Full Review

Contribution of genetics and epigenetics to progression of kidney fibrosis

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ABSTRACT

Chronic kidney disease (CKD) which can lead to end-stage renal failure remains a principal challenge in Nephrology. While mechanistic studies provided extensive insights into the common pathways of fibrogenesis which underlie the progression of CKD, these pre-clinical studies fail to fully explain the vastly different progression slopes of individual patients. Recent studies provide evidence that genetic polymorphisms and epigenetic variations determine the individual susceptibility of patients to develop chronic progressive kidney disease. Here, we review recent insights that were provided by genome-wide association studies (GWASs), gene-linkage studies and epigenome analysis.

The progression of CKD towards end-stage renal failure remains a principal unsolved problem in Nephrology as effective therapies and predictive tests are still not available [1, 2]. Chronic progressive kidney disease is caused by a wide range of diseases, with diabetes mellitus, hypertension and primary glomerulopathies being the most common causes in the Western world [3]. Infections, physical obstruction, interstitial nephritides and genetic cystic kidney diseases are also common causes of end-stage renal disease (ESRD) [3]. Regardless of the primary underlying disease, chronically injured kidneys are histomorphologically characterized by tubulointerstitial fibrosis [1]. In fact, the extent of tubulointerstitial fibrosis is the best predictor for kidney survival, irrespective of the underlying disease. For this reason, fibrosis is considered the common pathway of chronic progressive kidney disease [1]. Fibrogenesis is a pathological scarring process which involves accumulation of activated fibroblasts, excessive deposition of extracellular matrix, failed regeneration of tubular epithelium, microvascular rarefaction and (mostly sterile) inflammation [4]. Fibrogenesis depends on a complex inter-action of the involved cell types which is orchestrated by an extensive network of growth factors and signalling pathways (which are reviewed extensively elsewhere) [1]. In view of the detailed mechanistic knowledge of the pathways that orchestrate renal fibrogenesis, it is puzzling why progression rates of CKD differ dramatically among patients with identical underlying diseases [1, 2]. The fibrotic pathways are known, but the switches that control their intensities and which determine the speed at which fibrosis moves along the progression slope are not yet understood [1, 2].

The concept that genetic polymorphisms are the basis for individual progression rates of CKD is an obvious and attractive one. Distinct susceptibilities of different mouse and rat strains to experimental CKD are a strong testament of the impact of genetic variations on renal fibrogenesis. Identification of the underlying genetic polymorphisms and mechanistic proof of their involvement in the progression of CKD, however, is an ongoing challenge. There are two basic approaches: one strategy is to perform unbiased screening to identify genes which are associated with chronic progressive kidney disease and to then prove their mechanistic relevance in experimental studies (‘genotype to phenotype approach’). The second strategy is to selectively analyse polymorphisms of genes which have been identified in mechanistic studies as drivers of renal fibrogenesis with regard to their association with CKD (phenotype to genotype approach). The puzzling observation, however, is that genetic analysis and mechanistic studies so far rarely complement each other. The current state of affairs is reviewed in more detail below.

Keywords: DNA repair, epigenetics, fibrosis, genetics, GWAS, histone, methylation, SNP

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INSIGHTS FROM UNBIASED GENOMIC ANALYSIS

While any two unrelated individual patients share 99.5% of the DNA sequence, 0.5% of their DNA differs, accounting for their individuality. Variations in a single nucleotide are referred to as single-nucleotide polymorphism (SNP). Through the HapMap project more than 12 million SNPs with a frequency of >1% in the general population have been identified (http://hapmap.ncbi.nlm.nih.gov). With the emergence of high-throughput hybridization and sequencing technologies, it has become possible to analyse the association of disease traits with SNP frequencies in a genome-wide association studies (GWAS).

Since 2005 (when a polymorphism of the ‘complement factor H’ gene was linked to macular degeneration [5]) more than 1500 GWASs have been published and several studies were done to identify genetic polymorphisms that predispose to the progression of CKD. GWAS identified several genes which are associated with the chronic decline of kidney function (Table 1), notably ‘nonmuscle myosin heavy chain type 2 isoform A (MYH9), uromodulin (UMOD), methylenetetrahydrofolate synthetase (MTHFS), eyes absent homologue 1 (EYA1), transcription factor-7-like 2 (TCF7L2)’ (see Table 1). However, with the exception of uromodulin, none of the proteins encoded by these genes have yet been linked to the progression of CKD. Furthermore, genes which had been established as principal determinants of renal fibrogenesis through mechanistic studies, such as the gene encoding for transforming growth factor β1 (TGFβ1) as the most prominent example, were not re-discovered in GWASs. There are several explanations for this discrepancy: to link SNPs (with frequencies of 1–10% in the general population) with disease traits, large patient cohorts are required. For this reason, the CKD-GWAS focused on the elevation of serum creatinine and not on patients with biopsy-proven nephropathies. Furthermore, SNPs with frequencies of <1% were not assessed in these studies, a limitation which may be overcome through more advanced technologies (full-genome sequencing) may reveal the genetic origins of individual susceptibilities in the future.

