Injury and Kidney Cancer

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Abstract

Epidemiologic research shows a strong link between acute or chronic kidney injury and kidney tumors. However, it is unclear whether these associations are causally linked and in which direction. Data from basic and clinical research are now shedding light on this issue, prompting us to propose a new pathophysiological concept with immediate implications for the management of patients with kidney disease and kidney tumors. As a central paradigm, this review proposes kidney damage and repair mechanisms that are active not only during acute kidney injury but also during chronic kidney disease as triggers of DNA damage, promoting the expansion of (pre-) malignant cell clones. 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, as renal progenitors have been identified as the cell of origin for several benign and malignant kidney tumors by different studies. We show how known risk factors for kidney cancer are actually risk factors for kidney injury, which is an upstream cause of cancer. Finally, we propose a new role for nephrologists in the treatment of kidney cancer (i.e., the primary and secondary prevention and treatment of kidney injury to reduce incidence, prevalence, and recurrence of kidney cancer).

Keywords: Acute kidney injury • Chronic kidney disease • Kidney cancer • Risk factor • Surgery • Survival

Introduction

Cancerogenesis is a complex process that involves germline and/or somatic mutations that result in an uncontrolled proliferation of mutated cells. This frequently occurs in a series of steps in which numerous combinations of mutations only gradually pass the unrestricted cell growth threshold. Tissue injury is a known trigger of cancerogenesis for two reasons: its ability to induce DNA damage and somatic mutations, particularly in tissue-resident long-lived stem cells; and (ii) its ability to promote the expansion of such mutated cells during the tissue repair process [1]. These mechanisms, for example, contribute to colorectal cancer caused by inflammatory bowel disease and lung cancer caused by toxic smokes and dust particulates, atrophic gastritis-related gastric cancer6, and cirrhosis-related hepatocellular carcinoma. Several epidemiologic studies have found a link between Chronic Kidney Disease (CKD) and kidney cancer. Although both occur ideally in the second half of life, it is unclear whether and how these associations are causally linked.

Causation, for example, could be one way because tumor therapy, including surgery and antiangiogenic agents or Mechanistic Target of Rapamycin (mTOR) and immune checkpoint inhibitors are associated with an increased risk of AKI and CKD [2]. Similarly, it is unclear whether kidney injury causes kidney cancer, though some studies suggest that kidney cancer develops after an AKI episode or after years of CKD at the stage of kidney failure. We discuss the role of kidney injury as a cause of kidney cancer in this review. 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, beginning with epidemiologic and genetic evidence. We discuss recent findings regarding the putative cells of origin for benign and malignant kidney tumors, as well as how injury-mediated changes in the activation of distinct signaling pathways contribute to the various histotypes of kidney tumors. We also investigate how the intrinsic mechanisms of kidney repair that operate transiently during AKI episodes and persistently in CKD promote tumor growth and recurrence. Finally, we believe that preventing AKI and CKD is the best way to prevent the development of Renal Cell Carcinoma (RCC) and its consequences [3]. The concept of a bidirectional causal relationship between kidney disease and kidney tumors calls for the nephrologist to play a central role in the prevention and treatment of kidney cancer patients.

Epidemiologic studies uncover associations, but without confirming causation, such findings frequently lead to incorrect interpretations. In the search for unknown causes of kidney cancer, for example, epidemiologic studies identified several "risk factors" for which a direct causal link to cancerogenesis is not always obvious. Obesity, diabetes, hypertension, smoking, nephrotoxic drugs, and heavy metals all promote kidney injury, either AKI or CKD, and may be associated with an increase in injury-related kidney cancer rates. Indeed, nephrotoxic drugs and heavy metals cause toxic AKI with necroinflammation and oxidative stress. Obesity, diabetes, and smoking are all well-known risk factors for glomerular hyperfiltration and glomerulosclerosis-related CKD, resulting in nephron loss and significant adaptive cellular changes in the remaining nephrons to accommodate metabolic needs [4]. Finally, rather than being a cause, hypertension is frequently a result of kidney disease and a sensitive indicator of early CKD. Evidence suggests that the various subtypes of kidney tumors arise from cells located at the site of initial injury. Furthermore, the prevalence of various kidney cancer histotypes correlates with the prevalence of specific kidney injury triggers.

