




## CKJ REVIEW

## Oncogenic mechanisms in renal insufficiency

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### ABSTRACT

The prevalence of both cancer and end-stage renal disease is increasing. In addition, medical advances have meant increased survival rates for both diseases. Many chemotherapeutics are renally excreted, and conversely, renal insufficiency promotes a pro-neoplastic state, including genitourinary and other cancers. Dialysis prolongs life while increasing cancer risk. Proposed oncogenic mechanisms include immune dysfunction, chronic inflammation, changes in gut microbiota and stimulation of the renin–angiotensin system. This review summarizes current concepts in the relationship between cancer and renal insufficiency.

**Keywords:** cancer, carcinogenesis, end-stage renal disease, malignancy, renal transplant

### INTRODUCTION

Both cancer and end-stage renal disease (ESRD) are highly prevalent in the general population. The International Agency for Research on Cancer reported a global incidence for all cancers of 18 million and a 5-year prevalence of >43 million in 2018. Diagnostic and therapeutic advancements in recent decades in the management of cancer patients have led to improved survival, with 26% reduced mortality from cancer in the USA according to the Surveillance, Epidemiology, and End Results (SEER) Cancer Database.

ESRD increases mortality and morbidity through an increased risk of associated cardiovascular disease, diabetes and hypertension. Cancer incidence is reported to be higher in patients with ESRD compared with the general population [1–3], although the mechanisms involved are still not completely understood.

Both cancer and ESRD are more commonly diagnosed in older patients, such that there is overlapping of the two conditions in ageing individuals. Several cancer registry studies have reported [2, 3] a higher incidence of bladder [standardized incidence ratio (SIR) 1.5], kidney (SIR 3.6–4.03), liver, thyroid, head and neck and cervical cancer, as well as a higher incidence of multiple myeloma and non-Hodgkin’s lymphoma. This review summarizes current concepts in the relationship between cancer and kidney disease.

### RISK FACTORS

Although the mechanisms are still unknown, specific conditions that have linked ESRD and cancer include the following (Figures 1 and 2):

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- i. Acquired cystic disease of the kidney has been linked to a higher incidence of both clear cell and papillary renal cell carcinoma (RCC) in chronic kidney disease (CKD) patients [4]. Oya et al. [5] suggested possible activation of the proto-oncogene c-Jun in patients with ESRD, secondary to a chronic cytokine environment. ESRD patients have increased levels of inflammatory cytokines such as interleukin (IL)-1 $\beta$ , IL-6 and tumour necrosis factor (TNF)- $\alpha$  [6] due to oxidative stress in uraemia, leading to c-Jun activation and a higher risk of developing RCC. However, there seems to be a correlation with only low-stage and low-grade RCC. Another possible mechanism involves activation of the hepatocyte growth factor-c-Met pathway, leading to cyst formation and progression towards RCC [7]. Other anti-apoptotic molecules seem to be overexpressed, such as Bcl-2, leading to higher proliferative activity of the cystic epithelium.
- ii. Cyclophosphamide (CYC) use in patients with systemic autoimmune diseases can increase the risk of both solid tumours and myeloproliferative disorders [8, 9] due to direct chromosomal damage induced by cytotoxic and induced immunosuppression. Bladder and skin cancers were found to be more prevalent in patients previously treated with CYC compared with controls ( $P < 0.024$ ). The risk increased at 6 years post-treatment and continued to increase at 20 years [8], suggesting a need for prolonged surveillance in these patients. Moreover, there is a higher risk in male patients and those receiving a higher cumulative dose of CYC.
- iii. Viral infections [human papillomavirus (HPV), hepatitis B or C virus (HBV/HCV), Epstein-Barr virus (EBV)] in ESRD patients can increase the risk of cancer. Both haemodialysis (HD) and changes in innate and adaptive immunity [10, 11] are already known to increase the risk of infection in ESRD patients, increasing morbidity and mortality. It has been suggested that ~20% of HD patients become HBV carriers, whereas the prevalence in the general population is ~5% [12]. However, only 5% of these patients die from liver disease [13] such as cirrhosis or hepatocellular carcinoma, and other coexisting factors such as co-infection with HCV/human immunodeficiency virus, alcohol abuse and impaired

