From kidney injury to kidney cancer

OPEN

Anna Julie Peired[1,2], Elena Lazzeri[1,2], Francesco Guzzi[2], Hans-Joachim Anders[3] and Paola Romagnani[1,2,4]

[1]Excellence Centre for Research, Transfer and High Education for the Development of DE NOVO Therapies, University of Florence, Florence, Italy; [2]Department of Experimental and Clinical Biomedical Sciences "Mario Serio," University of Florence, Florence, Italy; [3]Division of Nephrology, Medizinische Klinik and Poliklinik IV, Ludwig Maximilian University Klinikum, Munich, Germany; and [4]Nephrology and Dialysis Unit, Meyer Children's University Hospital, Florence, Italy

Epidemiologic studies document strong associations between acute or chronic kidney injury and kidney tumors. However, whether these associations are linked by causation, and in which direction, is unclear. Accumulating data from basic and clinical research now shed light on this issue and prompt us to propose a new pathophysiological concept with immanent implications in the management of patients with kidney disease and patients with kidney tumors. As a central paradigm, this review proposes the mechanisms of kidney damage and repair that are active during acute kidney injury but also during persistent injuries in chronic kidney disease as triggers of DNA damage, promoting the expansion of (pre-)malignant cell clones. As renal progenitors have been identified by different studies as the cell of origin for several benign and malignant kidney tumors, we discuss how the different types of kidney tumors relate to renal progenitors at specific sites of injury and to germline or somatic mutations in distinct signaling pathways. We explain how known risk factors for kidney cancer rather represent risk factors for kidney injury as an upstream cause of cancer. Finally, we propose a new role for nephrologists in kidney cancer (i.e., the primary and secondary prevention and treatment of kidney injury to reduce incidence, prevalence, and recurrence of kidney cancer).

Kidney International (2021) **100,** 55–66; https://doi.org/10.1016/j.kint.2021.03.011

KEYWORDS: acute kidney injury; chronic kidney disease; kidney cancer; risk factor; surgery; survival

Correspondence: *Paola Romagnani, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Pieraccini 6, 50139 Firenze, Italy. E-mail: paola.romagnani@unifi.it*

Received 21 October 2020; revised 4 February 2021; accepted 17 February 2021; published online 29 March 2021

Cancerogenesis is a complex process involving germline and/or somatic mutations leading to an uncontrolled expansion of mutated cells. Frequently, this occurs in a series of steps in which numerous combinations of mutations only gradually pass the threshold for unrestricted cell growth.[1] Tissue injury is a known trigger of cancerogenesis for 2 reasons: (i) its potential to induce DNA damage and somatic mutations, especially in tissue-resident long-lived stem cells[2]; and (ii) its potential to promote the expansion of such mutated cells during the process of tissue repair.[3] For example, these 2 mechanisms contribute to inflammatory bowel disease–related colorectal cancer[4] and to lung cancer related to exposures to toxic smokes and dust particulates,[5] atrophic gastritis–related gastric cancer,[6] and cirrhosis-related hepatocellular carcinoma.[7]

Numerous epidemiologic studies report the association between chronic kidney disease (CKD) and kidney cancer (Table 1[8–15]). Although both occur preferably in the second half of life, it remains unclear whether and how these associations are linked by causation. For example, causation may be one way because tumor therapy, including surgery, and antiangiogenic agents or mechanistic target of rapamycin (mTOR) and immune checkpoint inhibitors involve an increased risk of acute kidney injury (AKI) and CKD.[16,17] Similarly, whether kidney injury causes kidney cancer is not clear at all, although some studies suggest that kidney cancer develops following an AKI episode or after years of CKD at the stage of kidney failure (Table 2[18–25]). In this review, we discuss the role of kidney injury as a driver of kidney cancer. Starting out with epidemiologic and genetic evidence, we discuss the evolving experimental support for kidney injury as a trigger of DNA damage and clonal proliferation of mutated kidney cells in different kidney compartments, determining the tumor histotype. We discuss the recent insights on the putative cells of origin for benign and malignant kidney tumors and explain how injury-mediated alterations in the activation of distinct signaling pathways contribute to the different histotypes of kidney tumors. We further explore how the intrinsic mechanisms of kidney repair that transiently operate on AKI episodes and that persistently operate in CKD promote tumor growth and tumor recurrence. Finally, we suggest that prevention of AKI and CKD is the best way to stop renal cell carcinoma (RCC) development and avoid its consequences. This concept of bidirectional causal

relationship between kidney disease and kidney tumors calls for a central role of the nephrologist in prevention and treatment of patients with kidney cancer.

The risk factors for kidney cancer are risk factors for kidney disease

Epidemiologic studies identify associations, but without confirming causation, such associations frequently trigger misleading interpretations. For example, in search for the unknown causes of kidney cancer, epidemiologic studies identified several "risk factors" for which a direct causative link to cancerogenesis is not always obvious (Table 3[26–43]). Obesity, diabetes, hypertension, smoking, nephrotoxic drugs, and heavy metals all promote kidney injury, either AKI or CKD, and may link indirectly to injury-related kidney cancer rates.[44–46] Indeed, nephrotoxic drugs and heavy metals induce episodes of toxic AKI associated with necroinflammation and oxidative stress.[45] Obesity, diabetes, and smoking are well-established risk factors for glomerular hyperfiltration and glomerulosclerosis-related CKD, imposing nephron loss and considerable adaptive cellular changes in the remnant nephrons to accommodate the metabolic needs.[46] Finally, hypertension, rather than a cause, is frequently a consequence of kidney disease and a sensitive indicator of early CKD.[44]

Site-specific kidney injuries cause unique subtypes of kidney cancer

Accumulating evidence suggests that the different subtypes of kidney tumors originate from cells located at the site of initial injury. In addition, the prevalence of different kidney cancer histotypes correlates with the prevalence of specific triggers of kidney injury.

Most frequent: clear cell carcinoma triggered by metabolic overload of the remnant nephron's proximal tubule in CKD (S1/S2 segment). Prospective studies suggest that CKD directly causes kidney cancer, particularly of the clear cell RCC (ccRCC) histotype that represents 70%–80% of kidney cancers. A follow-up study of 33,346 subjects, aged 26 to 61 years at baseline with a median follow-up of 28 years, showed that a moderate CKD at baseline increased the subsequent risk of kidney cancer.[19] Obesity and diabetes, which promote CKD, also drive RCC development. The link between these 2 conditions is represented by the metabolic overload of the cells of proximal tubule in remnant nephrons experiencing a drastically increased single-nephron hyperfiltration (and tubular hyperreabsorption).[47] This drives chronic cortical damage and CKD in patients with obesity and diabetes, with possible subsequent development of ccRCC, which typically originates from cells of the cortical proximal tubule (S1/S2 segment)[47] (Figure 1[25,44–46,48–57]).

Still frequent: papillary carcinoma triggered by ischemic necrosis of proximal tubules (S3 segment). Data obtained from Italian as well as Danish cohort studies indicate that patients with previous AKI episodes show an increased risk of developing papillary RCC (pRCC).[25] Further multicenter analysis showed that patients who underwent tumor resection for pRCC and experienced a postoperative AKI episode had a higher risk of tumor recurrence in comparison to those who did not experience a postoperative AKI, suggesting that ischemic injury promotes tumor growth.[25] This association was further confirmed in an experimental model of AKI, where the authors observed that postischemic AKI promotes long-term development of papillary tumors in mice by activating tumor growth–promoting pathways.[25] Direct evidence of the causative link between ischemic AKI and kidney cancer came from experiments showing onset of papillary adenomas 3 to 6 months after ischemia, which in some cases later transformed into pRCC in a classic adenoma-carcinoma sequence.[25] Papillary adenomas and carcinomas are mostly localized in the outer stripe of the outer medulla, where ischemic necrosis affects the cells of the S3 segment of proximal tubules[25] (Figure 1).

Table 1 | Epidemiological evidence that kidney cancer associates with kidney injury: increased risk for kidney disease in patients with kidney cancer

Exposure (risk factor or disease)	Outcome	Risk [95% CI]	Strength of evidence	Reference
Kidney cancer	CKD (stage ≥3)	21.4%	Crude prevalence at diagnosis	8
	AKI (+50% sCr)	IRR, 2.31 [2.05–2.60]	Multivariate analysis	9
	AKI (+50% sCr)	62.8% [57.6–67.5]	5-yr Cumulative incidence	9
	AKI-HA (severe)	13.9% [12.1–15.9]	5-yr Cumulative incidence	10
	AKI-D	1.7% [1.1–2.7]	5-yr Cumulative incidence	10
RCC	CKD (stage ≥3)	40.5%	3-yr Crude prevalence	11
	CKD (stage ≥4)	7.3%	32-mo Crude prevalence	12
	Rapid progressive CKD	2.1%	32-mo Crude prevalence	12
	ESKD	HR, 5.36 [4.37–7.24]	Multivariable analysis	13
	ESKD (men)	HR, 4.79 [3.37–6.82]	Multivariate analysis	13
	ESKD (women)	HR, 6.95 [4.82–10.1]	Multivariate analysis	13
	AKI-D or ESKD	CP, 2.0%	32-mo Crude prevalence	12
	Postoperative AKI	CP, 33.7%	Crude prevalence	14
RCC, RN vs. PN	CKD (stage ≥3)	HR, 1.9 [1.48–2.45]	Multivariate analysis	15
	ARF	HR, 1.41 [1.12–1.79]	Multivariate analysis	15

AKI, acute kidney injury; ARF, acute renal failure; CKD, chronic kidney disease; CI, cumulative incidence; CP, crude prevalence; ESKD, end-stage kidney disease; D, dialysis; HA, hospital acquired; HR, hazard ratio; IRR, incidence rate ratio; PN, partial nephrectomy; RCC, renal cell carcinoma; RN, radical nephrectomy.
Analysis of the literature highlights the link between increased risk for kidney disease in patients with kidney cancer and vice versa, as well as known risk factors for CKD and kidney cancer.

