# Doctoral (PhD) dissertation

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## End-Stage Kidney: Model for the relationship between inflammatory microenvironment and tumorgenesis

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**2022**

# End-stage renal disease

**End-stage kidney (ESRD) and it's significance**

Chronic kidney disease (CKD) is one of the major diseases today. By 2017, the number of patients had reached 700 million. It caused the deaths of 1,2 million patients, which is projected to rise further in the future, reaching 4 million deaths a year by 2040. Kidney failure is the last (fifth), most severe stage of CRD, defined as a GFR below 15 mL per minute per 1,73 $m^2$ body surface area. End-stage renal disease refers to an irreversible clinical process in which the patient permanently dependent upon renal replacement therapy (dialysis or kidney transplantation) in order to avoid life-threatening uremia.

The incidence and prevalence of ESRD show a steady increase. In the USA, according to the U.S. Renal Data System, the number of ESRD patients is growing by 20000 each year.

ESRD is multifactorial in origin. The increase in the number of patients can be attributed to a number of etiological factors. In the past decades, glomerulonephritis was one of the leading causes of the disease. Nowadays, the number of patients with ESRD of infectious origin is declining significantly, especially

in developed countries, however, it is still a significant etiological factor in developing countries. Recent studies identify hypertension and diabetes as the two main etiological factors. Among the etiological factors, it is important to mention polycystic kidney disease, long-term obstruction of the urinary system (regardless of the exact cause of the obstruction), vesico-ureteral reflux, recurrent pyelonephritis, and some medications such as non-steroid anti-inflammatory drugs (NSAID), calcinurin inhibitors and antiretroviral drugs. The life expectancy at birth is constantly increasing. Aging is also a risk factor for the kidney failure, the number of patients is increasing year by year, on the the other hand, more and more CKDis entering the end-stage “thanks” to the evolving medical science. 2,5 million patients worldwide receive kidney replacement therapy, but for the reasons detailed above, their number could reach 5,4 million by 2030.

Only 2% of CKDprogresses to end-stage, however, caring for this patient population places a significant burden and cost on health systems. The data show that we are facing not only a health problem, but also a serious economic problem. The prevention could be the key for the future.

**Histological aspects of ESRD**

Over time, CKD leads to the development of shrinking kidney. The common histopathologic features of the characteristically shrunken end-stage kidneys displaying tubular atrophy, interstitial inflammation and fibrosis, severe arterial, arteriolar and glomerular sclerosis result directly or indirectly from loss of functional and structural integrity. By the time of terminal uremia the kidneys may have much the same morphological appearance irrespectively of primary renal disease which excludes the exact recognition of original disease, particularly in kidneys of patients on chronic dialysis.

Renal replacement therapies prolong patient's life expectancy, especially if their disease is limited to the kidneys. After prolonged dialysis, a previously rarely seen, novel type of histological picture is called end-stage renal disease (ESRD).

If diffuse cystic lesions are also seen in the kidneys, we can speak of acquired cystic kidney disease (ACRD). In patients dialyzed for years, the histological picture of ACRD is often found, in which intense cell proliferation is observed with pre-neoplastic lesions and even rare clear-cell kidney cancer types.

The progressive structural changes, i.e. considerable fibrosis and intimal arterial thickening and widespraed deposition of

calcium, calcium oxalate or calcium phosphat crystals have already been mentioned in the previous decades. Renal epithelial cells respond with increased proliferation to calcium oxalate crystals. The characteristic histological changes of the end-stage kidney were already known.

Previous articles have reported microscopic cellular nodules of smooth muscle cell proliferation arising around arterial and arteriolar necrosis as well as the increase in arterial intimal thickness due the increased growth of endothelial and smooth muscle cells. The diverse froms of tubules of end-stage kidneys were classified into „classic" atrophic tubules, tubules showing „thyroidization", „endocrine" tubules and „super" tubules. Although the end-stage kidney is atrophic, scarred, it shows very significant proliferative activity, especially in the epithelium of the classical and super tubules.