INSIGHTS FROM CANDIDATE GENE ANALYSIS

As opposed to unbiased GWASs, numerous studies explored the association of genetic polymorphisms of genes which are known to be involved in renal fibrogenesis with progression of CKD in a biased fashion. Based on the concept that a dysregulation of growth factors underlies the progression of fibrosis, most of these studies focused on genetic polymorphisms involving growth factors with established fibrotic activities. Because TGFβ1 has been established in multiple mechanistic studies as a principal driver of fibrosis in the kidney (and in other organs such as liver, lung, heart and skin as well), most efforts focused on TGFβ1—with inconclusive results. Due to its outstanding role, studies involving TGFβ1 are discussed in detail below.

TGFβ1 is the prototypical (and first discovered) member of the TGF beta superfamily of structurally related cell regulatory proteins (which includes TGFβ proteins, bone morphogenetic proteins, activins and growth differentiation factors). Members of the TGFβ superfamily signal through cell surface serine/threonine-specific protein kinase receptors, and generate intracellular signals using a conserved family of proteins called SMADs. TGFβ1 was originally identified as a factor that induces the capacity of anchorage-independent growth, a hallmark of malignant transformation [6]. The prominent role of TGFβ1 in renal fibrogenesis was first demonstrated when neutralization of TGFβ1 with anti-serum ameliorated experimental fibrosis in the kidney (and in heart and liver as well) [7–10]. TGFβ1 is consistently upregulated in experimental models of renal fibrosis and in kidney biopsy specimen with fibrotic lesions, irrespective of the underlying disease [11–14].

Table 1: Overview of genes which were identified through GWASs of impaired kidney function

<table>
<thead>
<tr>
<th>Identified genes with SNPs associated with increased CKD risk</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMOD, SHROOM3, GATM-SPATA5L1, CST, STC1</td>
<td>GWAS on 41 343 European-ancestry individuals [39]</td>
</tr>
<tr>
<td>LASS2, GCKR, ALMS1, TFDLP, DAB2, SLC34A1, VEGFA, PRKAG2, PIP5K1B, ATXN2, DACH1, UBE2Q2, SLC7A9</td>
<td>GWAS on 67 093 individuals of European ancestry [40]</td>
</tr>
<tr>
<td>PAX8, LRIG1-KBTBD8, BCL6-LPP, SLC14A2, GNAS, MTK1-GABA, MECOM, UNC5, MPPED-DCCDS, WDR72, ALDH2, C12orf51, BCAS3, SHROOM3, MHC region, UMOD</td>
<td>Meta-analysis of 71 149 east Asian individuals from 18 studies as part of Asian Genetic Epidemiology Network [41]</td>
</tr>
<tr>
<td>MPPED, DDX1, SLC47A1, CDK12, CASP9, INO80</td>
<td>GWAS on 130 600 individuals of European ancestry stratified by age, sex, diabetes or hypertension status [42]</td>
</tr>
<tr>
<td>MTHFS, EYA1</td>
<td>Analysis of 70 987 SNPs in 1010 participants of Framingham Heart and Atherosclerosis Risk in Communities Study [43]</td>
</tr>
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In cell culture, TGFβ1 induces ‘pro-fibrotic’ responses in numerous cell types, including increased proliferation and increased extracellular matrix synthesis by renal fibroblasts and mesangial cells, chemokine release and epithelial-mesenchymal transition of tubular epithelial cells and endothelial-mesenchymal transition of endothelial cells and de-differentiation of podocytes. Overexpression of TGFβ1 in transgenic mice causes renal fibrosis, and inhibition of TGFβ1 has been demonstrated to ameliorate fibrosis in most models of experimental CKD. To our knowledge, the pivotal relevance of TGFβ1 for kidney fibrosis has not yet been disputed, making TGFβ1 a likely determinant of individual progression rates of fibrosis in patients with CKD [15].