Table 2 | Epidemiological evidence that kidney cancer associates with kidney injury: increased risk for kidney cancer in patients with kidney disease

Exposure (risk factor or disease)	Outcome	Risk [95% CI]	Strength of evidence	Reference
CKD (stage ≥3)	Death for kidney cancer	HR, 3.30 [1.24–8.81]	Multivariate analysis	18
	Death for urinary tract cancer	HR, 7.30 [2.48–21.46]	Multivariate analysis	18
	Kidney cancer	HR, 3.38 [1.48–7.71]	Multivariate analysis	19
CKD (stage 3A)	RCC	HR, 1.39 [1.22–1.58]	Multivariate analysis	20
CKD (stage 3B)	RCC	HR, 1.81 [1.51–2.17]	Multivariate analysis	20
CKD (stage 4)	RCC	HR, 2.28 [1.78–2.92]	Multivariate analysis	20
ESKD: dialysis	Kidney cancer	3.6 [3.5–3.8]	Standardized incidence ratio	21
	Kidney cancer	6.8 [5.1–8.9]	10-yr Standardized incidence ratio	21
	RCC	4.2%	1-yr Crude prevalence	22
	Oncocytomas	0.6%	1-yr Crude prevalence	22
Transplant vs. ESKD	Kidney cancer	HR, 0.77 [0.70–0.84]	Multivariate analysis	23
Transplant	RCC	5.68 [5.27–6.13]	Standardized incidence ratio	24
	pRCC	13.3 [11.5–15.3]	Standardized incidence ratio	24
	ccRCC	3.98 [3.47–4.55]	Standardized incidence ratio	24
AKI	pRCC	OR, 3.48 [1.14–10.67]	Multivariate analysis	25
	ccRCC	OR, 1.55 [0.51–4.67]	Multivariate analysis	25
Postoperative AKI	pRCC recurrence	OR, 7.24 [1.65–31.86]	Multivariate analysis	25

AKI, acute kidney injury; ccRCC, clear cell renal cell carcinoma; CKD, chronic kidney disease; CI, cumulative incidence; ESKD, end-stage kidney disease; HR, hazard ratio; OR, odds ratio; RCC, renal cell carcinoma; pRCC, papillary renal cell carcinoma.
Analysis of the literature highlights the link between increased risk for kidney disease in patients with kidney cancer and vice versa, as well as known risk factors for CKD and kidney cancer.

Rare but specific: lithium is toxic to collecting ducts and causes collecting duct cell–derived tumors. Lithium therapy is associated with collecting duct toxicity, leading to nephrogenic diabetes insipidus in up to 40% of patients.[58] Studies indicate that lithium causes the loss of the molecular water channel aquaporin-2. Lithium also alters the Notch pathway, which is involved in many aspects of cancer biology[59] and has an important role in regulating the maintenance of mature renal epithelial cell states.[60] Long-term exposure to lithium leads to tubulointerstitial nephritis and renal cysts, originating from distal tubules and collecting ducts.[58] Although long-term use of lithium is not associated with increased cumulative risk of kidney cancer,[61] lithium-treated patients show a high risk of developing oncocytomas/chromophobe RCC (that arise from a common progenitor lesion[62] and are histologically and morphologically similar[63]) and collecting duct carcinomas[49] (Figure 1). All these tumors originate from the collecting duct and are reported as rare.[48,49,64] However, the Pharmacovigilance Risk Assessment Committee of the European Medicine Agency has agreed that the evidence is sufficient to conclude that long-term use of lithium may induce microcysts, oncocytomas, and collecting duct renal carcinomas (http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2015/01/WC500181043.pdf). Consistently, animals treated with lithium presented an increased proliferation of principal cells, as well as an increased number of intercalated cells, possibly resulting from proliferation and differentiation of progenitor cells or the conversion of principal cells into intercalated cells.[50] Thus, lithium therapy–related oncocytomas and carcinomas of the collecting duct represent another example of injury site–specific cancerogenesis in the kidney.

Rare but specific: sickle cell anemia induces ischemic medulla injury and medullary carcinoma. Sickle cell anemia (SCA) is a monogenic hemoglobin disease associated with repetitive episodes of organ hypoperfusion, tissue ischemia, and necrosis.[65] Sickle cell nephropathy is a serious complication of SCA with possible progression to CKD and kidney failure.[66,67] In a cross-sectional study of children with SCA, elevated blood pressure and CKD were identified in 16.7% and 8.3% of patients, respectively.[67] Ischemia during sickling episodes can irreversibly injure the vascular architecture of the kidney medulla,[52] sometimes followed by the development of medullary carcinoma,[52,53] an aggressive form of kidney cancer almost exclusively associated with SCA.[51] Indeed, the extreme conditions of hypoxia and hypertonicity of the renal medulla, combined with regional ischemia induced by red blood cell sickling, activate DNA repair mechanisms to drive deletions and translocations in switch/sucrose nonfermentable–related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (*SMARCB1*), a tumor suppressor gene, which is localized in a fragile region of chromosome 22[68] (Figure 1).

This association indicates causation from injury to cancer because cancer cannot cause SCA, hemoglobin mutations cannot directly cause medullary cancer, and SCA-related medullary cancer does not occur without kidney injury.[52,53] Therefore, in contrast to monogenic forms of kidney cancer that directly involve mutations in kidney cells, SCA-related kidney cancer provides a strong clue for the role of injury in kidney cancer, as the causative gene is absent inside kidney cells and solely accounts for kidney injury as an upstream event of kidney cancerogenesis. Also, the role of analgesics and other potential third factors is unlikely in this context, because the medullary location of injury and the cancer subtype argue against a toxic trigger but support the causative

Table 3 | Epidemiological evidence that kidney cancer associates with kidney injury: risk factors for kidney cancer

Exposure (risk factor or disease)	Outcome	Risk (95% CI)	Strength of evidence	Reference
Obesity				
Per 5-kg/m^2 BMI increase	Kidney cancer (men)	RR, 1.24 [1.15–1.34]	Meta-analysis	26
	Kidney cancer (women)	RR, 1.34 [1.25–1.42]	Meta-analysis	26
BMI + 1 SD	RCC	OR, 1.56 [1.44–1.70]	Multivariate analysis	27
25 kg/m^2 ≤ BMI < 30 kg/m^2	Kidney cancer	RR, 1.35 [1.27–1.43]	Meta-analysis	28
BMI ≥ 30 kg/m^2	Kidney cancer	RR, 1.76 [1.61–1.91]	Meta-analysis	28
BMI ≥ 35 kg/m^2	Kidney cancer	HR, 1.71 [1.06–2.79]	Multivariate analysis	29
	RCC (men)	RR, 2.47 [1.72–3.53]	Multivariate analysis	30
	RCC (women)	RR, 2.59 [1.70–3.96]	Multivariate analysis	30
Diabetes				
DM type 1–2	Kidney cancer	RR, 1.42 [1.06–1.91]	Meta-analysis	31
DM type 1–2	Kidney cancer (men)	RR, 1.26 [1.06–1.49]	Meta-analysis	31
DM type 1–2	Kidney cancer (women)	RR, 1.70 [1.47–1.97]	Meta-analysis	31
DM type 2	RCC	HR, 1.83 [1.26–2.65]	Multivariate analysis	29
Fasting insulin + 1 SD	RCC	OR, 1.82 [1.30–2.55]	Multivariate analysis	27
HTN				
History of HTN	Kidney cancer	RR, 1.67 [1.46–1.90]	Meta-analysis	32
History of HTN	Kidney cancer (men)	RR, 1.51 [1.16–1.97]	Meta-analysis	32
History of HTN	Kidney cancer (women)	RR, 1.77 [1.50–2.08]	Meta-analysis	32
Per +10–mm Hg SYS	Kidney cancer	RR, 1.10 [1.05–1.14]	Meta-analysis	32
Per +10–mm Hg DIA	Kidney cancer	RR, 1.22 [1.10–1.34]	Meta-analysis	32
BP ≥ 130/80 mm Hg	Kidney cancer	HR, 1.29 [1.23–1.35]	Multivariate analysis	33
HTN with medications	Kidney cancer	HR, 1.74 [1.64–1.84]	Multivariate analysis	33
SYS ≥ 160 mm Hg	RCC	RR, 2.48 [1.53–4.02]	Multivariate analysis	34
DIA ≥ 100 mm Hg	RCC	RR, 2.34 [1.54–3.55]	Multivariate analysis	34
DIA + 1 SD	RCC	OR, 1.28 [1.11–1.47]	Multivariate analysis	27
Drugs				
Analgesics	RCC	OR, 1.5 [1.3–1.8]	Multivariate analysis	35
Dose: 4–8 g/wk	RCC	OR, 1.6 [1.2–2.2]	Multivariate analysis	35
Dose ≥8 g/wk	RCC	OR, 2.3 [1.7–3.1]	Multivariate analysis	35
ACE-i	Kidney cancer	RR, 1.50 [1.01–2.23]	Meta-analysis	36
Diuretics	RCC	OR, 1.55 [1.42–1.71]	Meta-analysis	37
	RCC (men)	OR, 1.69 [1.34–2.13]	Meta-analysis	37
	RCC (women)	OR, 2.01 [1.56–2.67]	Meta-analysis	37
	pRCC	OR, 3.1 [1.4–6.7]	Multivariate analysis	38
Lithium	RCC (men)	7.51 [1.51–21.95]	Standardized incidence ratio	39
	RCC (women)	13.69 [3.68–35.06]	Standardized incidence ratio	39
Smoking				
All smokers	RCC	RR, 1.31 [1.22–1.40]	Meta-analysis	40
Current smokers	RCC	RR, 1.36 [1.19–1.56]	Meta-analysis	40
Former smokers	RCC	RR, 1.16 [1.08–1.25]	Meta-analysis	40
Smoke ≥37 pack years	Kidney cancer	HR, 1.67 [1.16–2.42]	Multivariate analysis	29
Heavy metals				
Lead	RCC	OR, 1.55 [1.09–2.21]	Multivariate analysis	41
Lead (>13.3 g/m^3 yr)	RCC	OR, 2.25 [1.21–4.19]	Multivariate analysis	41
Cadmium + lead	RCC	OR, 2.77 [1.00–7.68]	Multivariate analysis	41
Cadmium	Kidney cancer	OR, 1.47 [1.27–1.71]	Meta-analysis	42
	RCC	OR, 1.40 [0.69–2.85]	Multivariate analysis	41
Arsenic	RCC	OR, 2.47 [1.52–4.01]	Multivariate analysis	43

