Review

Evolutionary trade-offs in kidney injury and repair

Yutian Lei and Hans-Joachim Anders

Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV der Ludwig-Maximilians Universität, Munich, Germany

Summary. Evolutionary medicine has proven helpful to understand the origin of human disease, e.g. in identifying causal roles of recent environmental changes impacting on human physiology (environment-phenotype mismatch). In contrast, diseases affecting only a limited number of members of a species often originate from evolutionary trade-offs for usually physiologic adaptations assuring reproductive success in the context of extrinsic threats. For example, the G1 and G2 variants of the APOL1 gene supporting control of Trypanosoma infection come with the trade-off that they promote the progression of kidney disease. In this review we extend the concept of evolutionary nephrology by discussing how the physiologic adaptations (danger responses) to tissue injury create evolutionary trade-offs that drive histopathological changes underlying acute and chronic kidney diseases. The evolution of multicellular organisms positively selected a number of danger response programs for their overwhelming benefits in assuring survival such as clotting, inflammation, epithelial healing and mesenchymal healing, i.e. fibrosis and sclerosis. Upon kidney injury these danger programs often present as pathomechanisms driving persistent nephron loss and renal failure. We explore how classic kidney disease entities involve insufficient or overshooting activation of these danger response programs for which the underlying genetic basis remains largely to be defined. Dissecting the causative and hierarchical relationships between danger programs should help to identify molecular targets to control kidney injury and to improve disease outcomes.

Key words: Regeneration, Fibrosis, Coagulation, Inflammation, Healing, Repair

Introduction

Evolutionary medicine can provide surprising explanations for pathomechanisms of human disease (Williams and Nesse, 1991). Phenotype adaption along evolution is driven by maintaining diversity in phenotypes and selection via reproductive success. Reproductive success requires reaching the reproductive phase of life and a certain fitness to get selected for mating. Evolutionary medicine has been explored in many directions but there is a relative paucity of concepts regarding kidney diseases and kidney pathology. Homer Smith presented a careful overview on the evolution of the kidney and salt handling (Vize and Smith, 2004). Robert L. Chevalier introduced the concept of evolutionary trade-offs versus mismatches to kidney disease (Chevalier, 2017). Here we approach the aspect of kidney pathology. Kidney injury can produce a large number of histopathological lesions because of the complex diverse cellular composition and the numerous functional compartments inside and outside the nephrons of the kidney. Kidney disease rarely involves mechanical trauma but is rather the consequence of triggers that set off intrinsic injurious pathomechanisms destroying the kidney. Interestingly, also concomitant healing responses trying to stabilize the remaining nephrons contribute to injury and malfunction. However, the number of cellular responses are limited, hence, different triggers can produce similar histopathological lesions such as focal segmental glomerulosclerosis (FSGS), mesangial proliferation, crescents arising from Bowman's capsule, thrombotic microangiopathy, tubular necrosis as well as interstitial fibrosis. Such nonspecific lesions require further diagnostic work-up. Here we present the view

from the angle of evolutionary medicine on how kidney injury generates distinct histopathogical lesions by interactions of a set of danger response programs (Anders, 2012). We start out by presenting such danger response programs assuring survival in multicellular organisms and how they may turn into pathomechanisms of kidney disease in humans as an evolutionary trade-off (Table 1) (Williams and Nesse, 1991). This conceptual approach can help to sort out the hierarchical relevance of certain histopathological lesions and to identify molecular and cellular elements central to the pathogenesis of kidney disease, potentially serving as therapeutic targets in the future.

Assuring reproductive success: response programs control dangers

Injuries require either regeneration or repair of tissue defects (Gurtner et al., 2008). Injured epithelial barriers involve the risks of fluid loss and microbial infection. From early on evolution positively selected those multicellular organisms equipped with adequate danger control mechanisms providing significant survival benefits that outweigh the trade-offs associated with collateral injuries or tissue remodeling. While such trade-offs can be acceptable for a species as a whole when assuring species survival, they can cause significant morbidity or even mortality for single individuals of that species. By concept, medicine is a cultural human trait that focusses on those individuals of the human species affected by trade-offs turning into disease such as kidney disease. We present four central danger response programs, positively selected by evolution to assure survival upon traumatic or toxic tissue injury, and how their evolutionary trade-offs contribute to the spectrum of kidney diseases listed in medical textbooks (Table 1). These danger response programs are coagulation, inflammation, re-epithelialization, and mesenchymal repair (Velnar et al.,

2009; Suarez-Alvarez et al., 2016).

Coagulation controls bleeding upon vascular injury

Vascular injury implies a barrier defect that cannot be regenerated in an instant, hence requires an immediate functional sealing to minimize the risk of hemorrhagic shock. Already present in arthropods, e.g. by haemolymph aggregation, the need for a balance between wanted and unwanted clotting evolved in the vertebrate as a complex interplay of endothelial cell activation, plasmatic enzymes and substrates, and platelets (Smith et al., 2015). While wanted clotting minimizes short term risks from bleeding, unwanted clotting presenting as diffuse intravascular coagulation or thromboembolism implies substantial trade-offs manifesting as tissue hypoperfusion, ischemia and fatal embolism or infarcts (Jennewein et al., 2011; Damman et al., 2015).

Inflammation creates a functional barrier to pathogens

Survival benefits provided by a balanced host defense against pathogenic threats are the driving element in the evolution of the immune system (Buchmann, 2014). Wounding external barriers holds the risk for infection and requires to rapidly re-install the barrier to limit pathogen entry and spreading. While re-epithelialization takes days, (Abais et al., 2014) local immune responses can create a functional barrier within few hours (Medzhitov, 2008; Hickey and Kubes, 2009). Pathogen-derived pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) released by dying parenchymal cells activate identical pattern recognition receptors in infectious and sterile forms of inflammation (Anders, 2010; Chan et al., 2012; Leventhal and Schroppel, 2012; Kaczmarek et al., 2013; McCarthy et al., 2014). There is a tight cross-talk between clotting and inflammation, e.g.

Table 1. Some examples of evolutionary trade-offs underlying kidney disease.

Kidney disease	Based on ancient evolutionary benefits on reproductive success
Hypertension-related kidney injury	Bipedal lifestyle on arid land
Gout, uric acid nephropathy	Loss of uricase activity in great apes and humans to increase serum uric acid levels for higher blood pressure, bipedal lifestyle on land when climate change created more arid biotopes, pseudogenization of uricase allows conversion of fructose into fat
Obesity-/T2D-related nephropathy	Energy storage for periods of food shortage
Accelerated CKD progression in patients with APOL-1 risk alleles	APOL-1 risk allele-related better host defense against *Trypanosoma* infection
Ischemic nephropathy (sickle cell disease)	Hemoglobin mutation-related benefits during *Plasmodium* infection
Thrombotic microangiopathy	Limiting blood loss upon trauma via coagulation
Renal abscess in pyelonephritis	Host defense to microbes, local barrier to avoid sepsis
Immune complex glomerulonephritis	Host defense to pathogens
Interstitial nephritis, allograft rejection	Host defense to pathogens
Crescent formation	Re-epithelialization in wound healing
Renal cyst, cell adenoma, carcinoma	Re-epithelialization in wound healing
Glomerulosclerosis, interstitial fibrosis	Stabilization of remnant parenchyma upon injury (wound healing)

T2D: type 2 diabetes, CKD: chronic kidney disease, APOL: apolipoprotein

platelet aggregation releases cytokines and chemokines from platelet granules promoting leukocyte influx and inflammation at the site of injury, i.e. immunothrombosis (Niessen et al., 2008; Delvaeye and Conway, 2009; Engelmann and Massberg, 2013; Wu, 2015). Also, the formation of neutrophil extracellular traps (NETs) releases lytic proteases and DAMPs that further fuel local inflammation (Palabrica et al., 1992; Semple et al., 2011; Martinod and Wagner, 2014). The inflammatory response triggers regulated forms of cell necrosis (Linkermann et al., 2014; Mulay et al., 2016a-c), e.g. in pyoderma gangraenosum but the same process can contribute to parenchymal losses in the kidney (Ahronowitz et al., 2012). Sepsis-related cytokine storm is the central cause of mortality in early sepsis, whereas the compensatory suppression of innate immunity implies a susceptibility for secondary infections in late sepsis (Hotchkiss et al., 2009).

Re-epithelialization (regeneration) reinstalls a structural barrier against fluid loss and pathogen entry

Epithelial injury implies barrier dysfunction, hence, rapid regeneration of the barrier is needed to limit fluid losses and pathogen entry, e.g. in skin burns or ulcerative colitis (Plikus et al., 2012; Sun et al., 2014). The epithelial layers in the kidney are not exposed to pathogens but anyway serve important barrier functions. For example, podocyte loss implies proteinuria (Reiser and Sever, 2013). While closing small gaps may be achieved by hypertrophy of the neighboring cells larger defects require *de novo* formation of epithelial cells and coordinated migration events initiated by signals acting on intrinsic cells with regenerative properties (Lasagni and Romagnani, 2010; Shankland et al., 2017). Already coagulation produces mitogenic factors that initiate cell cycle entry for either hypertrophy or proliferation of surviving epithelial cells (Nurden, 2011). Other mediators linking coagulation, inflammation, and re-epithelialization are growth factors (EGF, FGFs, HGF, TGF-β), cytokines (IL-6, IL-17, IL-22), chemokines (fractalkine, CXCL10) as well as microRNAs (Braun et al., 2008; Ishida et al., 2008; Pickert et al., 2009; Ebihara et al., 2011; Kroeze et al., 2012; McGee et al., 2013). Indeed, miRNAs evolve as important posttranscriptional regulators of the cell cycle machinery in cells that contribute to cutaneous wound healing (Lai and Siu, 2014). For example, miRNAs modulate human monocyte/macrophage differentiation (miR-424), TLR signaling (miR-147), collagen expression and wound contraction (miR-21) as well as the expression of the cell cycle master regulator p53 (miR-203) during keratinocyte differentiation (Lai and Siu, 2014).

The intrinsic regenerative capacity for re-epithelialization is largely provided by local progenitors committed to differentiate into the specific epithelial lineage (Romagnani, 2009; Plikus et al., 2012; Sallustio et al., 2013; Vaughan et al., 2015). Lack or delay of sufficient re-epithelialization fosters persistent barrier defects and may present as chronic dermal wounds or as proteinuria. Vice versa, "over re-epithelialization" can lead to epithelial hyperplasia (glomerular crescent formation) or (renal cell) carcinoma (Smeets et al., 2009; Ryu et al., 2012).

Fibrosis stabilizes functional integrity of remnant parenchyma

The reconstitution of parenchymal cell losses requires stabilizing scaffolds guiding regenerating elements to rebuild the precedent structural organization (Wynn, 2007). The obvious benefits of such a transient mesenchymal scaffold are well described during reconnecting broken bones, nerves, and blood vessels. Mesenchymal scaffolds are formed by mesenchymal cells surrounding the functional units of the organ, e.g. within muscle sheaths, periosteum, nerve sheaths, vascular pericytes, mesangial cells or interstitial fibroblasts. Upon injury, epithelial growth factors are released together with mesenchymal growth factors driving an early concomitant formation of a mesenchymal scaffold that stabilizes the injured units (Wynn, 2007). Once regeneration concluded these mesenchymal scaffolds disappear by degradation but whenever regeneration remains incomplete the scaffold persists as tissue fibrosis, a histopathological lesion obviously associated with poor outcomes as it indicates persistent parenchymal losses (Wynn, 2007). This association, however, does not necessarily imply that fibrosis causes tissue injury, a popular concept (Zeisberg and Neilson, 2010). Overshooting mesenchymal healing as it presents as keloid of the skin exists in certain individuals and might contribute to further tissue losses. But what are the elements that link insufficient re-epithelialization with tissue fibrosis? Epithelial-mesenchymal transition (EMT) and arrest in the G2/M phase of the cell cycle was reported to be associated with pro-fibrotic TGF-β cytokine secretion (Yang et al., 2010; Zeisberg and Duffield, 2010). Collagen-producing fibroblasts mainly originate from bone marrow-derived precursors via the circulation or from resident fibroblasts (Niedermeier et al., 2009; Chen et al., 2013; Xia et al., 2014). Instead, the interstitial fibroblasts pool was reported to take little from pericytes or endothelial cell transition (LeBleu et al., 2009; Humphreys et al., 2010; Falke et al., 2015), but the relative contribution could also depend on the type of kidney injury.