immune response contribute to a more rapid progression of HBV-related disease. According to the Dialysis Outcomes and Practice Patterns Study, the prevalence of HCV is nearly 10% [14], being lower in Western European countries and higher in Middle Eastern countries. Antiviral agents have been successfully used to improve outcomes in HCV patients with CKD, being associated with a significant survival benefit [15]. Both HBV and HCV infections lead to an increased risk of HCC, although the risk is higher with HBV [relative risk (RR) 2.49 versus 1.5] [16, 17]. As ESRD patients are generally immunocompromised due to immunosuppressive therapy used in the prevention of transplant rejection, an increased risk (RR 1.53) [18] of other viral infections such as HPV has been observed. Several studies have reported an increased risk of HPV-related cancers of between 1.8-fold and 8.6-fold [3, 18, 19], suggesting a possible theoretical benefit from HPV vaccination in this population. The prevalence of EBV infections in patients undergoing organ transplantation varies between 16% and 50% [20]. Persistent EBV infection may contribute to Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma and gastric cancer [21]. Alterations in the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway, PI3K (phosphatidylinositol 3-kinase) mutations and CpG methylation of the cell genome have been described in these patients. Moreover, EBV avoids immune surveillance through downregulation of the major histocompatibility complex (MHC) or programmed death-ligand 1 (PD-L1) expression, leading to inactivation of T cells.

- iv. Prolonged analgesic use has been linked to a 1.25–1.28 increased risk of kidney cancer in a large meta-analysis that included >8000 RCC patients [22]. One suggested mechanism is the alkylating effect of the accumulation of N-hydroxylated phenacetin metabolites in the kidney [23]. This also leads to stimulation of carcinogenesis in the kidney, ureters and bladder due to prolonged exposure and increased concentration of these substances.
- v. Balkan endemic nephropathy accompanied by urothelial carcinoma after exposure to aristolochic acid (AA) has been described in southeastern European populations [24, 25]. The prevalence of the disease varies between 0.5

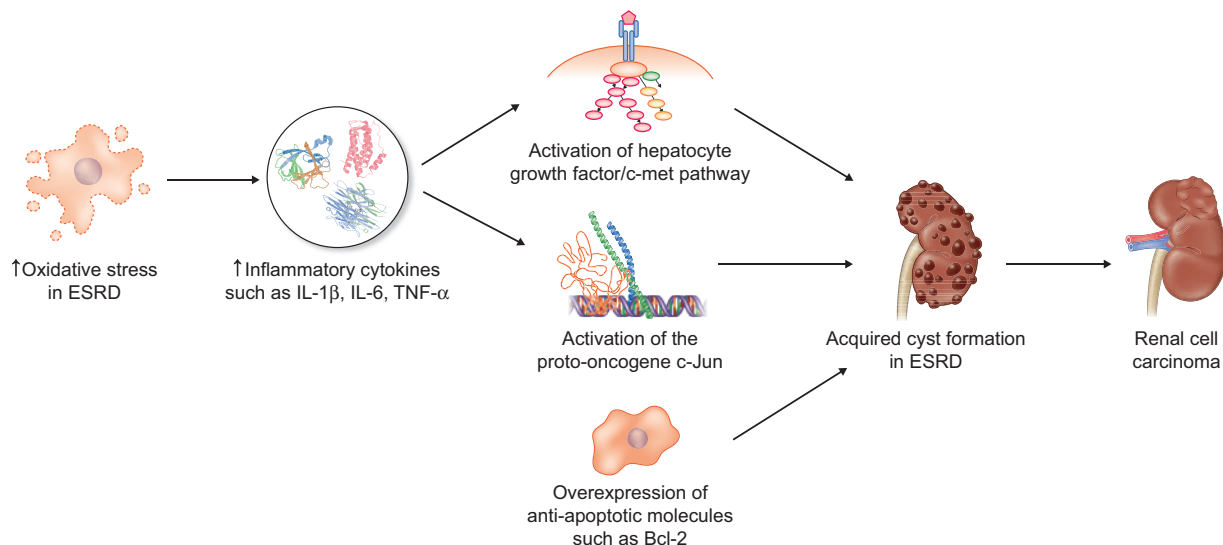


FIGURE 1: Mechanisms of renal cell carcinoma; ESRD - end stage renal disease; IL-1 $\beta$  - interleukin 1 beta; IL-6 - interleukin 6; TNF- $\alpha$  - tumor necrosis factor alpha; Bcl-2 - B-cell lymphoma 2.

