In The Name Of God

From kidney injury to kidney cancer

Acute kidney injury and kidney cancer

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Introduction

- Mechanisms of kidney damage and repair that are active during AKI as triggers of DNA damage, promoting the expansion of (pre-)malignant cell clones.

- Whether kidney injury causes kidney cancer is not clear at all, although some studies suggest that kidney cancer develops following an AKI episode .

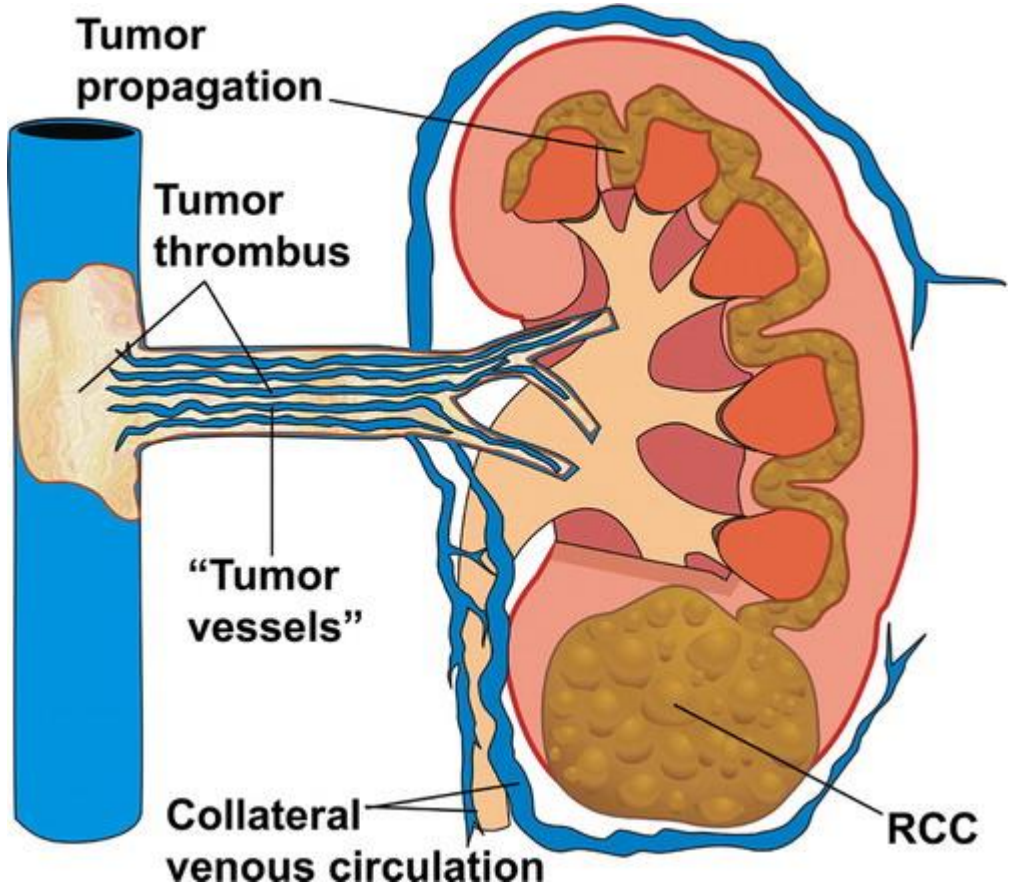
Introduction…

- 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.

- Primary and secondary prevention and treatment of kidney injury to reduce incidence, prevalence, and recurrence of kidney cancer.

The risk factors for kidney cancer

- ❑ Obesity
- ❑ Diabetes
- ❑ Hypertension
- ❑ Smoking
- ❑ Nephrotoxic drugs
- ❑ Heavy metals



Nat Rev Dis Primers, 3 (2017), p. 17088
J Am Soc Nephrol, 27 (2016), pp. 27-39

The risk factors for kidney cancer...

- **Nephrotoxic drugs and heavy metals** induce episodes of toxic AKI associated with necroinflammation and oxidative stress.