The trade-off: danger control programs as disease pathomechanisms

Well-balanced responses solve most incident problems without ending in acute organ failure or chronic damage. However, within a population, biological traits follow bell-shaped patterns. Hence, the human capacity to control dangers is not identical in all

members of the population. A bell-shaped distribution of the capacity to balance danger responses implies that some individuals will respond to the same type of insult either with exaggerated or insufficient coagulation, inflammation, re-epithelialization, and scaring, respectively (Fig. 1, Table 1). For example, genetic weaknesses in the expression or function of complement inhibitors promotes exaggerated complement-related inflammation, e.g. in atypical hemolytic uremic syndrome (aHUS) or C3 glomerulopathy (Noris and Remuzzi, 2013). It is likely that most kidney diseases result from genetically determined imbalances in danger control, where countless combinations of generic variants explain the wide spectrum of different manifestations of disease (Stokman et al., 2016). As such, genetic variants can exaggerate evolutionary trade-offs and produce drastic phenotypes in such unfortunate individuals. Indeed, our drive to categorize disease entities and classifying stages for medical teaching and administrative processing largely oversimplified a biology driven by countless combinations among genes and epigenetic as well as environmental factors.

Coagulation as pathomechanism

Exaggerated clotting

Unbalanced coagulation is a central element in thrombotic microangiopathies involving microvascular endothelial cell injury, activation of platelets, and plasma coagulation factors (Chapman et al., 2012). In the kidney thrombotic microangiopathies cause ischemic necrosis. Exaggerated clotting also contributes to crescentic glomerulonephritis. For example, in renal vasculitis complement-driven vascular injuries activate clotting inside glomerular capillaries, which becomes evident by fibrin deposition in capillary loops (Sorensen et al., 2011; Srivastava et al., 2013). In Alport nephropathy, a non-inflammatory form of glomerular vascular injury, progressive GBM disintegration associates with hematuria, fibrinogen conversion to fibrin, and plasma leakage into Bowman's space, a process that contributes
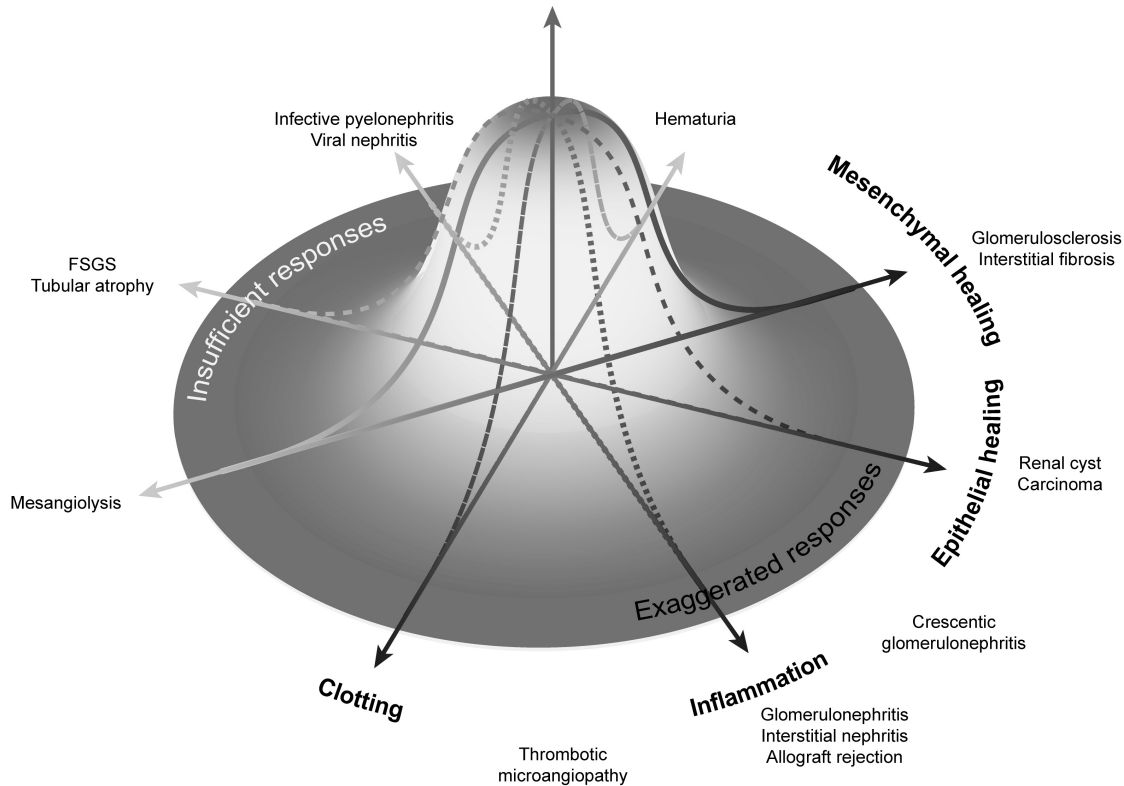

Fig. 1. 3D Gaussian distribution of danger response programs in kidney disease. Danger responses are well-balanced in the majority of the population and can usually help to regain homeostasis upon minor insults in the majority of the population (illustrated by the y-axis as being the peak of bell-shaped curves). However, a subset of the population being affected either by stronger injurious triggers or by genetic alterations resulting in exaggerated or insufficient danger responses suffer from a spectrum of different kidney diseases. The numerous combinations of genetic profiles and diverse environmental factors explain the broad spectrum of clinical manifestations. Current definitions of disease entities as well as guideline medicine often fall short in matching with the complexity of these biological processes. FSGS: Focal segmental glomerulosclerosis.

to glomerular pathology (Ryu et al., 2012).

Insufficient clotting

Insufficient clotting manifests by persistent bleeding. Vice versa persistent bleeding can relate to insufficient clotting. Certain glomerular diseases are associated with persistent microhematuria, Microhematuria implies capillary wall injury in few glomeruli (Vivante et al., 2013; Yuste et al., 2015). It remains uncertain if persistent hematuria originates from persistent vascular lesions of always the same glomeruli that do not heal or whether clotting stops vascular leakage in some glomeruli, while others start to bleed with persistent hematuria as a net effect. Episodes of intermittent macrohematuria occur in IgA nephropathy and other renal disorders and can last several days implying insufficient clotting (Gutierrez et al., 2012). The fibrinolytic activity of urokinase that is highly expressed in the urinary tract may contribute to this phenomenon.

Inflammation as pathomechanism

Exaggerated inflammation

Inflammation is a central element of host defense often turning into a predominant pathomechanism underlying organ failure (Medzhitov, 2008). In sterile inflammation the trade-off of inflammation is particularly obvious as there are few and often no benefits associated with this response (Rock et al., 2010). For example, traumatic or toxic sterile injuries still benefit from the release of growth factors from infiltrating leukocytes that contribute to tissue regeneration but inflammation related to crystal formation, e.g. in gout or crystal nephropathies does not share the same benefits (Mulay and Anders, 2016, 2017). Sterile inflammation is the most prevalent form of renal inflammation, e.g. in glomerulonephritis, allograft rejection, ischemic or toxic tubular necrosis, interstitial nephritis as well as during tissue remodeling along progressive CKD (Anders and Schaefer, 2014). Resident and infiltrating macrophages are equipped with numerous pattern recognition receptors translating PAMPs and DAMPs into local cytokine release and subsequent local inflammation (Anders, 2010; Nelson et al., 2012). Because renal parenchymal cells express only a limited number of such pattern recognition receptors they contribute less to the overall secretion of pro-inflammatory cytokines (Anders et al., 2004a). For example, renal cells lack TLR7 and TLR9 and, therefore, do not respond to certain forms of immunostimulatory nucleic acids (Anders, 2007; Anders and Schlondorff, 2007). In addition, renal cells produce only little IL-1β by activation of the NLRP3 inflammasome, a response strongly active in macrophages and dendritic cells (Anders and Muruve, 2011; Lichtnekert et al., 2011; Abais et al., 2014;

Shahzad et al., 2015; Anders, 2016).

Renal cell necrosis strongly contributes to intrarenal inflammation via the passive release of DAMPs activating pattern recognition receptors (Mulay et al., 2016a). For example, tubular cell necrosis releases the TLR2 and -4 agonist HMGB1, driving inflammation during acute kidney injuries (Wu, 2010; Mudaliar et al., 2013; Nair et al., 2015). A kidney-specific DAMP is Tamm-Horsfall protein/uromodulin, i.e. exclusively expressed within the cells of the thick ascending limb of the loop of Henle (Garimella and Sarnak, 2017). Upon injury in this area Tamm-Horsfall protein leaks into the interstitial space and activates dendritic cells via TLR4 as well as the NLRP3 inflammasome (Darisipudi et al., 2012). TLRs- and inflammasome-mediated DAMP recognition as a signal of renal cell necrosis is a central element also of rapid-progressive glomerulonephritis, thrombotic microangiopathies, and acute tubular necrosis (Andersen et al., 2014; Leemans et al., 2014; Anders, 2016). The subsequent release of TNF-α induces further regulated cell necrosis, e.g. by triggering RIPK3- and MLKL-mediated necroptosis (Linkermann and Green, 2014). This auto-amplification loop of necrosis-related inflammation and inflammation-related necrosis is referred to as "necroinflammation" (Linkermann et al., 2014; Mulay et al., 2016b). The molecular mechanisms of renal necroinflammation are counter-regulated as numerous levels to limit expanding renal cell necrosis (Mulay et al., 2016a). Inhibitors of TLR signaling suppress the activation of immune and non-immune cells and thereby limit immune-mediated kidney diseases (Lech et al., 2007, 2010, 2014; Noris et al., 2009; Lassen et al., 2010; Gunthner et al., 2013). Extracellular histones have a particular role in renal necroinflammation as they promote immunostimulatory as well as cytotoxic effects (Allam et al., 2014). Renal cell necrosis as well as NET formation both release histones into the extracellular space where they elicit cytotoxic effects on other cells by direct charge-mediated plasma membrane disruption (Allam et al., 2012; Nakazawa et al., 2017). A vicious circle further promotes histone- and DAMP-mediated necroinflammation (Allam et al., 2013; Nakazawa et al., 2017). When dying neutrophils release NETs they become an important source of extracellular histones killing endothelial cells and more tubular cells cells, e.g. in septic acute tubular necrosis or in crescentic glomerulonephritis, respectively (Kumar et al., 2015). Histones are also mediators of remote tissue injuries, e.g. in the lung that occur in the context of acute tubular necrosis (Nakazawa et al., 2017).

Extrarenal infections often trigger flares of chronic glomerulonephritis or renal vasculitis because circulating pathogen products activate pattern recognition receptors on non-immune and immune cells of the kidney (Pawar et al., 2006; Allam and Anders, 2008; Allam et al., 2008; Pawar et al., 2009), which promotes the intrarenal release of cytokines that increase renal inflammation and renal cell loss (Ryu et al., 2011;

Brahler et al., 2012). In lupus nephritis (or renal vasculitis) pathogen-derived nucleic acids activate dendritic cells, macrophages, and B cells, a process that can trigger expansion of the pathogenic lymphocyte clones and disease activity of these chronic autoimmune diseases (Leadbetter et al., 2002; Wen et al., 2007; Villanueva et al., 2011). In particular, IFN-α triggers a systemic "pseudoantiviral" immune response that mimics the clinical manifestations of viral infection (Anders, 2009; Migliorini and Anders, 2012). Also, mesangial cells and glomerular endothelial cells recognize such immunostimulatory nucleic acids and secrete type I interferons, a phenomenon linked to podocyte loss and glomerular scaring during viral glomerulonephritis (Allam et al., 2009; Flur et al., 2009; Hagele et al., 2009a; Anders et al., 2010; Migliorini et al., 2013b).