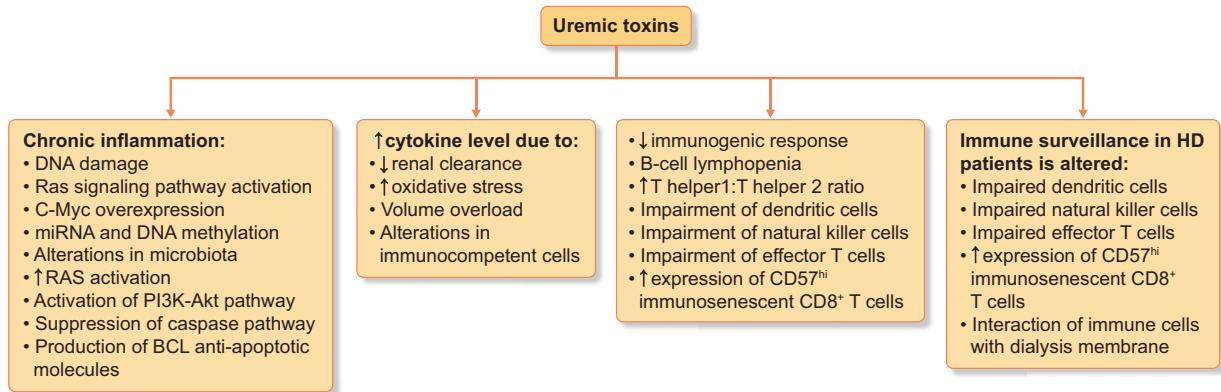


FIGURE 2: Effects of uremic toxins in ESRD patients; miRNA - microRNA; HD - hemodialysis.

and 4.4 in those with a genetic predisposition after exposure to plants of the genera *Aristolochia* and *Asarum*. Besides nephrotoxicity, AA has been linked to upper urinary tract cancer. Its carcinogenic potential has been indicated by the overexpression of p53 in these patients, suggesting a role for p53 gene mutations and the presence of AA DNA adducts in the kidney [26, 27].

- vi. Genetic factors. Inherited genetic mutations lead to 10% of all cancers, thus a detailed assessment of the family cancer history may indicate a hereditary cancer syndrome. RCC can be linked to a *VHL* gene abnormality in 1 of 36 000 individuals [28] who are at risk of developing multiple renal cysts and multicentric and bilateral clear cell carcinoma of the kidney. Other genetic alterations, such as the BRCA1-associated protein-1 mutation responsible for encoding a nuclear deubiquitinase, polybromo-1 (PBRM1) gene mutation, inactivation of histone-modifying genes or alterations of the ubiquitin-mediated proteolysis pathway have been described in RCC [29–32]. The Cancer Genome Atlas Research Network documented *MET* germline mutations in patients with type 1 papillary RCC [33] and fumarate hydratase germline mutations in type 2 papillary RCC.
- vii. Ultraviolet light exposure has been linked to a 7.43% cumulative incidence of non-melanoma skin cancer [squamous cell carcinoma (SCC)] in organ transplant recipients [34] under immunosuppressive treatment. Induction of oxidative stress and DNA damage has been documented in patients on azathioprine, and a lower incidence of SCC has been observed with mammalian target of rapamycin-based immunosuppressants.
- viii. Glomerulonephritis (GN) in a study by Ryu et al. [35] has been associated with an increased risk of malignancy (colon cancer, lung cancer, multiple myeloma and Kaposi's sarcoma) via mechanisms that are not fully understood. The observed:expected cancer ratio varied between 0.8 and 28.57, being highest with amyloidosis. Traditionally GN has been considered as a paraneoplastic syndrome associated with cancer diagnosis, however, the use of immunosuppressive drugs interfering with the immune system may explain the higher observed cancer risk [36].