ACE-i, angiotensin-converting enzyme inhibitor; BMI, body mass index; BP, blood pressure; CI, cumulative incidence; DM, diabetes mellitus; DIA, diastolic blood pressure; HR, hazard ratio; HTN, hypertension; OR, odds ratio; RCC, renal cell carcinoma; pRCC, papillary renal cell carcinoma; RR, relative risk; SYS, systolic blood pressure.
Analysis of the literature highlights the link between increased risk for kidney disease in patients with kidney cancer and vice versa, as well as known risk factors for CKD and kidney cancer.

role of SCA-mediated ischemic injury in this location. Thus, SCA-related kidney cancer provides another proof of concept that kidney injury can be the trigger of kidney cancer.

Monogenic kidney cancers unravel essential signaling pathways in kidney cancerogenesis and kidney repair

Several monogenic forms of kidney cancer show that essential oncogenes and pathways involved in kidney cancerogenesis are also involved in the response to kidney injury and repair.[69]

Von Hippel-Lindau syndrome. Mutations in the *Von Hippel-Lindau* (*VHL*) tumor suppressor gene can cause an autosomal dominant cancer syndrome with visceral cysts in the kidney[70] and kidney cancer of the clear cell type (ccRCCs) in 24% to 45% of patients.[71] *Vice versa*, 90% of patients with sporadic ccRCC carry mutations leading to *VHL* inactivation.[72] VHL is a key regulator of proteins involved in oxygen sensing through the hypoxia-inducible factor (HIF) pathway. VHL mutations place affected cells in a state of

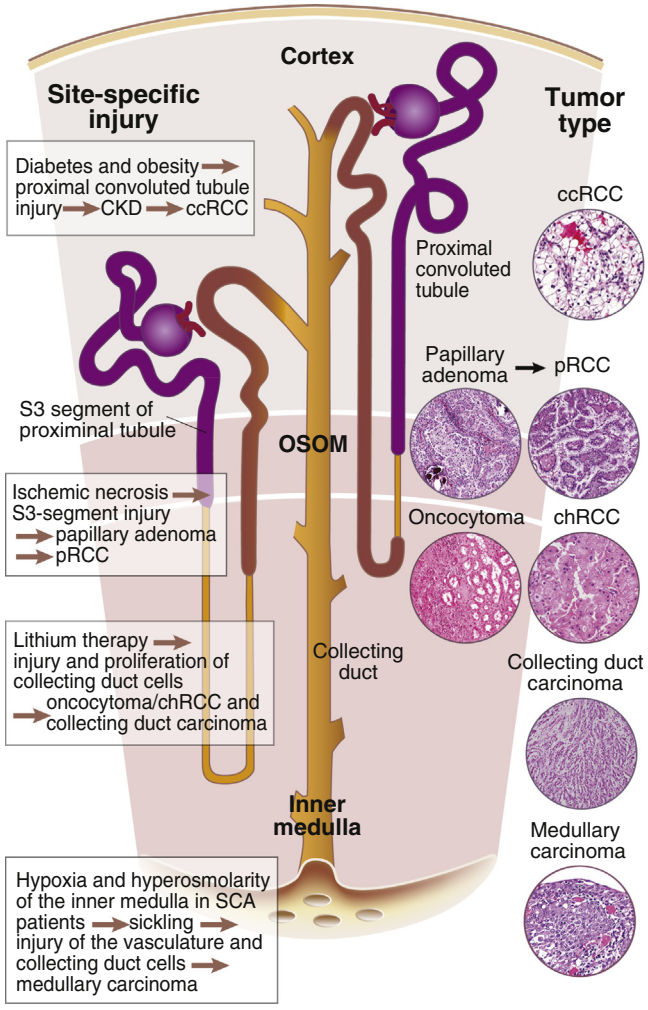

Figure 1 | Kidney injury causes benign tumor and cancer at the site of damage. Different kidney tumor histotypes develop at the site of damage in response to different injurious stimuli. Diabetes and obesity promote cortical injury through metabolic overload of proximal convoluted tubule in remnant nephrons. This drives chronic kidney disease (CKD) and subsequent development of clear cell renal cell carcinoma (ccRCC).[44–46] Ischemic necrosis affects cells of the S3 segment of the proximal tubule in the outer stripe of the outer medulla, driving the development of papillary adenomas followed by carcinomas.[25] Lithium therapy increases proliferation of cells in the collecting duct. This drives the development of oncocytomas/chromophobe and collecting duct carcinomas.[48–50] Hypoxia and hyperosmolarity of the inner medulla, along with ischemia induced by red blood cell sickling, injure the vascular architecture. This affects collecting duct cells, driving the development of medullary carcinoma.[51–54] chRCC, chromophobe renal cell carcinoma; pRCC, papillary renal cell carcinoma; OSOM, outer stripe of outer medulla; SCA, sickle cell anemia. ccRCC image adapted with permission by Bonert M. 2011. Available at: https://commons.wikimedia.org/wiki/User:Nephron. Accessed October 15, 2020.[55] Copyright © 2011 Michael Bonert. Creative Commons Attribution International License (CC BY-SA 3.0), https://creativecommons.org/licenses/by-sa/3.0/legalcode. Papillary adenoma image adapted with permission by Bonert M. 2011. Available at: https://commons.wikimedia.org/wiki/User:Nephron. Accessed October 15, 2020.[55] Copyright © 2011 Michael Bonert. Creative Commons Attribution International License (CC BY-SA 3.0), https://creativecommons.org/licenses/by-sa/3.0/legalcode. pRCC image adapted with permission by Busset C, Vijgen S, Lhermitte B, Pu Y. A case report of papillary renal (continued)

pseudohypoxia, promoting a unique angiogenic state and continuous mitogenic signaling.[71] Interestingly, VHL mutations are highly prevalent in acquired cystic kidney disease and in ccRCCs of patients in end-stage kidney disease, suggesting that kidney injury may exert a selection pressure for cells carrying the VHL mutations and HIF activation.[73] In addition, the metabolic stress in remnant nephrons of CKD kidneys translates into pseudohypoxia at the cellular level that permanently triggers HIF activation, which drives a chronic mitogenic response to replace tubular epithelial cells succumbing to metabolic stress.[74] These observations could provide the rationale behind the association between ccRCC and precedent CKD and explain why ccRCC derives from the proximal convoluted tubule, where metabolic overload primarily occurs. Moreover, this could explain why ccRCC, being related to CKD that is highly prevalent in the population, is the most frequent kidney cancer. Finally, hypoxia is the major trigger of AKI, and the HIF pathway is strongly activated following AKI episodes to drive the mitogenic response needed to replace necrotic tubular epithelial cells.[75]

Autosomal dominant polycystic kidney disease. Mutations in polycystic kidney disease (PKD) 1 (encoding polycystin-1) or PKD2 (encoding polycystin-2)[76] cause progressively enlarging multiple bilateral renal cysts, which lead to kidney failure in 50% of autosomal dominant polycystic kidney disease (ADPKD) patients by the age of 60 years.[76] Cystic and solid kidney tumors share many similarities in terms of uncontrolled hyperplasia of renal epithelial cells[77] because of many biological similarities between ADPKD and cancer. Available data for cancer incidence in patients with ADPKD on dialysis,[78] or after transplantation,[22,79] showed an increased risk of kidney neoplasms when compared with the general population, but not to other patients on renal replacement therapy without ADPKD.[80] More recently, in a

Figure 1 | (continued) cell carcinoma seeding along a percutaneous biopsy tract. *Open J Pathol.* 2018;8:139–146.[56] Copyright © 2018 by authors and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0), http://creativecommons.org/licenses/by/4.0. Oncocytoma image adapted with permission by Bonert M. 2011. Available at: https://commons.wikimedia.org/wiki/User:Nephron. Accessed October 15, 2020.[55] Copyright © 2011 Michael Bonert. Creative Commons Attribution International License (CC BY-SA 3.0), https://creativecommons.org/licenses/by-sa/3.0/legalcode. chRCC image adapted with permission by Uthman E. Chromophobe renal cell carcinoma from a slide study set. Available at: https://www.flickr.com/photos/euthman/4669534681/. Accessed October 15, 2020.[57] Copyright © Ed Uthman. Creative Commons Attribution International License (CC BY 2.0), https://creativecommons.org/licenses/by/2.0/. Image of collecting duct carcinoma adapted with permission by George J. Netto. Copyright © 2016 George J. Netto. Creative Commons Attribution International License (CC BY-SA 4.0), https://creativecommons.org/licenses/by/4.0/. Image of renal medullary carcinoma adapted with permission by Bonert M. 2011. Available at: https://commons.wikimedia.org/wiki/User:Nephron. Accessed October 15, 2020.[55] Copyright © 2011 Michael Bonert. Creative Commons Attribution International License (CC BY-SA 3.0), https://creativecommons.org/licenses/by-sa/3.0/legalcode.

