



Review

The Role of the PAX Genes in Renal Cell Carcinoma

Lei Li ¹, Sultana Mehbuba Hossain ^{1,2} and Michael R. Eccles ^{1,2,*} 

¹ Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin 9016, New Zealand; lile2757@student.otago.ac.nz (L.L.); mehbuba.hossain@otago.ac.nz (S.M.H.)

² Maurice Wilkins Centre for Molecular Biodiscovery, Level 2, 3A Symonds Street, Auckland 1010, New Zealand

* Correspondence: michael.eccles@otago.ac.nz

Abstract: Renal cell carcinoma (RCC) is a significant oncological challenge due to its heterogeneous nature and limited treatment options. The *PAX* developmental gene family encodes nine highly conserved transcription factors that play crucial roles in embryonic development and organogenesis, which have been implicated in the occurrence and development of RCC. This review explores the molecular landscape of RCC, with a specific focus on the role of the *PAX* gene family in RCC tumorigenesis and disease progression. Of the various RCC subtypes, clear cell renal cell carcinoma (ccRCC) is the most prevalent, characterized by the loss of the von Hippel–Lindau (*VHL*) tumor suppressor gene. Here, we review the published literature on the expression patterns and functional implications of *PAX* genes, particularly *PAX2* and *PAX8*, in the three most common RCC subtypes, including ccRCC, papillary RCC (PRCC), and chromophobe RCC (ChRCC). Further, we review the interactions and potential biological mechanisms involving *PAX* genes and *VHL* loss in driving the pathogenesis of RCC, including the key signaling pathways mediated by *VHL* in ccRCC and associated mechanisms implicating *PAX*. Lastly, concurrent with our update regarding *PAX* gene research in RCC, we review and comment on the targeting of *PAX* towards the development of novel RCC therapies.

Keywords: renal cell carcinoma; subtypes; *PAX* genes; *VHL*; clear cell renal cell carcinoma



Citation: Li, L.; Hossain, S.M.; Eccles, M.R. The Role of the *PAX* Genes in Renal Cell Carcinoma. *Int. J. Mol. Sci.* **2024**, *25*, 6730. <https://doi.org/10.3390/ijms25126730>

Academic Editors: Joaquim Calado and José Rueff

Received: 29 April 2024

Revised: 10 June 2024

Accepted: 16 June 2024

Published: 19 June 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Renal cell carcinoma (RCC) is the predominant form of kidney cancer, representing approximately 80–90% of kidney cancers, and it primarily originates from the renal tubular epithelium or renal cortex [1,2]. According to the 2020 Globocan Registry, RCC ranks as the 12th most common cancer globally, with 1.2 million cases reported over the past five years [3]. In 2020, the global age-standardized incidence rate (ASR) for RCC was 4.6 per 100,000 individuals. The ASR for men (6.1 per 100,000) was nearly double that for women (3.2 per 100,000) [3]. The incidence of RCC varies significantly by region, with higher rates generally observed in Europe and North America [4]. The gradual increase in the risk of RCC over the past decade is noteworthy and warrants greater attention.

With its diverse histological and molecular characteristics, RCC is classified into three main subtypes: clear cell renal cell carcinoma (ccRCC), papillary renal cell carcinoma (PRCC), and chromophobe renal cell carcinoma (ChRCC). Among these, ccRCC is the most prevalent, accounting for approximately 70–90% of cases, followed by PRCC with 10–15% of cases, and ChRCC with 3–5% of cases [5,6]. Additionally, rare types of RCC account for less than 1% of incidence each. Approximately 90% of sporadic ccRCC cases exhibit an alteration of the Von Hippel–Lindau tumor-suppressor gene (*VHL*), located on chromosome 3 [7].

Normal kidney development is a highly orchestrated process involving a multitude of genes that regulate the rapid proliferation and differentiation of embryonic tissues. *PAX*

proteins are vital for organ development, but their expression typically diminishes post-development [8]. The *PAX* genes (*PAX1*–*PAX9*) regulate cell processes, including proliferation, differentiation, apoptosis, migration, and stem cell maintenance [8,9]. Dysregulation of the *PAX* genes has been linked to a variety of diseases, including cancer [8,9]. *PAX2* and *PAX8* are frequently expressed during kidney development, whereas other *PAX* genes either show low expression or are not expressed [10,11]. As the nascent nephron matures, *PAX2* expression is downregulated in the pedunculated progenitor cells of the developing glomerulus and subsequently in all proximal and distal tubules of the nephron [12,13]. *PAX8* is still persistently expressed in epithelial cells of fully developed nephrons [14]. However, it is noteworthy that *PAX2* was found to be reactivated in renal cell carcinoma and that around 90% of renal cell carcinoma patients have high *PAX2* and *PAX8* expression levels [5,15].

PAX genes are thought to originate during evolution from a proto-*PAX* ancestor. The highly conserved PD (N-terminal paired domain) motif, which contains 128 amino acids, is present in all *PAX* proteins [16]. The genetic and functional homology observed in *PAX* genes across species highlights their evolutionary stability, suggesting strong evolutionary pressure to preserve these motifs due to their critical roles in development and cellular function. The *PAX* gene family is categorized into subgroups I–IV based on the presence or absence of an octapeptide region and the presence, absence, or truncation of a homeodomain. Of these, both the PD and homeodomain (HD) motifs show DNA binding ability [16], although only a partial HD is observed in the *PAX2* and *PAX8* genes. The DNA binding motifs enable *PAX* proteins to function as transcription factors and play crucial roles in embryonic development. During embryogenesis, mutations in subgroup I members (*PAX1* or *PAX9*) have been associated with congenital vertebral malformations, Klippel–Feil syndrome, and oligodontia [17,18]. Mutations in the *PAX2* gene cause coloboma syndrome [19]. Interestingly, *PAX2* is not normally expressed in healthy adult kidneys, although it becomes reactivated in RCC [20,21]. In our previous investigations, we found that the knockdown of *PAX2* sensitized RCC cells to cisplatin-induced apoptosis [22]. *PAX3* has been associated with the survival of melanoma cells and is considered essential for the viability of melanoma cell lines [23]. *PAX4* predominantly exhibits expression in the pancreas during embryonic development, and mutations in the *PAX4* gene have been implicated in the development of diabetes mellitus [24]. *PAX5* serves as a key driver in B-cell malignancies [25]. Mutations in *PAX6* lead to conditions like “small eye” in mice and aniridia, congenital cataracts, or Peter’s anomaly in humans [26]. *PAX8* was found to be frequently expressed in RCC patients, and validation from a large-scale functional genomic screen confirmed that *PAX8* silencing leads to reduced proliferation of RCC cell lines [27]. Moreover, disturbances in *PAX* function are linked to cancerous growth in humans, such as rhabdomyosarcoma (involving *PAX3* and *PAX7*), non-Hodgkin lymphoma (involving *PAX5*), follicular thyroid carcinoma (involving *PAX8*), and RCC (involving *PAX2* and *PAX8*) further implicating the functional significance of *PAX* genes (Table 1) [28–30].

Several members of the *PAX* gene family have been found to be expressed in RCC, and their expression was found to be diagnostic and potentially a therapeutic target for RCC [20,27,31]. In this review, we discuss the expression characteristics and potential roles of *PAX* genes in RCC. In addition, we discuss the molecular characteristics of different RCC subtypes, especially regarding the identified relationship between *VHL* mutations and the potential role of *PAX* genes in RCC.

Table 1. *PAX* family members.

Groups	* <i>PAX</i> Genes	HL	Structural	EA	ER	RC	References
I	<i>PAX1</i>	20p11	PD+OCT	Skeleton, thymus	No or low expression	Netural or favourable	[8,17,18]
	<i>PAX9</i>	14q12	PD+OCT	Skeleton, craniofacial, tooth	No or low expression	Netural or favourable	[12,17,18]
II	<i>PAX2</i>	10q24	PD+OCT+partial HD	CNS, kidney, eye, ear	High expression	Tumor-promoting	[19–22]
	<i>PAX5</i>	9p13	PD+OCT+partial HD	CNS, B cells, testis	No or low expression	Netural or favourable	[8,12,25]
	<i>PAX8</i>	2q12	PD+OCT+partial HD	CNS, kidney, thyroid	High expression	Tumor-promoting	[8,10,27]
III	<i>PAX3</i>	2q35	PD+OCT+HD	CNS, neural crest, skeletal muscle	No or low expression	Netural or favourable	[8,12,23]
	<i>PAX7</i>	1p36	PD+OCT+HD	CNS, craniofacial, skeletal muscle	No or low expression	Netural or favourable	[8,12]
IV	<i>PAX4</i>	7q32	PD+HD	CNS, Pancreas	No or low expression	Netural or favourable	[8,12,24]
	<i>PAX6</i>	11p13	PD+HD	CNS, eye, pancreas	No or low expression	Netural or favourable	[8,26]

* The *PAX* family may be categorized into four subgroups (Groups I–IV) based on the distinctive assembly of three structural motifs: the amino (N)-terminal paired domain (PD), the octapeptide (OCT), and the homeodomain (HD). Both the PD and HD motifs demonstrate DNA binding capabilities. The highly conserved PD motif comprises 128 amino acids and is ubiquitous among all *PAX* proteins. Group I (*PAX1* and *PAX9*) entirely lack HD, while group IV members (*PAX4* and *PAX6*) have a complete HD but lack an OCT domain. Group III members (*PAX3* and *PAX7*) feature a complete HD and an OCT domain, whereas Group II members (*PAX2*, *PAX5*, and *PAX8*) possess a partial HD. HL: human chromosome location; EA: expression area; CNS: central nervous system; ER: expression levels in RCC; RC: RCC contribution.

2. Recruitment of *PAX* Gene Expression Enables Renal Cell Carcinomas to Survive, Proliferate, and Metastasize

The *PAX* family of proteins comprises developmental regulatory proteins crucial for normal tissue development [8,9]. These proteins possess DNA binding domains that encode partially or fully functional transcription factor-associated domains to regulate the expression of a range of downstream genes [9,32]. *PAX* gene expression undergoes tight regulation during development. *PAX2* and *PAX8* are expressed during the early stages of urogenital development [33,34], playing a crucial role in the differentiation of renal precursor cells in the intermediate mesoderm and the transformation of metanephric mesenchymal cells into epithelial cells within developing kidney nephrons [34,35]. In general, *PAX* genes are not expressed in adult proximal and distal tubules. However, the *PAX2* gene is selectively re-expressed to modulate and enhance kidney regeneration, such as after renal tissue injury [36]. While *PAX* genes are transiently expressed during kidney development, their deregulation has been associated with certain kidney cell abnormalities in humans [8,35]. The recruitment of *PAX* gene expression, especially *PAX2* and *PAX8*, plays an important regulatory role in the survival, proliferation, and metastasis of RCC (Figure 1).