- **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.

- **Hypertension**, rather than a cause, is frequently a consequence of kidney disease and a sensitive indicator of early CKD

Clin Kidney J, 13 (2020), pp. 504-509
J Urol, 190 (2013), pp. 1657-1661

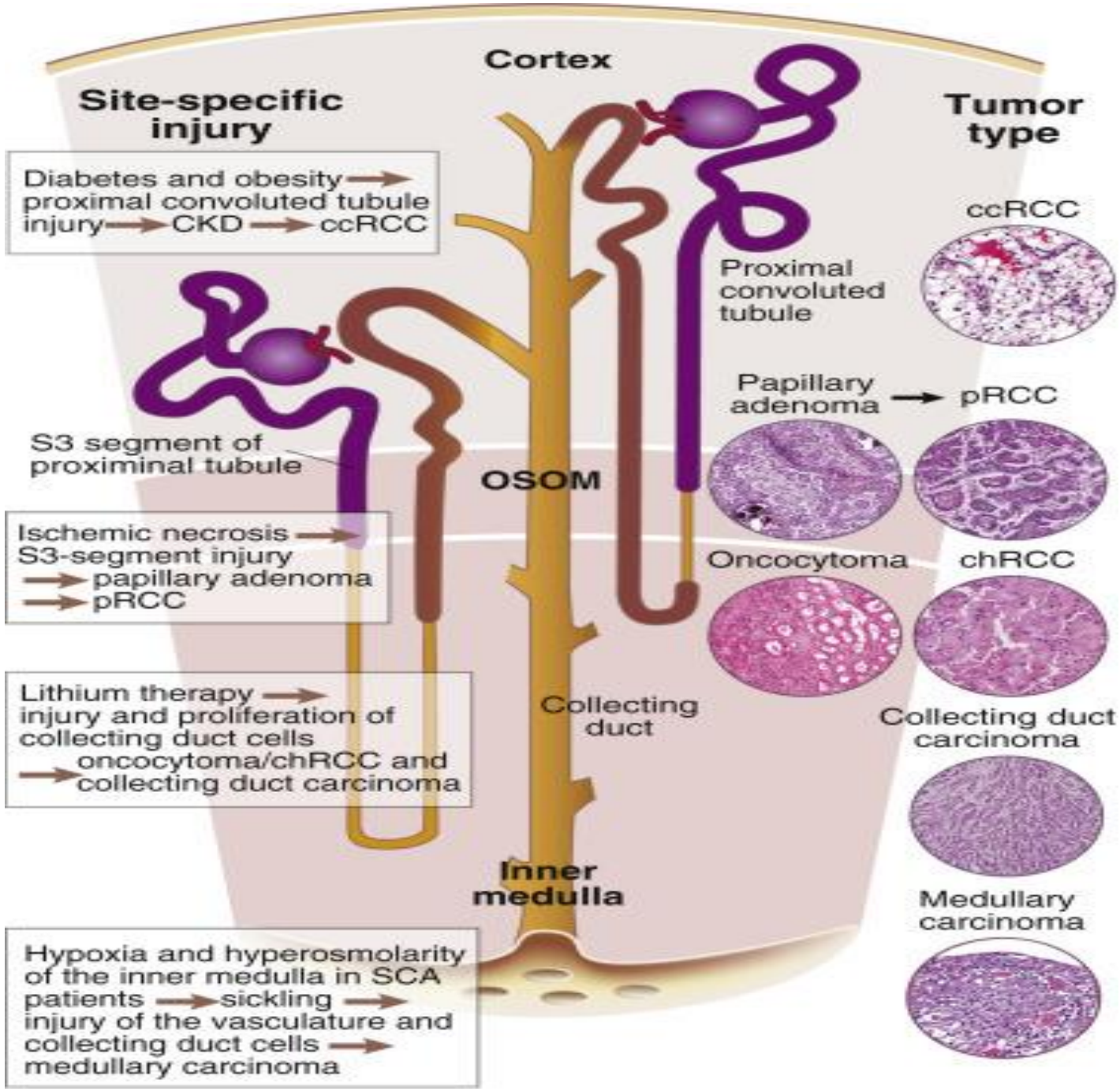
Table 1. Cancer-specific risk factors for AKI