**Cystic lesions of the kidney, acquired cystic kidney disease (ACRD)**

Cystic lesions in both kidneys following prolonged dialysis have been described previously. In acquired cystic kidney disease, the integrity of the normal tissue structure is compromised and replaced by chronic inflammation and

fibrosis. The diagnosis of ACRD accepted generally requires the presence of more than 3 cysts or more than 25% of tissue involvement in each kidney and the exclusion of hereditary cystic kidney diseases. Most cysts develop mainly in the cortical region, but the renal parenchyma can be affected anywhere. In the walls of larger cysts, the cell proliferation is more intense than in the smaller ones.

Renal replacement therapy may result diffuse cystic lesions in both kidneys, however, it is important to emphasize that in these patients the primary disease is not prone to cyst formation. The histological picture that also develops as a result of dialysis is called acquired cystic kidney disease. Renal cell tumor is more common in patients with ESRD and acquired cystic kidney disease than in the normal population. In a prospective study, the incidence of clinically confirmed renal cell tumors in patients awaiting kidney transplantation was 3,8%. In the normal population, the risk of renal cell tumor is 0,04%, which makes it easy to recognize the contrast between the two populations.

The duration of dialysis clearly negatively affects the development of acquired cystic kidney disease. With 10 years of dialysis, the probability of developing the disease is 100%. The significance of ACRD can be attributed to the many

complications it causes. The most common is haematuria due to rupture and infection of the cysts, which can also occur in the form of micro- and macrohaematuria. Although the development of a renal cell tumor is not the most common lesion among patients with acquired renal cysts, it is still the most important for both the patient and the clinician.

**Renal cell tumors in ESRD/ACRD**

In dialysed patients, the relative risk of renal cell tumors is significantly higher compared to the average population. Tumor prevalence in dialysed patients is 1,4-1,7%. Renal cell tumors associated with ACRD develop earlier in time, are bilateral in 10%-, and multifocal in 33% of cases. Although often multifocal or bilateral the tumor, it rarely gives symptoms and its size is usually smaller than 3cm.

Among patients with ESRD, the proportion of papillary tumors is significantly higher. In half of the cases, papillary kidney tumor develops, while in the average population, conventional kidney tumor develops in 90%-, and papillary only in 10% of the cases. Various histologic types renal cell tumors-, specific only in renal cell tumors in ESRD patients have been

described previously. Calcium oxalate deposits are observed in tumors and large eosinophil cells may be present.

Based on molecular genetic analysis, the genetic changes in some ESRD/ACRD tumors are similar to the general population, while others show only the most characteristic chromosome changes or not at all. With unusual tumor morphology, the diagnosis of some ESRD / ACRD-associated tumors is uncertain even after clinical symptoms and molecular characterization. Although further studies are required, the available data suggest that the development of ESRD / ACRD-associated renal cell tumors may differ from the normal population.

**Pathogenesis of ESRD/ACRD and tumours**

In spite of histochemical and molecular genetic studies, the biology of proliferating parenchymal and interstitial cells as well as the molecular mechanisms leading to formation of multiple cysts, remodelling the kidney parenchyma and development of unique type of tumours remains unknown. During chronic renal failure, structural integrity is disrupted, scarring caused by chronic inflammation first determines the microscopic image, followed by the damage of nephrons. The name of the end-stage

kidney is not idle, because there is very intense cell proliferation in the cells of atrophic tubules and stromal cells in these kidneys.

Most cysts in the kidney are lined with a single layer of squamous or cubic epithelium. In end-stage kidneys, the epithelium lining the cyst, or even the epithelium found in the tubules, shows intense hyperplastic activity. Hyperplasia is most pronounced in atypical cysts, in which the wall of the cysts is composed of atypical cells that often form papillary-growing precancerous lesions. The liquid inside the cysts is usually clear or yellow, possibly reddish or brownish due to cystrupture or bleeding. Cysts origins from the dilated tubules, with the increased proliferation of tubular cells and closure of the proximal and distal parts of the tubule.