The local expression of chemokines initiates a sequential recruitment of various leukocyte subsets but it is the local microenvironment within different tissue compartments that determines their functional status and phenotype (Anders and Ryu, 2011; Lech et al., 2012). Indeed, macrophages, T cells, and B cells come in functionally distinct subsets that enforce different aspects of danger control (Weidenbusch and Anders, 2012; Kurts et al., 2013; Minton, 2015; Mauri and Menon, 2017). For example, bacterial products induce neutrophils to undergo NET formation or activate infiltrating or resident macrophages to acquire a pro-inflammatory (M1) phenotype (Anders et al., 2003, 2004; Brinkmann et al., 2004). Blocking the CC-chemokine CCL2 or its receptor CCR2 reduces the intrarenal numbers of classically-activated (M1) macrophages, which can prevent damage and remodeling in glomeruli and the tubulointerstitium (Kulkarni et al., 2007, 2009; Ninichuk et al., 2008; Sayyed et al., 2011; Urushihara et al., 2011; Seok et al., 2013).

Thus, unbalanced inflammation is a common trade-off, especially in sterile forms of renal inflammation, and largely contributes to tissue injury in transient and persistent forms of kidney disease.

Insufficient inflammation

The evolutionary origins of inflammation arise from the benefits associated with host defense (Medzhitov, 2008), which in kidney disease relate to renal infections. For example, PAMP-driven and TLR/inflammasome-mediated immune activation are absolutely required to limit BK virus replication in kidney allografts (Babel et al., 2011; Ribeiro et al., 2012). The same applies to the control of *Escherichia coli* and other uropathogenic bacteria during bacterial pyelonephritis (Anders and Patole, 2005; Abraham and Miao, 2015). Inflammation is designed to enforce local pathogen killing and to limit pathogen spreading from local to systemic infection (Godaly et al., 2015; Behzadi and Behzadi, 2016), as

happens in mice that lack pattern recognition receptors such as in TLR4-deficient mice (Patole et al., 2005). The lack of pathogen control involves in turn benefits on collateral tissue injuries such as renal abscess formation, which are absent in TLR4-mutant mice (Patole et al., 2005). However, less immunopathology at the pathogen entry site comes at the cost of fatal gram negative sepsis (Abraham and Miao, 2015). Along the same line, TLR2 recognizes leptospiral outer membrane proteins in proximal tubular epithelial cells with similar implication for leptospirosis (Yang et al., 2006).

Together, the evolutionary trade-off to host defense is that a wide range of triggers initiate sterile inflammation causing unnecessary tissue injury, especially inside the kidney. Insufficient inflammation refers to lack of pathogen control in renal infection in immunocompromised hosts.

Re-epithelialization as pathomechanism

"The kidney" is actually a collection of up to 1 million independent functional units, i.e. the nephrons. Nephron structure and function is largely determined by an epithelial monolayer along the glomerular tuft and all tubular segments up to the collecting ducts opening into the renal pelvis. No matter in which segment it occurs, renal epithelial injury requires rapid re-epithelialization to avoid functional and structural problems (Rabelink and Little, 2013; Romagnani et al., 2013). Re-epithelialization is supported by surviving epithelial cells via cell division (proliferation = regeneration) or via increasing cell size without cell division (hypertrophy = reconstitution), two distinct processes that both imply cell cycle cycle activation and therefore are detected by "proliferation markers" such as immunolabeling (Thomasova and Anders, 2015). Although not formally proven by lineage tracing using clonal analysis it is widely assumed that functional recovery after acute tubular necrosis is associated with sufficient tubular epithelial cell regeneration (Bonventre, 2003; Duffield et al., 2005a). Growth factors like platelet derived growth factor (PDGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF) and bone morpho-genetic proteins (BMPs) induce re-epithelialization of injured epithelial monolayers (Werner and Grose, 2003; Sugimoto et al., 2012). Murine double minute (MDM)-2 supports cell cycle entry of surviving tubular cells by inhibiting p53-dependent cell cycle arrest in G1 (Mulay et al., 2012, 2013). MDM2 as well as numerous other molecules and mediators form close links between inflammation and regeneration (Thomasova et al., 2012; Ebrahim et al., 2015; Mulay et al., 2016c). Re-epithe-lialization requires first a resolution of inflammation because many pro-inflammatory elements suppress epithelial healing (Anders, 2014). The phenotype switch from "pro-inflammatory" (M1) to "wound healing" (M2) macrophages is important in this process. M2 macrophage-related CSF-1 secretion drives local M2

macrophage proliferation in an autocrine manner (Duffield et al., 2005b; Alikhan et al., 2011; Iwata et al., 2012). A tight regulation of re-epithelialization is essential because both overshooting as well as insufficient epithelial healing can contribute to aberrant kidney remodeling and organ failure.

Exaggerated re-epithelialization

Pro-mitotic signals without concomitant signals for differentiation promote cellular hyperplasia rather than epithelial healing (Lasagni and Romagnani, 2010), conceptually like in myeloproliferative disorders. For example, in crescentic glomerulonephritis renal progenitors within the parietal epithelial cell (PEC) layer of the Bowman's capsule no longer differentiate into podocytes to replace lost podocytes but rather produce hyperplastic lesions creating cellular crescents that obstruct the Bowman's space (Smeets et al., 2009; Bollee et al., 2011; Ryu et al., 2012). Not only inflammatory signals drive crescent formation. Indeed, crescent formation from PEC hyperplasia can occur also only upon plasma leakage from broken glomerular capillaries, conceptually similar to the mitogenic effect of serum components on cultured epithelial cells *in vitro* (Ryu et al., 2012). Indeed, under homeostatic conditions glomerular epithelial cells are never exposed to serum apart from vascular injury.

Insufficient epithelial regeneration

Insufficient re-epithelialization upon podocyte loss is a common cause for aging- or injury-related CKD (Hodgin et al., 2015). Differentiated podocytes lack the capacity to complete mitosis to replace lost podocytes next to them, because podocytes put all their cytoskeleton into the foot processes (Lasagni et al., 2013). Simplifying cell shape and recruiting the cytoskeleton to form the mitotic spindle is no option for differentiated podocytes as both processes would be incompatible with maintaining the filtration barrier (Lasagni et al., 2013). Thus, podocyte loss can only be compensated by hypertrophy of remnant podocytes or by *de novo* production of podocytes from local progenitors (Hagen et al., 2016). Under certain circumstances strong mitogenic signals force podocytes to bypass cell cycle restriction points, as evident from some multinucleated podocytes, but such podocytes rapidly detach and die, i.e. mitotic catastrophe (Liapis et al., 2013). Hypertrophy of remnant podocytes can compensate a loss of up to 20-30% of podocytes but losses exceeding this number often result in focal segmental glomerulosclerosis (FSGS) (Fukuda et al., 2012). *De novo* podocytes formation was clearly demonstrated by lineage tracing using the podocyte specific expression of the tomato-GFP reporter (Wanner et al., 2014). The source of such new podocytes remains an area of intense research activities (Shankland et al.,

2017). Some studies suggest that bone marrow-derived progenitor cells are able to replace lost podocytes (Prodromidi et al., 2006; Sugimoto et al., 2006; Zoja et al., 2012), whilst others propose that podocytes originate from local Pax2+ podocyte progenitors residing among the PECs or migrating onto the glomerular tuft from a pool of renin+ cells at the juxtaglomerular apparatus (Shankland et al., 2013; Lasagni et al., 2015; Lichtnekert et al., 2016). The capacity of podocyte progenitors to replace lost podocytes in the adult kidney seems very limited. Notch and Wnt signaling, EGF and SDF-1/CXCL12 regulate the behavior of PECs in glomerular injury (Lasagni et al., 2010; Darisipudi et al., 2011). Histone H3K9, H3K23 (acetylation), H3K4 (dimethylation) and H3K4 phosphorylation at serine 10 are associated with incomplete podocyte recovery and glomerulosclerosis (Gaikwad et al., 2010; Sayyed et al., 2010).

Repetitive or persistent injuries together with persistence of classically-activated (M1) macrophages impair tubular re-epithelialization after acute tubular necrosis (Duffield et al., 2005b; Anders, 2014; Lech et al., 2014). Tubular cells secrete the cytokine CSF-1 that enforces the expansion of macrophages inside the kidney but also enforces re-epithelialization of tubule segments (Menke et al., 2009). Severe injuries also eradicate those tubular cell progenitors more resistant to cell death and found scattered along the tubule, re-epithelialization may no longer be possible (Angelotti et al., 2012). The concept that bone marrow stem cells invade the injured tubulus to replace tubular cells by differentiation was experimentally excluded, but such cells may still provide paracrine support to the regenerating tubule cells from outside (Humphreys et al., 2011; Romagnani, 2011). Inability to rebuild the tubular epithelial monolayer leads to atrophy of the entire nephron.

In summary, both insufficient and exaggerated re-epithelialization contribute to kidney disease. Identifying the predominant pathomechanism in a clinical setting and identifying drugs that have the capacity to correct the abnormal response remains a challenge.

Fibrosis/sclerosis as pathomechanism

Mesenchymal structures stabilize the different compartments of the nephrons. Mesangial cells produce the mesangial matrix that stabilizes the glomerular tuft of capillaries. Similarly, interstitial fibroblasts produce the interstitial matrix that stabilizes the tubules. Pericytes stabilize intrarenal blood vessels especially upon injury by secreting TIMP3 and ADAMTS1 (Schrimpf et al., 2012; Smith et al., 2012). Nephron injury or microvascular damage activate such mesenchymal elements to expand and to produce more matrix enforcing the stabilization of the nephron compartments and to support the scaffold for parenchymal regeneration (Gurtner et al., 2008). Once nephrons undergo atrophy and are irreversibly lost

during injury, these mesenchymal elements fill the space with extracellular matrix, a process required to assure the functional integrity of the kidney as a whole. Nevertheless, nephron loss in CKD is associated with a declining kidney mass, because scar tissue does not exceed parenchymal losses.

Exaggerated mesenchymal healing

Mesangial cells lost during injury are usually rapidly replaced from several sources including potentially remnant mesangial cells, renin-producing cells from the extraglomerular mesangium, or mesangial cell precursors from the bone marrow (Imasawa et al., 2001; Ikarashi et al., 2005; Daniel et al., 2008; Starke et al., 2015). Mesangial repair upon mesangiolysis can be conveniently studied using the rat anti-Thy1.1 model (Eitner et al., 1997; Hugo et al., 1997). In contrast, mesangial hyperplasia is found in "mesangio-proliferative" and "membranoproliferative glomerulo-nephritis" (Sethi and Fervenza, 2012). The stabilizing function of scar formation also becomes obvious looking at insufficient podocyte regeneration. Whenever podocyte loss cannot any more be compensated by remnant podocyte hypertrophy or *de novo* podocyte formation, focal adhesions between the glomerular tuft and Bowman's capsule allow PECs to migrate onto the tuft (Smeets et al., 2011; Peired et al., 2013). There they lay down extracellular matrix and generate lesions referred to as FSGS (Smeets et al., 2011). Thus, whenever PECs are unable to contribute to re-epithelialization, e.g. by a lack of differentiation into podocytes they instead contribute to mesenchymal repair (Shankland et al., 2013, 2017). Like other scars FSGS lesions stabilize the rest of the glomerular tuft and minimize protein loss across the denudated GBM (Kriz and Lemley, 1999). However, the dynamics of hyperfiltration-related additional stress on the remaining podocytes can foster further podocyte loss and drive the progression to global glomerulosclerosis (Kriz and Lemley, 1999; Helal et al., 2012).

