two of the five most significantly mutated in ccRCC [18]. PBRM1 and SETD2 are both classified as tumor suppressor genes (TSGs) given that the majority of their mutations are inactivating [39] [7]. Tumors with PBRM1 mutations appear to have distinct biology from those with SETD2 mutations [18]. PBRM1-mutated ccRCCs exhibit a two-fold lower mutation burden than wild-type tumors and are the most common type of ccRCC defined by chromosome aberrations [44]. In contrast, either PBRM1 or SETD2 can drive a high number of copy number variations (CNVs), which are in turn associated with a worse outcome [45]. This integrated analysis asserts the unique contributions of PBRM1 and SETD2 in driving ccRCC genomic instability and tumor progression and adds a new layer of understanding to the complex biology of ccRCC [18].

SIMILARITIES AND DIFFERENCES IN FUNCTION

PBRM1 and SETD2 mutations are the 1st and 3rd most frequent gene mutations (~40% and ~20% mutation rate in ccRCC tumors) in ccRCCs, respectively [18][44]. Both genes function in a chromatin remodeling context, but PBRM1 is a SWI/SNF family chromatin remodeler and a regulator of transcription while SETD2 encodes a histone methyltransferase. The results of this review suggest that the two genes share several functional similarities (tumor suppression, alteration of cell cycle regulation and genomic integrity), but the context of PBRM1 and SETD2 mutations will have discordant genetic interactions and associated pathways [46]. Elucidating these distinctions in ccRCC tumorigenesis will be important to understand how PBRM1 and SETD2 mutations influence clinical outcomes and response to therapeutics [47]. Taken together, this comparative dialogue will provide insight into the gene-specific roles of PBRM1 and SETD2 in ccRCC carcinogenesis and will ultimately help to optimize patient therapies. Loss-of-function mutations in the Polybromo-1 (PBRM1) and SET Domain Containing 2 (SETD2) genes in renal cell carcinoma (RCC) patients have been highly associated with tumor aggressiveness and poor patient prognosis [25]. Genomic analysis of primary and metastatic RCC tumors has revealed a connection between the timing of PBRM1 and SETD2 mutations and disease state progression, where PBRM1 mutations are earlier events that alter chromatin accessibility, and later acquisition of SETD2 mutations exacerbates these changes [31].

IMPACT ON DISEASE PROGRESSION

The impact of PBRM1 and SETD2 mutations on determining either association with decreased survival or propensity to metastasize is analyzed and discussed, while summarizing and reviewing recent reports directed at this each aim [18]. The role of the two genes in the development of consecutive primary clear cell renal cell carcinoma (ccRCC) is also assessed, examining the molecular profile of the two genes for possible clonal relations, and investigating whether the development of metastasis is dependent on the multi-regionally heterogeneous aspect of these genes [48]. Comparatively few reports deal with the clinical effect of PBRM1 and SETD2 gene mutations on renal cell carcinoma (RCC), currently the third most deadly genitourinary tract cancer [18]. However, as their biological effects on RCC and

ccRCC are elucidated, analyses encompassing larger cohorts of RCC and ccRCC patients either with or without gene mutations are being reported [49]. Thus, current knowledge comprising this review mostly focuses on alterations to PBRM1 and SETD2 genes found in ccRCC and gnom AD information considering their changes in RCC pan-cancer cohorts [50]. Adverse clinical results are more apparent in ccRCC patients experiencing changes in both genes when analyzed in all commonly altered kidney cancer genes [51]. In addition, based on single-nucleotide variant (SNV) and copy number variant (CNV) data of PBRM1 and SETD2, a gene set enrichment analysis (GSEA) is also reviewed for insight into the biological effect these changes bring to ccRCCs [52]. The correlation between changes to two genes and the formation of metastasis in ccRCC is then looked upon through histopathologic and molecular observations made on primary sites and its metastasized sites in ccRCC patients [53]. Ultimately, it is hoped a push is given to oncologists in paying regards to these genes mutations in molecular profiling of ccRCC patients, which in turn may influence decisions made on how best to manage such individuals [29].

CLINICAL IMPLICATIONS AND THERAPEUTIC STRATEGIES

In this precision medicine era, advances in technologies are providing the opportunities to detect various molecular abnormalities that can be targets for individualized treatment approaches [54]. Starting from inherited genes, the spectrum of these molecular targets has been expanded to somatically acquired changes, and companion diagnostics in therapeutic strategies [55]. However, many clinicians do not yet integrate genetic profiling into routine oncological practice [56]. This text aims to summarize the recently defined implications of PBRM1 and SETD2 genes in renal cell carcinoma (RCC)-genealogies, prognosis, preferred therapeutic strategies, and challenges [55]. A good understanding of genetic contexts underlying PBRM1 and SETD2 abnormalities can offer essential information to the considerations of therapeutic strategy [44][47]. Additionally, it is worthy for researchers to further elucidate the mechanisms of the pronounced mutagenicity of PBRM1 and SETD2 mutations and to develop drugs targeting distinctive pathways and diseases caused by the alterations of these genes [52]. Advanced clear cell Renal Cell Carcinoma (ccRCC) has a poor prognosis and is generally refractory to standard chemotherapy and/or radiation therapy, so novel therapies are urgently needed [57]. RCC provides an attractive case study for this challenge, due to the remarkable progress in understanding molecular pathogenesis [29]. Large efforts have been made in identifying and understanding the alterations that drive RCC and kill off key checkpoints [15]. Therapy approaches in RCC, including the most recent ones [17]. In recent years, a deeper understanding of the molecular basis of RCC was obtained, and several new drugs have been tested in clinical trials, demonstrating additional to significant therapeutic promise [58]. Various promising strategies are currently under investigation, including targeted therapies, immunotherapies, and their combinations [59]. Using genetic information to stratify patients and to select more appropriate treatments is a crucial point in the decision-making process that can significantly improve the ability to benefit from therapy and, therefore, enhance outcomes [60]. Further research and, above all, the integration of genetic research into ongoing clinical trials and routine clinical practice aim to adjust the current strategy and help the development of novel efficient therapeutic approaches [61].