TGFβ1 is encoded by the TGFBI gene located at chromosome 19q13.1. The coding region contains seven exons and six introns encoding for a 390 amino acid (aa) polypeptide, which consists of a signal peptide (aa 1–29), a latency-associated peptide (aa 30–278) and the TGFβ1 domain (aa 279–390) (Figure 1). A homodimer of the C-terminal 112 aa TGFβ1 domain constitutes the biologically active TGFβ1. There are currently 483 polymorphisms of TGFβ1 known. Epidemiological and functional studies focus on six SNPs (which with an allele frequency of higher than 0.1 are among the most common in the White population) with three of them involved in the promoter region (C−988→A, C−800→A, C−509→T), and three of them involved in the coding region (T869→C, G914→C, C1628→T) (Figure 1). The C−800→A polymorphism (SNP rs1800468) is located within a cAMP-response element binding site and has been linked to reduced TGFβ1 expression [16]. The C−509→T (SNP rs 18000469) is located within an YY1 consensus binding site and the T allele has been linked to increased promoter activity and increased TGFβ1 plasma levels [17]. No functional consequence has yet been linked to the C−988→A polymorphism (rs1800820). Both the T869→C (syn. Leu10→Pro, codon 10 polymorphism, rs1800470) and G914→C (syn. Arg25→Pro, codon 25 polymorphism, rs1800471) polymorphisms encode amino acid substitutions within the signal peptide of the TGFβ1 precursor [18]. The 869T allele leads to increased cellular TGFβ1 secretion (10Pro variant) and has been linked to elevated TGFβ1 serum levels [19]. Similarly, the G914→C polymorphism (Arg25→Pro) has been associated with increased TGFβ1 secretion in vitro [20]. The C1628→T (syn. Thr263→Ile, rs 1800472) polymorphism is located within the cleaved part of the TGFβ1 precursor, and is considered to enhance the cleavage of the LAP domain and subsequent activation of TGFβ1 [21]. Overall, based on the central functional role of TGFβ1 in the progression of renal fibrogenesis, association of TGFBI SNPs and CKD progression slopes is less prominent (Table 2). SNPs involved in the promoter region (C−800→A, C−509→T) display a more conclusive association when compared with SNPs which are involved in the coding region (Table 2). Since these SNPs are not detected through current exome-sequencing strategies, lack of data on promoter regions and introns may contribute to the failure of GWAS to detect TGFBI (and other established growth factors) as determinants of CKD progression. Nevertheless, it is becoming evident that most SNPs are not impactful enough on gene product activity, to single-handedly alter the course of disease progression, and identification of gene clusters may be required to successfully link genetics to the progression of CKD.

**FIGURE 1**: TGFβ1 polymorphisms. The schematic illustrates TGFβ1 protein (top) and TGFBI gene (bottom) with their corresponding polymorphisms. TGFβ1 is synthesized as a 390 aa protein, consisting of a signal peptide (aa1-29, yellow), a latency associated peptide (aa30-278), blue) and the TGFβ1 domain (aa279-390). One kilobase of the proximal promoter region and the coding region consisting of seven exons and six introns of the TGFβ1 gene are displayed below (colours correspond to encoded TGFβ1 domains). Of the six most studied polymorphisms, three are located in the promoter region (C−988→A, C−800→A and C−509→T), and three are located in the coding region T869→C (corresponding to aa exchange Leu10→Pro), G914→C (corresponding to aa exchange Arg25→Pro) and C1628→T (corresponding to Thr263→Ile). None of the polymorphisms involve the active TGFβ1 peptide.
of a complete epigenome reference, the epigenetic heterogeneity within an organ due to specific epigenomes of each cell type and the still evolving technologies, epigenome-wide screening studies are still difficult and knowledge about the impact of epigenetics on the progression of renal fibrogenesis is just evolving.