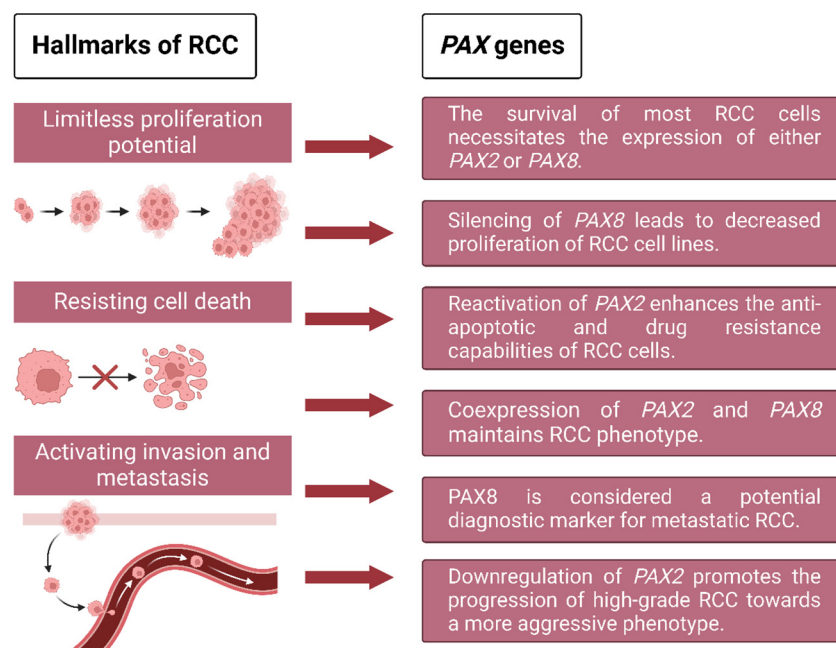


Figure 1. The hallmarks of RCC: exploring the potential role of PAX genes. PAX genes primarily participate in three hallmarks of RCC: cell survival, proliferation, and metastasis. Among these hallmarks, PAX2 and PAX8 are implicated in the transformation of RCC phenotype, either individually or cooperatively.

2.1. PAX Genes in Renal Cell Carcinoma Survival and Proliferation

Cancer entails a multi-step process characterized by cumulative alterations in both positive and negative regulators of cell proliferation and survival. The frequent expression of PAX genes in cancer is deemed essential for cancer cell growth and survival [33]. Distinct survival dependencies on PAX2 are observed in ovarian and bladder cancer cell lines [33]. Additionally, overexpression of PAX2 in Kaposi's sarcoma cells was found to enhance their resistance to apoptotic signals [37]. Other PAX genes are also involved in cell survival. In melanoma cell lines, for example, the inhibition of PAX3 induces apoptosis and markedly impedes cell survival [33]. Additionally, PAX4 functions as a survival gene in INS-1E insulinoma cells [38]. Notably, PAX8 is recognized as the prototypical lineage survival oncogene in epithelial ovarian cancer, and dysregulation of PAX8 promotes the progression of ovarian cancer [39].

In RCC, PAX2 and PAX8 exhibit heightened expression levels compared to other PAX genes [5]. PAX2 is among the earliest genes expressed in the kidney lineage and plays a crucial role in the survival, proliferation, and functional differentiation of kidney lineage cells [19]. Reactivation of PAX2 expression in RCC correlates with the anti-apoptotic capacity of RCC cells, while its inhibition helps to promote RCC cell apoptosis and sensitization to chemotherapy drugs such as cisplatin [22,31]. During epithelial-to-mesenchyme (EMT) transition of RCC cells, silencing of PAX2 expression reduces ADAM10 expression, which induces L1-CAM-dependent activation of the PI3K/Akt pathway, which is crucial for RCC cell survival [40].

Similarly, PAX8 plays a pivotal role in the survival and proliferation of epithelial cells [41]. The silencing of PAX8 leads to decreased proliferation in RCC cell lines [27], inducing apoptosis through a p53-dependent pathway, which involves caspase-3 activation and poly(ADP)ribose polymerase cleavage [41]. Notably, within the metabolic dysregulation hallmark of renal cell carcinoma, PAX8 is implicated in activating metabolic genes via enhancer elements [27]. Interaction of the PAX8 protein with hypoxia inducible factor 2 subunit alpha (HIF2 α) recruits the latter to transcriptional enhancers, promoting downstream oncogenic signaling pathways and supporting the expression of typical oncogenes like CCND1 and MYC [42,43].

Moreover, *PAX2*, *PAX8*, and the paralogous *PAX5* have been demonstrated to inhibit tumor suppressor gene *TP53* expression by directly binding to its first exon, thereby suppressing apoptosis and promoting tumor progression [44]. This inappropriate expression of *PAX* genes not only impedes *TP53* tumor suppressor function but also activates specific target genes that facilitate tumorigenesis [44,45].

2.2. *PAX* Genes in Renal Cell Carcinoma Metastasis

EMT involves a cellular mechanism wherein epithelial cells undergo a phenotypic change, adopting a mesenchymal phenotype characterized by enhanced motility and invasiveness [46]. Local and distant dissemination constitutes one of the hallmarks of tumor progression, with EMT significantly contributing to the metastatic potential of tumors. The expression profile and biological properties of EMT underscore its potential as a therapeutic target in cancer, including RCC. In RCC, EMT signifies a transient shift of tumor cells from an epithelial to a mesenchymal state, facilitating tumor cell motility, invasion, and metastasis in advanced stages. Conversely, mesenchymal–epithelial transition (MET) halts cell migration and promotes colonization in distant organs [46]. Loss of, or suppression of E-cadherin expression emerges as a pivotal event in EMT, associated with heightened expression of transcriptional repressors such as ZEB1, ZEB2, Slug, Snail, and Twist [47], some of which are known to repress E-cadherin expression. Additionally, EMT has been associated with an elevated risk of recurrence and poorer overall survival (OS) in RCC patients [47]. Targeting dysregulatory factors that drive EMT may improve the prognosis of patients with RCC.

The expression of both *PAX2* and *PAX8* is positive in most patients with metastatic RCC [20]. The reactivation of *PAX2* in the early stages of RCC is fundamental to the development of the RCC phenotype. *PAX2* is involved in a complex interplay with *ADAM10* and the TGF- β 1 signaling pathway, exerting regulatory control over RCC progression and metastasis [40,48]. *ADAM10*, which is a member of a family of transmembrane and secreted proteins, plays an important role in the progression and metastasis of various cancers [40]. *PAX2* binds to the promoter of the *ADAM10* gene in RCC and regulates *ADAM10* protein expression in RCC cells [40]. Moreover, silencing *PAX2* expression results in decreased *ADAM10* expression, leading to a more scattered cell phenotype accompanied by induction of *SNAIL2* (Slug) expression and loss of *CDH1* expression (E-cadherin), which is observed during EMT. Furthermore, downregulation of *ADAM10* reduces RCC cell proliferation, while *PAX2* knockdown results in increased L1 cell adhesion molecule (L1CAM) expression, which then induces endothelial cell proliferation and RCC cell migration. Some studies have noted a decline in *PAX2* expression levels in high-grade RCC [49,50]. It is thought this reduction in *PAX2* expression plays a contributory role in driving RCC towards a more aggressive phenotype.

PAX8 is recognized as a promising diagnostic marker for metastatic RCC, demonstrating higher sensitivity compared to *PAX2* [20]. Several groups have identified key target genes regulated by *PAX8*, among them being GATA binding protein 3 (*GATA3*), LIM homeobox protein 1 (*LHX1*), and Wilms tumor 1 (*WT1*) transcription factor [51,52]. These transcription factors, along with *PAX2* and *PAX8*, collectively form a core transcription factor circuit that plays a crucial role in driving proximal tubular epithelial fates. *PAX8* has been implicated in regulating the tumor microenvironment by enhancing fibronectin and collagen expression while increasing TGF- β 1 secretion [53]. *PBRM1* deletion was found to be the second most prevalent genetic alteration in RCC [54], and loss of *PBRM1* coactivator in RCCs is thought to lead to an imbalance in coregulator content within a *PAX8*-associated master transcription factor hub for the kidney lineage. This imbalance favors the over-representation of co-repressors, resulting in the repression of the terminal proximal tubule epithelial program [55].

3. Different Renal Cell Carcinoma Subtypes Are Distinguished by Molecular Features with Various Roles

Determining the source/origin of metastatic cancer is important, as it greatly influences the choice of local treatment strategy and systemic therapy. Different levels of *PAX* gene expression are observed in different RCC subtypes. Gupta et al. conducted a study involving 200 renal tumors and found that almost all ccRCC were immunoreactive for *PAX2* (28/30, 93%), whereas more than half (53%) of PRCC expressed *PAX2*, while most of ChRCC (94%) were non-immunoreactive for *PAX2* [15]. We previously also found high expression of *PAX2* and *PAX8* mRNA in ccRCC and PRCC cell lines, whereas these genes were expressed at low levels or not at all in ChRCC cell lines [5,32].

3.1. Molecular Features of Different Renal Cell Carcinoma Subtypes

Classical PRCC is often associated with concurrent gains of chromosomes 7 and 17, alongside infrequent gains of chromosomes 2, 3, 12, 16, or 20 [56,57]. Chromosome 7 contains several potential oncogenes, including *MET*, *EGFR*, and *BRAF* [57]. Somatic activating mutations of *MET* have been identified in a subset of classical PRCC cases, while hereditary PRCC stems from germline activating mutations of *MET* [57]. An analysis conducted by TCGA revealed somatic or germline *MET* mutations in 18.6% of classical PRCC cases, accompanied by occurrences of somatically acquired alternative *MET* RNA transcripts and *MET* gene fusions [58]. These alterations, along with the frequent gain of chromosome 7, were found to collectively contribute to *MET* modifications in classical PRCC. Genetic studies on metastatic ChRCC have revealed high-risk features associated with unfavorable survival outcomes, such as *TP53* mutations, *PTEN* mutations, DNA hypermethylation, and imbalanced chromosome duplication [59]. Most ChRCCs exhibit complete losses of several chromosomes (1, 2, 6, 10, 13, 17, and 21) [60,61].

ccRCC is characterized by a near-total deletion of the short arm of chromosome 3, resulting in the loss of multiple tumor suppressor genes [62]. Additionally, numerous genomic alterations have been identified in ccRCC, primarily involving epigenetic reprogramming and modifications in oncogenic metabolism pathways [63]. Frequently mutated genes include those regulating the cellular oxygen pathway (e.g., *VHL*) and maintaining chromatin structure integrity (e.g., *PBRM1* and *BAP1*) [64,65]. *BAP1* and *PBRM1* are situated near the *VHL* region on chromosome 3p [66,67]. The *VHL* protein (pVHL) is a crucial component of the oxygen-sensing system responsible for hypoxia inducible factor (HIF) degradation. Mutations or loss of function in the *VHL* gene result in the stabilization of HIF-1/2- α subunits, activating HIF target genes [68,69]. This pathway is implicated in various processes such as tumor angiogenesis, invasion, cancer metabolic reprogramming, and metastasis. Although *VHL* inactivation is nearly ubiquitous in ccRCC, it alone is insufficient to cause the disease. Preneoplastic cysts have been observed with *VHL* loss, and even mice with *VHL* disruption in the kidneys do not develop ccRCC, even when both alleles of *VHL* are inactivated in the appropriate kidney compartment [70,71]. These findings suggest that ccRCC tumorigenesis requires additional driver mutations to cooperate.

3.2. The Role of *VHL* Loss in Clear Cell Renal Cell Carcinoma

VHL functions as a subunit in a larger protein complex that recognizes specific protein substrates, initiating their ubiquitination and subsequent degradation by the proteasome [72,73]. This enables *VHL* to regulate cellular responses to fluctuating oxygen levels, ensuring appropriate cellular adaptations to hypoxic environments (Figure 2). Loss of *VHL* can disrupt hypoxia signaling pathways in ccRCC, impairing HIF regulation and leading to HIF α accumulation and constitutive expression of HIF target genes. Elevated HIF α levels then interact with hypoxia-responsive components, resulting in abnormal upregulation of genes like *VEGF*, platelet-derived growth factor (*PDGF*), *CA-IX*, *TGF α* , and *PAX2* which contribute to ccRCC development [74,75].