Most of the cysts and tumors develop from the proximal tubules. The exact molecular mechanism of renal structural transformation is unknown, but several factors that play an important role in the process are already known. Due to insufficient renal excretory function, potentially toxic agents accumulate in the body that would be excreted in the urine of a healthy person. The clinical picture is called uremia. Uremia affects all organs. Increased amounts of toxic substances damage the DNA in the cells. In 1988, sibling chromatid

exchange or micronucleus formation associated with uremia was described. The effectiveness of DNA repair mechanisms in uraemic patients decreases to around 60%, which can be increased to normal levels with renal replacement therapies.

Toxic agents in uremic patients can cause severe mitochondrial damage. Mitochondrial DNA is much more sensitive to genotoxic effects and therefore mutations are more common. The higher incidence of mutations can be explained by the lack of different protective and repair mechanisms. Due to mutations in mitochondrial DNA, increased production of intracellular reactive oxygen species (ROS) is expected due to the defect ofelectron transport chain. Elevated ROS levels can further cause tumor formation by damaging the DNA. End-stage kidneys tumors significantly differ from tumors in non-renal defficient patients in both genetic and histological characteristics. Genetic studies have identified chromosomal and DNA mutations that are absent in sporadically occurring renal tumors. The frequency of precursor lesions, the unique histological and genetic characteristics of tumors in ESRD / ACRD, suggest an alternative pathogenesis in which changes in the microenvironment are likely to play main role.

## The role of the microenvironment in ESRD / ACRD-associated tumors

In uraemia, increased amounts of potentially toxic compounds keep epithelial cells under toxic stress. In addition, increased expression of growth factors such as hepatocyte growth factor (HGF), hepatocyte growth factor receptor (MET) and insulin-like growth factor (IGF-1) contributes to increased proliferation of renal cells and thus to renal remodeling. Other studies highlight the importance of the role of hypoxia-inducible factor-2 (HIF-2) and hypoxia-inducible factor-1α (HIF-1α), which may lead to renal neovascularization. The carcinogenic effect of oxidative stress caused by inflammation has long been known. Oxidative and metabolic stress on cells and ROS induced by various cytokines, including interleukin 6 (IL-6), lead to increased expression of hypoxia-inducible factor-1 (HIF-1). HIF-1 leads to the synthesis of various pro-inflammatory proteins in the nuclear factor kappa beta (NFκB) pathway that play a significant role in the inflammatory cascade in the ESRD and ACRD kidneys. In normal cells, thioredoxin-interacting protein (TXNIP) and thioredoxin (TXN) regulate the appropriate ROS levels required for cell function. Increased

expression of TXNIP promotes the formation of intracellular ROS by inhibiting TXN function.

Altered expression of proto-oncogenes, amplification of c-erbB-2, activation of c-jun, and hypermethylation of connexin 32 have been reported. Increased expression of cytokines such as IL-6, interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF) in ESRD / ACRD kidneys has been described. In nephropathy (DNP) due to diabetes, damage to the proximal tubules leads to the expression of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) and the initiation of an inflammatory process. A global gene expression assay described a specific gene expression fingerprint characteristic of the ESRD / ACRD kidneys in which functionally linked genes such as cytokines and chemokines and keratins were present. In addition, a number of genes involved in cell proliferation have been identified. Real-time polymerase chain reaction (RT-PCR) and immunohistological examination confirmed that a significant part of the genes are indeed expressed only in ESRD / ACRD kidneys.

Patients with ESRD have lower levels of 1,25- (OH) 2D3 (vitamin D) in the blood. Vitamin D has been implicated in the regulation of cell proliferation and its antitumor activity has also

been demonstrated. Circulating vitamin D levels in the kidney are regulated by two hydroxylases. 1α-hydroxylase (CYP27B1) is responsible for the synthesis of the biologically active form of vitamin D, while 24-hydroxylase (CYP24A1) regulates the catabolism of vitamin D (14). Our experimental work has suggested that impaired vitamin D metabolism may be associated with carcinogenesis.

