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CRITICAL CARE

REVIEW

Heart–kidney crosstalk and role of humoral signaling in critical illness

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Abstract

Organ failure in the heart or kidney can initiate various complex metabolic, cell-mediated and humoral pathways affecting distant organs, contributing to the high therapeutic costs and significantly higher morbidity and mortality. The universal outreach of cells in an injured state has myriad consequences to distant organ cells and their milieu. Heart performance and kidney function are closely interconnected and communication between these organs occurs through a variety of bidirectional pathways. The term cardiorenal syndrome (CRS) is often used to describe this condition and represents an important model for exploring the pathophysiology of cardiac and renal dysfunction. Clinical evidence suggests that tissue injury in both acute kidney injury and heart failure has immune-mediated inflammatory consequences that can initiate remote organ dysfunction. Acute cardiorenal syndrome (CRS type 1) and acute renocardiac syndrome (CRS type 3) are particularly relevant in high-acuity medical units. This review briefly summarizes relevant research and focuses on the role of signaling in heart–kidney crosstalk in the critical care setting.

Introduction

Heart performance and kidney function are closely interconnected, and communication between these organs occurs through a variety of bidirectional pathways. The severity of the failing organ can initiate various complex metabolic, cell-mediated and humoral pathways affecting distant organs, contributing to the high therapeutic costs and significantly higher morbidity and mortality. Both acute and chronic cardiac disease can directly contribute to concurrent acute/chronic worsening kidney function and the converse [1,2]. The term cardiorenal syndrome (CRS) is often used to describe this condition, representing an important model for exploring the pathophysiology of cardiac and renal dysfunction [1,3]. The CRS classification system includes a vast array of acute or chronic conditions in these two important organs, where the primary failing organ can be either the heart or the kidneys. The current definition has been expanded into five subtypes whose etymology reflects the primary and secondary pathology, the time frame, as well as cardiac and renal co-dysfunction secondary to systemic disease [1] (Table 1). Epidemiological studies of CRS indicate that patients transition between different CRS subtypes [4]. There are a number of potential contributing factors for CRS that may predispose a patient to the development of this syndrome and which are relevant for the susceptibility, etiology, severity and duration of the disease state. The intersection of cardiac and renal disorders has important therapeutic and prognostic implications; this new classification represents a step towards a better understanding of the pathophysiology and management strategies of this bidirectional crosstalk.

Clinical evidence suggests that tissue injury such as acute kidney injury (AKI) is not an isolated event and it has become apparent that much of the increased risk of death is derived from distant complications [5,6]. A recent multicenter, multinational study reported that 5 to 6% of these at-risk patients suffer from AKI and subsequently are treated with renal replacement therapy (RRT) [7]. Twenty-five percent of patients in the ICU develop AKI [8,9]. RRT is the only US Food and Drug Administration-approved treatment for AKI [10,11]. For more than 40 years, despite the advent of RRT, there has been limited improvement in the mortality rate associated with AKI [12]. In the critical care setting, AKI remains an important predictor of outcome, and frequently results in remote organ dysfunction involving the heart, lung, liver, intestines, and brain through

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Table 1 Cardiorenal syndrome classification system

Classification	Abbreviation	Characteristic
Acute cardiorenal syndrome	CRS type 1	Abrupt worsening of cardiac function leading to acute kidney injury; for example, acute coronary syndrome causing acute heart failure and then renal dysfunction
Chronic cardiorenal syndrome	CRS type 2	Chronic abnormalities in cardiac function causing progressive chronic kidney disease; for example, congestive cardiac failure
Acute renocardiac syndrome	CRS type 3	Sudden worsening of renal function causing acute cardiac dysfunction; for example, uremic cardiomyopathy secondary to acute renal failure
Chronic renocardiac syndrome	CRS type 4	Condition of primary chronic kidney disease leading to an impairment of the cardiac function and/or increased risk of adverse cardiovascular events; for example, left ventricular hypertrophy and diastolic heart failure secondary to renal failure
Secondary cardiorenal syndrome	CRS type 5	Systemic disorders causing both cardiac and renal dysfunction; for example, septic shock, vasculitis

CRS, cardiorenal syndrome.

immune-mediated inflammatory mechanisms [13-15]. In the organ crosstalk, the combination of AKI with acute lung injury remains a formidable challenge for clinicians treating critically ill patients. New experimental data have emerged in recent years focusing on the interactive effects of kidney and lung dysfunction, and providing evidence that kidney–lung crosstalk occurs and can be bidirectionally deleterious. These studies have highlighted the pathophysiological importance of proinflammatory and proapoptotic pathways in the kidney–lung crosstalk [16,17]. Inflammatory dysregulation resulting from each organ failure results in rising levels of circulating chemokines, cytokines and activated lymphocytes [17]. Cellular (for example, neutrophils) as well as soluble mediators (cytokines) contribute to the inflammatory dysregulation under these circumstances [18].