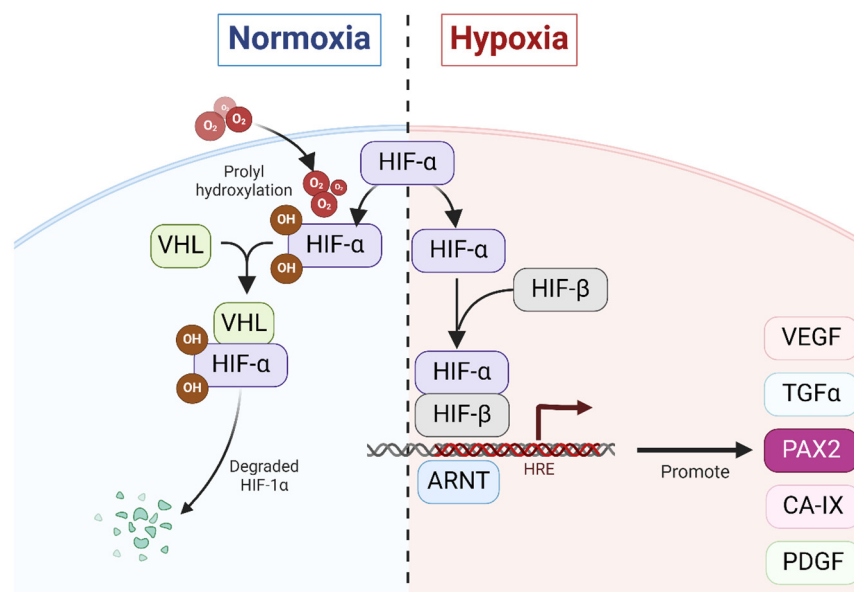


Figure 2. *VHL* signaling participates in the regulation of cellular adaptation to hypoxia and contributes to reactivated *PAX2* expression in ccRCC. During normoxic conditions, HIF- α undergoes hydroxylation by prolyl hydroxylases (PHD) and subsequently becomes recognized by the VHL protein. Upon binding of VHL to HIF- α , the latter undergoes ubiquitination and subsequent degradation through the proteasome machinery. Conversely, under hypoxic conditions, HIF- α remains un-hydroxylated, leading to its accumulation within the cytosol. This accumulated HIF- α then translocates into the nucleus, where it forms a heterodimer with its counterpart, HIF- β . The resultant complex drives the transcription of genes possessing a hypoxia-responsive element (HRE) within their promoters and further promotes the expression of their potential target genes (including *VEGF*, *PDGF*, *CA-IX*, *TGF α* , and *PAX2*). Furthermore, it is noteworthy that in ccRCC, *PAX2* reactivation is driven by HIF-dependent mechanisms following pVHL loss [36].

Following *VHL* loss, overexpression of HIF-2 α is necessary and sufficient for tumor growth [76]. In addition, *VHL* deficiency can lead to mitochondrial dysfunction [77]. Perrotta et al. found that *VHL* defects affect energy metabolism and impair mitochondrial function [77]. Mitochondrial dysfunction encompasses structural damage, defects in the respiratory chain, genetic abnormalities, reduced mitochondrial number, and altered oxidative protein activity [78]. The kidney is one of the body's highest energy-demanding organs, second only to the heart in oxygen consumption and mitochondrial abundance [79]. Aerobic respiration is the primary mechanism for production of adenosine triphosphate (ATP) [80]. Renal tubular epithelial cells are highly dependent on ATP production via oxidative phosphorylation (OXPHOS) for epithelial transport functions [81]. The persistence of mitochondrial dysfunction underscores the protraction of tubular injury, thereby potentially impeding the process of renal recuperation following an episode of acute kidney injury (AKI). Moreover, this unrelenting dysfunction serves as a catalyst for the advancement of chronic kidney disease (CKD) [82].

Mitochondrial dysfunction occupies a pivotal role in the developmental trajectory of RCC [42,83]. Most cancer cells, instead of relying on OXPHOS for ATP production even when sufficient oxygen is available, primarily derive ATP from glycolysis [84]. This phenomenon, termed "aerobic glycolysis", was identified by Warburg many years ago [85]. In ccRCC, this shift to aerobic glycolysis is attributed to hypoxia-induced stabilization of the transcription factor HIF, which is further facilitated by *VHL* inactivation [86]. Mitochondrial transcription factor A (*TFAM*) plays a crucial role in activating mitochondrial transcription and replication [87]. EGLN3 hydroxylates *TFAM*, and hydroxylated *TFAM* then binds to pVHL. This binding with pVHL stabilizes *TFAM*, protecting it from mitochondrial protein hydrolysis [87]. Furthermore, a deficiency of *TFAM* was shown to trigger mitochondrial

dysfunction in HK2 (Human Kidney-2) cells [87]. Metabolic perturbations are characteristic of many tumor types, especially RCC [88]. Mitochondrial dysfunction engenders augmented reliance on substrate-level phosphorylation for energy production [89]. These *VHL* tumors have been found to display reduced mitochondrial content, indicating that dysfunctional mitochondrial biogenesis might be linked to *VHL* tumorigenesis.

4. Signaling Pathways with Important Roles in Renal Cell Carcinoma and Their Relationship to *PAX*

The occurrence and progression of cancer are frequently linked to the dysregulation of signaling pathways. Within RCC, a diverse range of histological subtypes exists, each characterized not only by distinct molecular signatures but also increasingly by unique molecular pathways that undergo deregulation in each subtype [90]. Loss of *VHL* triggers the accumulation and nuclear translocation of HIF α , subsequently activating crucial oncogenic signaling pathways in RCC. The absence of *VHL* seems to serve as an early foundation for RCC development, with the *PAX* genes also contributing and being upregulated by the *VHL*-mediated hypoxia signaling pathway (Figure 3).

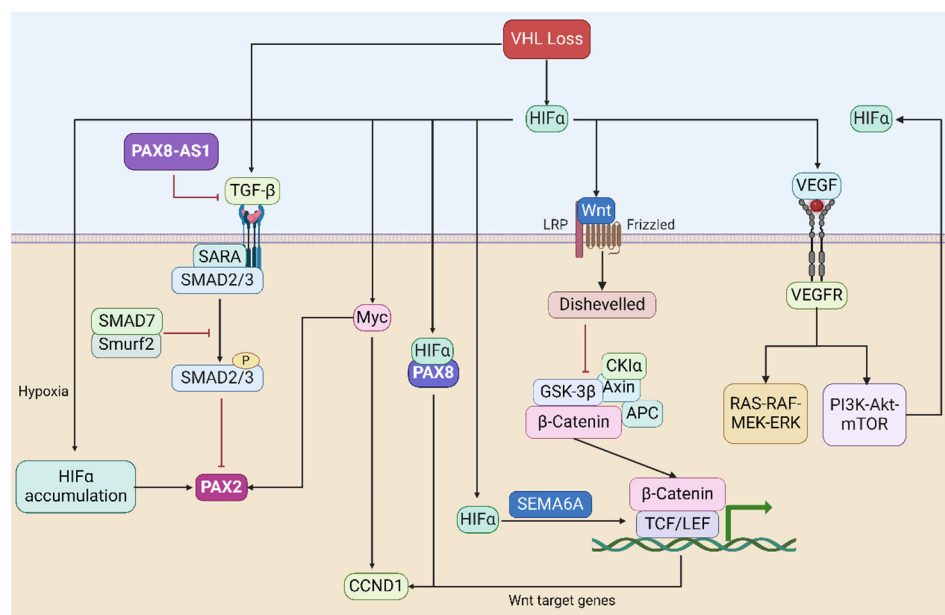


Figure 3. *VHL*-mediated signaling/regulatory pathways in ccRCC with respect to *PAX* involvement. The loss of *VHL* leads to HIF α accumulation and translocation into the nucleus, which subsequently activates the transcription of HIF target genes that are involved in critical oncogenic pathways (such as HIF-based hypoxia signaling pathway, TGF- β signaling pathway, VEGF-related signaling pathways, MYC-related signaling pathways, and Wnt/ β -catenin signal pathway). Loss of *VHL* promotes the progression and metastasis of RCC, wherein *PAX* genes also exert a positive contribution.

4.1. The HIF-Based Hypoxia Signaling Pathway

Hypoxia (a state of oxygen deficiency) is a prominent characteristic within numerous solid malignancies, primarily attributed to inadequate perfusion and/or the development of poorly or non-functional blood vessels within neoplasms. This phenomenon is particularly pronounced in rapidly proliferating tumors. In most ccRCC, hypoxia-inducible factors (HIFs), which are global transcriptional regulators of the hypoxic response, are persistently activated through the inactivation of a component of the E3 ubiquitin ligase complex, the *VHL* tumor-suppressor protein [91].

The *VHL* tumor-suppressor gene mediates and participates in the transduction of the hypoxia signaling pathway through HIF α [91] (see Figure 3). Luu et al. showed that *PAX2* reactivation in ccRCC is induced by hypoxia and depends on the functional integrity of pVHL and that *PAX2* reactivation after pVHL loss is driven by HIF-dependent

mechanisms [92]. HIF is a heterodimer complex comprising a labile α subunit and a stable β subunit [93]. The α subunit is the major regulatory subunit of HIF. Its level is mainly regulated by intracellular oxygen concentration. Under normoxic conditions, hydroxylation of the HIF α subunit enables its recognition and ubiquitination by the pVHL complex [94], thereby keeping intracellular HIF α levels low. Conversely, during hypoxia, HIF α remains unhydroxylated, resulting in its non-interaction with VHL proteins and consequent lack of degradation. Isono et al. found that HIF2 α is overexpressed in VHL-deficient RCC cells, leading to higher cell viability in tumor cells [95]. Additionally, in a ccRCC xenograft model, HIF-2 α overexpression in RCC cells contributes to increased tumor burden [76]. When HIF-1 α was overexpressed, a reduction in tumor size was observed, whereas the knockdown of HIF-1 α increased RCC cell proliferation [76]. Therefore, HIF-1 α may exert a tumor suppressor function in the context of RCC.

4.2. The TGF- β Signaling Pathway

In RCC, the TGF- β pathway is often dysregulated, leading to tumor promotion [96]. TGF- β acts as a tumor suppressor in the early stages of RCC, inhibiting cell proliferation and promoting differentiation. However, in later stages, TGF- β may promote tumor progression by inducing EMT. TGF- β 1 can exert its functions through both canonical (Smad-dependent) and non-canonical (Smad-independent) signaling pathways [97]. Canonical TGF- β 1 signaling (Smad-based) can promote RCC progression by promoting invasion and metastasis and inducing EMT [98]. TGF- β signaling has been found to interact with HIF to promote renal fibrosis [99]. Inhibition of PAX2 transcription in ccRCC cells through classical TGF- β signaling has been reported [48] (see Figure 3). *LncRNA-PAX8-AS1* was found to be located in chromosome 2q13 upstream of the PAX8 gene and has a negative regulatory effect on PAX8 [100]. PAX8-AS1 can bind to *miR-96-5p* to inhibit the malignant phenotype of papillary thyroid carcinoma cells [101]. In renal peduncle cells, PAX8-AS1 reduces renal peduncle apoptosis and inhibits the expression of *VEGF/TGF- β 1* [102]. Shang et al. showed that TGF- β 1 may be a direct target of VHL rather than regulating TGF- β 1 expression through the HIF pathway [103]. Furthermore, the inactivation of VHL in ccRCC may enhance the metastatic ability of RCC cells by increasing TGF- β 1 expression [103].