Retrospective studies [2, 3] suggest a higher risk of cancer of the bladder (SIR 1.5) and kidney or renal pelvis (SIR 3.6–4.3) among ESRD patients. In a retrospective cohort study of Taiwanese dialysis patients [37], the highest cancer risk was in the younger population, unlike in the previously mentioned studies. A meta-analysis of prospective studies [38] suggests a correlation between renal function decline and a trend towards an increased risk of urinary tract cancers {hazard ratio [HR] 2.34 [95% confidence interval (CI) 1.31–4.18];  $P = 0.06$ }.

## MECHANISMS INVOLVED IN CARCINOGENESIS

The management of cancer is often complicated by coexisting ESRD, and there is interest in early detection of this overlap population whose survival is doubly negatively impacted (Figures 2 and 3).

Studies reporting an increased cancer incidence in ESRD patients [39–41] offer valuable epidemiologic information regarding cancer risk in this specific population. These observational studies show an increased incidence of colon and lung cancers after transplantation, as well as virus-associated cancers, possibly as a result of immunosuppressive drugs; endocrine-related cancers such as breast, prostate and ovarian cancers have a similar rate; several cancers related to kidney dysfunction are more frequently diagnosed, such as kidney and urinary tract cancers, myeloma and lymphoma; geographic differences in viral patterns may influence cancer risk in some areas; and differences in cancer screening strategies may also impact cancer diagnosis and influence reported outcomes in these studies.

### Immune dysfunction in ESRD

Both innate and adaptive immunity play a major role in immune surveillance, with different specificity of recognition and speed of response. The innate immune response is less specific in target recognition but compensates in the speed of the response. On the other side, the adaptive immune response has a higher target specificity but offers a more delayed, but durable, response. Cancer cells can elude the immune system by

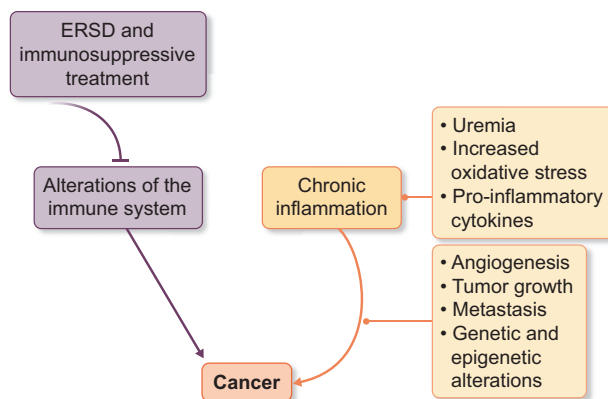


FIGURE 3: Chronic inflammation and cancer; ESRD - end stage renal disease.

blocking the ‘immune checkpoint molecules’, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programme cell death protein 1 (PD-1) and PD-L1 expression by tumour cells, which represents an important mechanism of tumour immune evasion. Modulating the immune response with checkpoint inhibitors has been recognized as a standard of care for many types of cancers in the last decade.

In ESRD patients, changes in the immune system have been observed in the context of both the condition itself and the immunosuppressive treatment. In the context of decreased renal clearance, increased oxidative stress and volume overload, hypercytokinaemia has been observed [42, 43]. Moreover, uraemia has also been associated with immunosuppression, as demonstrated by changes in immunocompetent cells. In terms of innate immunity changes, an increased production of pro-inflammatory cytokines has been described, such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , as a consequence of decreased renal function [43]. Chronic inflammation has also been observed, as neutrophils are more prone to apoptosis, as a direct effect of the uraemic milieu [44].

A reduced immunogenic response has been observed in ESRD patients undergoing vaccination [45], as a consequence of the uraemic milieu [46]. Only 50–75% of HD patients who receive the usual HBV vaccine develop protective antibody levels, compared with 90% in the general population. This has also been observed when HD patients were vaccinated against influenza virus, *Clostridium tetani* and *Corynebacterium diphtheriae* [45]. The most important adaptive immune system representatives are B cells and T helper (Th) lymphocytes. Th lymphocytes activate macrophages and neutrophils and also play a role in promoting humoral immunity. In HD patients, there is an altered Th1:Th2 ratio in favour of Th1 due to increased Th1 differentiation induced by the production of IL-2 [47, 48]. Another change in the immune system in HD patients is B cell lymphopenia due to increased apoptosis [49].