The well-documented association between interstitial fibrosis and poor renal function has led to the assumption that fibrosis drives nephron loss and CKD progression rather than simply being a marker of preceding nephron loss (Bohle et al., 1992; Zeisberg and Neilson, 2010). There is little evidence on a causal role of fibrosis for GFR decline and further nephron loss. There are no obvious genetic diseases causing primary fibrosis of the kidney, not even diffuse scleroderma presents with renal fibrosis (Bussone et al., 2011), and also genome-wide association studies on CKD cohorts did not identify risk genes pointing towards fibrogenesis (Boger et al., 2011). Indeed, ubiquitous presence of renal fibrosis in CKD implies it to be mesenchymal healing of secondary nature related to precedent insufficient epithelial healing (Anders and Schaefer, 2014). For example, tubular epithelial cells unable to regenerate were reported to be arrested in the G2/M phase and to produce tumor growth factor-beta as occurs in Chinese herb nephropathy (Yang et al., 2010). Leukocytes contribute to mesenchymal healing of the kidney demonstrated by interventions inhibiting leukocyte influx (Anders et al., 2002, 2003b, 2006; Vielhauer et al., 2004; Ninichuk et al., 2005; Furuichi et al., 2006; Ninichuk et al., 2007; Clauss et al., 2009). Indeed, inhibition, deletion or depletion of alternatively-activated (M2) macrophages abrogates intrarenal fibrogenesis (Lee et al., 2011; Braga et al., 2012; Chen et al., 2012; Cao et al., 2015). In addition, Ly6G+ collagen-producing "fibrocytes" from the bone marrow invade the kidney via CCL21-CCR7 and contribute to local collagen secretion (Sakai et al., 2006; Reich et al., 2013). Finally, pericyte-derived fibroblasts produce collagen and contribute to renal interstitial fibrosis (Lin et al., 2008; Smith et al., 2012; Kramann et al., 2015, 2017).

Insufficient mesenchymal healing

Insufficient scaring is a less prevalent problem in kidney disease. Mesangiolysis noted on a kidney biopsy implies insufficient regeneration from mesangial cell progenitors, e.g. in atypical hemolytic uremic syndrome, immune complex glomerulonephritis or C3 glomerulo-pathy (Bomback and Appel, 2012; Migliorini et al., 2013a). Hyperglycemia in diabetes is another state known to compromise mesangial healing. For example, Kimmelstiel-Wilson nodules in diabetic nephropathy are thought to result from mesangiolysis that cannot be restored from cellular sources and is rather filled by nodular matrix deposits (Stout et al., 1993).

In summary, mesenchymal repair serves an important function, i.e. to stabilize remnant parenchymal tissue to to serve as a scaffold during tissue regeneration. By contrast, insufficient mesenchymal healing is a rare problem in the kidney.

Concluding remarks

Diseases are often manifestations of evolutionary trade-offs. Evolution selected danger responses to cope with potentially life-threatening risks but such danger responses need to be balanced to avoid collateral damage implying other morbidities and even fatal consequences. Clotting, inflammation, epithelial and mesenchymal healing are excellent examples of life saving danger response programs that under certain circumstances can cause disease (Hagemann et al., 2013). Overshooting or insufficient responses can occur due to genetic or environmental insults and can become predominant pathomechanisms of disease. Identifying the predominant pathomechanism in individual patients and identifying specific drugs to correct the abnormal tissue response are the central challenges for translational research in the following years.

References

Abais J.M., Xia M., Li G., Chen Y., Conley S.M., Gehr T.W., Boini K.M. and Li P.L. (2014). Nod-like receptor protein 3 (nlrp3) inflammasome activation and podocyte injury via thioredoxin-interacting protein (txnip) during hyperhomocysteinemia. J. Biol. Chem. 289, 27159-27168.

Abraham S.N. and Miao Y. (2015). The nature of immune responses to urinary tract infections. Nat. Rev. Immunol. 15, 655-663.

Ahronowitz I., Harp J. and Shinkai K. (2012). Etiology and management of pyoderma gangrenosum: A comprehensive review. Am. J. Clin. Dermatol.

Alikhan M.A., Jones C.V., Williams T.M., Beckhouse A.G., Fletcher A.L., Kett M.M., Sakkal S., Samuel C.S., Ramsay R.G., Deane J.A., Wells C.A., Little M.H., Hume D.A. and Ricardo S.D. (2011). Colony-stimulating factor-1 promotes kidney growth and repair via alteration of macrophage responses. Am. J. Pathol. 179, 1243-1256.

Allam R. and Anders H.J. (2008). The role of innate immunity in autoimmune tissue injury. Curr. Opin. Rheumatol. 20, 538-544.

Allam R., Darisipudi M.N., Tschopp J. and Anders H.J. (2013). Histones trigger sterile inflammation by activating the nlrp3 inflammasome. Eur. J. Immunol. 43, 3336-3342.

Allam R., Kumar S.V., Darisipudi M.N. and Anders H.J. (2014). Extracellular histones in tissue injury and inflammation. J. Mol. Med. (Berl.) 92, 465-472.

Allam R., Lichtnekert J., Moll A., Taubitz A., Vielhauer V. and Anders H.J. (2009). Viral RNA and DNA sense common antiviral responses including type I interferons in mesangial cells. J. Am. Soc. Nephrol. 20, 1986-1996.

Allam R., Pawar R.D., Kulkarni O.P., Hornung V., Hartmann G., Segerer S., Akira S., Endres S. and Anders H.J. (2008). Viral 5'-triphosphate rna and non-cpg DNA aggravate autoimmunity and lupus nephritis via distinct tlr-independent immune responses. Eur. J. Immunol. 38, 3487-3498.

Allam R., Scherbaum C.R., Darisipudi M.N., Mulay S.R., Hagele H., Lichtnekert J., Hagemann J.H., Rupanagudi K.V., Ryu M., Schwarzenberger C., Hohenstein B., Hugo C., Uhl B., Reichel C.A., Krombach F., Monestier M., Liapis H., Moreth K., Schaefer L. and Anders H.J. (2012). Histones from dying renal cells aggravate kidney injury via tlr2 and tlr4. J. Am. Soc. Nephrol. 23, 1375-1388.

Anders H.J. (2007). Innate pathogen recognition in the kidney: Toll-like receptors, nod-like receptors, and rig-like helicases. Kidney Int. 72, 1051-1056.

Anders H.J. (2009). Pseudoviral immunity - a novel concept for lupus. Trends Mol. Med. 15, 553-561.

Anders H.J. (2010). Toll-like receptors and danger signaling in kidney injury. J. Am. Soc. Nephrol. 21, 1270-1274.

Anders H.J. (2012). Four danger response programs determine glomerular and tubulointerstitial kidney pathology: Clotting, inflammation, epithelial and mesenchymal healing. Organogenesis 8, 29-40.

Anders H.J. (2014). Immune system modulation of kidney regeneration--mechanisms and implications. Nat. Rev. Nephrol. 10, 347-358.

Anders H.J. (2016). Of inflammasomes and alarmins: Il-1beta and il-1alpha in kidney disease. J. Am. Soc. Nephrol. 27, 2564-2575.

Anders H.J. and Patole P.S. (2005). Toll-like receptors recognize uropathogenic escherichia coli and trigger inflammation in the urinary tract. Nephrol. Dial. Transplant. 20, 1529-1532.

Anders H.J. and Schlondorff D. (2007). Toll-like receptors: Emerging concepts in kidney disease. Curr. Opin. Nephrol. Hypertens. 16, 177-183.

Anders H.J. and Ryu M. (2011). Renal microenvironments and macrophage phenotypes determine progression or resolution of renal inflammation and fibrosis. Kidney Int. 80, 915-925.

Anders H.J. and Muruve D.A. (2011). The inflammasomes in kidney disease. J. Am. Soc. Nephrol. 22, 1007-1018.

Anders H.J. and Schaefer L. (2014). Beyond tissue injury-damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis. J. Am. Soc. Nephrol. 25, 1387-1400.

Anders H.J., Vielhauer V., Frink M., Linde Y., Cohen C.D., Blattner S.M., Kretzler M., Strutz F., Mack M., Grone H.J., Onuffer J., Horuk R., Nelson P.J. and Schlondorff D. (2002). A chemokine receptor ccr-1 antagonist reduces renal fibrosis after unilateral ureter ligation. J. Clin. Invest. 109, 251-259.

Anders H.J., Vielhauer V. and Schlondorff D. (2003a). Chemokines and chemokine receptors are involved in the resolution or progression of renal disease. Kidney Int. 63, 401-415.

Anders H.J., Banas B., Linde Y., Weller L., Cohen C.D., Kretzler M., Martin S., Vielhauer V., Schlondorff D. and Grone H.J. (2003b). Bacterial cpg-DNA aggravates immune complex glomerulonephritis: Role of tlr9-mediated expression of chemokines and chemokine receptors. J. Am. Soc. Nephrol. 14, 317-326.

Anders H.J., Banas B. and Schlondorff D. (2004a). Signaling danger: Toll-like receptors and their potential roles in kidney disease. J. Am. Soc. Nephrol. 15, 854-867.

Anders H.J., Vielhauer V., Eis V., Linde Y., Kretzler M., Perez de Lema G., Strutz F., Bauer S., Rutz M., Wagner H., Grone H.J. and Schlondorff D. (2004b). Activation of toll-like receptor-9 induces progression of renal disease in mrl-fas(lpr) mice. FASEB J. 18, 534-536.

Anders H.J., Ninichuk V. and Schlondorff D. (2006). Progression of kidney disease: Blocking leukocyte recruitment with chemokine receptor ccr1 antagonists. Kidney Int. 69, 29-32.

Anders H.J., Lichtnekert J. and Allam R. (2010). Interferon-alpha and -beta in kidney inflammation. Kidney Int. 77, 848-854.

Andersen K., Eltrich N., Lichtnekert J., Anders H.J. and Vielhauer V. (2014). The nlrp3/asc inflammasome promotes t-cell-dependent immune complex glomerulonephritis by canonical and noncanonical mechanisms. Kidney Int. 86, 965-978.

Angelotti M.L., Ronconi E., Ballerini L., Peired A., Mazzinghi B., Sagrinati C., Parente E., Gacci M., Carini M., Rotondi M., Fogo A.B., Lazzeri E., Lasagni L. and Romagnani P. (2012). Characterization of renal progenitors committed toward tubular lineage and their regenerative potential in renal tubular injury. Stem Cells 30, 1714-1725.

Babel N., Volk H.D. and Reinke P. (2011). Bk polyomavirus infection and nephropathy: The virus-immune system interplay. Nat Rev Nephrol 7, 399-406.

Behzadi E. and Behzadi P. (2016). The role of toll-like receptors (tlrs) in urinary tract infections (utis). Cent European J. Urol. 69, 404-410.

Boger C.A., Gorski M., Li M., Hoffmann M.M., Huang C., Yang Q., Teumer A., Krane V., O'Seaghdha C.M., Kutalik Z., Wichmann H.E., Haak T., Boes E., Coassin S., Coresh J., Kollerits B., Haun M., Paulweber B., Kottgen A., Li G., Shlipak M.G., Powe N., Hwang S.J., Dehghan A., Rivadeneira F., Uitterlinden A., Hofman A., Beckmann J.S., Kramer B.K., Witteman J., Bochud M., Siscovick D., Rettig R., Kronenberg F., Wanner C., Thadhani R.I., Heid I.M., Fox C.S., Kao W.H. and Consortium C.K. (2011). Association of EGFR-related loci identified by gwas with incident CKD and ESRD. PLoS Genet 7, e1002292.