large cohort study conducted in Taiwan, Yu *et al.* reported an increased susceptibility to kidney cancer in patients with ADPKD before receiving renal replacement therapy, when compared with patients without the disease but with a similar (or no) degree of renal impairment,[81] even after adjustment for all potentially confounding factors. This supports the hypothesis that the typical renal cystic changes in patients with ADPKD, and particularly cluster-like papillary hyperplasia, may represent precancerous lesions that can evolve in RCC, usually of the papillary histotype.[82,83] Another possible explanation is overactivation in cyst-lining epithelial cells[84] of pathways involved in kidney injury[85,86] as well as in the pathogenesis of kidney cancer (i.e., aberrant activation of Notch and HIF-1a).[87,88]

Tuberous sclerosis complex. Tuberous sclerosis complex (TSC) is an autosomal dominant disease[89] due to germline inactivating mutations of either of *TSC1* (encoding hamartin) or *TSC2* (encoding tuberin) genes, forming a complex that negatively regulates mTOR complex 1, a master regulator of cell proliferation and differentiation.[90] Manifestations include multifocal angiomyolipomas, epithelial cysts, and RCC in up to 5% of patients, including ccRCC,[90] pRCC,[90] chromophobe RCC,[91] and neuroendocrine tumors.[89] Second hits can be identified in the remaining allele of *TSC1* or *TSC2* in most sporadic angiomyolipomas[92] and TSC-related RCCs.[93] Mutations in *TSC2* were observed in 60% of acquired cystic kidney disease patients,[94] suggesting a role in the development of sporadic cysts/RCC. A strong association between age, angiomyolipoma size, and CKD has been reported; patients with worse CKD stage tend to be older and have more advanced angiomyolipoma.[95] CKD can develop as a consequence of surgical removal of renal parenchyma because of growth of angiomyolipoma or cysts, or acute hemorrhage from angiomyolipomas and/or RCCs.[96,97] The fact that mTOR overactivation is responsible for renal lesions in TSC patients is demonstrated by efficacy of treatment with mTOR inhibitors.[90,98] In addition, mTOR inhibitors improve glomerular hypertrophy and hyperfiltration in patients with diabetes-related CKD, suggesting that this pathway plays a crucial role in kidney injury and repair.[87,99]

Hereditary pRCC. Hereditary papillary renal cancers are observed in different rare genetic syndromes.[72,100] In particular, hereditary pRCC of type 1 is associated with frequent gains of chromosome 7 involving activating mutations of MET.[72] Likewise, somatic or germline mutations or other genetic alterations involving the MET gene are observed in 81.3% of type 1 pRCCs.[101] MET gene codes for a tyrosine kinase receptor that binds hepatocyte growth factor that protects against tubular cell death[102] and is involved in AKI.

Kidney injury drives cancerogenesis from long-lived progenitor cells that proliferate during kidney repair

A growing body of evidence suggests that putative renal progenitors represent a crucial link between many types of kidney cancer,[103–105] AKI,[25] and CKD.[106–109] Renal progenitors are immature precursors of epithelial cells localized in the glomerulus and in all segments of the nephron and in the collecting duct.[108–115] In contrast to the highly proliferative phenotype of tissue-resident progenitors in high turnover organs, such as the skin or gut, renal progenitors are mostly quiescent and show a limited spontaneous proliferative capacity to replace physiological losses of podocytes and tubular epithelial cells.[108,109,111] The traditional view of kidney repair suggests that most tubular epithelial cells are capable of proliferation, undergoing dedifferentiation on injury.[116,117] However, more recent data propose that rather a preexisting population of putative renal progenitors undergo clonal proliferation to replace differentiated epithelial cells lost by detachment (e.g., podocytes) or necrosis (e.g., tubular epithelial cells).[109,111,118,119]

In 2011, Lindgren *et al.* demonstrated a significant similarity at transcriptional and protein levels between renal progenitors and pRCCs as well as papillary adenomas.[112] A further study showed that the vascular cell adhesion molecule-1–positive subset of renal progenitors is endowed with high resistance to death, proliferative capacity, and multipotent differentiation capacity.[108] In 2017, Cho *et al.* and Goncalves *et al.* suggested the origin of angiomyolipomas from multipotent kidney epithelial cells localized inside the tubule undergoing clonal expansion in response to *TSC* gene deletion.[103,104] Both studies proposed these cells could be renal progenitors[103,104] that are endowed with multilineage differentiation capacity[113] and that in certain conditions generate the multiple lineages coexisting in sporadic angiomyolipomas and angiomyolipomas associated with TSC[103,104] (Figure 2[25,103–105,112]). In 2018, Young *et al.* used single-cell RNA sequencing technology to identify the cell of origin of ccRCC and pRCC.[105] They identified the cluster proximal tubule 1, composed of a specific subtype of scattered vascular cell adhesion molecule-1–positive cells in convoluted proximal tubule that matched the canonical cancer transcriptome of pRCC and ccRCC.[105] A recent reanalysis of the Young *et al.* The single-cell RNA sequencing database showed that proximal tubule 1 shared similarities with human renal progenitor cells[25] (Figure 2). Finally, by using a lineage tracing approach based on the Confetti reporter,[25] Peired *et al.* directly proved that pRCC is derived by clonal expansion of renal progenitors through an adenoma-carcinoma sequence in response to AKI.[25] Renal progenitors represent a population endowed with a high proliferative capacity and resistance to death and form clones that generate whole tubule segments after AKI.[111] Overactivation of the Notch1 pathway, which is crucially involved in the response to AKI by promoting renal progenitor proliferation,[120] can also reproduce papillary adenomas and pRCC formation in transgenic animal models[25] (Figure 2). In the collecting ducts, renal progenitors were proposed as the cell of origin of collecting duct–derived oncocytoma and carcinoma RCC.[50,62] Why can renal progenitors originate multiple kidney tumors? and How is this linked to the kidney repair process?

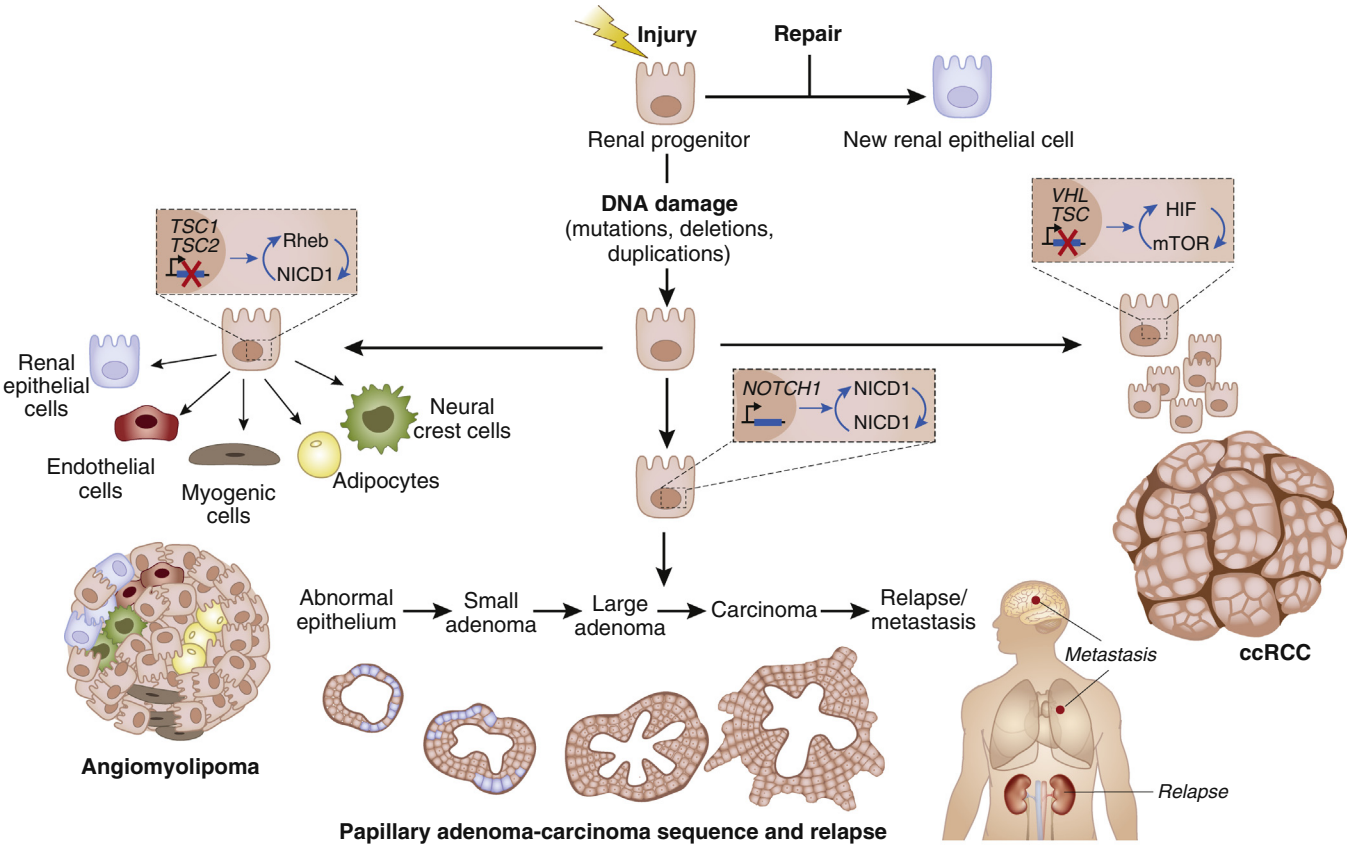

Figure 2 | Mechanistic insights in the development of different types of kidney tumors. DNA damage and mutations in renal progenitors during their clonal expansion on injury induces transformation of renal progenitors into a tumor-initiating cell. Hyperactivation or deletion of different signaling pathways related to the repair response promotes the development of different kidney tumors.[25,103–105,112] ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; mTOR, mechanistic target of rapamycin; NICD1, Notch1 intracellular domain; Rheb, Ras homolog enriched in brain; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau.