Such an imbalance has been correlated with the development of SCC in post-transplant patients [50, 51]. Due to impairment of dendritic cells, natural killer cells and effector T cells, combined with an increased expression of CD57<sup>hi</sup> immunosenescent CD8<sup>+</sup> T cells (cells with impaired cytotoxic activity), the immune surveillance in HD patients is altered. A possible role of

$\gamma\delta$  T cells in SCC carcinogenesis has been suggested by Rei et al. [52], who observed a direct association between cancer incidence and the number of  $\gamma\delta$  T cells. The authors suggested patient stratification according to the CD8<sup>+</sup>CD57<sup>hi</sup> phenotype when assessing cancer risk in post-transplant patients.

### Chronic inflammation in ESRD/inflammation and oxidative stress

Various transcriptional and epigenetic changes can contribute to the progression of renal damage through oxidative stress, inflammation and uraemic toxins, as identified in genome-wide association studies.

HD may cause acquired immunodeficiency over time [53]. The dialysis membrane used for the procedure and the bacterial products present in the dialysis water may abnormally activate a series of immune cells, such as monocytes. This phenomenon has been mostly observed with cellulose membranes, compared with non-cellulose membranes, and was dependent on interaction with the dialysis membrane. The authors also observed an increased expression of adhesion molecules such as CD18, CD49, CD54 and the lipopolysaccharide ligand CD14. Moreover, HD induces the expression of complement factors and endotoxins, further contributing to cellular activation, with several consequences such as cytokine secretion and induced apoptosis of cells coming into contact with the membrane. As back-filtration and back-diffusion of contaminated dialysate have been linked to cytokine production during the process, the use of ultrapure dialysis fluid may decrease IL-6 and C-reactive protein (CRP) levels, thus reducing the inflammatory process [54, 55]. Compared with HD, peritoneal dialysis (PD) seems to induce a modest inflammatory response [56], although the prevalence of chronic inflammation is similar in both [57]. This is probably due to the fact that PD relies on the use of a physiological membrane, not an artificial one.

Genetic factors are involved in the development of chronic inflammation, which explains variations in the prevalence and consequences of inflammation in various patient groups. Studies of patients of Asian descent showed a lower predisposition towards chronic inflammation, along with better survival

outcome [58, 59]. Szalai *et al.* [60] identified a single-nucleotide polymorphism (SNP) in the CRP gene that caused increased CRP levels in Caucasians compared with Asian populations. Decreased IL-10 production associated with a SNP can also lead to a more active inflammatory response [61], while a SNP in the LGALS2 gene that encodes galectin-2 was found to have a regulatory role in inflammation [62]. Although genetic polymorphism suggests differences in inflammatory response, it has not been established yet if this translates into differences in inflammatory response during dialysis treatment in both HD and PD.

There is growing evidence that suggests increased levels of oxidative stress in CKD patients, especially in later stages, where there seems to be an inverse correlation between the two [63], promoting inflammation. Moreover, HD can decrease antioxidant levels during the procedure, favouring the accumulation of various oxidative products [64]. Therefore it has been speculated that supplementation of various antioxidants (vitamins E and C) may reduce oxidative stress in these patients, although interventional studies have been inconclusive [65]. Increased oxidative damage to DNA, such as single- or double-strand breakage, base modifications or DNA cross-linking, may increase the mutational load and play an important role in carcinogenesis [66, 67]. Activation of the Ras signalling pathway, as well as c-Myc overexpression, can increase genomic instability and promote DNA damage [68, 69].

During carcinogenesis, the chronic inflammatory milieu can influence the immune response and induce angiogenesis, tumour growth and metastasis [70]. Further genomic instability and accumulation of mutations lead to cancer due to oncogene activation and tumour suppressor gene inactivation. Several pathways are altered in most solid tumours, some being driven by inflammatory conditions, leading to a malignant phenotype [71].