4.3. The VEGF-Related Signaling Pathway

VEGF is a cytokine that plays a central role in promoting the formation of angiogenesis [104]. In cancer, increased VEGF expression and angiogenesis are crucial for tumor growth and metastasis [104]. VEGF was found to be a potential HIF α target in ccRCC, and knockdown of HIF α decreased the expression level of VEGF [105]. Elevated VEGF expression is frequently linked to poor prognosis in RCC patients [106]. VEGF, upon binding to its corresponding cell surface receptors such as VEGFR, induces tyrosine phosphorylation of the receptor, initiating downstream signaling through various kinase-dependent pathways, including the PI3K-Akt-mTOR pathway and the RAS-RAF-MEK-ERK pathway [107,108] (see Figure 3). PAX2 has been reported to be related to angiogenesis in RCC [109]. Research by Fonsato et al. shows that PAX2 may participate in the Akt pathway and affect angiogenesis by regulating PTEN [109]. PTEN is a phosphatase that regulates PI3K-dependent activation of Akt. PAX8 was found to promote angiogenesis in ovarian cancer by interacting with SOX17, but whether it is related to angiogenesis in RCC remains unclear [110]. It is important to highlight that mTOR is among the downstream effectors of PI3K/AKT, and its activation results in increased expression levels of HIF α [107]. Notably, an aberrant VHL function can establish a harmful positive feedback loop. The absence of VHL leads to impaired degradation of HIF α , causing its accumulation at high levels. Subsequently, elevated HIF α levels further stimulate the abnormal expression of VEGF, which binds to VEGFR, activating the PI3K-Akt pathway. Consequently, mTOR is also activated through this pathway, leading to even higher HIF α levels. This vicious positive feedback loop exacerbates the defects caused by aberrant VHL function, thereby promoting the onset and progression of ccRCC.

4.4. The MYC-Related Signaling Pathway

MYC is a family of regulatory and proto-oncogenes encoding transcription factors (-MYC (MYC), *L-MYC* (MYCL), and *N-MYC* (MYCN)) [111,112]. MYC regulates various biological processes, including cell differentiation, cell growth, apoptosis, and stem cell self-renewal [111,112]. Hwang et al. showed that pVHL can bind to the *C-MYC* promoter along with *C-MYC* and then transcriptionally repress the *C-MYC* gene [113]. In metanephric mesenchyme cells, *N-MYC* acting downstream of *PAX2* may restore *PAX2* expression at the transcriptional level and thus regulate cell proliferation and apoptosis [114]. HIF-2 α can promote *C-MYC* activity and induce cell cycle progression in ccRCC cells [115]. On the other hand, HIF-1 α acts as an inhibitor of *C-MYC* activity, leading to reduced levels of E2F and cyclin D2 while concurrently enhancing the expression of cell cycle progression inhibitors p21 and p27 [115,116]. Another significant discovery is that HIF-1 inhibits mitochondrial biogenesis and cellular respiration in *VHL*-deficient renal cell carcinoma by impeding *C-MYC* activity [117]. *C-MYC* can transactivate *CCND1* expression [118] (see Figure 3). *CCND1* plays a tumor-promoting role in RCC, and its knockdown has been shown to attenuate xenograft growth in vivo [119]. Additionally, *CCND1* is considered a potential downstream gene of HIF-2 α . Its expression decreases upon HIF-2 α inhibition and increases upon re-expression of HIF-2 α in vitro [76]. Notably, HIF-2 α and *PAX8* interact with each other at the level of chromatin, and they may be synergistically involved in the regulation of *CCND1* expression [120].

4.5. The Wnt/ β -Catenin Signaling Pathway

Wnts represent a family of secreted glycoproteins responsible for regulating essential cellular processes, including cell proliferation, differentiation, and migration [121]. Multiple lines of evidence suggest the involvement of the Wnt/ β -catenin signaling pathway in RCC [122,123] (see Figure 3). Blockade of the WNT signaling pathway inhibits the migration and invasion ability of *PAX2*-positive cells [124]. Wnt1 was found to be significantly overexpressed in ccRCC, and high levels of Wnt1 are associated with more aggressive RCC cells and worse prognosis in patients [123]. Among the intracellular signal transducers, β -catenin plays a crucial role as a participant in the canonical Wnt signaling pathway [125,126]. Unphosphorylated β -catenin can interact with members of the LEF and TCF families, thereby further promoting the transcription of Wnt target genes (such as *C-MYC* and *CCND1*) [127,128]. While β -catenin-activating point mutations are not common in RCC, studies have demonstrated that inducing overexpression of β -catenin leads to the development of renal tumors in mice [129]. Ji et al. showed that activation of the Wnt/ β -catenin pathway correlates with the expression of *SEMA6A* in ccRCC [122]. The *VHL*-HIF-2 α axis can stabilize β -catenin and promote ccRCC progression by inducing *SEMA6A* upregulation [122].

5. The Development of *PAX*-Related Therapeutic Strategies in Renal Cell Carcinoma

In recent years, advancements in medicine have continuously updated and optimized the treatment of RCC. Surgery remains the primary treatment for RCC, especially for localized and locally advanced renal cancer. However, the emergence of immune checkpoint inhibitors (ICIs) has dramatically transformed the treatment prospects for RCC. Currently, the standard first-line treatment for advanced ccRCC includes ICI combinations. The dual immune checkpoint blockade with ipilimumab and nivolumab, targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), respectively, is the first ICI combination approved by the US Food and Drug Administration (FDA) under the CheckMate 214 trial [130,131]. ICI combination therapy has brought overall survival benefits and improved prognostic characteristics to some patients. Nevertheless, a significant number of patients exhibit primary resistance to ICI combinations or develop acquired resistance, ultimately succumbing to the disease [131]. Therefore, the development of new treatment options and the identification of novel therapeutic targets to enhance the prognosis of RCC remain the primary focus of current RCC research.

Genetic loss-of-function studies suggest that *PAX* genes, particularly *PAX2* and *PAX8*, which are highly expressed in RCC, are crucial for the continued proliferation and/or survival of RCC cells. Consequently, targeting *PAX2* or *PAX8* may represent a potentially effective therapeutic approach for the treatment of RCC (Table 2). Previous studies have utilized small interfering RNA (siRNA) to knock down *PAX2*, demonstrating that *PAX2* knockdown sensitized RCC cells to cisplatin-induced apoptosis, resulting in the death of 50–60% of cisplatin-resistant ACHN and CAKI-1 cells [22]. Further animal experiments have corroborated these findings, indicating that silencing *PAX2* expression could partially overcome the resistance of RCC to chemotherapy in vivo [31]. Additionally, large-scale functional genomic screening validated that *PAX8* silencing led to reduced proliferation of RCC cell lines [27]. Grimley et al. have screened large chemical libraries and identified a compound, EG1, that can effectively block *PAX2* activity and DNA binding through the *PAX2* paired domain [132]. Their findings revealed that EG1 can significantly inhibit the proliferation of *PAX2*-positive RCC cells while having minimal impact on *PAX2*-negative RCC cells. Recently, Bradford et al. [133] discovered three triazolo pyrimidine derivatives that inhibit *PAX*-mediated reporter gene transcriptional activation. Analysis of cultured renal epithelial cells demonstrated that these small molecules specifically inhibit *PAX2* and *PAX8* function by preventing the recruitment of the adaptor protein PTIP and the assembly of histone methylation complexes at target promoters. Furthermore, these compounds can specifically slow the proliferation of *PAX2*-positive RCC cells [133]. Combining *PAX* targeting with immunotherapy may represent a promising therapeutic direction. However, progress in developing therapeutic strategies targeting *PAX* proteins remains inadequate, particularly regarding the development of *PAX*-related inhibitors, which face significant obstacles. One major challenge arises from the inherently disordered structure of *PAX* proteins, rendering direct targeting approaches complex. Additionally, the predominant nuclear localization of *PAX* proteins poses significant hurdles to effective drug delivery. Addressing these challenges demands concerted efforts to explore novel methodologies and deepen our understanding of *PAX* genes, thereby facilitating the development of more efficacious therapeutic interventions.

Table 2. Strategies used for *PAX*-related therapeutic approaches in RCC.

<i>PAX</i>	Methods	Model	Main Outcomes	Authors, Year [Reference]
<i>PAX2</i>	SiRNA inactivation of <i>PAX2</i>	RCC cell lines	<i>PAX2</i> inactivation enhances cisplatin-induced apoptosis in renal carcinoma cells	Hueber et al., 2006 [22]
<i>PAX2</i>	shRNA targeting <i>PAX2</i>	RCC cell lines and nude mice	Subcutaneous ACHN/sh <i>PAX2</i> xenografts in nude mice respond better to cisplatin therapy than control ACHN tumors	Hueber et al., 2008 [31]
<i>PAX2</i>	Virtual screening and experimental validation	RCC cell lines	A small molecule inhibitor (EG1) targeting the DNA binding domain of <i>PAX2</i>	Grimley et al., 2017 [132]
<i>PAX8</i>	Large-scale functional genomic screens (ChIP-seq, RNA-seq, and ATAC-seq)	RCC cell lines	<i>PAX8</i> silencing results in decreased proliferation of RCC cell lines	Bleu et al., 2019 [27]
<i>PAX2</i>	Unbiased cell-based high-throughput screening assay	RCC cell lines	Three triazolo pyrimidine derivatives were identified that inhibited <i>PAX</i> -mediated transcriptional activation of reporter genes and suppressed proliferation of <i>PAX2</i> -positive RCC cells.	Bradford et al., 2022 [133]

6. Conclusions

The *PAX* gene family plays an important role in the occurrence and development of RCC [8,9]. *PAX2* undergoes reactivation during the early stages of ccRCC [12,13]. Approx-

imately 90% of RCC tumors exhibit high *PAX2* and *PAX8* expression levels, while other *PAX* genes have low or no expression in RCC [5,15]. Moreover, it is noteworthy that *PAX2* and *PAX8* exhibit heightened expression frequencies in both ccRCC and PRCC, while their expression remains either low or entirely absent in ChRCC. The upregulation of *PAX2* and *PAX8* within the context of RCC may be intricately linked to the maintenance of the epithelial phenotype during the process of EMT. Several lines of evidence implicate *PAX2* and *PAX8* as promising, emerging potential therapeutic targets for the treatment of RCC.

The most frequently mutated gene in ccRCC is *VHL*, where approximately 90% of sporadic ccRCC cases show alterations in the *VHL* gene located on chromosome 3 [7]. Notably, the loss of *VHL* function results in the upregulation of *PAX2* expression in ccRCC. Loss of *VHL* alone is insufficient to induce ccRCC, which requires additional epigenetic events to occur. When the *VHL* gene mutates or loses its function, the HIF-1/2- α subunit becomes stable, leading to the activation of *HIF* target genes and their downstream signaling pathways [72,73,92]. *HIF-2 α* is preferentially recruited to *PAX8*-bound transcriptional enhancers, which together coordinate the expression of the oncogene *CCND1* [120]. In conclusion, the loss of *VHL* in ccRCC may be involved in the occurrence and development of ccRCC in conjunction with *PAX* gene expression through *HIF*-mediated downstream target genes and signaling pathways.

Targeting *PAX2* or *PAX8* may be a potentially valuable treatment approach for RCC [12,31]. Small molecule compounds that target *PAX* have been developed and employed in targeted cancer therapy (non-clinical), which yielded promising in vitro results [132,133]. However, it is important to note that the expression levels of *PAX2* undergo dynamic changes during RCC development, reflecting a phenotypic shift in RCC. *PAX2* is reactivated in early ccRCC, but its expression levels begin to decline in high-grade ccRCC. This coincides with ccRCC transitioning towards a more aggressive phenotype and favoring glycolysis for energy production. Consequently, in patients with high-grade ccRCC, regardless of whether *PAX2* is targeted or not, its expression has decreased. The potential reasons for this phenomenon could include metabolic reprogramming of RCC and alterations in the tumor microenvironment, although the specific mechanisms remain unclear. Therefore, the clinical application of *PAX* gene inhibitors will require a further understanding of the role of *PAX* genes in cancer.