## Aim of the study

It is known from the literature to date that renal tumors with histological and genetic characteristics different from those in the normal population are more common in the kidney of ESRD. An earlier hypothesis is that the microenvironment developed in the kidney of the ESRD may play a role in this. To confirm this, we examined the expression of genes involved in the development of the inflammatory microenvironment by immunohistology:

a, cell-bound expression of cytokines such as IL-6, Colony stimulating factor 2 (CSF2), Transforming growth factor β (TGFβ), and Interleukin 1β (IL1β) was determined

b, we examined the expression of genes involved in fibrotic stroma formation and renal remodeling, such as α smooth muscle actin (αSMA), Fibronectin 1 (FN1), Laminin subunit α 3 (LAMA3), Laminin subunit β 3 (LAMB3) , and Laminin subunit γ 2 (LAMC2).

c, we examined the expression of metalloproteinases such as Matrix metallopeptidase 9 (MMP9) and Matrix metallopeptidase 12 (MMP12), which are required for rearrangement of renal structure and tumorigenesis.

d, we are looking for a correlation between the significantly reduced number of tubules in the ESRD kidney and the tissue expression of the vitamin D receptor and CYP24A1 and CYP27B1.

e, we examined the effect of the TXNIP-TXN redox system involved in the regulation of ROS induced by inflammatory stress.

# Patients and Methods

## Sample collection and histological diagnosis

We have collected 12 kidneys from ESRD/ACRD cases removed due to cancer. The formalin fixed kidney specimens were obtained from the Departments of Urology, University of Heidelberg, of District Hospital Bad-Hersfeld, Germany and of Radcliffe Hospital, Cambridge, United Kingdom and of Institute of Pathology, University of Ljubljana, Slovenia. Six kidneys were classified as ESRD and six ones with an intensive cystic changes as ACRD. In all cases, nephrectomy was performed and non-of the patients had kidney transplantation. Samples underwent immediate processing after nephrectomy. Each kidney was processed in several hundreds of paraffin blocks for histological analysis. The hematoxylin and eosin stained slides were scored for cysts, small precursor lesions and tumors. The diagnosis of the main tumors was established according to the Heidelberg Classification and as proposed by Tickoo et al. Five tumours were diagnosed as papillary RCC and another 6 as conventional RCC. We also found one oncocytoma, two ACRD-associated eosinophylic-vacuolated tumors, two chromophobe-like tumors, and one clear cell papillary RCC in the 12 kidneys. Altogether, 65 small papillary, 42 chromophobe-like and 24

eosinophilic vacuolated pre-cancerous lesions were detected in the 12 kidneys. The use of this material has been authorized by the Ethics Committee of the Universities of Heidelberg and Pécs. (No. 5343/2014) Embryonic kidneys were processed from the Department of Gynecology, Pécs, in connection with legal abortion.

**Tissue microarray (TMA)**

Tissue multi array (TMA) of ESRD/ACRD associated tumors was constructed from paraffin embedded tumors after marking the areas of interest on H&E stained slides. Core biopsies of 0.6 mm in diameter were placed within a recipient block by the Manual Tissue Arrayer (MTA1, Beecher Instruments, Inc. USA). Foetal kidneys were obtained from autopsy whereas adult kidney tissues from radical nephrectomy.

**Immunohistochemistry**

Sixteen representative paraffin blocks from ESRD/ACRD kidneys were selected for immunohistochemistry. Serial sections were used to be able to compare the results obtained by different antibodies. We have also analysed foetal and adult kidneys for the cellular localisation of the antibodies. A TMA containing 3-5 core biopsies of each ESRD/ACRD associated tumor has also been analysed.