CURRENT THERAPIES TARGETING PBRM1 AND SETD2

Clear cell Renal Cell Carcinoma (ccRCC) is one of the tumors with a complicated genetic background, in which PBRM1 gene is one of the most frequently altered genes [22]. SMARCB1/2 mostly contain genes that encode the SWI/SNF complex, which can help generate an open chromatin state by moving or ejecting nucleosomes [62]. BRG1 and BRM encode a DNA-dependent ATPase of the SWI/SNF complex [63]. It is known that mutations in PBRM1 often occur in the domain encoding the protein-protein interaction (PPI) site of the SWI/SNF complex [62]. PBRM1 has three KID domains, two BAH domains and one HMG box domain. Acetylation and methylation marks are involved in chromatin remodeling, which can be recognized by chromatin remodeling complexes and modified the nucleosome structure, impacting the accessibility of other proteins to DNA [64]. CC2D1A, BCL11A, BRD7, and UAP1 are mutated in less than 10% of ccRCC samples, and KDM5C, SETD2, BAP1, and TCEB1 are more susceptible to biallelic inactivation [63]. SET domain containing 2 (SETD2) gene RING-type E3 ligase comprises an array of RING finger proteins and really interesting new gene finger domain proteins are components of distinct E3 ubiquitin ligases, which mediate ubiquitination of target proteins [65]. RING finger proteins often act in complexes with specific E2 ubiquitin-conjugating enzymes [64], ccRCC is one of the most common malignant tumor types in the world, accounting for approximately 65,000 to 100,000 deaths worldwide [66]. The development of surgery, includ-

ing targeted molecular therapy, has led to increased disease-free survival rates. However, patients with advanced and metastatic RCC have limited treatment options, including surgical tumor resection, radiotherapy, new drug therapy, and immunotherapy [67].

CONCLUSIONS

Synthesizing the invaluable insights and extensive knowledge gained throughout the rigorous and comprehensive review serves as a crucial reminder that renal cell carcinoma (RCC) is an intricate, polygenetic, and invasive type of solid tumor that is driven by a diverse and multifaceted array of genetic alterations. Within this complex landscape, the PBRM1 and SETD2 genes frequently play critical and pivotal roles during the evolutionary stages of clear cell renal cell carcinoma (ccRCC) and exhibit a wide range of variable subclonal genetic alterations that significantly expand their already expansive clonal evolutionary history over time. However, a thorough and comprehensive understanding of the driver genetic alterations that influence RCC is not only absolutely necessary but could also provide fundamental and essential genetic insights that are invaluable for advancing clinical practices in oncology. The analyses reviewed in this context not only substantiate but also reinforce the vital relationship between mutations in PBRM1 and SETD2 and the complex genetic evolution of ccRCC. Given the notable and high prevalence of genetic alterations involving PBRM1 and SETD2 in ccRCC cases, these significant findings might possess substantial practical and implicational values that could influence the field of oncology. Specifically, (i) PBRM1 mutation could serve as a tumor co-initiator that actively cooperates with other driver gene mutations in the formation of the preneoplastic cell population, thus highlighting its essential role in the process of tumorigenesis. (ii) Furthermore, the formation of a subclonal copy number loss could act as a new and distinctive branch, promoting the advancement of the PBRM1 mutated clone to a more dominant and predominant status within the tumor hierarchy itself. (iii) Moreover, the cooperation of SETD2 mutation with PBRM1 mutation is absolutely crucial in establishing the potential for distant metastatic spread of the disease, enhancing the complexity of the tumor environment. The above predictions and hypotheses may pave the way for the development of collaborative and innovative therapeutic avenues and fundamentally reinforce the pressing necessity for the ongoing exploration and investigation of PBRM1 and SETD2 genes in this crucial context. Furthermore, the pharmacologic studies undertaken thus far suggest the considerable potential for identifying promising and innovative treatment strategies that could prove to be effective against RCC. By actively integrating those crucial discoveries into larger and more diverse RCC research communities and institutions, there exists significant potential for transformational novel therapies to emerge in the future landscape of cancer treatment that could positively impact patient outcomes. These informative and promising prospects illustrate the hopeful benefits and positive impacts of the emerging genetic findings combined with advanced technologies in the understanding, prevention, and comprehensive management of renal cell carcinoma in both clinical and research settings.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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