The generation of small molecule compounds that directly target *PAX* proteins is at a relatively early stage in terms of *PAX* inhibitor drug development because in vivo delivery of *PAX*-targeting small molecules is a significant barrier. Similarly, in vivo stability and delivery of siRNAs against *PAX* mRNAs are also significant barriers. Consequently, there remain significant gaps in the development of targeted therapies for *PAX* in RCC. Additionally, there continues to be ongoing debate regarding the use of *PAX2* expression levels as a metastatic marker for RCC. One potential reason for this debate may be the discrepancies in methods used to quantify gene expression, whether through the detection of RNA or protein markers. Although mRNA levels are early indicators of gene expression, they do not necessarily correlate directly with protein levels due to the influence of various regulatory factors such as translation efficiency and protein degradation rates. Furthermore, the expression of *PAX* genes varies in different regions of RCC at different times.

Future investigations could prioritize the elucidation of the potential mechanisms associated with *PAX* involvement in RCC and advancing therapeutic strategies targeting *PAX*. Presently, the precise mechanisms underlying *PAX*-mediated RCC onset and progression remain elusive. Notably, *PAX* genes are frequently expressed during developmental processes and are implicated in tissue regeneration and repair. Emerging research suggests a correlation between *PAX* expression and signaling pathways associated with stemness, indicating that the reactivation of *PAX* genes in RCC may contribute to the manifestation of cancer stemness characteristics [134,135]. Moreover, combination therapies targeting multiple pathways hold promise as a burgeoning approach. Identified potential targets upregulated in RCC, such as MUC1, AXL, EGFR, C-MET, PD-L1, VEGF, HIF, etc., could be

targeted in combination with targeting *PAX*, offering valuable support in the development of potential therapeutic strategies for RCC [134–138].

Author Contributions: Conceptualization, L.L., S.M.H. and M.R.E.; writing—original draft preparation, L.L.; writing—review and editing, S.M.H. and M.R.E. All authors have read and agreed to the published version of the manuscript.

Funding: L.L. is supported by a PhD scholarship from the Chinese Scholarship Council–New Zealand–China Research Collaboration Centres (CSC–NZ CRCC) joint funding program and the New Zealand–China Non-Communicable Diseases Research Collaboration Centre (NCD CRCC). S.M.H. is supported by a Postdoctoral Fellowship from the New Zealand Institute for Cancer Research Trust. Additionally, the authors received funding support from the Maurice Wilkins Centre for Molecular Biodiscovery, and Dunedin School of Medicine, University of Otago.

Acknowledgments: Figures 1–3 were produced using Biorender software (URL accessed on 19 April 2024; www.biorender.com).

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Rini, B.I.; Campbell, S.C.; Escudier, B. Renal cell carcinoma. *Lancet* **2009**, *373*, 1119–1132. [[CrossRef](#)] [[PubMed](#)]
2. Chen, Y.W.; Wang, L.; Panian, J.; Dhanji, S.; Derweesh, I.; Rose, B.; Bagrodia, A.; McKay, R.R. Treatment Landscape of Renal Cell Carcinoma. *Curr. Treat. Options Oncol.* **2023**, *24*, 1889–1916. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
3. Cirillo, L.; Innocenti, S.; Becherucci, F. Global epidemiology of kidney cancer. *Nephrol. Dial. Transplant.* **2024**, *39*, 920–928. [[CrossRef](#)] [[PubMed](#)]
4. Bukavina, L.; Bensalah, K.; Bray, F.; Carlo, M.; Challacombe, B.; Karam, J.A.; Kassouf, W.; Mitchell, T.; Montironi, R.; O’Brien, T.; et al. Epidemiology of Renal Cell Carcinoma: 2022 Update. *Eur. Urol.* **2022**, *82*, 529–542. [[CrossRef](#)] [[PubMed](#)]
5. Li, L.; Li, C.G.; Almomani, S.N.; Hossain, S.M.; Eccles, M.R. Co-Expression of Multiple PAX Genes in Renal Cell Carcinoma (RCC) and Correlation of High PAX Expression with Favorable Clinical Outcome in RCC Patients. *Int. J. Mol. Sci.* **2023**, *24*, 11432. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
6. Linehan, W.M.; Ricketts, C.J. The Cancer Genome Atlas of renal cell carcinoma: Findings and clinical implications. *Nat. Rev. Urol.* **2019**, *16*, 539–552. [[CrossRef](#)] [[PubMed](#)]
7. Hu, J.; Tan, P.; Ishihara, M.; Bayley, N.A.; Schokrpur, S.; Reynoso, J.G.; Zhang, Y.; Lim, R.J.; Dumitras, C.; Yang, L.; et al. Tumor heterogeneity in VHL drives metastasis in clear cell renal cell carcinoma. *Signal Transduct. Target. Ther.* **2023**, *8*, 155. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
8. Thompson, B.; Davidson, E.A.; Liu, W.; Nebert, D.W.; Bruford, E.A.; Zhao, H.; Dermitzakis, E.T.; Thompson, D.C.; Vasiliou, V. Overview of PAX gene family: Analysis of human tissue-specific variant expression and involvement in human disease. *Hum. Genet.* **2021**, *140*, 381–400. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
9. Li, C.G.; Eccles, M.R. PAX Genes in Cancer; Friends or Foes? *Front. Genet.* **2012**, *3*, 6. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
10. Bouchard, M.; Souabni, A.; Mandler, M.; Neubüser, A.; Busslinger, M. Nephric lineage specification by Pax2 and Pax8. *Genes Dev.* **2002**, *16*, 2958–2970. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
11. Narlis, M.; Grote, D.; Gaitan, Y.; Boualia, S.K.; Bouchard, M. Pax2 and pax8 regulate branching morphogenesis and nephron differentiation in the developing kidney. *J. Am. Soc. Nephrol.* **2007**, *18*, 1121–1129. [[CrossRef](#)] [[PubMed](#)]
12. Grimley, E.; Dressler, G.R. Are Pax proteins potential therapeutic targets in kidney disease and cancer? *Kidney Int.* **2018**, *94*, 259–267. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
13. Patel, S.R.; Dressler, G.R. The genetics and epigenetics of kidney development. *Semin. Nephrol.* **2013**, *33*, 314–326. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
14. Kakun, R.R.; Melamed, Z.; Perets, R. PAX8 in the Junction between Development and Tumorigenesis. *Int. J. Mol. Sci.* **2022**, *23*, 7410. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
15. Gupta, R.; Balzer, B.; Picken, M.; Osunkoya, A.O.; Shet, T.; Alsabeh, R.; Luthringer, D.; Paner, G.P.; Amin, M.B. Diagnostic implications of transcription factor Pax 2 protein and transmembrane enzyme complex carbonic anhydrase IX immunoreactivity in adult renal epithelial neoplasms. *Am. J. Surg. Pathol.* **2009**, *33*, 241–247. [[CrossRef](#)] [[PubMed](#)]
16. Shaw, T.; Barr, F.G.; Üren, A. The PAX Genes: Roles in Development, Cancer, and Other Diseases. *Cancers* **2024**, *16*, 1022. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
17. Peters, H.; Wilm, B.; Sakai, N.; Imai, K.; Maas, R.; Balling, R. Pax1 and Pax9 synergistically regulate vertebral column development. *Development* **1999**, *126*, 5399–5408. [[CrossRef](#)] [[PubMed](#)]
18. Ogasawara, M.; Shigetani, Y.; Hirano, S.; Satoh, N.; Kuratani, S. Pax1/Pax9-Related genes in an agnathan vertebrate, *Lampetra japonica*: Expression pattern of LjPax9 implies sequential evolutionary events toward the gnathostome body plan. *Dev. Biol.* **2000**, *223*, 399–410. [[CrossRef](#)] [[PubMed](#)]