Several studies have established a direct link between resident stem cells and the pathogenesis of cancer in many organs of the body.[1–3] Pivotal examples are those of the skin, or of the gut, where accumulation of DNA damage and mutations in the resident stem cell initiate the oncogenic process.[1–3] Key to the process is that resident stem cells are long-lived cells that are highly resistant to death and undergo multiple cycles of cell division during life to deal with the organ turnover or the response to injury.[2] This favors accumulation of DNA damage without cell clearance, promoting cancerogenesis.[1] Emerging evidence suggests similar phenomena occur also in the kidney. Similar to resident stem cells of other organs, renal progenitors are long-lived cells[100,111] with high resistance to death[108,111,121] that undergo a slow turnover during kidney lifespan[109,111] and clonally amplify, undergoing numerous divisions in response to injury.[122] Analysis of somatic mutations[123] in the subset of renal progenitors matching the proximal tubule 1 phenotype found by Young *et al.*[105] revealed an enrichment in active chromatin, regulatory, and transcribed regions, which increased gradually over the years, leading to an enhanced risk of tumoral transformation.[123] Ischemic injury, exposure to nephrotoxic agents, such as chemotherapeutics, is associated with single-stranded breaks, double-stranded breaks, covalently bound chemical DNA adducts, oxidative-induced lesions, and DNA-DNA or DNA-protein cross-links.[124] Activation of tissue injury–related pathways that push fast proliferation can provide a second hit to the progenitors, favoring the accumulation of further DNA damage and faster carcinogenesis.[125]

Kidney cancer development following injury is induced through activation of specific pathways

Each type of injury, occurring in distinct locations, preferentially activates a different pathway involved in tissue injury and repair. Consistently, many recent studies suggest that the mechanisms leading to the transformation of renal progenitors into a tumor-initiating cell are also linked to activation of signaling pathways,[25] such as HIF, Notch, mTOR, and Hippo (Figure 2). Evidence of this interconnection comes not only from monogenic syndromes, but also from shared risk factors as well as from animal models.

VHL-HIF pathway. The hypoxia response through the HIF pathway plays an important role in kidney injury and repair in patients affected by AKI and CKD[75] and ccRCC.[126]

Similarly, in hypertensive patients, hypoxia and HIF pathway, resulting from the constriction of blood vessels due to the renin-angiotensin system, prostaglandins, and endothelin,[127,128] is a possible mechanism leading to kidney cancer and CKD. In animal models, continuous transgenic expression of HIF-2α in tubular cells leads to renal fibrosis and insufficiency, next to multiple renal cysts.[129] Transgenic mice with renal epithelial-specific *VHL* deletion failed to develop ccRCC, suggesting that second-hit loss-of-function mutations were needed.[130] Models combining *VHL* deletion with *PTEN*, *KIF3a*, *TRP53*, or *BAP1* loss, or with activation of the intracellular part of Notch1, caused the formation of simple and atypical cystic lesions, nests of dysplastic cells with a clear cytoplasm, or even small tumors, mimicking ccRCC precursor lesions[130] (Figure 2). Ultimately, the deletion of *VHL* together with *TRP53* and *RB1* led to the formation of lesions highly similar to human ccRCC.[130] Interestingly, all pathways activated by Pten, Kif3a, Trp53, Bap1, Rb1, and Notch1 are involved in the process of kidney repair from injury, underlining the interconnection between kidney disease and kidney cancer and suggesting that the second hit may often come from kidney injury.[25] As further evidence, adult mice with kidney-specific inactivation of *KIF3a* developed cysts rapidly, in a similar way than in *VHL KIF3a* double-knockout mouse,[131] only when subjected to an AKI episode.[132]

mTOR pathway. In diabetes mellitus, protein kinase B/mTOR pathway, together with hyperglycemia- and hyperinsulinemia-prompted activation of molecular pathways, contributes to the development of RCC and diabetic kidney disease.[133,134] Mutation of phosphoinositide 3-kinase–protein kinase B–mTOR pathway genes (including *PTEN*, *MTOR*, and *PIK3CA*) were frequently reported in RCC.[135] In addition, mutations in *TSC1/TSC2* result in activation of mTOR signaling through the Ras homolog enriched in brain (RHEB)–Notch-RHEB regulatory loop,[90,103,104] leading to angiomyolipoma development (Figure 2).

Notch pathway. Aberrant Notch signaling can cause several pathologies, including cancer, in a variety of organs, through preservation of self-renewal and amplification of cancer stem cells.[136] Activation of the Notch pathway plays a major role in kidney injury and repair[120] but can also induce malignant transformation of renal progenitors and development of papillary adenomas and RCC in humans and mice[25] (Figure 2). Experiments conducted in transgenic mice overexpressing Notch1 intracellular domain in tubular cells showed development of CKD as well as pRCC and acceleration of cancerogenesis induced by AKI episodes, further confirming the tight link between AKI, CKD, and pRCC.[25] Notch has an important role in control of polarity and orientation of the mitotic spindle in several cell types.[25,137–139] Indeed, aberrant Notch activation disrupted cell polarity signaling, leading to a notable number of abnormal mitoses in renal progenitors, through the deregulation of pathways involved in cell cycle checkpoints and/or mitotic spindle control.[25]

Hippo pathway. A deregulated Hippo pathway (yes-associated protein 1/transcriptional coactivator with PDZ-binding motif [YAP/TAZ] downstream target) is seen in several forms of cystic kidney disease,[140,141] in response to AKI,[142] and in several sporadic cancers, suggesting this pathway can also be a link between cell proliferation in cyst formation and RCC.[143,144] Downregulation of Salvador homolog-1 (SAV1), a component of the Hippo pathway, due to copy number loss is involved in the pathogenesis of high-grade ccRCC by regulating the proliferation of RCC cells through Hippo-YAP1 signaling.[145] In addition, loss of chromosome 22, which contains the tumor suppressor genes *NF2* (encoding a Hippo pathway regulator, SAV1)[72] and *SMARCB1* (encoding a protein of the chromatin-modifying switch/sucrose nonfermentable complex), is associated with sporadic pRCC.[146] Finally, The Cancer Genome Atlas analysis of pRCC revealed a high number of mutations in both type 1 and type 2 tumors involving Hippo signaling pathway (2.8% and 10.0%, respectively).[72] Targeted deletion of SAV1 in tubular epithelial cells causes YAP1 nuclear translocation, indicative of inactive Hippo pathway.[147] Moreover, SAV1-knockout ($SAV1^{fl/fl}$) mice demonstrated morphologic abnormalities in the renal tubules, such as large irregular nuclei, augmented cellularity, a multilayered epithelium, and the formation of renal cysts.[147]

c-Met–hepatocyte growth factor pathway. Iron overload has been associated with carcinogenesis in humans.[41] In mice, repeated iron administration causes the intracellular release of reactive oxygen species (i.e., a Fenton reaction) in renal proximal tubules, which ultimately leads to a high incidence of RCC.[148] The animals presented extensive genomic alterations, and 2 of the most commonly altered loci corresponded to a *MET* amplification and a *CDKN2a/2b* deletion.[148] Interestingly, tumor sizes were proportionally associated with Met expression and/or amplification, as confirmed by clustering analysis.[148]

Chromatin remodeling. Aberrations in chromatin remodeling proteins are associated with human diseases, including cancer.[149,150] Chromatin remodeling pathways are activated after DNA damage, response to injury, and response to carcinogens, including smoking.[124] In ccRCC, the pathways involved are chromosome arm 3p genes polybromo 1 (*PBRM1*), SET domain-containing protein 2 (*SETD2*), and BRCA-associated protein-1 (*BAP1*) or in *SMARCB1*.[151,152] Loss of *CDKN2A* owing to mutation, deletion, or promoter hypermethylation and mutation of TP53 were also frequently reported in ccRCC.[72,152]

A call for a new role for nephrologists in kidney cancer care

Injury involving DNA damage is a known driver of malignant transformation of proliferating cells.[3] This concept derives from irradiation-related leukemia and translates into solid tumors arising from long-lived tissue-resident progenitor/stem cells.[2] Increasing evidence now demonstrates the same for the non-Mendelian forms of kidney cancer.[153] Sickle cell disease–related kidney cancer is a paradigmatic example of how repetitive ischemic kidney injury can cause kidney cancer in the injured area of the kidney.[52–54] Epidemiologic and experimental studies now demonstrate the same for a wider

range of kidney cancers, and suggest a putative premalignant condition, just about the time new strategies for kidney cancer screening are debated.[154] But why do we observe a relatively low RCC prevalence despite the high prevalence of CKD/AKI patients? First, benign/early forms of kidney tumors go frequently undetected as they appear in older patients and take time to develop into malignant forms. As a significant example, autopsy studies suggest that papillary adenomas are common, with a prevalence ranging from 5% to 10% before the age of 40 years and increasing to almost 40% above the age of 70 years.[155] In addition, transition from benign to malignant tumors represents a multihit process that requires further environmental or genetic factors besides CKD/AKI to fully develop.[25] Finally, AKI and CKD patients have shorter life expectancy,[156] particularly when associated with obesity and diabetes. Treatment of CKD with renin-angiotensin system blockers not only delays CKD progression, but also lowers the incidence of RCC,[157] providing the proof of concept that treatment of kidney injury may be an efficient approach to prevent development of kidney tumors.