Age >65 years
Congestive heart failure (i.e., exposure to anthracyclines, trastuzumab)
CKD
Hypovolemia (i.e., chemotherapy-related nausea and vomiting, acute graft-versus-host disease)
Distant metastases
Multiple myeloma
Liver cancer
Nephrectomy for renal cell carcinoma
Induction chemotherapy for acute lymphoma or leukemia

Site-specific kidney injuries cause unique subtypes of kidney cancer

- Different subtypes of kidney tumors originate from cells located at the site of initial injury

- The prevalence of different kidney cancer histotypes correlates with the prevalence of specific triggers of kidney injury.



Kidney International 2021

Still frequent: papillary carcinoma

triggered by ischemic necrosis of proximal tubules (S3 segment)

Cohort studies indicate that patients with previous AKI episodes show an increased risk of developing papillary RCC (pRCC)

Multicenter analysis :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**

Sci Transl Med, 12 (2020), Article eaaw6003

Still frequent: papillary carcinoma…

- Onset of papillary adenomas **3 to 6 months after** ischemia, which in some cases **later transformed into pRCC** in a classic adenoma-carcinoma sequence.

- 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**

Sci Transl Med, 12 (2020), Article eaaw6003

Cont…

- 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.
- Overactivation of the **Notch1 pathway**, which is crucially involved in the response to AKI by promoting renal progenitor proliferation, can also reproduce papillary adenomas and pRCC formation in transgenic **animal models**.
- In the collecting ducts, renal progenitors were proposed as the cell of origin of collecting duct–derived oncocytoma and carcinoma RCC.

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

Cont…

- **AKI** is a risk factor for the development and recurrence of **pRCC** in **humans** and that **NOTCH1** overexpression could be the mechanism by which pRCC is induced after AKI.

- Thus, AKI prevention and risk stratification programmes should be developed to prevent and monitor the development of pRCC after AKI.

Sci. Transl Med. 12, eaaw6003 (2020)

Rare but specific: lithium

- Toxic to collecting ducts and causes collecting duct cell–derived tumors.

- Alters the **Notch pathway**, which is involved in many aspects of cancer biology and has an important role in regulating the maintenance of mature renal epithelial cell states

Nat Rev Drug Discov, 20 (2021), pp. 125-144
J Am Soc Nephrol, 30 (2019), pp. 110-126

Rare but specific: lithium…

- Long-term use of lithium may induce microcysts, oncocytomas, and collecting duct renal carcinomas.

- High risk of developing oncocytomas/ chromophobe RCC (that arise from a common progenitor lesion and are histologically and morphologically similar).

Rare but specific: sickle cell anemia

- Anemia induces ischemic medulla injury and **medullary carcinoma**.
- Sickle cell anemia associated with repetitive episodes of organ hypoperfusion, tissue ischemia, and necrosis.
- **Sickle cell nephropathy** is a serious complication of SCA with possible AKI and progression to CKD and kidney failure.
- Ischemia during sickling episodes can **irreversibly** injure the vascular architecture of the kidney medulla, sometimes followed by the development of **medullary carcinoma**.

BMC Nephrol. 2013;14:237
nephropathy: from sickle cell disease to sickle trait. Expert Rev Hematol. 2017;10:1087–1094.

Kidney cancer development following injury : activation of specific pathways

- ❑HIF
- ❑Notch
- ❑ mTOR
- ❑Hippo

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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 and ccRCC**.

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mTOR pathway

- **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**.
- Mutation of phosphoinositide 3-kinase–protein kinase B–mTOR pathway genes (including PTEN, MTOR, and PIK3CA) were frequently reported in **RCC.**
- **Angiomyolipoma development**

Notch pathway

- Notch is a **highly conserved cell-cell communication mechanism that regulates development, tissue homeostasis and repair**. Recent studies indicate that Notch plays a key role in kidney development by establishing proximal tubular epithelial cell fate and cell type specification in the renal collecting system.