19. Amiel, J.; Audollent, S.; Joly, D.; Dureau, P.; Salomon, R.; Tellier, A.L.; Augé, J.; Bouissou, F.; Antignac, C.; Gubler, M.C.; et al. PAX2 mutations in renal-coloboma syndrome: Mutational hotspot and germline mosaicism. *Eur. J. Hum. Genet.* **2000**, *8*, 820–826. [[CrossRef](#)] [[PubMed](#)]
20. Ozcan, A.; de la Roza, G.; Ro, J.Y.; Shen, S.S.; Truong, L.D. PAX2 and PAX8 expression in primary and metastatic renal tumors: A comprehensive comparison. *Arch. Pathol. Lab. Med.* **2012**, *136*, 1541–1551. [[CrossRef](#)] [[PubMed](#)]
21. Knoepp, S.M.; Kunju, L.P.; Roh, M.H. Utility of PAX8 and PAX2 immunohistochemistry in the identification of renal cell carcinoma in diagnostic cytology. *Diagn. Cytopathol.* **2012**, *40*, 667–672. [[CrossRef](#)] [[PubMed](#)]
22. Hueber, P.A.; Waters, P.; Clark, P.; Eccles, M.; Goodyer, P. PAX2 inactivation enhances cisplatin-induced apoptosis in renal carcinoma cells. *Kidney Int.* **2006**, *69*, 1139–1145, Erratum in *Kidney Int.* **2006**, *70*, 1666. [[CrossRef](#)] [[PubMed](#)]
23. Liu, Y.; Cui, S.; Li, W.; Zhao, Y.; Yan, X.; Xu, J. PAX3 is a biomarker and prognostic factor in melanoma: Database mining. *Oncol. Lett.* **2019**, *17*, 4985–4993. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
24. Ko, J.; Fonseca, V.A.; Wu, H. Pax4 in Health and Diabetes. *Int. J. Mol. Sci.* **2023**, *24*, 8283. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
25. Nasri Nasrabadi, P.; Martin, D.; Gharib, E.; Robichaud, G.A. The Pleiotropy of PAX5 Gene Products and Function. *Int. J. Mol. Sci.* **2022**, *23*, 10095. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
26. Azuma, N.; Yamaguchi, Y.; Handa, H.; Tadokoro, K.; Asaka, A.; Kawase, E.; Yamada, M. Mutations of the PAX6 gene detected in patients with a variety of optic-nerve malformations. *Am. J. Hum. Genet.* **2003**, *72*, 1565–1570. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
27. Bleu, M.; Gaulis, S.; Lopes, R.; Sprouffske, K.; Apfel, V.; Holwerda, S.; Pregnolato, M.; Yildiz, U.; Cordo', V.; Dost, A.F.M.; et al. PAX8 activates metabolic genes via enhancer elements in Renal Cell Carcinoma. *Nat. Commun.* **2019**, *10*, 3739. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
28. Wachtel, M.; Schäfer, B.W. Unpeaceful roles of mutant PAX proteins in cancer. *Semin. Cell Dev. Biol.* **2015**, *44*, 126–134. [[CrossRef](#)] [[PubMed](#)]
29. Dumont, S.N.; Lazar, A.J.; Bridge, J.A.; Benjamin, R.S.; Trent, J.C. PAX3/7-FOXO1 fusion status in older rhabdomyosarcoma patient population by fluorescent in situ hybridization. *J. Cancer Res. Clin. Oncol.* **2012**, *138*, 213–220. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
30. Sorensen, P.H.; Lynch, J.C.; Qualman, S.J.; Tirabosco, R.; Lim, J.F.; Maurer, H.M.; Bridge, J.A.; Crist, W.M.; Triche, T.J.; Barr, F.G. PAX3-FKHR and PAX7-FKHR gene fusions are prognostic indicators in alveolar rhabdomyosarcoma: A report from the children's oncology group. *J. Clin. Oncol.* **2002**, *20*, 2672–2679. [[CrossRef](#)] [[PubMed](#)]
31. Hueber, P.A.; Iglesias, D.; Chu, L.L.; Eccles, M.; Goodyer, P. In vivo validation of PAX2 as a target for renal cancer therapy. *Cancer Lett.* **2008**, *265*, 148–155. [[CrossRef](#)] [[PubMed](#)]
32. Robson, E.J.; He, S.J.; Eccles, M.R. A PANorama of PAX genes in cancer and development. *Nat. Rev. Cancer* **2006**, *6*, 52–62. [[CrossRef](#)] [[PubMed](#)]
33. Muratovska, A.; Zhou, C.; He, S.; Goodyer, P.; Eccles, M.R. Paired-Box genes are frequently expressed in cancer and often required for cancer cell survival. *Oncogene* **2003**, *22*, 7989–7997. [[CrossRef](#)] [[PubMed](#)]
34. Patel, S.R.; Ranghini, E.; Dressler, G.R. Mechanisms of gene activation and repression by Pax proteins in the developing kidney. *Pediatr. Nephrol.* **2014**, *29*, 589–595. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
35. Sharma, R.; Sanchez-Ferras, O.; Bouchard, M. Pax genes in renal development, disease and regeneration. *Semin. Cell Dev. Biol.* **2015**, *44*, 97–106. [[CrossRef](#)] [[PubMed](#)]
36. Jiang, Y.S.; Jiang, T.; Huang, B.; Chen, P.S.; Ouyang, J. Epithelial-mesenchymal transition of renal tubules: Divergent processes of repairing in acute or chronic injury? *Med. Hypotheses* **2013**, *81*, 73–75. [[CrossRef](#)] [[PubMed](#)]
37. Buttiglieri, S.; Deregibus, M.C.; Bravo, S.; Cassoni, P.; Chiarle, R.; Bussolati, B.; Camussi, G. Role of Pax2 in apoptosis resistance and proinvasive phenotype of Kaposi's sarcoma cells. *J. Biol. Chem.* **2004**, *279*, 4136–4143. [[CrossRef](#)] [[PubMed](#)]
38. Brun, T.; Duhamel, D.L.; Hu He, K.H.; Wollheim, C.B.; Gauthier, B.R. The transcription factor PAX4 acts as a survival gene in INS-1E insulinoma cells. *Oncogene* **2007**, *26*, 4261–4271. [[CrossRef](#)] [[PubMed](#)]
39. Shi, K.; Yin, X.; Cai, M.C.; Yan, Y.; Jia, C.; Ma, P.; Zhang, S.; Zhang, Z.; Gu, Z.; Zhang, M.; et al. PAX8 regulon in human ovarian cancer links lineage dependency with epigenetic vulnerability to HDAC inhibitors. *eLife* **2019**, *8*, e44306. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
40. Doberstein, K.; Pfeilschifter, J.; Gutwein, P. The transcription factor PAX2 regulates ADAM10 expression in renal cell carcinoma. *Carcinogenesis* **2011**, *32*, 1713–1723. [[CrossRef](#)] [[PubMed](#)]
41. Di Palma, T.; Filippone, M.G.; Pierantoni, G.M.; Fusco, A.; Soddu, S.; Zannini, M. Pax8 has a critical role in epithelial cell survival and proliferation. *Cell Death Dis.* **2013**, *4*, e729. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
42. Wang, J.; Zhao, X.; Qi, J.; Yang, C.; Cheng, H.; Ren, Y.; Huang, L. Eight proteins play critical roles in RCC with bone metastasis via mitochondrial dysfunction. *Clin. Exp. Metastasis* **2015**, *32*, 605–622. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
43. Hoefflin, R.; Harlander, S.; Schäfer, S.; Metzger, P.; Kuo, F.; Schönenberger, D.; Adlesic, M.; Peighambari, A.; Seidel, P.; Chen, C.Y.; et al. HIF-1 α and HIF-2 α differently regulate tumour development and inflammation of clear cell renal cell carcinoma in mice. *Nat. Commun.* **2020**, *11*, 4111. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
44. Stuart, E.T.; Haffner, R.; Oren, M.; Gruss, P. Loss of p53 function through PAX-mediated transcriptional repression. *EMBO J.* **1995**, *14*, 5638–5645. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]

45. Frost, V.; Grocott, T.; Eccles, M.R.; Chantry, A. Self-regulated Pax gene expression and modulation by the TGFbeta superfamily. *Crit. Rev. Biochem. Mol. Biol.* **2008**, *43*, 371–391. [[CrossRef](#)] [[PubMed](#)]
46. Pei, D.; Shu, X.; Gassama-Diagne, A.; Thiery, J.P. Mesenchymal-epithelial transition in development and reprogramming. *Nat. Cell Biol.* **2019**, *21*, 44–53. [[CrossRef](#)] [[PubMed](#)]
47. Harada, K.; Miyake, H.; Kusuda, Y.; Fujisawa, M. Expression of epithelial-mesenchymal transition markers in renal cell carcinoma: Impact on prognostic outcomes in patients undergoing radical nephrectomy. *BJU Int.* **2012**, *110 Pt C*, E1131–E1137. [[CrossRef](#)] [[PubMed](#)]
48. Kaur, G.; Li, C.G.; Chantry, A.; Stayner, C.; Horsfield, J.; Eccles, M.R. SMAD proteins directly suppress PAX2 transcription downstream of transforming growth factor-beta 1 (TGF- β 1) signalling in renal cell carcinoma. *Oncotarget* **2018**, *9*, 26852–26867. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
49. Mazal, P.R.; Stichenwirth, M.; Koller, A.; Blach, S.; Haitel, A.; Susani, M. Expression of aquaporins and PAX-2 compared to CD10 and cytokeratin 7 in renal neoplasms: A tissue microarray study. *Mod. Pathol.* **2005**, *18*, 535–540. [[CrossRef](#)] [[PubMed](#)]
50. Truong, L.D.; Shen, S.S. Immunohistochemical diagnosis of renal neoplasms. *Arch. Pathol. Lab. Med.* **2011**, *135*, 92–109. [[CrossRef](#)] [[PubMed](#)]
51. Grote, D.; Souabni, A.; Busslinger, M.; Bouchard, M. Pax 2/8-regulated Gata 3 expression is necessary for morphogenesis and guidance of the nephric duct in the developing kidney. *Development* **2006**, *133*, 53–61. [[CrossRef](#)] [[PubMed](#)]
52. Boualia, S.K.; Gaitan, Y.; Tremblay, M.; Sharma, R.; Cardin, J.; Kania, A.; Bouchard, M. A core transcriptional network composed of Pax2/8, Gata3 and Lim1 regulates key players of pro/mesonephros morphogenesis. *Dev. Biol.* **2013**, *382*, 555–566. [[CrossRef](#)] [[PubMed](#)]
53. Salvi, A.; Hardy, L.R.; Heath, K.N.; Watry, S.; Pergande, M.R.; Cologna, S.M.; Burdette, J.E. PAX8 modulates the tumor microenvironment of high grade serous ovarian cancer through changes in the secretome. *Neoplasia* **2023**, *36*, 100866. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
54. Aili, A.; Wen, J.; Xue, L.; Wang, J. Mutational Analysis of PBRM1 and Significance of PBRM1 Mutation in Anti-PD-1 Immunotherapy of Clear Cell Renal Cell Carcinoma. *Front. Oncol.* **2021**, *11*, 712765. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
55. Gu, X.; Enane, F.; Tohme, R.; Schuerger, C.; Radivoyevitch, T.; Parker, Y.; Zuberi, E.; Przychodzen, B.; Jha, B.K.; Lindner, D.; et al. PBRM1 loss in kidney cancer unbalances the proximal tubule master transcription factor hub to repress proximal tubule differentiation. *Cell Rep.* **2021**, *36*, 109747. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
56. Jiang, F.; Richter, J.; Schraml, P.; Bubendorf, L.; Gasser, T.; Sauter, G.; Mihatsch, M.J.; Moch, H. Chromosomal imbalances in papillary renal cell carcinoma: Genetic differences between histological subtypes. *Am. J. Pathol.* **1998**, *153*, 1467–1473. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
57. Durinck, S.; Stawiski, E.W.; Pavía-Jiménez, A.; Modrusan, Z.; Kapur, P.; Jaiswal, B.S.; Zhang, N.; Toffessi-Tcheuyap, V.; Nguyen, T.T.; Pahuja, K.B.; et al. Spectrum of diverse genomic alterations define non-clear cell renal carcinoma subtypes. *Nat. Genet.* **2015**, *47*, 13–21. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
58. Cancer Genome Atlas Research Network; Linehan, W.M.; Spellman, P.T.; Ricketts, C.J.; Creighton, C.J.; Fei, S.S.; Davis, C.; Wheeler, D.A.; Murray, B.A.; Schmidt, L.; et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N. Engl. J. Med.* **2016**, *374*, 135–145. [[CrossRef](#)] [[PubMed](#)]
59. Casuscelli, J.; Weinhold, N.; Gundem, G.; Wang, L.; Zabor, E.C.; Drill, E.; Wang, P.I.; Nanjangud, G.J.; Redzematovic, A.; Nargund, A.M.; et al. Genomic landscape and evolution of metastatic chromophobe renal cell carcinoma. *JCI Insight* **2017**, *2*, e92688. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
60. Speicher, M.R.; Schoell, B.; du Manoir, S.; Schröck, E.; Ried, T.; Cremer, T.; Störkel, S.; Kovacs, A.; Kovacs, G. Specific loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 in chromophobe renal cell carcinomas revealed by comparative genomic hybridization. *Am. J. Pathol.* **1994**, *145*, 356–364. [[PubMed](#)] [[PubMed Central](#)]
61. Davis, C.F.; Ricketts, C.J.; Wang, M.; Yang, L.; Cherniack, A.D.; Shen, H.; Buhay, C.; Kang, H.; Kim, S.C.; Fahey, C.C.; et al. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell* **2014**, *26*, 319–330. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
62. Mitchell, T.J.; Turajlic, S.; Rowan, A.; Nicol, D.; Farmery, J.H.R.; O'Brien, T.; Martincorena, I.; Tarpey, P.; Angelopoulos, N.; Yates, L.R.; et al. TRACERx Renal Consortium. Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal. *Cell* **2018**, *173*, 611–623.e17. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
63. El-Mokadem, I.; Fitzpatrick, J.; Bondad, J.; Rauchhaus, P.; Cunningham, J.; Pratt, N.; Fleming, S.; Nabi, G. Chromosome 9p deletion in clear cell renal cell carcinoma predicts recurrence and survival following surgery. *Br. J. Cancer* **2014**, *111*, 1381–1390. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
64. Dalgliesh, G.L.; Furge, K.; Greenman, C.; Chen, L.; Bignell, G.; Butler, A.; Davies, H.; Edkins, S.; Hardy, C.; Latimer, C.; et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. *Nature* **2010**, *463*, 360–363. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
65. Brannon, A.R.; Reddy, A.; Seiler, M.; Arreola, A.; Moore, D.T.; Pruthi, R.S.; Wallen, E.M.; Nielsen, M.E.; Liu, H.; Nathanson, K.L.; et al. Molecular Stratification of Clear Cell Renal Cell Carcinoma by Consensus Clustering Reveals Distinct Subtypes and Survival Patterns. *Genes Cancer* **2010**, *1*, 152–163. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]