1. **Table.** Used antibodies

| Antibody | Manufacturer |
|---|---|
| anti-VDR, ab134826 | Abcam, Cambridge,UK |
| anti-CYP27B1, EPR20271 | Abcam, Cambridge UK |
| anti-CYP24A1, HPA022261 | Sigma-Aldrich, St-Louis, MO, USA |
| anti IL6 PA1-26811 | Thermo Fisher, Budapest, Hungary |
| anti-CSF2, TA808009 | Origene, Rockville, MD, USA |
| anti-TGFβ, PA1-26811 | Thermo Fisher, Budapest, Hungary |
| anti-αSMA, ab124964 | Abcam, Cambridge, UK |
| anti FAPa ab207178 | Abcam, Cambridge, UK |
| anti-FN1, ab32419 | Abcam, Cambridge, UK |
| anti-MMP12, NBP1-31225 | Novus Biologicals, Littleton, CO, USA |
| anti-LAMA3 HPA009309 | Sigma-Aldrich, Budapest, Hungary |
| anti-LAMB3 HPA008069 | Sigma-Aldrich, Budapest, Hungary |
| anti-LAMC2 HPA024638 | Sigma-Aldrich, Budapest, Hungary |
| anti-TXN, HPA055752 | Atlas Antibodies, Bromma, Sweden |
| anti-TXNIP, EPR14774 | Abcam, Cambridge, UK |
| anti HIF1a ab51608 | Abcam, Cambridge, UK |

# Results

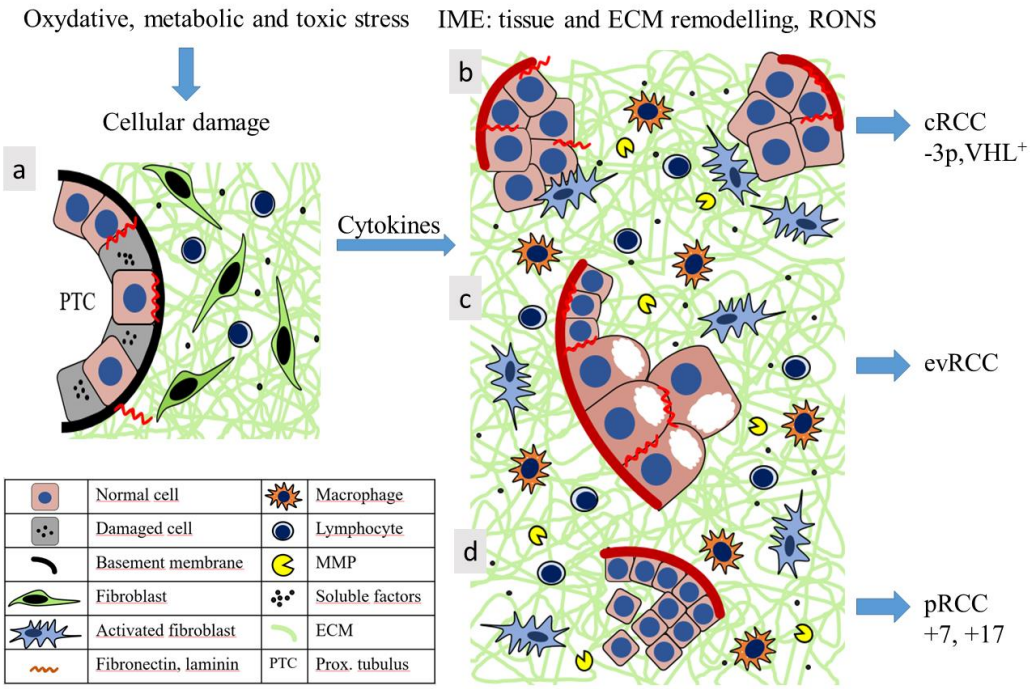
Detailed clinical and histological data on ESRD / ACRD cases and their tumors are provided in the dissertation.

### ESRD kidney and increased tumorgenesis

The histological image of ESRD is dominated by the chronic inflammatory microenvironment in which epithelial cells are confined to either cystically transformed or completely disordered cell clusters. A significant portion of the inflammatory microenvironment is comprised of ECM and its dissolved growth factors, cytokines, and proteinases. In the inflammatory microenvironment, many cellular elements occur, which are activated by fibroblasts, immune cells, macrophages, lymphocytes. Proliferating endothelial cells and pericytes are also part of the microenvironment. These mesenchymal cells interact with epithelial cells. The continuous expression of cytokines, the constant presence of activated fibroblasts, the resulting oxidative and metabolic stress, and the resulting genetic instability play a significant role in the development of renal tumors. Added to this is the fact that epithelial cells themselves undergo significant transformation because, in the

absence of function, they alter their cytoskeletal profile and become more plastic. Under these conditions, in addition to increased cytokine and growth factor production, it is not unexpected to observe that the ESRD kidney is not a resting organ but a significant cell proliferation organ.