- Notch signaling may play a tumor suppressor role in the kidney .Hence, both increased and decreased levels of Notch signaling have been correlated with kidney cancers.

- development of **papillary adenomas and RCC** in humans and mice

Biol. 2010;337:386–395.
Biomolecules. 2019 Nov; 9(11): 692

Hippo pathway

A deregulated Hippo pathway is seen in several forms of **cystic kidney disease**, **in response to AKI**, and in several **sporadic cancers**, suggesting this pathway can also be a link between cell proliferation in **cyst formation and RCC.**

Review

The link between kidney disease and cancer: complications and treatment

Jolanta Malyszko, Petra Tesarova, Giovambattista Capasso, Anna Capasso

Acute and chronic kidney disease encompasses a complex set of diseases that can both lead to, and result from, cancer. In particular, kidney disease can arise from the use of chemotherapeutic agents. Many of the current and newly developed cancer chemotherapeutic agents are nephrotoxic and can promote kidney dysfunction, which frequently manifests during the terminal stages of cancer. Given the link between kidney disease and cancer development and treatment, the aim of this Review is to highlight the importance of multidisciplinary collaboration between oncologists and nephrologists to predict and prevent chemotherapeutic-induced nephrotoxicity. As new therapies are introduced to treat cancer, new renal toxicities require proper diagnosis and management. We anticipate that multidisciplinary collaborations will lead to the development and implementation of guidelines for clinicians to improve the therapeutic management of patients with both cancer and renal impairment.

Lancet 2020; 396: 277–87

Department of Nephrology, Dialysis and Internal Medicine, Medical University of Warsaw, Poland (Prof J Malyszko MD); Department of Oncology, Charles University, Prague, Czech Republic (Prof P Tesarova MD); Department of Translational Medical Sciences, University

Lancet 2020; 396: 277–87

	Indication
Minimal change disease	Lung cancer, colon cancer, pancreatic cancer, bladder cancer, renal cell carcinoma, ovarian cancer, mesothelioma, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, and myeloma
Membranoproliferative glomerulonephritis	Lung cancer, renal cell carcinoma, breast cancer, oesophageal cancer, gastric cancer, Wilms tumour, melanoma, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, monoclonal gammopathy of undetermined significance, and myeloma
Mesangioproliferative glomerulonephritis	Lung cancer, renal cell carcinoma, non-melanoma skin cancer, gastric cancer, pancreatic cancer, liver cancer, and myeloma
IgA nephropathy	Lung cancer, pancreatic cancer, renal cell carcinoma, head and neck cancer, tongue cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma
Focal segmental glomerulosclerosis	Lung cancer, renal cell carcinoma, breast cancer, oesophageal cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, T-cell leukaemia, and myeloma
Membranous nephropathy	Lung cancer, colon cancer, pancreatic cancer, stomach cancer, prostate cancer, breast cancer, head and neck cancer, Wilms tumour, teratoma, ovarian cancer, cervical cancer, endometrial cancer, melanoma, non-melanoma skin cancer, pheochromocytoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, and chronic lymphocytic leukaemia
Crescentic glomerulonephritis	Lung cancer, colon cancer, renal cell carcinoma, prostate cancer, gastric cancer, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, and chronic lymphocytic leukaemia
Thrombotic microangiopathy	Lung cancer, breast cancer, and gastric cancer
Amyloid A amyloidosis	Renal cell carcinoma, gastrointestinal stromal tumour, spleen sarcoma, and Hodgkin lymphoma
Anti-glomerular basement membrane glomerulonephritis	Hodgkin lymphoma
ANCA-associated vasculitis	Prostate cancer, bladder cancer, non-Hodgkin lymphoma, leukaemia, non-melanoma skin cancer, and lung cancer

ANCA=antineutrophil cytoplasmic antibody.

Table 1: **Paraneoplastic glomerulopathies in cancer patients**

Conclusion

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).

Conclusion

- **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.


Thanks