Our own research group investigated the impact of DNA hypermethylation on renal fibrogenesis. ‘DNA methylation’ refers to clustering of methylated cytosine bases within a specific promoter region (CpG island promoters) [23]. Such methylation completely silences transcription of the affected gene [23]. Our efforts to investigate DNA methylation originated from the observation that experimental renal fibrosis in mice is ameliorated when the de-methylating agent 5’Azacytidine is administered [24]. To gain insights into hypermethylated candidate genes, we focused on fibroblasts (the principal cell type that drives fibrogenesis). Genome-wide methylation screening comparing fibroblasts from fibrotic kidney biopsies with fibroblasts from non-fibrotic kidneys revealed 12 genes which were hypermethylated in all tested fibrotic fibroblasts (DLG2, Enc, EYA1, Ltz1, HIPK1, HIPK2, HIPK3, Lrnf2, Oddi1, Pax3, RASAL1 and Zu5) [24]. Of these genes, hypermethylation of RASAL1 is not limited to renal fibrosis, but it has been identified as being hypermethylated in liver fibrosis and colorectal cancer as well [25, 26]. Methylation of the RASAL1 CpG island promoter silences RASAL1 expression, resulting in increased intrinsic Ras-GTP activity in affected cells. Increased Ras-GTP contributes to fibroblast activation, ultimately contributing to renal fibrogenesis [24]. As analysis of RASAL1 methylation in larger patient cohorts to investigate its association with steeper progression slopes is underway, pre-clinical studies provided evidence that DNA methylomics play a role in renal fibrogenesis, that they are more relevant to gene expression/activity than most SNPs and that methylomics may be a powerful tool for risk stratification of individual CKD patients in the future.

The role of histone modifications in renal fibrogenesis is poorly understood [22]. Histone modifications refer not only to chemical modifications of the side chains of the H2A, H2B, H3 and H4 core, but also to substitution of the prototypical core histones by variant histones such as H2AX or H2AZ (which are different gene products that can replace H2A) [22].

Histone modifications impact gene expression as they determine gene accessibility to polymerases. As DNA is regularly spun (147 bp are spun around each histone core with ~50 bp between cores) around histone cores, each gene is associated with multiple histones—all of which can be individually modified. As ChIP-Seq technologies to perform large-scale histone analysis are still limited, and specific inhibitors or inducers of select histone modifications are not yet available, and insights into the role of histone modifications in renal fibrosis are limited to pre-clinical beneficial effects of histone deacetylase inhibitors such as trichostatin [22].

In addition to classical epigenetic mechanisms of DNA methylation and histone modifications, microRNAs (miRs) have entered the field of epigenomics. MiRs are short single-stranded RNA molecules, which regulate gene expression post-transcriptionally through capturing target mRNAs. To date, over 700 miRs have been found in humans and ~5500 genes are considered miR targets (about 30% of the human genome). The field is very much in flux as the list of miRs is still growing and matching miRs to target genes is still far from done. Among the epigenetic mechanisms, regulation of gene expression through miRs is the most dynamic (which is why miRs are often excluded from the list of epigenomics). There is particular interest in miRs, because they can be therapeutically interfered with (either antagonized with so-called antagonomirs or they can be overexpressed). With regard to chronic progressive kidney disease, miR-21, miR-29 and miR-200 have been best established [27]. MiR-21 was originally discovered to enhance fibrosis in the heart through enhancing MAPK signalling (by means of targeting the MAPK inhibitor ‘sprouty’) [28]. In the kidney, miR-21 is responsible for ischaemic pre-conditioning (protecting the kidney from further injury through inhibiting pro-apoptotic programmed cell death protein 4 PMCD4) [29]. Sustained miR21 expression,
however, contributes to renal fibrogenesis (through targeting peroxisome proliferator-activated receptor-α PPARα) [30] (for extensive review, see [27]). Why miR-21 has distinct mRNA preferences in distinct contexts (accounting for its opposing functions) is not yet known.

In summary, epigenetic modifications of selected genes are more likely to impact disease progression than genetic polymorphisms, because they can efficiently shut down gene expression. Unlike genetic polymorphisms, epigenetic modifications can be therapeutically modified, and hence there is optimism that further insights into the epigenetics of renal fibrosis may lead to development of therapeutic stratification tools in the future.

INSIGHTS PROVIDED BY ANALYSIS OF AUTOSOMAL RECESSIVE INTERSTITIAL FIBROSIS

By discovering a monogenic cause of a rare form hereditary chronic kidney failure with implications for common pathways of CKD, a recent study by a group led by Friedhelm Hildebrandt provided novel insights into the genetics of renal fibrosis through an entirely different approach [31]. The Hildebrandt group performed genetic analysis on patients with karyomegalic interstitial nephritis (KIN), a rare hereditary CKD (12 known families worldwide) [31]. Affected patients display markedly enlarged hyperchromatic nuclei (karyomegaly) in kidney, liver and brain and develop CKD associated with interstitial fibrosis, tubular atrophy and microcyst formation (similar to presentation of nephronophthisis) after the third decade (KIN was initially named ‘Systemic karyomegaly associated with chronic interstitial nephritis’) [32]. The Hildebrandt group successfully linked KIN to mutations of the FAN1 gene, which encodes for Fanconi anaemia protein1 (FAN1), which plays a role in the repair of interstrand DNA crosslinks (ICLs), and thus provided a link between renal fibrosis DNA damage and DNA damage repair [31].