Bohle A., Wehrmann M., Bogenschutz O., Batz C., Vogl W., Schmitt H., Muller C.A. and Muller G.A. (1992). The long-term prognosis of the primary glomerulonephritides. A morphological and clinical analysis of 1747 cases. Pathol. Res. Pract. 188, 908-924.

Bollee G., Flamant M., Schordan S., Fligny C., Rumpel E., Milon M., Schordan E., Sabaa N., Vandermeersch S., Galaup A., Rodenas A., Casal I., Sunnarborg S.W., Salant D.J., Kopp J.B., Threadgill D.W., Quaggin S.E., Dussaule J.C., Germain S., Mesnard L., Endlich K., Boucheix C., Belenfant X., Callard P., Endlich N. and Tharaux P.L. (2011). Epidermal growth factor receptor promotes glomerular injury and renal failure in rapidly progressive crescentic glomerulonephritis. Nat. Med. 17, 1242-1250.

Bomback A.S. and Appel G.B. (2012). Pathogenesis of the c3 glomerulopathies and reclassification of mpgn. Nat. Rev. Nephrol 8, 634-642.

Bonventre J.V. (2003). Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. J. Am. Soc. Nephrol. 14 (Suppl. 1), S55-61.

Braga T.T., Correa-Costa M., Guise Y.F., Castoldi A., de Oliveira C.D., Hyane M.I., Cenedeze M.A., Teixeira S.A., Muscara M.N., Perez K.R., Cuccovia I.M., Pacheco-Silva A., Goncalves G.M. and Camara N.O. (2012). Myd88 signaling pathway is involved in renal fibrosis by favoring a th2 immune response and activating alternative m2 macrophages. Mol. Med. 18, 1231-1239.

Brahler S., Ising C., Hagmann H., Rasmus M., Hoehne M., Kurschat C., Kisner T., Goebel H., Shankland S., Addicks K., Thaiss F., Schermer B., Pasparakis M., Benzing T. and Brinkkoetter P.T. (2012). Intrinsic proinflammatory signaling in podocytes contributes to podocyte damage and prolonged proteinuria. Am. J. Physiol. Renal Physiol. 303, F1473-1485.

Braun R.K., Ferrick C., Neubauer P., Sjoding M., Sterner-Kock A., Kock M., Putney L., Ferrick D.A., Hyde D.M. and Love R.B. (2008). Il-17 producing gammadelta t cells are required for a controlled inflammatory response after bleomycin-induced lung injury. Inflammation 31, 167-179.

Brinkmann V., Reichard U., Goosmann C., Fauler B., Uhlemann Y., Weiss D.S., Weinrauch Y. and Zychlinsky A. (2004). Neutrophil extracellular traps kill bacteria. Science 303, 1532-1535.

Buchmann K. (2014). Evolution of innate immunity: Clues from invertebrates via fish to mammals. Front. Immunol. 5, 459.

Bussone G., Berezne A., Pestre V., Guillevin L. and Mouthon L. (2011). The scleroderma kidney: Progress in risk factors, therapy, and prevention. Curr. Rheumatol. Rep. 13, 37-43.

Cao Q., Harris D.C. and Wang Y. (2015). Macrophages in kidney injury, inflammation, and fibrosis. Physiology (Bethesda) 30, 183-194.

Chan J.K., Roth J., Oppenheim J.J., Tracey K.J., Vogl T., Feldmann M., Horwood N. and Nanchahal J. (2012). Alarmins: Awaiting a clinical response. J. Clin. Invest. 122, 2711-2719.

Chapman K., Seldon M. and Richards R. (2012). Thrombotic microangiopathies, thrombotic thrombocytopenic purpura, and adamts-13. Semin. Thromb. Hemost. 38, 47-54.

Chen G., Chen H., Wang C., Peng Y., Sun L., Liu H. and Liu F. (2012). Rapamycin ameliorates kidney fibrosis by inhibiting the activation of mtor signaling in interstitial macrophages and myofibroblasts. PLoS One 7, e33626.

Chen L., Guo S., Ranzer M.J. and DiPietro L.A. (2013). Toll-like receptor 4 has an essential role in early skin wound healing. J. Invest. Dermatol. 133, 258-267.

Chevalier R.L. (2017). Evolutionary nephrology. Kidney Int. Rep. 2, 302-317.

Clauss S., Gross O., Kulkarni O., Avila-Ferrufino A., Radomska E., Segerer S., Eulberg D., Klussmann S. and Anders H.J. (2009). Ccl2/mcp-1 blockade reduces glomerular and interstitial macrophages but does not ameliorate renal pathology in collagen4a3-deficient mice with autosomal recessive alport nephropathy. J. Pathol. 218, 40-47.

Damman J., Bloks V.W., Daha M.R., van der Most P.J., Sanjabi B., van der Vlies P., Snieder H., Ploeg R.J., Krikke C., Leuvenink H.G. and Seelen M.A. (2015). Hypoxia and complement-and-coagulation pathways in the deceased organ donor as the major target for intervention to improve renal allograft outcome. Transplantation 99, 1293-1300.

Daniel C., Albrecht H., Ludke A. and Hugo C. (2008). Nestin expression in repopulating mesangial cells promotes their proliferation. Lab. Invest. 88, 387-397.

Darisipudi M.N., Kulkarni O.P., Sayyed S.G., Ryu M., Migliorini A., Sagrinati C., Parente E., Vater A., Eulberg D., Klussmann S., Romagnani P. and Anders H.J. (2011). Dual blockade of the homeostatic chemokine cxcl12 and the proinflammatory chemokine ccl2 has additive protective effects on diabetic kidney disease. Am. J. Pathol. 179, 116-124.

Darisipudi M.N., Thomasova D., Mulay S.R., Brech D., Noessner E., Liapis H. and Anders H.J. (2012). Uromodulin triggers il-1beta-dependent innate immunity via the nlrp3 inflammasome. J. Am. Soc. Nephrol. 23, 1783-1789.

Delvaeye M. and Conway E.M. (2009). Coagulation and innate immune responses: Can we view them separately? Blood 114, 2367-2374.

Duffield J.S., Park K.M., Hsiao L.L., Kelley V.R., Scadden D.T., Ichimura T. and Bonventre J.V. (2005a). Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. J. Clin. Invest. 115, 1743-1755.

Duffield J.S., Forbes S.J., Constandinou C.M., Clay S., Partolina M., Vuthoori S., Wu S., Lang R. and Iredale J.P. (2005b). Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J. Clin. Invest. 115, 56-65.

Ebihara N., Matsuda A., Nakamura S., Matsuda H. and Murakami A. (2011). Role of the il-6 classic- and trans-signaling pathways in corneal sterile inflammation and wound healing. Invest. Ophthalmol. Vis. Sci. 52, 8549-8557.

Ebrahim M., Mulay S.R., Anders H.J. and Thomasova D. (2015). Mdm2 beyond cancer: Podoptosis, development, inflammation, and tissue regeneration. Histol. Histopathol. 30, 1271-1282.

Eitner F., Westerhuis R., Burg M., Weinhold B., Grone H.J., Ostendorf

T., Ruther U., Koch K.M., Rees A.J. and Floege J. (1997). Role of interleukin-6 in mediating mesangial cell proliferation and matrix production *in vivo*. Kidney Int. 51, 69-78.

Engelmann B. and Massberg S. (2013). Thrombosis as an intravascular effector of innate immunity. Nat. Rev. Immunol. 13, 34-45.

Falke L.L., Gholizadeh S., Goldschmeding R., Kok R.J. and Nguyen T.Q. (2015). Diverse origins of the myofibroblast-implications for kidney fibrosis. Nat. Rev. Nephrol. 11, 233-244.

Flur K., Allam R., Zecher D., Kulkarni O.P., Lichtnekert J., Schwarz M., Beutler B., Vielhauer V. and Anders H.J. (2009). Viral rna induces type i interferon-dependent cytokine release and cell death in mesangial cells via melanoma-differentiation-associated gene-5: Implications for viral infection-associated glomerulonephritis. Am. J. Pathol. 175, 2014-2022.

Fukuda A., Chowdhury M.A., Venkatareddy M.P., Wang S.Q., Nishizono R., Suzuki T., Wickman L.T., Wiggins J.E., Muchayi T., Fingar D., Shedden K.A., Inoki K. and Wiggins R.C. (2012). Growth-dependent podocyte failure causes glomerulosclerosis. J. Am. Soc. Nephrol. 23, 1351-1363.

Furuichi K., Gao J.L. and Murphy P.M. (2006). Chemokine receptor cx3cr1 regulates renal interstitial fibrosis after ischemia-reperfusion injury. Am. J. Pathol. 169, 372-387.

Gaikwad A.B., Sayyed S.G., Lichtnekert J., Tikoo K. and Anders H.J. (2010). Renal failure increases cardiac histone h3 acetylation, dimethylation, and phosphorylation and the induction of cardiomyopathy-related genes in type 2 diabetes. Am. J. Pathol. 176, 1079-1083.

Garimella P.S. and Sarnak M.J. (2017). Uromodulin in kidney health and disease. Curr. Opin. Nephrol. Hypertens. 26, 136-142.

Godaly G., Ambite I. and Svanborg C. (2015). Innate immunity and genetic determinants of urinary tract infection susceptibility. Curr. Opin. Infect. Dis. 28, 88-96.

Gunthner R., Kumar V.R., Lorenz G., Anders H.J. and Lech M. (2013). Pattern-recognition receptor signaling regulator mrna expression in humans and mice, and in transient inflammation or progressive fibrosis. Int. J. Mol. Sci. 14, 18124-18147.

Gurtner G.C., Werner S., Barrandon Y. and Longaker M.T. (2008). Wound repair and regeneration. Nature 453, 314-321.

Gutierrez E., Egido J., Rubio-Navarro A., Buendia I., Blanco Colio L.M., Toldos O., Manzarbeitia F., de Lorenzo A., Sanchez R., Ortiz A., Praga M. and Moreno J.A. (2012). Oxidative stress, macrophage infiltration and cd163 expression are determinants of long-term renal outcome in macrohematuria-induced acute kidney injury of iga nephropathy. Nephron. Clin. Pract. 121, c42-53.

Hagele H., Allam R., Pawar R.D. and Anders H.J. (2009a). Double-stranded rna activates type i interferon secretion in glomerular endothelial cells via retinoic acid-inducible gene (rig)-1. Nephrol. Dial. Transplant. 24, 3312-3318.

Hagele H., Allam R., Pawar R.D., Reichel C.A., Krombach F. and Anders H.J. (2009b). Double-stranded DNA activates glomerular endothelial cells and enhances albumin permeability via a toll-like receptor-independent cytosolic DNA recognition pathway. Am. J. Pathol. 175, 1896-1904.

Hagemann J.H., Haegele H., Muller S. and Anders H.J. (2013). Danger control programs cause tissue injury and remodeling. Int. J. Mol. Sci. 14, 11319-11346.

Hagen M., Pfister E., Kosel A., Shankland S., Pippin J., Amann K. and Daniel C. (2016). Cell cycle re-entry sensitizes podocytes to injury induced death. Cell Cycle 15, 1929-1937.

Helal I., Fick-Brosnahan G.M., Reed-Gitomer B. and Schrier R.W. (2012). Glomerular hyperfiltration: Definitions, mechanisms and clinical implications. Nat. Rev. Nephrol. 21, 293-300.

Hickey M.J. and Kubes P. (2009). Intravascular immunity: The host-pathogen encounter in blood vessels. Nat. Rev. Immunol. 9, 364-375.