The liver and kidney are important regulators of body homeostasis and are involved in excreting the toxic byproducts of metabolism and exogenous drugs [19]. Liver injury often correlates with severity of kidney injury. AKI induces oxidative stress and promotes inflammation (production of TNFα, IL-1, IL-6), apoptosis and tissue damage in hepatocytes [20-23]. Another important mechanism of end-organ dysfunction in kidney–liver crosstalk is the development of hepatorenal syndrome, a functional renal failure that often occurs in patients with cirrhosis and ascites. Two different types of hepatorenal syndrome have been described. Hepatorenal syndrome type 1 develops as a consequence of a severe reduction of effective circulating volume due to both an extreme splanchnic arterial vasodilatation and a reduction of cardiac output. Hepatorenal syndrome type 2 is characterized by a stable or slowly progressive renal failure, so that its main clinical consequence is not acute renal failure but refractory astrocytes, and its impact on prognosis is less negative [24,25]. Effects of AKI on the brain and the nervous system include several clinical signs [26]. In addition, cerebral inflammation and functional changes were demonstrated after AKI [27,28]. AKI also led to increased levels of proinflammatory chemokines, keratinocyte-derived chemoattractant, and granulocyte colony-stimulating factor in the cerebral cortex and hippocampus, which may function to recruit neutrophils to sites of neuronal damage, and to increased expression of glial fibrillary acidic protein in astrocytes in the cortex and corpus callosum [23]. AKI also induces a cell-mediated inflammatory response in the brain by activation of microglial cells (brain macrophages) [23].

In cardiorenal crosstalk, acute cardiorenal syndrome (CRS type 1) and acute renocardiac syndrome (CRS type 3) are particularly relevant in high-acuity medical units; in particular, CRS type 1 is often seen in the coronary care unit and in the ICU (Figure 1). The purpose of this review is to examine the burden of concomitant heart and renal dysfunction in critically ill patients. Recent work on AKI has shown that inflammatory cascades, cell adhesion molecule, cytokine and chemokine upregulated expression, neutrophil migration, leukocyte trafficking, caspase-mediated apoptosis, and oxidative stress putatively induce distant organ dysfunction [27]. During AKI, chemokines recruit neutrophil infiltration into the heart and cause myocyte apoptosis [29,30]. Additional complications include oxidative loss of redox homeostasis in reactive oxygen species (ROS) and reactive nitrogen species, resulting in a proinflammatory and profibrotic milieu via distinct mechanisms that promote cardiovascular and renal structural and functional abnormalities, including ischemia/reperfusion injury (IRI) [31,32]. The physiological crosstalk is necessary to maintain regular homeostasis and normal functioning of the organism. However, in the diseased state, the immediate and concomitant induction of toxic cell signaling by the primary damaged organ can induce structural and functional dysfunction in distant organs [33].

The evaluation of known mechanisms and putative targets underlying the pathophysiology of heart–kidney crosstalk encompasses innate and adaptive immunity,