Currently, the involvement of nephrologists in the management of patients with kidney cancer is often limited to treatment of CKD after surgery and, once needed, kidney replacement therapy. However, the injury concept of kidney cancer implies new opportunities for nephrologists to prevent kidney cancer and to improve outcomes of patients with kidney cancer.

- Together with primary care physicians, nephrologists may increase awareness for kidney disease in the community, ameliorate blood pressure control, promote healthy lifestyle education, and facilitate avoidance or correct use of nephrotoxic medications (primary prevention).
- Nephrologists may participate in the identification of those patients at risk who will benefit the most from targeted kidney cancer screening programs.
- Nephrologists can contribute to limit kidney injury and, once it occurs, provide straightforward treatment (e.g., by identifying the causative drug and stopping exposure in acute toxic injury or detecting and treating subacute and chronic kidney injury as early as possible). This may require to first increase awareness in decision makers, to ensure referral of patients to nephrologists as early as at the stage of urinary abnormalities and not only once CKD stage 3 or 4 has been reached, which is far too late to limit the impact of kidney injury on cancerogenesis.
- Nephrologists may take a central role in secondary prevention of kidney injury to limit tumor growth by providing an optimized CKD care, by reducing CKD risk factors, by limiting metabolic stress to remnant nephrons, and eventually by considering tumor screening with periodical ultrasound examinations in patients at greater risk.
- Nephrologists could work hand in hand with urologists and oncologists to reduce the impact of surgical and medical treatment on kidney injury, thereby reducing the risk of tumor recurrence.

"From kidney injury to kidney cancer" as a novel concept may define kidney cancer as a new long-term outcome of AKI and CKD, increase more attention on preventing kidney injury in patients with kidney cancer, and create a new role for nephrologists in the management of patients with kidney cancer.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This project has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement 648274) and by the Associazione Italiana per la Ricerca sul Cancro and Fondazione CR Firenze under IG 2018—ID.21821 project—to PR. H-JA was supported by the Deutsche Forschungsgemeinschaft (AN372/23-1, 24-1, and 27-1). AJP is a recipient of the Fondazione Umberto Veronesi fellowship.

REFERENCES

1. Kiwerska K, Szyfter K. DNA repair in cancer initiation, progression, and therapy-a double-edged sword. *J Appl Genet*. 2019;60:329–334.
2. Tomasetti C, Vogelstein B. Cancer etiology: variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*. 2015;347:78–81.
3. Basu AK. DNA damage, mutagenesis and cancer. *Int J Mol Sci*. 2018;19:970.
4. Greuter T, Vavricka S, König AO, et al. Malignancies in inflammatory bowel disease. *Digestion*. 2020;101(suppl 1):136–145.
5. Lipfert FW, Wyzga RE. Longitudinal relationships between lung cancer mortality rates, smoking, and ambient air quality: a comprehensive review and analysis. *Crit Rev Toxicol*. 2019;49:790–818.
6. Vannella L, Lahner E, Osborn J, et al. Systematic review: gastric cancer incidence in pernicious anaemia. *Aliment Pharmacol Ther*. 2013;37:375–382.
7. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. *Hepatology*. 2006;43:1303–1310.
8. Na SY, Sung JY, Chang JH, et al. Chronic kidney disease in cancer patients: an independent predictor of cancer-specific mortality. *Am J Nephrol*. 2011;33:121–130.
9. Christiansen CF, Johansen MB, Langeberg WJ, et al. Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. *Eur J Intern Med*. 2011;22:399–406.
10. Kitchlu A, McArthur E, Amir E, et al. Acute kidney injury in patients receiving systemic treatment for cancer: a population-based cohort study. *J Natl Cancer Inst*. 2019;111:727–736.
11. Kim WH, Shin KW, Ji SH, et al. Robust association between acute kidney injury after radical nephrectomy and long-term renal function. *J Clin Med*. 2020;9:619.
12. Klarenbach S, Moore RB, Chapman DW, et al. Adverse renal outcomes in subjects undergoing nephrectomy for renal tumors: a population-based analysis. *Eur Urol*. 2011;59:333–339.
13. Hung PH, Tsai HB, Hung KY, et al. Increased risk of end-stage renal disease in patients with renal cell carcinoma: a 12-year nationwide follow-up study. *Medicine (Baltimore)*. 2014;93:e52.
14. Cho A, Lee JE, Kwon GY, et al. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol Dial Transplant*. 2011;26:3496–3501.
15. Sun M, Bianchi M, Hansen J, et al. Chronic kidney disease after nephrectomy in patients with small renal masses: a retrospective observational analysis. *Eur Urol*. 2012;62:696–703.
16. Erman M, Benekli M, Basaran M, et al. Renal cell cancer: overview of the current therapeutic landscape. *Expert Rev Anticancer Ther*. 2016;16:955–968.

17. Porta C, Cosmai L, Leibovich BC, et al. The adjuvant treatment of kidney cancer: a multidisciplinary outlook. *Nat Rev Nephrol*. 2019;15:423–433.
18. Weng PH, Hung KY, Huang HL, et al. Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort. *Clin J Am Soc Nephrol*. 2011;6:1121–1128.
19. Christensson A, Savage C, Sjoberg DD, et al. Association of cancer with moderately impaired renal function at baseline in a large, representative, population-based cohort followed for up to 30 years. *Int J Cancer*. 2013;133:1452–1458.
20. Lowrance WT, Ordonez J, Udaltsova N, et al. CKD and the risk of incident cancer. *J Am Soc Nephrol*. 2014;25:2327–2334.
21. Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol*. 2003;14:197–207.
22. Denton MD, Magee CC, Ovuworie C, et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. *Kidney Int*. 2002;61:2201–2209.
23. Yanik EL, Clarke CA, Snyder JJ, et al. Variation in cancer incidence among patients with ESRD during kidney function and nonfunction intervals. *J Am Soc Nephrol*. 2016;27:1495–1504.
24. Karami S, Yanik EL, Moore LE, et al. Risk of renal cell carcinoma among kidney transplant recipients in the United States. *Am J Transplant*. 2016;16:3479–3489.
25. Peired AJ, Antonelli G, Angelotti ML, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. *Sci Transl Med*. 2020;12:eaaw6003.
26. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371:569–578.
27. Johansson M, Carreras-Torres R, Scelo G, et al. The influence of obesity-related factors in the etiology of renal cell carcinoma-a mendelian randomization study. *PLoS Med*. 2019;16:e1002724.
28. Liu X, Sun Q, Hou H, et al. The association between BMI and kidney cancer risk: an updated dose-response meta-analysis in accordance with PRISMA guideline. *Medicine (Baltimore)*. 2018;97:e12860.
29. Macleod LC, Hotaling JM, Wright JL, et al. Risk factors for renal cell carcinoma in the VITAL study. *J Urol*. 2013;190:1657–1661.
30. Adams KF, Leitzmann MF, Albanes D, et al. Body size and renal cell cancer incidence in a large US cohort study. *Am J Epidemiol*. 2008;168:268–277.
31. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia*. 2011;54:1013–1018.
32. Hidayat K, Du X, Zou SY, et al. Blood pressure and kidney cancer risk: meta-analysis of prospective studies. *J Hypertens*. 2017;35:1333–1344.
33. Kim CS, Han KD, Choi HS, et al. Association of hypertension and blood pressure with kidney cancer risk: a nationwide population-based cohort study. *Hypertension*. 2020;75:1439–1446.
34. Weikert S, Boeing H, Pischon T, et al. Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Am J Epidemiol*. 2008;167:438–446.
35. Gago-Dominguez M, Yuan JM, Castelao JE, et al. Regular use of analgesics is a risk factor for renal cell carcinoma. *Br J Cancer*. 1999;81:542–548.
36. Yoon C, Yang HS, Jeon I, et al. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and cancer risk: a meta-analysis of observational studies. *CMAJ*. 2011;183:E1073–E1084.
37. Grossman E, Messerli FH, Goldbourt U. Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol*. 1999;83:1090–1093.
38. Colt JS, Hofmann JN, Schwartz K, et al. Antihypertensive medication use and risk of renal cell carcinoma. *Cancer Causes Control*. 2017;28:289–297.
39. Zaidan M, Stucker F, Stengel B, et al. Increased risk of solid renal tumors in lithium-treated patients. *Kidney Int*. 2014;86:184–190.
40. Cumberbatch MG, Rota M, Catto JW, et al. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. *Eur Urol*. 2016;70:458–466.
41. Boffetta P, Fontana L, Stewart P, et al. Occupational exposure to arsenic, cadmium, chromium, lead and nickel, and renal cell carcinoma: a case-control study from Central and Eastern Europe. *Occup Environ Med*. 2011;68:723–728.
42. Song J, Luo H, Yin X, et al. Association between cadmium exposure and renal cancer risk: a meta-analysis of observational studies. *Sci Rep*. 2015;5:17976.
43. Mostafa MG, Cherry N. Arsenic in drinking water and renal cancers in rural Bangladesh. *Occup Environ Med*. 2013;70:768–773.
44. Carriazo S, Vanessa Perez-Gomez M, Ortiz A. Hypertensive nephropathy: a major roadblock hindering the advance of precision nephrology. *Clin Kidney J*. 2020;13:504–509.
45. Mulay SR, Linkermann A, Anders HJ. Necroinflammation in kidney disease. *J Am Soc Nephrol*. 2016;27:27–39.
46. Romagnani P, Remuzzi G, Glassock R, et al. Chronic kidney disease. *Nat Rev Dis Primers*. 2017;3:17088.
47. Polascik TJ, Bostwick DG, Cairns P. Molecular genetics and histopathologic features of adult distal nephron tumors. *Urology*. 2002;60:941–946.
48. Ambrosiani L, Pisanu C, Deidda A, et al. Thyroid and renal tumors in patients treated with long-term lithium: case series from a lithium clinic, review of the literature and international pharmacovigilance reports. *Int J Bipolar Disord*. 2018;6:17.
49. Rookmaaker MB, van Gerven HA, Goldschmeding R, et al. Solid renal tumours of collecting duct origin in patients on chronic lithium therapy. *Clin Kidney J*. 2012;5:412–415.
50. Christensen BM, Kim YH, Kwon TH, et al. Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. *Am J Physiol Renal Physiol*. 2006;291:F39–F48.
51. Davis CJ Jr, Mostofi FK, Sesterhenn IA. Renal medullary carcinoma: the seventh sickle cell nephropathy. *Am J Surg Pathol*. 1995;19:1–11.
52. Naik RP, Derebail VK. The spectrum of sickle hemoglobin-related nephropathy: from sickle cell disease to sickle trait. *Expert Rev Hematol*. 2017;10:1087–1094.
53. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. *Nat Rev Nephrol*. 2015;11:161–171.
54. Nnaji UM, Ogoke CC, Okafor HU, et al. Sickle cell nephropathy and associated factors among asymptomatic children with sickle cell anaemia. *Int J Pediatr*. 2020;2020:1286432.
55. Images of histopathology by Bonert, M. 2011. Available at: https://commons.wikimedia.org/wiki/User:Nephron. Accessed October 15, 2020.
56. Busset C, Vijgen S, Lhermitte B, Pu Y. A case report of papillary renal cell carcinoma seeding along a percutaneous biopsy tract. *Open J Pathol*. 2018;8:139–146.
57. Uthman E. Chromophobe renal cell carcinoma from a slide study set. Available at: https://www.flickr.com/photos/euthman/4669534681/. Accessed October 15, 2020.
58. Grunfeld JP, Rossier BC. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*. 2009;5:270–276.
59. Majumder S, Crabtree JS, Golde TE, et al. Targeting Notch in oncology: the path forward. *Nat Rev Drug Discov*. 2021;20:125–144.
60. Mukherjee M, deRiso J, Otterpohl K, et al. Endogenous Notch signaling in adult kidneys maintains segment-specific epithelial cell types of the distal tubules and collecting ducts to ensure water homeostasis. *J Am Soc Nephrol*. 2019;30:110–126.
61. Pottegard A, Hallas J, Jensen BL, et al. Long-term lithium use and risk of renal and upper urinary tract cancers. *J Am Soc Nephrol*. 2016;27:249–255.
62. Tickoo SK, Reuter VE, Amin MB, et al. Renal oncocytosis: a morphologic study of fourteen cases. *Am J Surg Pathol*. 1999;23:1094–1101.
63. Brennan K, Metzner TJ, Kao CS, et al. Development of a DNA methylation-based diagnostic signature to distinguish benign oncocytoma from renal cell carcinoma. *JCO Precis Oncol*. 2020;4. PO.20.00015.
64. Lindgren D, Eriksson P, Krawczyk K, et al. Cell-type-specific gene programs of the normal human nephron define kidney cancer subtypes. *Cell Rep*. 2017;20:1476–1489.
65. Taylor SM, Parobek CM, Fairhurst RM. Haemoglobinopathies and the clinical epidemiology of malaria: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12:457–468.
66. Naik RP, Irvin MR, Judd S, et al. Sickle cell trait and the risk of ESRD in Blacks. *J Am Soc Nephrol*. 2017;28:2180–2187.
67. Bodas P, Huang A, O'Riordan MA, et al. The prevalence of hypertension and abnormal kidney function in children with sickle cell disease -a cross sectional review. *BMC Nephrol*. 2013;14:237.