Hodgin J.B., Bitzer M., Wickman L., Afshinnia F., Wang S.Q., O'Connor C., Yang Y., Meadowbrooke C., Chowdhury M., Kikuchi M., Wiggins J.E. and Wiggins R.C. (2015). Glomerular aging and focal global glomerulosclerosis: A podometric perspective. J. Am. Soc. Nephrol. 26, 3162-3178.

Hotchkiss R.S., Coopersmith C.M., McDunn J.E. and Ferguson T.A. (2009). The sepsis seesaw: Tilting toward immunosuppression. Nat. Med. 15, 496-497.

Hugo C., Shankland S.J., Bowen-Pope D.F., Couser W.G. and Johnson R.J. (1997). Extraglomerular origin of the mesangial cell after injury. A new role of the juxtaglomerular apparatus. J. Clin. Invest. 100, 786-794.

Humphreys B.D., Czerniak S., DiRocco D.P., Hasnain W., Cheema R. and Bonventre J.V. (2011). Repair of injured proximal tubule does not involve specialized progenitors. Proc. Natl. Acad. Sci. USA 108, 9226-9231.

Humphreys B.D., Lin S.L., Kobayashi A., Hudson T.E., Nowlin B.T., Bonventre J.V., Valerius M.T., McMahon A.P. and Duffield J.S. (2010). Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. Am. J. Pathol. 176, 85-97.

Ikarashi K., Li B., Suwa M., Kawamura K., Morioka T., Yao J., Khan F., Uchiyama M. and Oite T. (2005). Bone marrow cells contribute to regeneration of damaged glomerular endothelial cells. Kidney Int. 67, 1925-1933.

Imasawa T., Utsunomiya Y., Kawamura T., Zhong Y., Nagasawa R., Okabe M., Maruyama N., Hosoya T. and Ohno T. (2001). The potential of bone marrow-derived cells to differentiate to glomerular mesangial cells. J. Am. Soc. Nephrol. 12, 1401-1409.

Ishida Y., Gao J.L. and Murphy P.M. (2008). Chemokine receptor cx3cr1 mediates skin wound healing by promoting macrophage and fibroblast accumulation and function. J. Immunol. 180, 569-579.

Iwata Y., Bostrom E.A., Menke J., Rabacal W.A., Morel L., Wada T. and Kelley V.R. (2012). Aberrant macrophages mediate defective kidney repair that triggers nephritis in lupus-susceptible mice. J. Immunol. 188, 4568-4580.

Jennewein C., Paulus P. and Zacharowski K. (2011). Linking inflammation and coagulation: Novel drug targets to treat organ ischemia. Curr. Opin. Anaesthesiol. 24, 375-380.

Kaczmarek A., Vandenabeele P. and Krysko D.V. (2013). Necroptosis: The release of damage-associated molecular patterns and its physiological relevance. Immunity 38, 209-223.

Kramann R., Wongboonsin J., Chang-Panesso M., Machado F.G. and Humphreys B.D. (2017). Gli1+ pericyte loss induces capillary rarefaction and proximal tubular injury. J. Am. Soc. Nephrol. 28, 776-784.

Kramann R., Schneider R.K., DiRocco D.P., Machado F., Fleig S., Bondzie P.A., Henderson J.M., Ebert B.L. and Humphreys B.D. (2015). Perivascular gli1+ progenitors are key contributors to injury-induced organ fibrosis. Cell Stem Cell 16, 51-66.

Kriz W. and Lemley K.V. (1999). The role of the podocyte in glomerulosclerosis. Curr. Opin. Nephrol. Hypertens. 8, 489-497.

Kroeze K.L., Boink M.A., Sampat-Sardjoepersad S.C., Waaijman T., Scheper R.J. and Gibbs S. (2012). Autocrine regulation of re-

epithelialization after wounding by chemokine receptors ccr1, ccr10, cxcr1, cxcr2, and cxcr3. J. Invest. Dermatol. 132, 216-225.

Kulkarni O., Eulberg D., Selve N., Zollner S., Allam R., Pawar R.D., Pfeiffer S., Segerer S., Klussmann S. and Anders H.J. (2009). Anti-ccl2 spiegelmer permits 75% dose reduction of cyclophosphamide to control diffuse proliferative lupus nephritis and pneumonitis in mrl-fas(lpr) mice. J. Pharmacol. Exp. Ther. 328, 371-377.

Kulkarni O., Pawar R.D., Purschke W., Eulberg D., Selve N., Buchner K., Ninichuk V., Segerer S., Vielhauer V., Klussmann S. and Anders H.J. (2007). Spiegelmer inhibition of ccl2/mcp-1 ameliorates lupus nephritis in mrl-(fas)lpr mice. J. Am. Soc. Nephrol. 18, 2350-2358.

Kumar S.V., Kulkarni O.P., Mulay S.R., Darisipudi M.N., Romoli S., Thomasova D., Scherbaum C.R., Hohenstein B., Hugo C., Muller S., Liapis H. and Anders H.J. (2015). Neutrophil extracellular trap-related extracellular histones cause vascular necrosis in severe gn. J. Am. Soc. Nephrol. 26, 2399-2413.

Kurts C., Panzer U., Anders H.J. and Rees A.J. (2013). The immune system and kidney disease: Basic concepts and clinical implications. Nat. Rev. Immunol. 13, 738-753.

Lai W.F. and Siu P.M. (2014). MicroRNAs as regulators of cutaneous wound healing. J. Biosci. 39, 519-524.

Lasagni L. and Romagnani P. (2010). Glomerular epithelial stem cells: The good, the bad, and the ugly. J. Am. Soc. Nephrol. 21, 1612-1619.

Lasagni L., Lazzeri E., Shankland S.J., Anders H.J. and Romagnani P. (2013). Podocyte mitosis - a catastrophe. Curr. Mol. Med. 13, 13-23.

Lasagni L., Ballerini L., Angelotti M.L., Parente E., Sagrinati C., Mazzinghi B., Peired A., Ronconi E., Becherucci F., Bani D., Gacci M., Carini M., Lazzeri E. and Romagnani P. (2010). Notch activation differentially regulates renal progenitors proliferation and differentiation toward the podocyte lineage in glomerular disorders. Stem Cells 28, 1674-1685.

Lasagni L., Angelotti M.L., Ronconi E., Lombardi D., Nardi S., Peired A., Becherucci F., Mazzinghi B., Sisti A., Romoli S., Burger A., Schaefer B., Buccoliero A., Lazzeri E. and Romagnani P. (2015). Podocyte regeneration driven by renal progenitors determines glomerular disease remission and can be pharmacologically enhanced. Stem Cell Reports 5, 248-263.

Lassen S., Lech M., Rommele C., Mittruecker H.W., Mak T.W. and Anders H.J. (2010). Ischemia reperfusion induces ifn regulatory factor 4 in renal dendritic cells, which suppresses postischemic inflammation and prevents acute renal failure. J. Immunol. 185, 1976-1983.

Leadbetter E.A., Rifkin I.R., Hohlbaum A.M., Beaudette B.C., Shlomchik M.J. and Marshak-Rothstein A. (2002). Chromatin-igg complexes activate b cells by dual engagement of igm and toll-like receptors. Nature 416, 603-607.

LeBleu V., Sugimoto H., Mundel T.M., Gerami-Naini B., Finan E., Miller C.A., Gattone V.H. 2nd, Lu L., Shield C.F. 3rd, Folkman J. and Kalluri R. (2009). Stem cell therapies benefit alport syndrome. J. Am. Soc. Nephrol. 20, 2359-2370.

Lech M., Grobmayr R., Weidenbusch M. and Anders H.J. (2012). Tissues use resident dendritic cells and macrophages to maintain homeostasis and to regain homeostasis upon tissue injury: The immunoregulatory role of changing tissue environments. Mediators Inflamm. 2012, 951390.

Lech M., Garlanda C., Mantovani A., Kirschning C.J., Schlondorff D. and Anders H.J. (2007). Different roles of tir8/sigirr on toll-like receptor signaling in intrarenal antigen-presenting cells and tubular epithelial cells. Kidney Int. 72, 182-192.

Lech M., Skuginna V., Kulkarni O.P., Gong J., Wei T., Stark R.W., Garlanda C., Mantovani A. and Anders H.J. (2010). Lack of sigirr/tir8 aggravates hydrocarbon oil-induced lupus nephritis. J. Pathol. 220, 596-607.

Lech M., Grobmayr R., Ryu M., Lorenz G., Hartter I., Mulay S.R., Susanti H.E., Kobayashi K.S., Flavell R.A. and Anders H.J. (2014). Macrophage phenotype controls long-term aki outcomes--kidney regeneration versus atrophy. J. Am. Soc. Nephrol. 25, 292-304.

Lee S., Huen S., Nishio H., Nishio S., Lee H.K., Choi B.S., Ruhrberg C. and Cantley L.G. (2011). Distinct macrophage phenotypes contribute to kidney injury and repair. J. Am. Soc. Nephrol. 22, 317-326.

Leemans J.C., Kors L., Anders H.J. and Florquin S. (2014). Pattern recognition receptors and the inflammasome in kidney disease. Nat. Rev. Nephrol. 10, 398-414.

Leventhal J.S. and Schroppel B. (2012). Toll-like receptors in transplantation: Sensing and reacting to injury. Kidney Int. 81, 826-832.

Liapis H., Romagnani P. and Anders H.J. (2013). New insights into the pathology of podocyte loss: Mitotic catastrophe. Am. J. Pathol. 183, 1364-1374.

Lichtnekert J., Kaverina N.V., Eng D.G., Gross K.W., Kutz J.N., Pippin J.W. and Shankland S.J. (2016). Renin-angiotensin-aldosterone system inhibition increases podocyte derivation from cells of renin lineage. J. Am. Soc. Nephrol. 27, 3611-3627.

Lichtnekert J., Kulkarni O.P., Mulay S.R., Rupanagudi K.V., Ryu M., Allam R., Vielhauer V., Muruve D., Lindenmeyer M.T., Cohen C.D. and Anders H.J. (2011). Anti-gbm glomerulonephritis involves il-1 but is independent of nlrp3/asc inflammasome-mediated activation of caspase-1. PLoS One 6, e26778.

Lin S.L., Kisseleva T., Brenner D.A. and Duffield J.S. (2008). Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. Am. J. Pathol. 173, 1617-1627.

Linkermann A. and Green D.R. (2014). Necroptosis. N. Engl. J. Med. 370, 455-465.

Linkermann A., Stockwell B.R., Krautwald S. and Anders H.J. (2014). Regulated cell death and inflammation: An auto-amplification loop causes organ failure. Nat. Rev. Immunol. 14, 759-767.

Martinod K. and Wagner D.D. (2014). Thrombosis: Tangled up in nets. Blood 123, 2768-2776.

Mauri C. and Menon M. (2017). Human regulatory b cells in health and disease: Therapeutic potential. J. Clin. Invest. 127, 772-779.

McCarthy C.G., Goulopoulou S., Wenceslau C.F., Spitler K., Matsumoto T. and Webb R.C. (2014). Toll-like receptors and damage-associated molecular patterns: Novel links between inflammation and hypertension. Am. J. Physiol. Heart Circ. Physiol. 306, H184-196.

McGee H.M., Schmidt B.A., Booth C.J., Yancopoulos G.D., Valenzuela D.M., Murphy A.J., Stevens S., Flavell R.A. and Horsley V. (2013). Il-22 promotes fibroblast-mediated wound repair in the skin. J. Invest. Dermatol. 133, 1321-1329.

Medzhitov R. (2008). Origin and physiological roles of inflammation. Nature 454, 428-435.

Menke J., Iwata Y., Rabacal W.A., Basu R., Yeung Y.G., Humphreys B.D., Wada T., Schwarting A., Stanley E.R. and Kelley V.R. (2009). Csf-1 signals directly to renal tubular epithelial cells to mediate repair in mice. J. Clin. Invest. 119, 2330-2342.