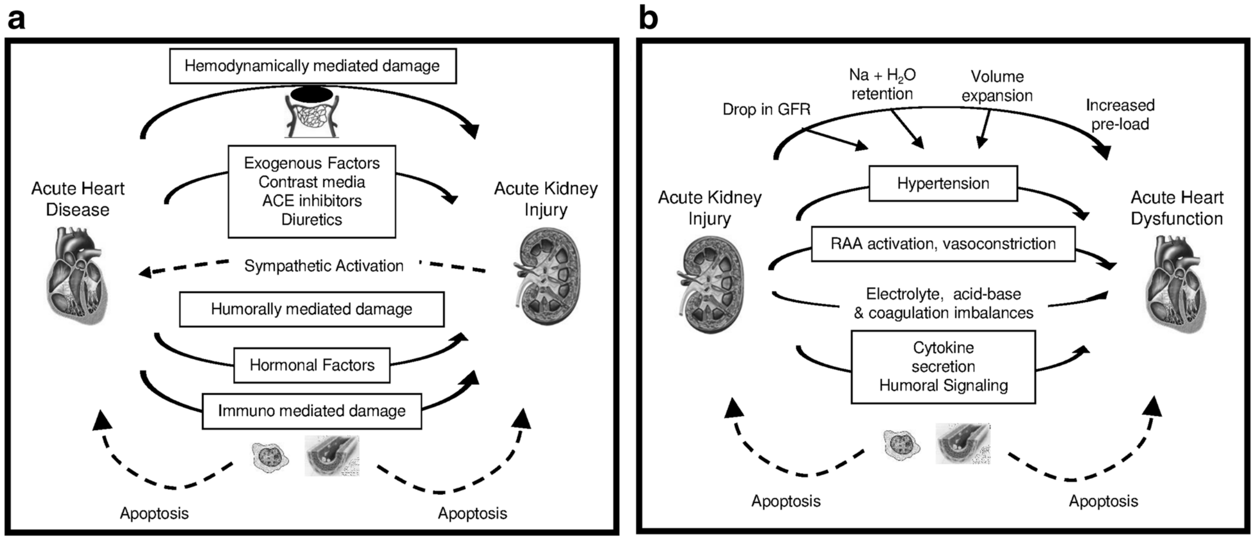

Figure 1 Cardiorenal syndrome type 1 and cardiorenal syndrome type 3. (a) Cardiorenal syndrome (CRS) type 1 is characterized by acute worsening of heart function leading to acute kidney injury (AKI) and/or dysfunction. Acute cardiac events that may contribute to AKI include acute decompensated heart failure, acute coronary syndrome, cardiogenic shock and cardiac surgery-associated low cardiac output syndrome. **(b)** CRS type 3 is characterized by acute worsening of kidney function leading to acute cardiac injury and/or dysfunction, such as acute myocardial infarction, congestive heart failure, or arrhythmia. Conditions that may contribute to this syndrome include cardiac surgery-associated AKI, AKI after major noncardiac surgery, contrast-induced AKI, other drug-induced nephropathies, and rhabdomyolysis. ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; RAA, rennin-angiotensin-aldosterone.

inflammation, cytokine and chemokine release, cell apoptosis, renal tubular epithelium and renal vascular endothelium alterations.

Renal tubular epithelium and renal vascular endothelium

The proximal tubular epithelial cells reabsorb numerous substances from the 140 liters of plasma ultrafiltrate that the normal kidney produces each day, substances that include small peptides and immune regulatory molecules as well as electrolytes and nitrogenous waste products [34]. Proximal tubular cells also actively secrete molecules from the peritubular capillary bed into the tubular lumen. Finally, proximal tubular cells are immunologically active, presenting antigen and producing a variety of inflammatory mediators [35-39].

The CD40/CD40-ligand (CD40L) pathway is a key mediator of cellular responses to injury and the resulting vascular pathophysiology. CD40 is a cell surface glycoprotein that belongs to the TNF-receptor superfamily, largely expressed on the cellular surface of antigen-presenting cells, including B lymphocytes, macrophages, and dendritic cells. CD40 is also present in some non-lymphoid cells, such as tubular epithelial cells, where it has been suggested to play a role in the pathogenesis of renal inflammatory response [40,41]. Stimulation in response to injury of CD40 receptor–CD40L has pleiotropic effects both on immune and nonimmune cells including downstream cellular and humoral immune response, microglial activation, and TNFα production. CD40/CD40L interaction induces *in vitro* the production of different proinflammatory cytokines, including IL-8, monocyte chemoattractant protein-1, and RANTES, by proximal tubular epithelial cells and modulates the response to inflammatory stimuli [40,42]. These different cytokines, chemokines, and adhesion molecules serve as chemoattractants for additional leukocytic infiltrates, including monocytes and T lymphocytes [43,44]. In particular, Laxmanan and colleagues found that human renal proximal tubular epithelial cells treated with soluble CD40L to ligate CD40 showed a significant increase in the generation of proinflammatory ROS; however, CD40-activated cells did not undergo apoptosis [45].

Recently, some studies focused on the contribution of tubular epithelial cells to the typical systemic inflammatory response of CRS and other pathologic conditions [29,46]. Complex signaling systems including crosstalks, feedback and feedforward loops polarize the cellular milieu in the pathophysiological profile, and include the expression of co-stimulatory pathways. An inexorable assemblage of evidence indicates that the clinical patterns in heart and kidney dysfunction are a direct result of cellular and subcellular remodeling processes [47-52]. Furthermore, renal tubular cells play a critical role in the handling of inflammatory mediators and in their resulting efflux into systemic circulation [50,53]. These cells contribute to the circulating levels of inflammatory mediators by different mechanisms, including epigenetic processes. These processes are driven by changes in covalent modifications of DNA and associated proteins, alterations in chromatin structure, and recruitment of a diversity of signal responsive transcription factors and enzymes [54,55]. In particular, Zager and Johnson demonstrated the upregulation of histone-modifying enzyme systems and the alteration of histone expression at proinflammatory and profibrotic genes such as TNFα and monocyte chemoattractant protein-1 in IRI [56-58].