66. Bihr, S.; Ohashi, R.; Moore, A.L.; Rüschhoff, J.H.; Beisel, C.; Hermanns, T.; Mischo, A.; Corro, C.; Beyer, J.; Beerenwinkel, N.; et al. Expression and Mutation Patterns of PBRM1, BAP1 and SETD2 Mirror Specific Evolutionary Subtypes in Clear Cell Renal Cell Carcinoma. *Neoplasia* **2019**, *21*, 247–256. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
67. Brugarolas, J. PBRM1 and BAP1 as novel targets for renal cell carcinoma. *Cancer J.* **2013**, *19*, 324–332. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
68. Mazumder, S.; Higgins, P.J.; Samarakoon, R. Downstream Targets of VHL/HIF- α Signaling in Renal Clear Cell Carcinoma Progression: Mechanisms and Therapeutic Relevance. *Cancers* **2023**, *15*, 1316. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
69. Zhang, J.; Zhang, Q. VHL and Hypoxia Signaling: Beyond HIF in Cancer. *Biomedicines* **2018**, *6*, 35. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
70. Kaelin, W.G., Jr. The von Hippel-Lindau tumor suppressor protein and clear cell renal carcinoma. *Clin. Cancer Res.* **2007**, *13 Pt 2*, 680s–684s. [[CrossRef](#)] [[PubMed](#)]
71. Lonser, R.R.; Glenn, G.M.; Walther, M.; Chew, E.Y.; Libutti, S.K.; Linehan, W.M.; Oldfield, E.H. von Hippel-Lindau disease. *Lancet* **2003**, *361*, 2059–2067. [[CrossRef](#)] [[PubMed](#)]
72. Iwai, K.; Yamanaka, K.; Kamura, T.; Minato, N.; Conaway, R.C.; Conaway, J.W.; Klausner, R.D.; Pause, A. Identification of the von Hippel-Lindau tumor-suppressor protein as part of an active E3 ubiquitin ligase complex. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 12436–12441. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
73. Siemeister, G.; Weindel, K.; Mohrs, K.; Barleon, B.; Martiny-Baron, G.; Marmé, D. Reversion of deregulated expression of vascular endothelial growth factor in human renal carcinoma cells by von Hippel-Lindau tumor suppressor protein. *Cancer Res.* **1996**, *56*, 2299–2301. [[PubMed](#)]
74. Gudas, L.J.; Fu, L.; Minton, D.R.; Mongan, N.P.; Nanus, D.M. The role of HIF1 α in renal cell carcinoma tumorigenesis. *J. Mol. Med.* **2014**, *92*, 825–836. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
75. Kamura, T.; Sato, S.; Iwai, K.; Czyzyk-Krzeska, M.; Conaway, R.C.; Conaway, J.W. Activation of HIF1 α ubiquitination by a reconstituted von Hippel-Lindau (VHL) tumor suppressor complex. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 10430–10435. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
76. Raval, R.R.; Lau, K.W.; Tran, M.G.; Sowter, H.M.; Mandriota, S.J.; Li, J.L.; Pugh, C.W.; Maxwell, P.H.; Harris, A.L.; Ratcliffe, P.J. Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. *Mol. Cell Biol.* **2005**, *25*, 5675–5686. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
77. Perrotta, S.; Roberti, D.; Bencivenga, D.; Corsetto, P.; O'Brien, K.A.; Caiazza, M.; Stampone, E.; Allison, L.; Fleck, R.A.; Scianguetta, S.; et al. Effects of Germline VHL Deficiency on Growth, Metabolism, and Mitochondria. *N. Engl. J. Med.* **2020**, *382*, 835–844. [[CrossRef](#)] [[PubMed](#)]
78. Brand, M.D.; Nicholls, D.G. Assessing mitochondrial dysfunction in cells. *Biochem. J.* **2011**, *435*, 297–312, Erratum in *Biochem. J.* **2011**, *437*, 575. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
79. Wang, Z.; Ying, Z.; Bosy-Westphal, A.; Zhang, J.; Schautz, B.; Later, W.; Heymsfield, S.B.; Müller, M.J. Specific metabolic rates of major organs and tissues across adulthood: Evaluation by mechanistic model of resting energy expenditure. *Am. J. Clin. Nutr.* **2010**, *92*, 1369–1377. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
80. Lunt, S.Y.; Vander Heiden, M.G. Aerobic glycolysis: Meeting the metabolic requirements of cell proliferation. *Annu. Rev. Cell Dev. Biol.* **2011**, *27*, 441–464. [[CrossRef](#)] [[PubMed](#)]
81. Natarajan, B.; Arige, V.; Khan, A.A.; Reddy, S.S.; Barthwal, M.K.; Mahapatra, N.R. Hypoxia-mediated regulation of mitochondrial transcription factors in renal epithelial cells: Implications for hypertensive renal physiology. *Hypertens. Res.* **2021**, *44*, 154–167. [[CrossRef](#)] [[PubMed](#)]
82. Szeto, H.H.; Liu, S.; Soong, Y.; Seshan, S.V.; Cohen-Gould, L.; Manichev, V.; Feldman, L.C.; Gustafsson, T. Mitochondria Protection after Acute Ischemia Prevents Prolonged Upregulation of IL-1 β and IL-18 and Arrests CKD. *J. Am. Soc. Nephrol.* **2017**, *28*, 1437–1449. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
83. Yang, O.C.; Maxwell, P.H.; Pollard, P.J. Renal cell carcinoma: Translational aspects of metabolism and therapeutic consequences. *Kidney Int.* **2013**, *84*, 667–681. [[CrossRef](#)] [[PubMed](#)]
84. Fukushi, A.; Kim, H.D.; Chang, Y.C.; Kim, C.H. Revisited Metabolic Control and Reprogramming Cancers by Means of the Warburg Effect in Tumor Cells. *Int. J. Mol. Sci.* **2022**, *23*, 10037. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
85. Koppenol, W.H.; Bounds, P.L.; Dang, C.V. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat. Rev. Cancer* **2011**, *11*, 325–337, Erratum in *Nat. Rev. Cancer* **2011**, *11*, 618. [[CrossRef](#)] [[PubMed](#)]
86. Hervouet, E.; Simonnet, H.; Godinot, C. Mitochondria and reactive oxygen species in renal cancer. *Biochimie* **2007**, *89*, 1080–1088. [[CrossRef](#)] [[PubMed](#)]
87. Li, S.; Li, W.; Yuan, J.; Bullova, P.; Wu, J.; Zhang, X.; Liu, Y.; Plescher, M.; Rodriguez, J.; Bedoya-Reina, O.C.; et al. Impaired oxygen-sensitive regulation of mitochondrial biogenesis within the von Hippel-Lindau syndrome. *Nat. Metab.* **2022**, *4*, 739–758, Erratum in *Nat. Metab.* **2022**, *4*, 1421. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
88. Lu, J.; Tan, M.; Cai, Q. The Warburg effect in tumor progression: Mitochondrial oxidative metabolism as an anti-metastasis mechanism. *Cancer Lett.* **2015**, *356 Pt A*, 156–164. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
89. Chinopoulos, C.; Seyfried, T.N. Mitochondrial Substrate-Level Phosphorylation as Energy Source for Glioblastoma: Review and Hypothesis. *ASN Neuro* **2018**, *10*, 1759091418818261. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]

90. Banumathy, G.; Cairns, P. Signaling pathways in renal cell carcinoma. *Cancer Biol. Ther.* **2010**, *10*, 658–664. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
91. Schödel, J.; Grampp, S.; Maher, E.R.; Moch, H.; Ratcliffe, P.J.; Russo, P.; Mole, D.R. Hypoxia, Hypoxia-inducible Transcription Factors, and Renal Cancer. *Eur. Urol.* **2016**, *69*, 646–657. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
92. Luu, V.D.; Boysen, G.; Struckmann, K.; Casagrande, S.; von Teichman, A.; Wild, P.J.; Sulser, T.; Schraml, P.; Moch, H. Loss of VHL and hypoxia provokes PAX2 up-regulation in clear cell renal cell carcinoma. *Clin. Cancer Res.* **2009**, *15*, 3297–3304. [[CrossRef](#)] [[PubMed](#)]
93. Maxwell, P.H.; Wiesener, M.S.; Chang, G.W.; Clifford, S.C.; Vaux, E.C.; Cockman, M.E.; Wykoff, C.C.; Pugh, C.W.; Maher, E.R.; Ratcliffe, P.J. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* **1999**, *399*, 271–275. [[CrossRef](#)] [[PubMed](#)]
94. Ivan, M.; Kondo, K.; Yang, H.; Kim, W.; Valiando, J.; Ohh, M.; Salic, A.; Asara, J.M.; Lane, W.S.; Kaelin, W.G., Jr. HIF α targeted for VHL-mediated destruction by proline hydroxylation: Implications for O₂ sensing. *Science* **2001**, *292*, 464–468. [[CrossRef](#)] [[PubMed](#)]
95. Isono, T.; Chano, T.; Yoshida, T.; Kageyama, S.; Kawauchi, A.; Suzaki, M.; Yuasa, T. Hydroxyl-HIF2- α is potential therapeutic target for renal cell carcinomas. *Am. J. Cancer Res.* **2016**, *6*, 2263–2276. [[PubMed](#)] [[PubMed Central](#)]
96. Gao, S.L.; Yin, R.; Zhang, L.F.; Wang, S.M.; Chen, J.S.; Wu, X.Y.; Yue, C.; Zuo, L.; Tang, M. The oncogenic role of MUC12 in RCC progression depends on c-Jun/TGF- β signalling. *J. Cell Mol. Med.* **2020**, *24*, 8789–8802. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
97. Peng, D.; Fu, M.; Wang, M.; Wei, Y.; Wei, X. Targeting TGF- β signal transduction for fibrosis and cancer therapy. *Mol. Cancer* **2022**, *21*, 104. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
98. Tretbar, S.; Krausbeck, P.; Müller, A.; Friedrich, M.; Vaxevanis, C.; Bukur, J.; Jasinski-Bergner, S.; Seliger, B. TGF- β inducible epithelial-to-mesenchymal transition in renal cell carcinoma. *Oncotarget* **2019**, *10*, 1507–1524. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
99. Hanna, C.; Hubchak, S.C.; Liang, X.; Rozen-Zvi, B.; Schumacker, P.T.; Hayashida, T.; Schnaper, H.W. Hypoxia-inducible factor-2 α and TGF- β signaling interact to promote normoxic glomerular fibrogenesis. *Am. J. Physiol. Renal Physiol.* **2013**, *305*, F1323–F1331. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
100. Han, J.; Zhou, W.; Jia, M.; Wen, J.; Jiang, J.; Shi, J.; Zhang, K.; Ma, H.; Liu, J.; Ren, J.; et al. Expression quantitative trait loci in long non-coding RNA PAX8-AS1 are associated with decreased risk of cervical cancer. *Mol. Genet. Genom.* **2016**, *291*, 1743–1748. [[CrossRef](#)] [[PubMed](#)]
101. Zhou, P.; Xu, T.; Hu, H.; Hua, F. Overexpression of PAX8-AS1 Inhibits Malignant Phenotypes of Papillary Thyroid Carcinoma Cells via miR-96-5p/PKN2 Axis. *Int. J. Endocrinol.* **2021**, *2021*, 5499963. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
102. Shen, Y.; Tong, Z.W.; Zhou, Y.; Sun, Y.; Xie, Y.; Li, R.; Liu, H. Inhibition of lncRNA-PAX8-AS1-N directly associated with VEGF/TGF- β 1/8-OHdG enhances podocyte apoptosis in diabetic nephropathy. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 6864–6872. [[CrossRef](#)] [[PubMed](#)]
103. Shang, D.; Liu, Y.; Yang, P.; Chen, Y.; Tian, Y. TGFBI-promoted adhesion, migration and invasion of human renal cell carcinoma depends on inactivation of von Hippel-Lindau tumor suppressor. *Urology* **2012**, *79*, 966.e1–966.e7. [[CrossRef](#)] [[PubMed](#)]
104. Siveen, K.S.; Prabhu, K.; Krishnankutty, R.; Kuttikrishnan, S.; Tsakou, M.; Alali, F.Q.; Dermime, S.; Mohammad, R.M.; Uddin, S. Vascular Endothelial Growth Factor (VEGF) Signaling in Tumour Vascularization: Potential and Challenges. *Curr. Vasc. Pharmacol.* **2017**, *15*, 339–351. [[CrossRef](#)] [[PubMed](#)]
105. Cho, H.; Du, X.; Rizzi, J.P.; Liberzon, E.; Chakraborty, A.A.; Gao, W.; Carvo, I.; Signoretti, S.; Bruick, R.K.; Josey, J.A.; et al. On-target efficacy of a HIF-2 α antagonist in preclinical kidney cancer models. *Nature* **2016**, *539*, 107–111. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
106. Mei, X.; Shu, J.; Huang, R.; Chu, X.; Tian, Y. Expression of VEGF, CD73 and their relationship with clinical pathology, microvessel density, and prognosis in renal cell carcinoma. *Transl. Androl. Urol.* **2020**, *9*, 1366–1373. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
107. Wang, Y.; Lu, Y.H.; Tang, C.; Xue, M.; Li, X.Y.; Chang, Y.P.; Cheng, Y.; Li, T.; Yu, X.C.; Sun, B.; et al. Calcium Dobesilate Restores Autophagy by Inhibiting the VEGF/PI3K/AKT/mTOR Signaling Pathway. *Front. Pharmacol.* **2019**, *10*, 886. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
108. Su, C.C. Tanshinone IIA inhibits gastric carcinoma AGS cells by decreasing the protein expression of VEGFR and blocking Ras/Raf/MEK/ERK pathway. *Int. J. Mol. Med.* **2018**, *41*, 2389–2396. [[CrossRef](#)] [[PubMed](#)]
109. Fonsato, V.; Buttiglieri, S.; Deregiibus, M.C.; Puntorieri, V.; Bussolati, B.; Camussi, G. Expression of Pax2 in human renal tumor-derived endothelial cells sustains apoptosis resistance and angiogenesis. *Am. J. Pathol.* **2006**, *168*, 706–713. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
110. Chaves-Moreira, D.; Mitchell, M.A.; Arruza, C.; Rawat, P.; Sidoli, S.; Nameki, R.; Reddy, J.; Corona, R.I.; Afeyan, L.K.; Klein, I.A.; et al. The transcription factor PAX8 promotes angiogenesis in ovarian cancer through interaction with SOX17. *Sci. Signal.* **2022**, *15*, eabm2496. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
111. Baluapuri, A.; Wolf, E.; Eilers, M. Target gene-independent functions of MYC oncoproteins. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 255–267. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
112. Solé, X.; Hernández, P.; de Heredia, M.L.; Armengol, L.; Rodríguez-Santiago, B.; Gómez, L.; Maxwell, C.A.; Aguiló, F.; Condom, E.; Abril, J.; et al. Genetic and genomic analysis modeling of germline c-MYC overexpression and cancer susceptibility. *BMC Genom.* **2008**, *9*, 12. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]