Migliorini A. and Anders H.J. (2012). A novel pathogenetic concept-antiviral immunity in lupus nephritis. Nat. Rev. Nephrol. 8, 183-189.

Migliorini A., Ebid R., Scherbaum C.R. and Anders H.J. (2013a). The danger control concept in kidney disease: Mesangial cells. J. Nephrol. 26, in press.

Migliorini A., Angelotti M.L., Mulay S.R., Kulkarni O.O., Demleitner J., Dietrich A., Sagrinati C., Ballerini L., Peired A., Shankland S.J., Liapis H., Romagnani P. and Anders H.J. (2013b). The antiviral cytokines ifn-alpha and ifn-beta modulate parietal epithelial cells and promote podocyte loss: Implications for ifn toxicity, viral glomerulonephritis, and glomerular regeneration. Am. J. Pathol. 183, 431-440.

Minton K. (2015). T cell responses: A long-chain reaction. Nat. Rev. Immunol. 15, 726-727.

Mudaliar H., Pollock C., Komala M.G., Chadban S., Wu H. and Panchapakesan U. (2013). The role of toll-like receptor proteins (tlr) 2 and 4 in mediating inflammation in proximal tubules. Am. J. Physiol. Renal Physiol. 305, F143-154.

Mulay S.R. and Anders H.J. (2016). Crystallopathies. N. Engl. J. Med. 374, 2465-2476.

Mulay S.R. and Anders H.J. (2017). Crystal nephropathies: Mechanisms of crystal-induced kidney injury. Nat. Rev. Nephrol. 13, 226-240.

Mulay S.R., Thomasova D., Ryu M. and Anders H.J. (2012). MDM2 (murine double minute-2) links inflammation and tubular cell healing during acute kidney injury in mice. Kidney Int. 81, 1199-1211.

Mulay S.R., Thomasova D., Ryu M., Kulkarni O.P., Migliorini A., Bruns H., Grobmayr R., Lazzeri E., Lasagni L., Liapis H., Romagnani P. and Anders H.J. (2013). Podocyte loss involves mdm2-driven mitotic catastrophe. J. Pathol. 230, 322-335.

Mulay S.R., Linkermann A. and Anders H.J. (2016a). Necroinflammation in kidney disease. J. Am. Soc. Nephrol. 27, 27-39.

Mulay S.R., Kumar S.V., Lech M., Desai J. and Anders H.J. (2016b). How kidney cell death induces renal necroinflammation. Semin. Nephrol. 36, 162-173.

Mulay S.R., Romoli S., Desai J., Honarpisheh M.M., Kumar S.V., Anders H.J. and Thomasova D. (2016c). Murine double minute-2 inhibition ameliorates established crescentic glomerulonephritis. Am. J. Pathol. 186, 1442-1453.

Nair A.R., Ebenezer P.J., Saini Y. and Francis J. (2015). Angiotensin ii-induced hypertensive renal inflammation is mediated through hmgb1-tlr4 signaling in rat tubulo-epithelial cells. Exp. Cell Res. 335, 238-247.

Nakazawa D., Kumar S.V., Marschner J., Desai J., Holderied A., Rath L., Kraft F., Lei Y., Fukasawa Y., Moeckel G.W., Angelotti M.L., Liapis H. and Anders H.J. (2017). Histones and neutrophil extracellular traps enhance tubular necrosis and remote organ injury in ischemic aki. J. Am. Soc. Nephrol. 28, 1753-1768.

Nelson P.J., Rees A.J., Griffin M.D., Hughes J., Kurts C. and Duffield J. (2012). The renal mononuclear phagocytic system. J. Am. Soc. Nephrol. 23, 194-203.

Niedermeier M., Reich B., Rodriguez Gomez M., Denzel A., Schmidbauer K., Gobel N., Talke Y., Schweda F. and Mack M. (2009). Cd4+ t cells control the differentiation of gr1+ monocytes into fibrocytes. Proc. Natl. Acad. Sci. USA 106, 17892-17897.

Niessen F., Schaffner F., Furlan-Freguia C., Pawlinski R., Bhattacharjee G., Chun J., Derian C.K., Andrade-Gordon P., Rosen H. and Ruf W. (2008). Dendritic cell par1-s1p3 signalling couples coagulation and inflammation. Nature 452, 654-658.

Ninichuk V., Clauss S., Kulkarni O., Schmid H., Segerer S., Radomska E., Eulberg D., Buchner K., Selve N., Klussmann S. and Anders H.J. (2008). Late onset of ccl2 blockade with the spiegelmer mnox-e36-3'peg prevents glomerulosclerosis and improves glomerular filtration rate in db/db mice. Am. J. Pathol. 172, 628-637.

Ninichuk V., Khandoga A.G., Segerer S., Loetscher P., Schlapbach A., Revesz L., Feifel R., Khandoga A., Krombach F., Nelson P.J., Schlondorff D. and Anders H.J. (2007). The role of interstitial macrophages in nephropathy of type 2 diabetic db/db mice. Am. J. Pathol. 170, 1267-1276.

Ninichuk V., Gross O., Reichel C., Khandoga A., Pawar R.D., Ciubar R., Segerer S., Belemezova E., Radomska E., Luckow B., Perez de Lema G., Murphy P.M., Gao J.L., Henger A., Kretzler M., Horuk R., Weber M., Krombach F., Schlondorff D. and Anders H.J. (2005). Delayed chemokine receptor 1 blockade prolongs survival in collagen 4a3-deficient mice with alport disease. J. Am. Soc. Nephrol. 16, 977-985.

Noris M. and Remuzzi G. (2013). Overview of complement activation and regulation. Semin. Nephrol. 33, 479-492.

Noris M., Cassis P., Azzollini N., Cavinato R., Cugini D., Casiraghi F., Aiello S., Solini S., Cassis L., Mister M., Todeschini M., Abbate M., Benigni A., Trionfini P., Tomasoni S., Mele C., Garlanda C., Polentarutti N., Mantovani A. and Remuzzi G. (2009). The toll-il-1r member tir8/sigirr negatively regulates adaptive immunity against kidney grafts. J. Immunol. 183, 4249-4260.

Nurden A.T. (2011). Platelets, inflammation and tissue regeneration. Thromb. Haemost. 105 (Suppl. 1), S13-33.

Palabrica T., Lobb R., Furie B.C., Aronovitz M., Benjamin C., Hsu Y.M., Sajer S.A. and Furie B. (1992). Leukocyte accumulation promoting fibrin deposition is mediated *in vivo* by p-selectin on adherent platelets. Nature 359, 848-851.

Patole P.S., Schubert S., Hildinger K., Khandoga S., Khandoga A., Segerer S., Henger A., Kretzler M., Werner M., Krombach F., Schlondorff D. and Anders H.J. (2005). Toll-like receptor-4: Renal cells and bone marrow cells signal for neutrophil recruitment during pyelonephritis. Kidney Int. 68, 2582-2587.

Pawar R.D., Patole P.S., Wornle M. and Anders H.J. (2006). Microbial nucleic acids pay a toll in kidney disease. Am. J. Physiol. Renal Physiol. 291, F509-516.

Pawar R.D., Castrezana-Lopez L., Allam R., Kulkarni O.P., Segerer S., Radomska E., Meyer T.N., Schwesinger C.M., Akis N., Grone H.J. and Anders H.J. (2009). Bacterial lipopeptide triggers massive albuminuria in murine lupus nephritis by activating toll-like receptor 2 at the glomerular filtration barrier. Immunology 128, e206-221.

Peired A., Angelotti M.L., Ronconi E., la Marca G., Mazzinghi B., Sisti A., Lombardi D., Giocaliere E., Della Bona M., Villanelli F., Parente E., Ballerini L., Sagrinati C., Wanner N., Huber T.B., Liapis H., Lazzeri E., Lasagni L. and Romagnani P. (2013). Proteinuria impairs podocyte regeneration by sequestering retinoic acid. J. Am. Soc. Nephrol. 24, 1756-1768.

Pickert G., Neufert C., Leppkes M., Zheng Y., Wittkopf N., Warntjen M., Lehr H.A., Hirth S., Weigmann B., Wirtz S., Ouyang W., Neurath M.F. and Becker C. (2009). Stat3 links il-22 signaling in intestinal epithelial cells to mucosal wound healing. J. Exp. Med. 206, 1465-1472.

Plikus M.V., Gay D.L., Treffeisen E., Wang A., Supapannachart R.J. and Cotsarelis G. (2012). Epithelial stem cells and implications for wound repair. Semin. Cell Dev. Biol. 23, 946-953.

Prodromidi E.I., Poulsom R., Jeffery R., Roufosse C.A., Pollard P.J., Pusey C.D. and Cook H.T. (2006). Bone marrow-derived cells

contribute to podocyte regeneration and amelioration of renal disease in a mouse model of alport syndrome. Stem Cells 24, 2448-2455.

Rabelink T.J. and Little M.H. (2013). Stromal cells in tissue homeostasis: Balancing regeneration and fibrosis. Nat. Rev. Nephrol. 9, 747-753.

Reich B., Schmidbauer K., Rodriguez Gomez M., Johannes Hermann F., Gobel N., Bruhl H., Ketelsen I., Talke Y. and Mack M. (2013). Fibrocytes develop outside the kidney but contribute to renal fibrosis in a mouse model. Kidney Int. 84, 78-89.

Reiser J. and Sever S. (2013). Podocyte biology and pathogenesis of kidney disease. Annu. Rev. Med. 64, 357-366.

Ribeiro A., Wornle M., Motamedi N., Anders H.J., Grone E.F., Nitschko H., Kurktschiev P., Debiec H., Kretzler M., Cohen C.D., Grone H.J., Schlondorff D. and Schmid H. (2012). Activation of innate immune defense mechanisms contributes to polyomavirus bk-associated nephropathy. Kidney Int. 81, 100-111.

Rock K.L., Latz E., Ontiveros F. and Kono H. (2010). The sterile inflammatory response. Annual Review of Immunology, 28, 321-342.

Romagnani P. (2009). Toward the identification of a "renopoietic system"? Stem Cells 27, 2247-2253.

Romagnani P. (2011). Family portrait: Renal progenitor of bowman's capsule and its tubular brothers. Am. J. Pathol. 178, 490-493.

Romagnani P., Lasagni L. and Remuzzi G. (2013). Renal progenitors: An evolutionary conserved strategy for kidney regeneration. Nat. Rev. Nephrol. 9, 137-146.

Ryu M., Kulkarni O.P., Radomska E., Miosge N., Gross O. and Anders H.J. (2011). Bacterial cpg-DNA accelerates alport glomerulo-sclerosis by inducing an m1 macrophage phenotype and tumor necrosis factor-alpha-mediated podocyte loss. Kidney Int. 79, 189-198.

Ryu M., Migliorini M., Miosge N., Gross O., Shankland S., Brinkoetter P.T., Hagmann H., Romagnani P., Liapis H. and Anders H.J. (2012). Plasma leakage through glomerular basement membrane ruptures triggers the proliferation of parietal epithelial cells and crescent formation in non-inflammatory glomerular injury. J. Pathol. 228, 482-494.

Sakai N., Wada T., Yokoyama H., Lipp M., Ueha S., Matsushima K. and Kaneko S. (2006). Secondary lymphoid tissue chemokine (slc/ccl21)/ccr7 signaling regulates fibrocytes in renal fibrosis. Proc. Natl. Acad. Sci. USA 103, 14098-14103.

Sallustio F., Costantino V., Cox S.N., Loverre A., Divella C., Rizzi M. and Schena F.P. (2013). Human renal stem/progenitor cells repair tubular epithelial cell injury through tlr2-driven inhibin-a and microvesicle-shuttled decorin. Kidney Int. 83, 392-403.