Each cell in the human body is constantly challenged by damage to its DNA. Among the various types of DNA damage, covalent interstrand crosslinks (ICLs) are the most toxic, because ICLs prevent separation of DNA strands and thus, present a definitive block for DNA replication and transcription of affected genes [33]. ICLs can form under pressure of lipid metabolites and replication stress. Induction of ICLs through administration of crosslinking drugs (such as cisplatin) still remains a stronghold of anti-cancer chemotherapy [33]. Like for any other type of DNA damage, each cell in the body is equipped with highly specific repair mechanisms for crosslink repair [34].

FAN1 is part of the replication-dependent ICL repair pathway, which is the predominant mechanism of ICL repair in eukaryotes (Figure 2) [35]. During the S-phase, when converging replication forks encounter an ICL, they stall because the covalently crosslinked strands cannot separate [34]. Removal of the ICL and repair of the damaged chromosomes occur in several tightly controlled steps: the ICL is first encountered by the MCM complex which unwinds parental DNA ahead of replication forks, providing single-stranded DNA templates. When an ICL is encountered, replication forks pause at a 30 nucleotide distance before the leading strand of a single fork extends within one nucleotide of the lesion [33]. Two incisions of the non-template strand flanking ‘unhook’ the ICL [and create a double-strand break (DSB) which recruits γH2AX], allowing for extension of the leading strands towards the first Okazaki fragment of the converged replication fork [33]. The incision-generated break is then repaired through homologous recombination [33].

While understanding of the molecular events of ICL is still evolving, it is well established that the ‘Fanconi anaemia pathway’ plays a central role in the coordination of ICL repair [33]. Replication-dependent ICL repair mechanisms are also referred to as the ‘Fanconi anaemia pathway’ [36]. Fanconi anaemia is a rare disorder which presents with bone marrow failure and predisposition to cancer due to ICL repair deficiency. Mutation in any one of 14 ‘Fanconi anaemia genes’ (FANCA, FANCB, C, D1, D2, E, F, G, I, J, L, M, N, P) causes FA [36]. Fanconi anaemia proteins form three distinct functional groups (FA core complex, ID complex and downstream effector complex), which—in concert with associated proteins such as FAN1—facilitate ICL repair (Figure 2E). ICL repair is initiated through FANCM binding to an ICL and subsequent formation of the Fanconi anaemia core complex. The FA core complex then ubiquinates FANCl and FANCD2 (the ‘ID complex’) [36]. The monoubiquitinated ID complex then recruits polymerases (such as the translesion polymerase Pol v) and nucleases (such as FAN1) which are required for the repair of ICLs [36].

Through exome-sequencing and linkage analysis of two siblings, the Hildebrandt proved linkage of FAN1 mutations and KIN and confirmed FAN1 mutations in nine additional families, identifying recessive mutations of FAN1 as the cause of KIN [31]. Mechanistically, they demonstrated increased susceptibility to mitomycin1-induced DNA cross-linking and increased incidence of spontaneous chromatid breaks in cultured fibroblast cell lines established from KIN patients, and demonstrated that overexpression of competent FAN1 rescues the phenotype in these cells [31]. DNA instability in cell lines with FAN1 mutations was less pronounced than in cell lines from Fanconi anaemia patients with established FRANCA mutations (the central gene of the FA pathway) [31]. Expression analysis of FAN1 in adult tissues revealed that FAN1 is predominantly expressed in parenchymal tissues (such as kidney and liver), neuronal tissue and female reproductive organs, whereas FANCD2 is predominantly expressed in bone marrow (mutations of FANCD1 result in Fanconi anaemia, an integral part of the FA core complex) [31]. Additionally, FAN1 knockdown in zebrafish caused widespread DNA damage and apoptosis and formation of microcysts in zebrafish [31]. In summary, the Hildebrandt group indisputably identified FAN1 mutations as the cause of KIN [31]. Their mechanistic experiments also provide a conclusive explanation of why FAN1 mutations (an FA-pathway associated gene involved in ICL repair) do not cause Fanconi anaemia, but result in an entirely different clinical presentation (KIN) [31].
Of highest interest to the nephrologist, however, is the study’s possible implication for common pathways of CKD. As established in their analysis of FAN1-mutant fibroblasts and FAN1-morpholino zebrafish, the authors perform γH2AX immunostaining to analyse DNA damage in kidneys of fawn-hooded hypertensive rats (a well-established model of spontaneous CKD) and in three kidney transplant specimens and they found that fibrosis positively correlates with increased γH2AX immunolabelling and they speculate that accumulating DNA damage, and specifically DNA damage through decreased FAN1 activity (i.e. through hypomorphic FAN1 alleles), may play a role in renal fibrogenesis and may explain individual progression rates of CKD [31]. While this concept is too attractive to discount, several issues need further consideration. The FAN1 activity in diseased kidneys (other than in KIN patients) is not yet entirely clear (expression levels or existence of hypomorphic alleles were not assessed). γH2AX refers to the histone variant histone H2AX, which when phosphorylated at serine 139 (and possibly also at tyrosine 142) is referred to as γH2AX and binds to DSBs [37]. Among the numerous forms of DNA damage, DSBs are the most severe. So far, FAN1 has only been linked to DSBs that are generated as a consequence of the ICL repair pathway (in vitro generation of DSBs through the ICL repair is independent of FAN1) [35, 38]. Furthermore, DSB generation is part of the replication-dependent ICL repair pathway, which is limited to proliferating