Accumulation of genetic and epigenetic alterations induced by either environmental factors or chronic inflammation causes aberrant DNA methylation [72], and oncogenesis can be further stimulated by various carcinogenic exposures [73]. An epigenome-wide association study associated DNA methylation level in specific cytosine-phosphate-guanine sites with a reduction in estimated glomerular filtration rate, incidence of CKD and renal fibrosis in patients from the Atherosclerosis Risk in Communities and Framingham Heart Studies [74]. Moreover, increased levels of DNA methylation in certain genes, such as connective tissue growth factor, methylenetetrahydrofolate reductase (*MTHFR*) and insulin like growth factor binding protein 1 (*IGFBP1*), have been observed in ESRD patients [75–77]. Other mechanisms involved in the development of CKD include histone crotonylation and acetylation that can contribute to the inflammatory process [78] or higher levels of pro-inflammatory microRNA (miRNA) such as miR-34 [79]. Of note, miRNA and DNA methylation have been studied as biomarkers of CKD progression and these may become treatment targets in the future.

### Gut microbiota and inflammation

Gut microbiota are influenced by and maintain equilibrium via nutrition, metabolism and the immune system [80, 81]. Microbiota evolve with the host over time, with variations in genome, diet and lifestyle factors [82]. The Human Microbiome Project Consortium used next-generation sequencing and metagenomics in order to characterize the diversity of the human microbiome, mapping the microbial signature of normal individuals and highlighting the important role in various

physiological functions and its implications in various diseases [83, 84]. As gut microbiota represent a dynamic system, it has been suggested that alterations in commensal flora can contribute to the pathogenesis of various conditions, including CKD and cancer. Although several studies have focused on describing the microbiome composition and its impact on human health, there is a need for further research corroborated by results from larger clinical trials [85].

In CKD patients, the uraemic milieu influences the intestinal barrier, promoting chronic inflammation and translocation of bacteria and endotoxins across the intestinal wall. In turn, there is a decreased population of beneficial bacteria that produce short-chain fatty acids and an increase in uraemic toxin-producing bacteria [86], generating bound uraemic solutes produced by fermentation in the large intestine [87]. The continuous gut production of endotoxin (constituents of the outer membrane of Gram-negative bacteria) triggers an immune response through the activation of macrophages and endothelial cells, contributing to chronic inflammation in CKD patients [88, 89].

In ESRD patients, there is a bidirectional relationship between the microbiota and the uraemic milieu, as the uraemic milieu has a negative impact on the microbiota on the one hand and, on the other hand, alterations in the microbiota lead to uraemic toxin production [90]. As a consequence, dietary interventions in CKD patients seem to provide benefits in reducing uraemic toxin generation by both the microbiota and the disease itself.

The relationship between gut microbiota and cancer has been intensely studied and a link has been described with gastrointestinal tumours through either oncogene activation or tumour suppressor gene inactivation. A 'gut-brain axis' has been described, suggesting a crosstalk between the enteroendocrine system and the central nervous system, the hypothalamic-pituitary-adrenal axis, the autonomic nervous system and the enteric system [91]. The microbiome can modulate host metabolism, the immune system, xenobiotics and drug metabolism [92–94], being involved in both carcinogenesis through dysbiosis and inflammation and the modulation of treatment response in cancer patients treated with immunotherapy. Treating dysbiosis with probiotics or faecal microbiota transplantation has proven beneficial in preclinical studies, with some authors recommending integrating probiotics alongside anticancer therapy in order to modulate treatment response [95, 96].

Given the increased risk of gastrointestinal tumours in ESRD patients, one possible mechanism could be long-term alterations in gut microbiota, promoting carcinogenesis in this population. However, this association has not been confirmed yet in preclinical or clinical studies and further research is needed, especially in the context of possible modulation of dysbiosis with dietary interventions.