Prospective studies suggest that CKD causes kidney cancer, particularly Clear Cell RCC (ccRCC), which accounts for 70%-80% of all 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, found that having moderate CKD at the start increased the risk of developing kidney cancer later in life. Obesity and diabetes, which promote CKD, are also factors in the development of RCC. The metabolic overload of proximal tubule cells in remnant nephrons experiencing dramatically increased single-nephron hyperfiltration represents the link between these two conditions (and tubular hyperreabsorption). This causes chronic cortical damage and CKD in obese and diabetic patients, with the possibility of developing ccRCC, which typically originates from cortical proximal cells [5].

Data from Italian and Danish cohort studies show that patients who have had previous AKI episodes are more likely to develop papillary RCC (*pRCC*). Further multicenter analysis revealed that patients who had tumor resection for pRCC and had a postoperative AKI episode had a higher risk of tumor recurrence than those who did not have a

postoperative AKI episode, implying that ischemic injury promotes tumor growth. This link was confirmed in an AKI experimental model, where the authors discovered that postischemic AKI promotes the long-term development of papillary tumors in mice by activating tumor growth-promoting pathways.

Lithium therapy is linked to collecting duct toxicity, which can result in nephrogenic diabetes insipidus in up to 40% of patients. According to research, lithium causes the loss of the molecular water channel aquaporin-2. The Notch pathway, which is involved in many aspects of cancer biology and plays an important role in regulating the maintenance of mature renal epithelial cell states, is also altered by lithium. Long-term lithium exposure causes tubulointerstitial nephritis and renal cysts to form in the distal tubules and collecting ducts. Although long-term lithium use is not linked to an increased cumulative risk of kidney cancer.

Oncocytomas/chromophobe RCC (which arise from a common progenitor lesion and are histologically and morphologically similar) and collecting duct carcinomas are common in lithium-treated patients. All of these tumors are rare and originate in the collecting duct. However, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee agreed that the evidence is sufficient to conclude that long-term lithium use may cause microcysts, oncocytomas, and collecting duct renal carcinomas.

Animals treated with lithium consistently showed increased proliferation of principal cells as well as an increase in the number of intercalated cells, which could be attributed to progenitor cell proliferation and differentiation or the conversion of principal cells to intercalated cells. Thus, lithium therapy-related oncocytomas and collecting duct carcinomas are yet another example of injury-site-specific cancerogenesis in the kidney.

Sickle cell anemia is a rare but specific condition that causes ischemic medulla injury and medullary carcinoma.

Sickle Cell Anemia (SCA) is a hemoglobin disorder characterized by recurrent episodes of organ hypoperfusion, tissue ischemia, and necrosis. Sickle cell nephropathy is a severe complication of SCA that can lead to CKD and kidney failure. Elevated blood pressure and CKD were found in 16.7% and 8.3% of children with SCA, respectively, in a cross-sectional study. Ischemia during sickling episodes can permanently damage the vascular architecture of the kidney medulla, leading to the development of medullary carcinoma, an aggressive type of kidney cancer almost exclusively associated with SCA [6]. Indeed, the extreme conditions of renal medulla hypoxia and hypertonicity, combined with regional ischemia caused by red blood cell sickling, activate DNA repair mechanisms, resulting in deletions and translocations in switch/sucrose nonfermentable-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (*SMARCB1*), a tumor suppressor gene located in a fragile region of chromosome 22.

Because cancer cannot cause SCA, hemoglobin mutations cannot directly cause medullary cancer, and SCA-related medullary cancer does not occur without kidney injury, this association suggests that cancer is caused by injury. As a result, unlike monogenic forms of kidney cancer, which involve direct mutations in kidney cells, SCA-related kidney cancer provides a strong clue for the role of injury in kidney cancer because the causative gene is absent inside kidney cells and only accounts for kidney injury as an upstream event of kidney cancerogenesis. Furthermore, the role of analgesics and other potential third factors is unlikely in this context, as the medullary location of injury and cancer subtype argue against a toxic trigger while supporting the causative role of SCA-mediated ischemic injury in this location. Human diseases, including cancer, have been linked to changes in chromatin remodeling proteins. Chromatin remodeling pathways are activated in response to DNA damage, injury, and carcinogens such as smoking. Pathways involved in ccRCC include the Polybromo 1 (*PBRM1)*, SET Domain-Containing Protein 2 (*SETD2)*, and *BRCA*-Associated Protein-1 (*BAP1*) genes, as well as *SMARCB1*. *CDKN2A* loss due to mutation, deletion, or promoter hypermethylation, as well as *TP53* mutation, were also frequently reported in ccRCC [7].

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