**FIGURE 2:** (A–D) Replication-dependent repair of ICLs. (A) Replication fork stalling. A schematic of two replication forks converging towards an ICL (green box) is displayed. Replication stalls 20–40 nucleotides from the ICL, because strands fail to separate. (B) ICL unhooking. Dual incisions are made at the non-template strand (dark blue line), creating a DSB on the non-template strand, whereas the unhooked ICL nucleotides remain in the template strand red. This enables a TLS polymerase to extend on the template strand past the unhooked ICL (orange arrow). The generated DSB is recognized by histone variant γH2AX which serves to keep the DNA repair machinery in place. (C) Homologous recombination. A nucleoprotein filament containing the free 3’ end (light blue strand) invades the identical DNA duplex forming the displacement loop (D-loop) which enables extension of the free 3’end. (D) Synthesis-dependent strand ligation. The newly synthesized 3’ end of the invading strand anneals to the other 3’ end of the damaged chromosome. Gaps are then filled through complementary nucleotide synthesis and ligation. The unhooked ICL is excised. Upon repair of the DSB γH2AX is removed. The function of FAN1 in this process is to remove possible 3’ overhangs (‘3’ flaps’) which are generated when the invading strand re-anneals with its complementary damaged strand (blue strands). (E–G) FA pathway of repair of ICLs. (E) FANCM senses ICLs in stalling forks and binds to the lesion to initiate ICL repair. (F) FANCM initiates assembly of the Fanconi core complex which ubiquinates FANCD2 and FANCI (ID complex). FAN1 (yellow) is recruited to monoubiquinated FANCD2. (G) The activated ID complex recruits polymerases and nucleases which are required for repair of the lesion to the ICL.
cells. Hence, the link between the observed accumulation of DSBs (by means of γH2AX immunolabelling) and FAN1 in fibrotic kidneys is not entirely clear based on the existing literature, leaving the question of why DNA damage accumulates in fibrotic kidneys. In addition to environmental toxins and oxidative stress, replicative stress (kidney injury and fibrogenesis are associated with proliferation of numerous cell types) is an obvious candidate for causing the observed DSBs. In summary, the link of impaired DNA repair (i.e. through FAN1 polymorphisms), epigenetics (i.e. histone γH2AX) to functional changes reminiscent of ageing (age remains the highest risk factor for CKD) is highly attractive and deserves further consideration.

CONCLUSION

As technologies advance, evidence is increasing that genetic polymorphisms and epigenetic modifications are the basis for distinct susceptibilities to develop end-stage renal failure in individual patients. Through epigenetic and genetic analyses, new pathways of renal fibrogenesis such as Ras-GTP signalling (through association of RASAL1 methylation and progression of renal fibrosis) and DNA repair (through association of FAN1 mutations and hereditary interstitial fibrosis) have been highlighted. The results of GWASs and mechanistic insights on fibrogenesis still do not complement each other, but there is optimism that full-genome sequencing (including non-coding regions) may provide additional insights in the future.

CONFLICT OF INTEREST STATEMENT

None declared.

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