Sayyed S.G., Gaikwad A.B., Lichtnekert J., Kulkarni O., Eulberg D., Klussmann S., Tikoo K. and Anders H.J. (2010). Progressive glomerulosclerosis in type 2 diabetes is associated with renal histone h3k9 and h3k23 acetylation, h3k4 dimethylation and phosphorylation at serine 10. Nephrol. Dial. Transplant. 25, 1811-1817.

Sayyed S.G., Ryu M., Kulkarni O.P., Schmid H., Lichtnekert J., Gruner S., Green L., Mattei P., Hartmann G. and Anders H.J. (2011). An orally active chemokine receptor ccr2 antagonist prevents glomerulosclerosis and renal failure in type 2 diabetes. Kidney Int. 80, 68-78.

Schrimpf C., Xin C., Campanholle G., Gill S.E., Stallcup W., Lin S.L., Davis G.E., Gharib S.A., Humphreys B.D. and Duffield J.S. (2012). Pericyte timp3 and adamts1 modulate vascular stability after kidney injury. J. Am. Soc. Nephrol. 23, 868-883.

Semple J.W., Italiano J.E. Jr and Freedman J. (2011). Platelets and the immune continuum. Nat. Rev. Immunol. 11, 264-274.

Seok S.J., Lee E.S., Kim G.T., Hyun M., Lee J.H., Chen S., Choi R., Kim H.M., Lee E.Y. and Chung C.H. (2013). Blockade of ccl2/ccr2 signalling ameliorates diabetic nephropathy in db/db mice. Nephrol. Dial. Transplant. 28, 1700-1710.

Sethi S. and Fervenza F.C. (2012). Membranoproliferative glomerulonephritis--a new look at an old entity. N. Engl. J. Med. 366, 1119-1131.

Shahzad K., Bock F., Dong W., Wang H., Kopf S., Kohli S., Al-Dabet M.M., Ranjan S., Wolter J., Wacker C., Biemann R., Stoyanov S., Reymann K., Soderkvist P., Gross O., Schwenger V., Pahernik S., Nawroth P.P., Grone H.J., Madhusudhan T. and Isermann B. (2015). Nlrp3-inflammasome activation in non-myeloid-derived cells aggravates diabetic nephropathy. Kidney Int. 87, 74-84.

Shankland S.J., Anders H.J. and Romagnani P. (2013). Glomerular parietal epithelial cells in kidney physiology, pathology, and repair. Curr. Opin. Nephrol. Hypertens. 22, 302-309.

Shankland S.J., Freedman B.S. and Pippin J.W. (2017). Can podocytes be regenerated in adults? Curr. Opin. Nephrol. Hypertens. 26, 154-164.

Smeets B., Kuppe C., Sicking E.M., Fuss A., Jirak P., van Kuppevelt T.H., Endlich K., Wetzels J.F., Grone H.J., Floege J. and Moeller M.J. (2011). Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. J. Am. Soc. Nephrol. 22, 1262-1274.

Smeets B., Angelotti M.L., Rizzo P., Dijkman H., Lazzeri E., Mooren F., Ballerini L., Parente E., Sagrinati C., Mazzinghi B., Ronconi E., Becherucci F., Benigni A., Steenbergen E., Lasagni L., Remuzzi G., Wetzels J. and Romagnani P. (2009). Renal progenitor cells contribute to hyperplastic lesions of podocytopathies and crescentic glomerulonephritis. J. Am. Soc. Nephrol. 20, 2593-2603.

Smith S.A., Travers R.J. and Morrissey J.H. (2015). How it all starts: Initiation of the clotting cascade. Crit. Rev. Biochem. Mol. Biol. 50, 326-336.

Smith S.W., Schrimpf C., Parekh D.J., Venkatachalam M. and Duffield J.S. (2012). Kidney pericytes: A novel therapeutic target in interstitial fibrosis. Histol. Histopathol. 27, 1503-1514.

Sorensen I., Susnik N., Inhester T., Degen J.L., Melk A., Haller H. and Schmitt R. (2011). Fibrinogen, acting as a mitogen for tubulointerstitial fibroblasts, promotes renal fibrosis. Kidney Int. 80, 1035-1044.

Srivastava A., Rao G.K., Segal P.E., Shah M. and Geetha D. (2013). Characteristics and outcome of crescentic glomerulonephritis in patients with both antineutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody. Clin. Rheumatol. 32, 1317-1322.

Starke C., Betz H., Hickmann L., Lachmann P., Neubauer B., Kopp J.B., Sequeira-Lopez M.L., Gomez R.A., Hohenstein B., Todorov V.T. and Hugo C.P. (2015). Renin lineage cells repopulate the glomerular mesangium after injury. J. Am. Soc. Nephrol. 26, 48-54.

Stokman M.F., Renkema K.Y., Giles R.H., Schaefer F., Knoers N.V. and van Eerde A.M. (2016). The expanding phenotypic spectra of kidney diseases: Insights from genetic studies. Nat. Rev. Nephrol. 12, 472-483.

Stout L.C., Kumar S. and Whorton E.B. (1993). Focal mesangiolysis and the pathogenesis of the kimmelstiel-wilson nodule. Hum. Pathol. 24, 77-89.

Suarez-Alvarez B., Liapis H. and Anders H.J. (2016). Links between coagulation, inflammation, regeneration, and fibrosis in kidney pathology. Lab. Invest. 96, 378-390.

Sugimoto H., Mundel T.M., Sund M., Xie L., Cosgrove D. and Kalluri R. (2006). Bone-marrow-derived stem cells repair basement membrane collagen defects and reverse genetic kidney disease. Proc. Natl. Acad. Sci. USA 103, 7321-7326.

Sugimoto H., Lebleu V.S., Bosukonda D., Keck P., Taduri G., Bechtel W., Okada H., Carlson W., Bey P., Rusckowski M., Tampe B., Tampe D., Kanasaki K., Zeisberg M. and Kalluri R. (2012). Activin-like kinase 3 is important for kidney regeneration and reversal of fibrosis. Nat. Med. 18, 396-404.

Sun B.K., Siprashvili Z. and Khavari P.A. (2014). Advances in skin grafting and treatment of cutaneous wounds. Science 346, 941-945.

Thomasova D. and Anders H.J. (2015). Cell cycle control in the kidney. Nephrol. Dial. Transplant. 30, 1622-1630.

Thomasova D., Mulay S.R., Bruns H. and Anders H.J. (2012). P53-independent roles of mdm2 in nf-kappab signaling: Implications for cancer therapy, wound healing, and autoimmune diseases. Neoplasia 14, 1097-1101.

Urushihara M., Ohashi N., Miyata K., Satou R., Acres O.W. and Kobori H. (2011). Addition of angiotensin ii type 1 receptor blocker to ccr2 antagonist markedly attenuates crescentic glomerulonephritis. Hypertension 57, 586-593.

Vaughan A.E., Brumwell A.N., Xi Y., Gotts J.E., Brownfield D.G., Treutlein B., Tan K., Tan V., Liu F.C., Looney M.R., Matthay M.A., Rock J.R. and Chapman H.A. (2015). Lineage-negative progenitors mobilize to regenerate lung epithelium after major injury. Nature 517, 621-625.

Velnar T., Bailey T. and Smrkolj V. (2009). The wound healing process: An overview of the cellular and molecular mechanisms. J. Int. Med. Res. 37, 1528-1542.

Vielhauer V., Berning E., Eis V., Kretzler M., Segerer S., Strutz F., Horuk R., Grone H.J., Schlondorff D. and Anders H.J. (2004). Ccr1 blockade reduces interstitial inflammation and fibrosis in mice with glomerulosclerosis and nephrotic syndrome. Kidney Int. 66, 2264-2278.

Villanueva E., Yalavarthi S., Berthier C.C., Hodgin J.B., Khandpur R., Lin A.M., Rubin C.J., Zhao W., Olsen S.H., Klinker M., Shealy D., Denny M.F., Plumas J., Chaperot L., Kretzler M., Bruce A.T. and Kaplan M.J. (2011). Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. J. Immunol. 187, 538-552.

Vivante A., Calderon-Margalit R. and Skorecki K. (2013). Hematuria and risk for end-stage kidney disease. Curr. Opin. Nephrol. Hypertens. 22, 325-330.

Vize P.D. and Smith H.W. (2004). A homeric view of kidney evolution: A reprint of h.W. Smith's classic essay with a new introduction. Evolution of the kidney. 1943. Anat. Rec. A Discov. Mol. Cell. Evol. Biol. 277, 344-354.

Wanner N., Hartleben B., Herbach N., Goedel M., Stickel N., Zeiser R., Walz G., Moeller M.J., Grahammer F. and Huber T.B. (2014). Unraveling the role of podocyte turnover in glomerular aging and injury. J. Am. Soc. Nephrol. 25, 707-716.

Weidenbusch M. and Anders H.J. (2012). Tissue microenvironments define and get reinforced by macrophage phenotypes in homeostasis or during inflammation, repair, and fibrosis. J. Innate Immun. 4, 463-477.

Wen Z.K., Xu W., Xu L., Cao Q.H., Wang Y., Chu Y.W. and Xiong S.D. (2007). DNA hypomethylation is crucial for apoptotic DNA to induce systemic lupus erythematosus-like autoimmune disease in sle-non-susceptible mice. Rheumatology (Oxford) 46, 1796-1803.

Werner S. and Grose R. (2003). Regulation of wound healing by growth factors and cytokines. Physiol. Rev. 83, 835-870.

Williams G.C. and Nesse R.M. (1991). The dawn of darwinian medicine. Q. Rev. Biol. 66, 1-22.

Wu Y. (2015). Contact pathway of coagulation and inflammation. Thromb. J. 13, 17.

Wu H. P.J.M., Wyburn K.R., Chadban, S.J. (2010). Hmgb1 contributes to kidney ischemia reperfusion injury. J. Am. Soc. Nephrol. 21, in press.

Wynn T.A. (2007). Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J. Clin. Invest. 117, 524-529.

Xia Y., Yan J., Jin X., Entman M.L. and Wang Y. (2014). The chemokine receptor cxcr6 contributes to recruitment of bone marrow-derived fibroblast precursors in renal fibrosis. Kidney Int. 86, 327-337.

Yang C.W., Hung C.C., Wu M.S., Tian Y.C., Chang C.T., Pan M.J. and Vandewalle A. (2006). Toll-like receptor 2 mediates early inflammation by leptospiral outer membrane proteins in proximal tubule cells. Kidney Int. 69, 815-822.

Yang L., Besschetnova T.Y., Brooks C.R., Shah J.V. and Bonventre J.V. (2010). Epithelial cell cycle arrest in g2/m mediates kidney fibrosis after injury. Nat. Med. 16, 535-543.

Yuste C., Rubio-Navarro A., Barraca D., Aragoncillo I., Vega A., Abad S., Santos A., Macias N., Mahillo I., Gutierrez E., Praga M., Egido J., Lopez-Gomez J.M. and Moreno J.A. (2015). Haematuria increases progression of advanced proteinuric kidney disease. PLoS One 10, e0128575.

Zeisberg M. and Duffield J.S. (2010). Resolved: EMT produces fibroblasts in the kidney. J. Am. Soc. Nephrol. 21, 1247-1253.

Zeisberg M. and Neilson E.G. (2010). Mechanisms of tubulointerstitial fibrosis. J. Am. Soc. Nephrol. 21, 1819-1834.

Zoja C., Garcia P.B., Rota C., Conti S., Gagliardini E., Corna D., Zanchi C., Bigini P., Benigni A., Remuzzi G. and Morigi M. (2012). Mesenchymal stem cell therapy promotes renal repair by limiting glomerular podocyte and progenitor cell dysfunction in adriamycin-induced nephropathy. Am. J. Physiol. Renal Physiol. 303, F1370-1381.