68. Msaouel P, Tannir NM, Walker CL. A model linking sickle cell hemoglobinopathies and SMARCB1 loss in renal medullary carcinoma. *Clin Cancer Res*. 2018;24:2044–2049.
69. Perazella MA, Dreicer R, Rosner MH. Renal cell carcinoma for the nephrologist. *Kidney Int*. 2018;94:471–483.
70. Findeis-Hosey JJ, McMahon KQ, Findeis SK. Von Hippel-Lindau disease. *J Pediatr Genet*. 2016;5:116–123.
71. Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer*. 2002;2:673–682.
72. Linehan WM, Ricketts CJ. The Cancer Genome Atlas of renal cell carcinoma: findings and clinical implications. *Nat Rev Urol*. 2019;16:539–552.
73. Inoue H, Nonomura N, Kojima Y, et al. Somatic mutations of the von Hippel–Lindau disease gene in renal carcinomas occurring in patients with long-term dialysis. *Nephrol Dial Transplant*. 2007;22:2052–2055.
74. Fiseha T, Tamir Z. Urinary markers of tubular injury in early diabetic nephropathy. *Int J Nephrol*. 2016;2016:4647685.
75. Shu S, Wang Y, Zheng M, et al. Hypoxia and hypoxia-inducible factors in kidney injury and repair. *Cells*. 2019;8:207.
76. Grantham JJ. Clinical practice: autosomal dominant polycystic kidney disease. *N Engl J Med*. 2008;359:1477–1485.
77. Sun K, Xu D, Mei C. The association between autosomal dominant polycystic kidney disease and cancer. *Int Urol Nephrol*. 2019;51:93–100.
78. Orskov B, Sørensen VR, Feldt-Rasmussen B, et al. Changes in causes of death and risk of cancer in Danish patients with autosomal dominant polycystic kidney disease and end-stage renal disease. *Nephrol Dial Transplant*. 2011;27:1607–1613.
79. Schrem H, Schneider V, Kurok M, et al. Independent pre-transplant recipient cancer risk factors after kidney transplantation and the utility of G-chart analysis for clinical process control. *PLoS One*. 2016;11:e0158732.
80. Cachat F, Renella R. Risk of cancer in patients with polycystic kidney disease. *Lancet Oncol*. 2016;17:e474.
81. Yu TM, Chuang YW, Yu MC, et al. Risk of cancer in patients with polycystic kidney disease: a propensity-score matched analysis of a nationwide, population-based cohort study. *Lancet Oncol*. 2016;17:1419–1425.
82. Chen YB, Tickoo SK. Spectrum of preneoplastic and neoplastic cystic lesions of the kidney. *Arch Pathol Lab Med*. 2012;136:400–409.
83. Keith DS, Torres VE, King BF, et al. Renal cell carcinoma in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1994;4:1661–1669.
84. Idowu J, Home T, Patel N, et al. Aberrant regulation of Notch3 signaling pathway in polycystic kidney disease. *Sci Rep*. 2018;8:3340.
85. Sharma S, Sirin Y, Susztak K. The story of Notch and chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2011;20:56–61.
86. Tanaka S, Tanaka T, Nangaku M. Hypoxia and hypoxia-inducible factors in chronic kidney disease. *Ren Replace Ther*. 2016;2:25.
87. Ma MKM, Yung S, Chan TM. mTOR inhibition and kidney diseases. *Transplantation*. 2018;102:S32–S40.
88. Wetmore JB, Calvet JP, Yu AS, et al. Polycystic kidney disease and cancer after renal transplantation. *J Am Soc Nephrol*. 2014;25:2335–2341.
89. Henske EP, Jozwiak S, Kingswood JC, et al. Tuberous sclerosis complex. *Nat Rev Dis Primers*. 2016;2:16035.
90. Lam HC, Siroky BJ, Henske EP. Renal disease in tuberous sclerosis complex: pathogenesis and therapy. *Nat Rev Nephrol*. 2018;14:704–716.
91. Yang P, Cornejo KM, Sadow PM, et al. Renal cell carcinoma in tuberous sclerosis complex. *Am J Surg Pathol*. 2014;38:895–909.
92. Giannikou K, Malinowska IA, Pugh TJ, et al. Whole exome sequencing identifies TSC1/TSC2 biallelic loss as the primary and sufficient driver event for renal angiomyolipoma development. *PLoS Genet*. 2016;12:e1006242.
93. Tyburczy ME, Jozwiak S, Malinowska IA, et al. A shower of second hit events as the cause of multifocal renal cell carcinoma in tuberous sclerosis complex. *Hum Mol Genet*. 2015;24:1836–1842.
94. Shah A, Lal P, Toorens E, et al. Acquired cystic kidney disease-associated renal cell carcinoma (ACKD-RCC) harbor recurrent mutations in KMT2C and TSC2 genes. *Am J Surg Pathol*. 2020;44:1479–1486.
95. Kingswood JC, Bissler JJ, Budde K, et al. Review of the tuberous sclerosis renal guidelines from the 2012 consensus conference: current data and future study. *Nephron*. 2016;134:51–58.
96. Rouviere O, Nivet H, Grenier N, et al. Kidney damage due to tuberous sclerosis complex: management recommendations. *Diagn Interv Imaging*. 2013;94:225–237.
97. Rakowski SK, Winterkorn EB, Paul E, et al. Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. *Kidney Int*. 2006;70:1777–1782.
98. Pleniceanu O, Omer D, Azaria E, et al. mTORC1 inhibition is an effective treatment for sporadic renal angiomyolipoma. *Kidney Int Rep*. 2018;3:155–159.
99. Kingswood JC, Belousova E, Benedik MP, et al. Renal manifestations of tuberous sclerosis complex: key findings from the final analysis of the TOSCA study focussing mainly on renal angiomyolipomas. *Front Neurol*. 2020;11:972.
100. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. *Nat Genet*. 1997;16:68–73.
101. Linehan WM, Spellman PT, Ricketts CJ, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med*. 2016;374:135–145.
102. Gui Y, Lu Q, Gu M, et al. Fibroblast mTOR/PPARgamma/HGF axis protects against tubular cell death and acute kidney injury. *Cell Death Differ*. 2019;26:2774–2789.
103. Cho JH, Patel B, Bonala S, et al. Notch transactivates Rheb to maintain the multipotency of TSC-null cells. *Nat Commun*. 2017;8:1848.
104. Goncalves AF, Adlesic M, Brandt S, et al. Evidence of renal angiomyolipoma neoplastic stem cells arising from renal epithelial cells. *Nat Commun*. 2017;8:1466.
105. Young MD, Mitchell TJ, Vieira Braga FA, et al. Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. *Science*. 2018;361:594–599.
106. Maeshima A, Yamashita S, Nojima Y. Identification of renal progenitor-like tubular cells that participate in the regeneration processes of the kidney. *J Am Soc Nephrol*. 2003;14:3138–3146.
107. Smeets B, Kuppe C, Sicking EM, et al. Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. *J Am Soc Nephrol*. 2011;22:1262–1274.
108. Angelotti ML, Ronconi E, Ballerini L, et al. Characterization of renal progenitors committed toward tubular lineage and their regenerative potential in renal tubular injury. *Stem Cells*. 2012;30:1714–1725.
109. Lasagni L, Angelotti ML, Ronconi E, et al. Podocyte regeneration driven by renal progenitors determines glomerular disease remission and can be pharmacologically enhanced. *Stem Cell Rep*. 2015;5:248–263.
110. El-Dahr SS, Li Y, Liu J, et al. p63+ Ureteric bud tip cells are progenitors of intercalated cells. *JCI Insight*. 2017;2:e89996.
111. Lazzeri E, Angelotti ML, Peired A, et al. Endocycle-related tubular cell hypertrophy and progenitor proliferation recover renal function after acute kidney injury. *Nat Commun*. 2018;9:1344.
112. Lindgren D, Bostrom AK, Nilsson K, et al. Isolation and characterization of progenitor-like cells from human renal proximal tubules. *Am J Pathol*. 2011;178:828–837.
113. Sagrinati C, Netti GS, Mazzinghi B, et al. Isolation and characterization of multipotent progenitor cells from the Bowman's capsule of adult human kidneys. *J Am Soc Nephrol*. 2006;17:2443–2456.
114. Romagnani P. Toward the identification of a "renopoietic system"? *Stem Cells*. 2009;27:2247–2253.
115. Peired AJ, Melica ME, Molli A, et al. Molecular mechanisms of renal progenitor regulation: how many pieces in the puzzle? *Cells*. 2021;10:59.
116. Bonventre JV. Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. *J Am Soc Nephrol*. 2003;14(suppl 1):S55–S61.
117. Kusaba T, Lalli M, Kramann R, et al. Differentiated kidney epithelial cells repair injured proximal tubule. *Proc Natl Acad Sci U S A*. 2014;111:1527–1532.
118. Kang HM, Huang S, Reidy K, et al. Sox9-positive progenitor cells play a key role in renal tubule epithelial regeneration in mice. *Cell Rep*. 2016;14:861–871.
119. Rinkevich Y, Montoro DT, Contreras-Trujillo H, et al. In vivo clonal analysis reveals lineage-restricted progenitor characteristics in mammalian kidney development, maintenance, and regeneration. *Cell Rep*. 2014;7:1270–1283.
120. Lasagni L, Ballerini L, Angelotti ML, et al. Notch activation differentially regulates renal progenitors proliferation and differentiation toward the podocyte lineage in glomerular disorders. *Stem Cells*. 2010;28:1674–1685.