113. Hwang, I.Y.; Roe, J.S.; Seol, J.H.; Kim, H.R.; Cho, E.J.; Youn, H.D. pVHL-mediated transcriptional repression of c-Myc by recruitment of histone deacetylases. *Mol. Cells* **2012**, *33*, 195–201. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
114. Zhang, S.L.; Chen, Y.W.; Tran, S.; Liu, F.; Nestoridi, E.; Hébert, M.J.; Ingelfinger, J.R. Pax-2 and N-myc regulate epithelial cell proliferation and apoptosis in a positive autocrine feedback loop. *Pediatr. Nephrol.* **2007**, *22*, 813–824. [[CrossRef](#)] [[PubMed](#)]
115. Gordan, J.D.; Lal, P.; Dondeti, V.R.; Letrero, R.; Parekh, K.N.; Oquendo, C.E.; Greenberg, R.A.; Flaherty, K.T.; Rathmell, W.K.; Keith, B.; et al. HIF- α effects on c-Myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. *Cancer Cell* **2008**, *14*, 435–446. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
116. Gordan, J.D.; Thompson, C.B.; Simon, M.C. HIF and c-Myc: Sibling rivals for control of cancer cell metabolism and proliferation. *Cancer Cell* **2007**, *12*, 108–113. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
117. Zhang, H.; Gao, P.; Fukuda, R.; Kumar, G.; Krishnamachary, B.; Zeller, K.I.; Dang, C.V.; Semenza, G.L. HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity. *Cancer Cell* **2007**, *11*, 407–420. [[CrossRef](#)] [[PubMed](#)]
118. Yang, Z.; Xu, T.; Xie, T.; Yang, L.; Wang, G.; Gao, Y.; Xi, G.; Zhang, X. CDC42EP3 promotes glioma progression via regulation of CCND1. *Cell Death Dis.* **2022**, *13*, 290. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
119. Zhang, T.; Niu, X.; Liao, L.; Cho, E.A.; Yang, H. The contributions of HIF-target genes to tumor growth in RCC. *PLoS ONE* **2013**, *8*, e80544. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
120. Patel, S.A.; Hirosue, S.; Rodrigues, P.; Vojtasova, E.; Richardson, E.K.; Ge, J.; Syafruddin, S.E.; Speed, A.; Papachristou, E.K.; Baker, D.; et al. The renal lineage factor PAX8 controls oncogenic signalling in kidney cancer. *Nature* **2022**, *606*, 999–1006. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
121. Miller, J.R. The Wnts. *Genome Biol.* **2002**, *3*, REVIEWS3001. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
122. Ji, J.; Xu, Y.; Xie, M.; He, X.; Ren, D.; Qiu, T.; Liu, W.; Chen, Z.; Shi, W.; Zhang, Z.; et al. VHL-HIF-2 α axis-induced SEMA6A upregulation stabilized β -catenin to drive clear cell renal cell carcinoma progression. *Cell Death Dis.* **2023**, *14*, 83. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
123. Kruck, S.; Eyrich, C.; Scharpf, M.; Sievert, K.D.; Fend, F.; Stenzl, A.; Bedke, J. Impact of an altered Wnt1/ β -catenin expression on clinicopathology and prognosis in clear cell renal cell carcinoma. *Int. J. Mol. Sci.* **2013**, *14*, 10944–10957. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
124. Li, L.; Gong, L. Impact of WNT Pathway Blockade on the Biological Characteristics of Renal Tubular Epithelial Cells Stably Transfected with PAX2. *Ann. Clin. Lab. Sci.* **2021**, *51*, 368–375. [[PubMed](#)]
125. Nusse, R.; Clevers, H. Wnt/ β -Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell* **2017**, *169*, 985–999. [[CrossRef](#)] [[PubMed](#)]
126. Piotrowska, Ż.; Niezgoda, M.; Młynarczyk, G.; Acewicz, M.; Kasacka, I. Comparative Assessment of the WNT/ β -Catenin Pathway, CacyBP/SIP, and the Immunoproteasome Subunit LMP7 in Various Histological Types of Renal Cell Carcinoma. *Front. Oncol.* **2020**, *10*, 566637. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
127. Yang, C.M.; Ji, S.; Li, Y.; Fu, L.Y.; Jiang, T.; Meng, F.D. β -Catenin promotes cell proliferation, migration, and invasion but induces apoptosis in renal cell carcinoma. *Oncotargets Ther.* **2017**, *10*, 711–724. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
128. Ueno, K.; Hirata, H.; Majid, S.; Tabatabai, Z.L.; Hinoda, Y.; Dahiya, R. IGFBP-4 activates the Wnt/ β -catenin signaling pathway and induces M-CAM expression in human renal cell carcinoma. *Int. J. Cancer* **2011**, *129*, 2360–2369. [[CrossRef](#)] [[PubMed](#)]
129. Saadi-Kheddouci, S.; Berrebi, D.; Romagnolo, B.; Cluzeaud, F.; Peuchmaur, M.; Kahn, A.; Vandewalle, A.; Perret, C. Early development of polycystic kidney disease in transgenic mice expressing an activated mutant of the beta-catenin gene. *Oncogene* **2001**, *20*, 5972–5981. [[CrossRef](#)] [[PubMed](#)]
130. Atkins, M.B.; Clark, J.I.; Quinn, D.I. Immune checkpoint inhibitors in advanced renal cell carcinoma: Experience to date and future directions. *Ann. Oncol.* **2017**, *28*, 1484–1494. [[CrossRef](#)] [[PubMed](#)]
131. Gebrael, G.; Sahu, K.K.; Agarwal, N.; Maughan, B.L. Update on combined immunotherapy for the treatment of advanced renal cell carcinoma. *Hum. Vaccines Immunother.* **2023**, *19*, 2193528. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
132. Grimley, E.; Liao, C.; Ranghini, E.J.; Nikolovska-Coleska, Z.; Dressler, G.R. Inhibition of Pax2 Transcription Activation with a Small Molecule that Targets the DNA Binding Domain. *ACS Chem. Biol.* **2017**, *12*, 724–734. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
133. Bradford, S.T.J.; Grimley, E.; Laszczyk, A.M.; Lee, P.H.; Patel, S.R.; Dressler, G.R. Identification of Pax protein inhibitors that suppress target gene expression and cancer cell proliferation. *Cell Chem. Biol.* **2022**, *29*, 412–422.e4. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
134. Lasorsa, F.; Rutigliano, M.; Milella, M.; Ferro, M.; Pandolfo, S.D.; Crocetto, F.; Autorino, R.; Battaglia, M.; Ditunno, P.; Lucarelli, G. Cancer Stem Cells in Renal Cell Carcinoma: Origins and Biomarkers. *Int. J. Mol. Sci.* **2023**, *24*, 13179. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
135. Swetha, G.; Chandra, V.; Phadnis, S.; Bhonde, R. Glomerular parietal epithelial cells of adult murine kidney undergo EMT to generate cells with traits of renal progenitors. *J. Cell. Mol. Med.* **2011**, *15*, 396–413. [[CrossRef](#)]
136. Milella, M.; Rutigliano, M.; Lasorsa, F.; Ferro, M.; Bianchi, R.; Fallara, G.; Crocetto, F.; Pandolfo, S.D.; Barone, B.; d’Amati, A.; et al. The Role of MUC1 in Renal Cell Carcinoma. *Biomolecules* **2024**, *14*, 315. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]

137. Barata, P.C.; Rini, B.I. Treatment of renal cell carcinoma: Current status and future directions. *CA Cancer J. Clin.* **2017**, *67*, 507–524. [[CrossRef](#)]
138. Jin, J.; Xie, Y.; Zhang, J.S.; Wang, J.Q.; Dai, S.J.; He, W.F.; Li, S.Y.; Ashby, C.R., Jr.; Chen, Z.S.; He, Q. Sunitinib resistance in renal cell carcinoma: From molecular mechanisms to predictive biomarkers. *Drug Resist. Updates* **2023**, *67*, 100929. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.