Considering the detailed histological and immunohistochemical analysis and the data from the gene expression fingerprint, the following developmental pathways emerge for ESRD / ACRD-derived tumor types.




The putative pathomechanism of end-stage renal disease and the development of various tumors.

**Clear cell renal cell cancer (cRCC).** There are one or two epithelial cells or loosely connected epithelial cell groups in the fibrotic inflammatory kidney stroma that are likely to correspond to cells remaining after inflammatory, necrotic destruction of the proximal tubules. These cell groups are not surrounded by a basal membrane recognizable at the light microscopic level. In our opinion, these cells are a potential

starting point for cRCC. 95% of the cRCC is characterized by the loss of the short arm of one of chromosomes 3 and about 60% by a mutation in the Von Hippel-Lindau (VHL) gene. Preliminary studies indicate that loss of the 3p chromosome region due to increased mitotic activity in normal adult kidneys during embryonic development, with a copy of the VHL gene, is not uncommon. High concentrations of RONS may cause mutations in the VHL and / or Permeable reactive barrier myc box 1 (PRMB1) genes. If a VHL mutation occurs in a cell carrying a chromosomal change and that cell begins to proliferate under the influence of highly expressed growth factors in the microenvironment, a tumor may develop. Interestingly, no precursor lesions were detected in the general population (with the exception of VHL syndrome), but ESRD / ACRD kidneys have an average of 3-4 microscopic clear cell lesions. The finding also confirms that while cells in the poximal tubule in the average population are in a normal microenvironment, cell groups without a basement membrane in the ESRD kidney are embedded in a pro-tumorigenic microenvironment.

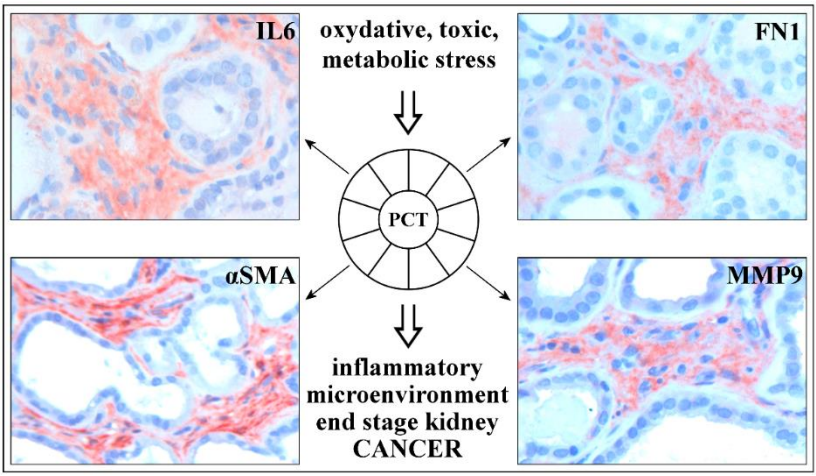
**Eosinophilic vacuolated renal cell carcinoma (evRCC)** occurs almost exclusively in end-stage ACRD kidneys. In a large, multi-institutional study, almost every second tumor in ACRD kidneys was diagnosed as evRCC. The occurrence of evRCC is associated with a number of pre-neoplastic lesions that show a similar histological pattern. Smaller or larger cysts lined with large eosinophil vacuolated cells are seen only in ACRD kidneys. In some cysts, a transition from small cubic cells to large eosinophil vacuolated cells was observed. In our opinion, evRCC ACRD is derived from similar cysts found in the kidneys.