121. Sallustio F, De Benedictis L, Castellano G, et al. TLR2 plays a role in the activation of human resident renal stem/progenitor cells. *FASEB J*. 2010;24:514–525.
122. Soteriou D, Fuchs Y. A matter of life and death: stem cell survival in tissue regeneration and tumour formation. *Nat Rev Cancer*. 2018;18:187–201.
123. Franco I, Helgadottir HT, Moggio A, et al. Whole genome DNA sequencing provides an atlas of somatic mutagenesis in healthy human cells and identifies a tumor-prone cell type. *Genome Biol*. 2019;20:285.
124. Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. *Nat Rev Cancer*. 2016;16:20–33.
125. Kim HS, Kim YJ, Seo YR. An overview of carcinogenic heavy metal: molecular toxicity mechanism and prevention. *J Cancer Prev*. 2015;20:232–240.
126. Chappell JC, Payne LB, Rathmell WK. Hypoxia, angiogenesis, and metabolism in the hereditary kidney cancers. *J Clin Invest*. 2019;129:442–451.
127. Welch WJ. Intrarenal oxygen and hypertension. *Clin Exp Pharmacol Physiol*. 2006;33:1002–1005.
128. Eckardt KU, Bernhardt WM, Weidemann A, et al. Role of hypoxia in the pathogenesis of renal disease. *Kidney Int Suppl*. 2005;(99):S46–S51.
129. Schietke RE, Hackenbeck T, Tran M, et al. Renal tubular HIF-2alpha expression requires VHL inactivation and causes fibrosis and cysts. *PLoS One*. 2012;7:e31034.
130. Sobczuk P, Brodziak A, Khan MI, et al. Choosing the right animal model for renal cancer research. *Transl Oncol*. 2020;13:100745.
131. Lehmann H, Vicari D, Wild PJ, et al. Combined deletion of Vhl and Kif3a accelerates renal cyst formation. *J Am Soc Nephrol*. 2015;26:2778–2788.
132. Patel V, Li L, Cobo-Stark P, et al. Acute kidney injury and aberrant planar cell polarity induce cyst formation in mice lacking renal cilia. *Hum Mol Genet*. 2008;17:1578–1590.
133. Labochka D, Moszczuk B, Kukwa W, et al. Mechanisms through which diabetes mellitus influences renal cell carcinoma development and treatment: a review of the literature. *Int J Mol Med*. 2016;38:1887–1894.
134. Anders HJ, Huber TB, Isermann B, et al. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol*. 2018;14:361–377.
135. Guo H, German P, Bai S, et al. The PI3K/AKT pathway and renal cell carcinoma. *J Genet Genomics*. 2015;42:343–353.
136. Meisel CT, Porcheri C, Mitsiadis TA. Cancer stem cells, quo vadis? the Notch signaling pathway in tumor initiation and progression. *Cells*. 2020;9:1879.
137. Charnley M, Ludford-Menting M, Pham K, Russell SM . A new role for Notch in the control of polarity and asymmetric cell division of developing T cells. *J Cell Sci*. 2019;133:jcs235358.
138. Regan JL, Sourisseau T, Soady K, et al. Aurora A kinase regulates mammary epithelial cell fate by determining mitotic spindle orientation in a Notch-dependent manner. *Cell Rep*. 2013;4:110–123.
139. Surendran K, Selassie M, Liapis H, et al. Reduced Notch signaling leads to renal cysts and papillary microadenomas. *J Am Soc Nephrol*. 2010;21:819–832.
140. Seeger-Nukpezah T, Geynisman DM, Nikonova AS, et al. The hallmarks of cancer: relevance to the pathogenesis of polycystic kidney disease. *Nat Rev Nephrol*. 2015;11:515–534.
141. Habbig S, Bartram MP, Muller RU, et al. NPHP4, a cilia-associated protein, negatively regulates the Hippo pathway. *J Cell Biol*. 2011;193:633–642.
142. Anorga S, Overstreet JM, Falke LL, et al. Deregulation of Hippo-TAZ pathway during renal injury confers a fibrotic maladaptive phenotype. *FASEB J*. 2018;32:2644–2657.
143. Zaytseva YY, Valentino JD, Gulhati P, et al. mTOR inhibitors in cancer therapy. *Cancer Lett*. 2012;319:1–7.
144. Wander SA, Hennessy BT, Slingerland JM. Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. *J Clin Invest*. 2011;121:1231–1241.
145. Matsuura K, Nakada C, Mashio M, et al. Downregulation of SAV1 plays a role in pathogenesis of high-grade clear cell renal cell carcinoma. *BMC Cancer*. 2011;11:523.
146. Lee S, Karas PJ, Hadley CC, et al. The role of Merlin/NF2 loss in meningioma biology. *Cancers (Basel)*. 2019;11:1633–1646.
147. Kai T, Tsukamoto Y, Hijiya N, et al. Kidney-specific knockout of Sav1 in the mouse promotes hyperproliferation of renal tubular epithelium through suppression of the Hippo pathway. *J Pathol*. 2016;239:97–108.
148. Akatsuka S, Yamashita Y, Ohara H, et al. Fenton reaction induced cancer in wild type rats recapitulates genomic alterations observed in human cancer. *PLoS One*. 2012;7:e43403.
149. Nair SS, Kumar R. Chromatin remodeling in cancer: a gateway to regulate gene transcription. *Mol Oncol*. 2012;6:611–619.
150. Le VH, Hsieh JJ. Genomics and genetics of clear cell renal cell carcinoma: a mini-review. *J Transl Genet Genom*. 2018;2:17.
151. Liao L, Testa JR, Yang H. The roles of chromatin-remodelers and epigenetic modifiers in kidney cancer. *Cancer Genet*. 2015;208:206–214.
152. Ricketts CJ, De Cubas AA, Fan H, et al. The Cancer Genome Atlas comprehensive molecular characterization of renal cell carcinoma. *Cell Rep*. 2018;23:313–326.e315.
153. Peired AJ, Sisti A, Romagnani P. Renal cancer stem cells: characterization and targeted therapies. *Stem Cells Int*. 2016;2016:8342625.
154. Usher-Smith J, Simmons RK, Rossi SH, et al. Current evidence on screening for renal cancer. *Nat Rev Urol*. 2020;17:637–642.
155. Eble JN, Togashi K, Pisani P. Renal cell carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press; 2004:110–123.
156. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care*. 2006;10:R73.
157. Sobczuk P, Szczylik C, Porta C, et al. Renin angiotensin system deregulation as renal cancer risk factor. *Oncol Lett*. 2017;14:5059–5068.