### Intrarenal renin-angiotensin system (RAS) activation as a hallmark of cancer

The RAS regulates haemodynamics [97] via renal sodium transport under both physiological and pathological conditions. However, preclinical studies have suggested that RAS is also involved in various other functions such as cell cycle regulation and angiogenesis inhibition [98]. In ESRD patients, higher intrarenal angiotensin II levels and angiotensin II receptor type 1 (AT1R) expression have been observed, secondary to RAS

activation, contributing to renal damage such as tubulointerstitial fibrosis [99].

The extravascular impact of RAS may be oncogenic. Several acquired properties of cancer cells, as defined in 2000 by Hanahan and Weinberg [100], include angiogenesis, cell proliferation, metastasis and alteration of metabolism and the micro-environment. The effects of the RAS on cancer cells seem to favour the described hallmarks. However, it is still unclear if RAS alterations are secondary to cancer development or if they play a role in carcinogenesis.

RAS signalling induces receptor-mediated cell proliferation and differentiation in vascular smooth muscle cells and breast, pituitary, adrenocortical and endometrial cells [101, 102]. One of the possible mechanisms by which angiotensin peptides are involved in cellular growth is through mitogen-activated protein kinase (MEK) and PI3K signalling [103], which are important signalling pathways overexpressed in various cancers. The receptor-mediated signalling of the RAS may be dependent on both the overexpression and the type of receptor, as AT1R is mainly responsible for cell proliferation and angiogenesis, whereas angiotensin II receptor type 2 (AT2R) has inhibitory effects, thus stimulating apoptosis [103].

Arrieta et al. [104] analysed the expression of AT1R and AT2R in high-grade astrocytoma, correlating receptor expression with the mitotic index and vascular density, suggesting a co-dependent relationship between the two receptors. Inhibition of AT1R may result in AT2R overexpression and activation of cell death through apoptosis.

RAS activation through AT1R may favour cancer cell survival through activation of the PI3K–Akt pathway, suppression of the caspase pathway and production of anti-apoptotic Bcl proteins [105]. It is involved in reshaping the tumour microenvironment through pro-inflammatory and pro-angiogenic signalling, along with generation of reactive oxygen species involved in DNA damage.

The RAS in tumour invasion and metastasis has been suggested by two trials that included gastric cancer [106] and renal cell cancer patients [107], where AT1R overexpression could have an impact on tumour behaviour, suggesting a possible link between RAS and tumour capacity for metastasis. Keizman et al. [107] retrospectively analysed the possible effects of adding an angiotensin-converting enzyme (ACE) inhibitor to sunitinib. The combination significantly improved patient outcome, with a 7-month progression-free survival benefit (HR 0.537;  $P=0.0055$ ), suggesting that adding an ACE inhibitor may decrease the expression of vascular endothelial growth factor and inhibit the growth factor receptor through a secondary mechanism.

Genetic determinants have been associated with an increased risk of cancer. In a population-based study, van der Knaap et al. [108] suggested that carriers of the high-activity DD genotype have an increased risk of breast cancer compared with those with the low-activity II/ID genotype [HR 1.47 (95% CI 1.05–2.04)]. Moreover, DD carriers who were exposed to long-term high-dose medication were at lower risk of cancer [HR 0.28 (95% CI 0.10–0.79)] and short-term high-dose patients had a higher risk of colorectal cancer progression in the II/ID stratum [HR 3.83 (95% CI 1.67–8.79)].

## CONCLUSIONS

Mechanisms related to immune dysfunction and inflammation have been suggested to be involved in promoting cancer in ESRD patients. Current data focus on the role the microbiota

and uraemic milieu play in modulating inflammation in CKD patients and on understanding their role in cancer initiation. In the ‘-omics’ era, identification of predictive biomarkers can better stratify patients at risk and incorporate better surveillance or preventive strategies for the CKD patient.

Onconephrology has already been recognized as an emerging field, due to the importance of a multidisciplinary approach of ESRD patients with cancer. Complex management strategies for these patients have influenced research strategies that have led to a better understanding of the underlying mechanisms of cancer in these patients. However, there is still an unmet need in the field, as the mechanisms involved in cancer initiation and progression in this particular setting are still not fully understood. The focus of future research will likely include preventive strategies that can lead to improved cancer screening and treatment in patients with CKD.

## CONFLICT OF INTEREST STATEMENT

None declared.

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