**Papillary renal cell carinoma (pRCC).** The origin of pRCCs in the normal population as well as in the kidney of the ESRD / ACRD is still under discussion. More than 25 years ago, it was suggested that pRCC is derived from non-fully differentiated embryonic cells that remain throughout life. This theory is supported by the fact that each pRCC in a normal population carries an average of 42 nephrogenic rest lesions and an average of 13 nephrogenic rest lesions associated with pRCC observed in ESRD / ACRD kidneys. The frequency of small papillary lesions / adenomas in the general population was documented by Apitz as early as 1944. He also suggested that adenoma is

caused by a disorder of embryonic kidney differentiation, and that kidney sclerosis only increases the number and magnitude of these lesions. The data suggest that papillary lesions detected in the kidney of sclerotic ESRD develop from embryonic dormant cells that have begun to grow under the influence of a tumor inflammatory microenvironment. The genetic changes in the vast majority of pRDs in the ESRD / ACRD are similar to those observed in non-ESRD / ACRD-related pRCCs in the general population.

**Conclusions**

Our study aimed at a better understanding of the pathomechanism leading to the development of ESRD / ACRD. The pathomechanism of the irreversible inflammatory microenvironment leading to complete structural remodeling of the kidney and thus to the narrowing or complete cessation of renal function was investigated by immunohistology.




Summary of end-stage renal changes and tumorigenesis.

a, Damage to the proximal tubules for any reason, due to oxidative, toxic, or metabolic stress, initiates an irreversible process that creates an inflammatory microenvironment.

b, Continuous expression of IL-6 plays a significant role in maintaining this, but other cytokines such as IL-8, CSF2, and TGFB are also involved in maintaining the inflammatory microenvironment and transforming the ECM.

c, The cellular component of the ECM is largely composed of activated fibroblasts and immune cells. αSMA-positive

activated fibroblasts play an important role in the formation of the fibrillar portion of the ECM and in constant communication with epithelial cells.

d, αSMA-positive myofibroblasts produce significant amounts of FN1. Fibronectin is essential in the assembly of the ECM fibrillar protein network, including collagen, fibrillin, fibrinogen, fibulin, integrin, and thrombospandin. Activated fibroblasts also play a significant role in the conversion of the ECM pro-tumorigenic gene.

e, The expression of MMPs as MMP9 and MMP12 plays a significant role in the reconstruction of the ESRD / ACRD kidneys, the degradation of the ECM around proliferating epithelial cells, and at the same time in the development of tumors.

f, A significant decrease in the expression of CYP27B1 and VDR in the fibrotically reconstituted kidney and its remaining epithelial cells, and thus the elimination of the protective effect of vitamin D, also contributes to the development of tumors.

g, Damage to the TXN / TXNIP redox system is associated with an inflammatory microenvironment in the kidney of the ESRD / ACRD. The altered expression of TXN / TXNIP in the evRCC associated with ESRD / ACRD and their precursor lesions suggests a causal role for the oxidative-reductive system lesion.

The association between inflammation and an increased risk of cancer has been well documented recently. For example, the association between viral hepatitis and liver cancer, Helicobacter pylori infection and gastric cancer, schistosomiasis and bladder cancer, or the development of human papilloma virus and cervical cancer is known. Based on our previous and present studies, we believe that the association between the inflammatory microenvironment in ESRD / ARCD and the associated common cancers can be added to these examples. The tumor is actually considered a wound that never heals. The irreversible, progressive inflammatory and fibrotic process observed in the kidney of ESRD / ACRD also corresponds to a never-healing wound, which may eventually lead to another never-healing wound, a tumor.

## Acknowledgement

First of all, I would like to thank my supervisor, Gyula Kovács, MD who gave me the opportunity to establish my research. It was an honor for me to work with Him. Throughout our work, he motivated, supported and taught me. In our joint work, he shared me his life experiences, with which he made a significant contribution to my development.

I would also like to thank the Department of Urology Pécs for allowing me to do my scientific work.

I am also grateful to my colleagues of the Department of Urology, University of Debrecen, who took into account my time spent writing the research work and writing the dissertation.

In addition to the above, I would like to thank the staff of the Heidelberg Molecular Oncology Laboratory for using the results of their previous work.

Last but not least, I am grateful to my family and wife, who supported me with their understanding and patience throughout.

## Közlemények

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