Allam and colleagues recently identified extracellular histones as mediators of postischemic and septic AKI. Histones are released from dying tubular epithelial cells and act as damage-associated molecular patterns, which require toll-like receptor (TLR)2 and TLR4 for the induction of proinflammatory cytokines; extracellular histones aggravate AKI via both its direct toxicity to renal endothelial cells and tubular epithelial cells and its proinflammatory effects [59].

Epigenetic changes, cellular signaling and humoral pathways create the cellular milieu and pathophysiological profile, depending on the timing, disease setting, and stimulation state. These biological events may play a role in heart–kidney crosstalk and in the increase of systemic inflammation and distant organ injury.

Renal vascular endothelial cells initiate early inflammatory responses in the injured kidney by direct contact with injurious agents [60]. The injured kidney is known to modulate the activity of leukocytes [61-63]. The ischemic injury damages the barrier function of endothelium, resulting in disorganization of endothelial integrity producing partial disappearance of cell–cell borders and disruption of cell–cell contacts [46]. Endothelial disintegration thus increases vascular permeability and facilitates leukocyte infiltration into the renal parenchyma. Recent studies have investigated the leukocyte–endothelium interactions. Down regulation of Netrin-1, a protein involved in development of the nervous system and epithelial tissues, in renal vascular endothelial cells in peritubular capillaries may promote endothelial cell activation, resulting in extravasation of leukocytes into the kidney and tubular injury [64,65]. Furthermore, sphingosine-1-phosphate maintains endothelial cell integrity and inhibits lymphocyte extravasations via the sphingosine-1-phospate receptor. A recent study showed that a sphingosine-1-phosphate selective agonist ameliorates ischemic acute renal failure [66]. In addition to changes in the integrity of the renal vascular endothelium layer, IRI upregulates the expression of adhesion molecules, in particular intracellular adhesion molecule-1, that promote and facilitate the interactions between leukocytes and the endothelium [29,67]. Leukocyte adhesion causes inflammation and extension of cellular injury. Renal tubular epithelium is a major site of cell injury and cell death during AKI and numerous studies have suggested that renal epithelial cells have a central role in inflammation during AKI. This effect could modulate cell behavior in distant organs, such as the heart and lung, with potentially deleterious effects and creating a vicious circle.

Immunomodulation: the role of innate and adaptive immunity

Recent studies have highlighted the importance of both innate and adaptive immune responses to endogenous molecules induced by either tissue damage or infection [68,69]. The innate immune system is immediately activated in infection states and inflammatory conditions in a nonantigenic-specific way. This activation is executed primarily by myeloid cells with the participation of some innate lymphocyte subpopulations and is comprised of neutrophils, monocytes/macrophages, dendritic cells (DCs), natural killer cells and natural killer T cells (Figure 2). Leukocytes such as DCs and macrophages play important functions in both types of immunity by generating cytokines, chemokines and presenting antigens to lymphocytes [29,68]. Adaptative immunity is a second line of defense responding to specific antigens in cellular and humoral response pathways. T-cell polarization in response to DC activation is complex and involves myriads of signaling cascades. Critical signaling cascades from both intrinsic and extrinsic factors come down to a single bridge. Activation of both innate and adaptive immune responses is regulated by the TLR pathways. Briefly, DC maturation and antigen presentation, CD4 and CD8 lymphocyte proliferation and stimulation, and consequently T-lymphocyte to B-lymphocyte interactions lead to specific morphological and cell signaling upregulation. Specific subpopulations of T cells have been implicated in deleterious cell fate pathways, contributing to organ damage [70]. Proposed initiators of the innate immune response during AKI include the activation of TLRs and the release of ROS, reactive nitrogen species and mitochondrial products [71]. TLRs are the major pattern recognition receptors, binding to a wide range of different molecules and, in particular, endogenous ligands produced as a consequence of tissue injury. This pathogenesis, specifically TLR signaling, causes a rapid response mechanism to local tissue damage and is involved in early activation of the immune response in AKI events [15].

The adaptive immune system is stimulated by the specificity of antigen receptors on B and T lymphocytes that react to several antigenic molecular structures. Once stimulated, B cells produce specific antibodies, perform opsonization to encourage phagocytosis, and activate the complement system [15]. Antigen-dependent T-cell activation has been demonstrated in experimental models of renal IRI [61,72]. Inflammation of renal tissue stimulates

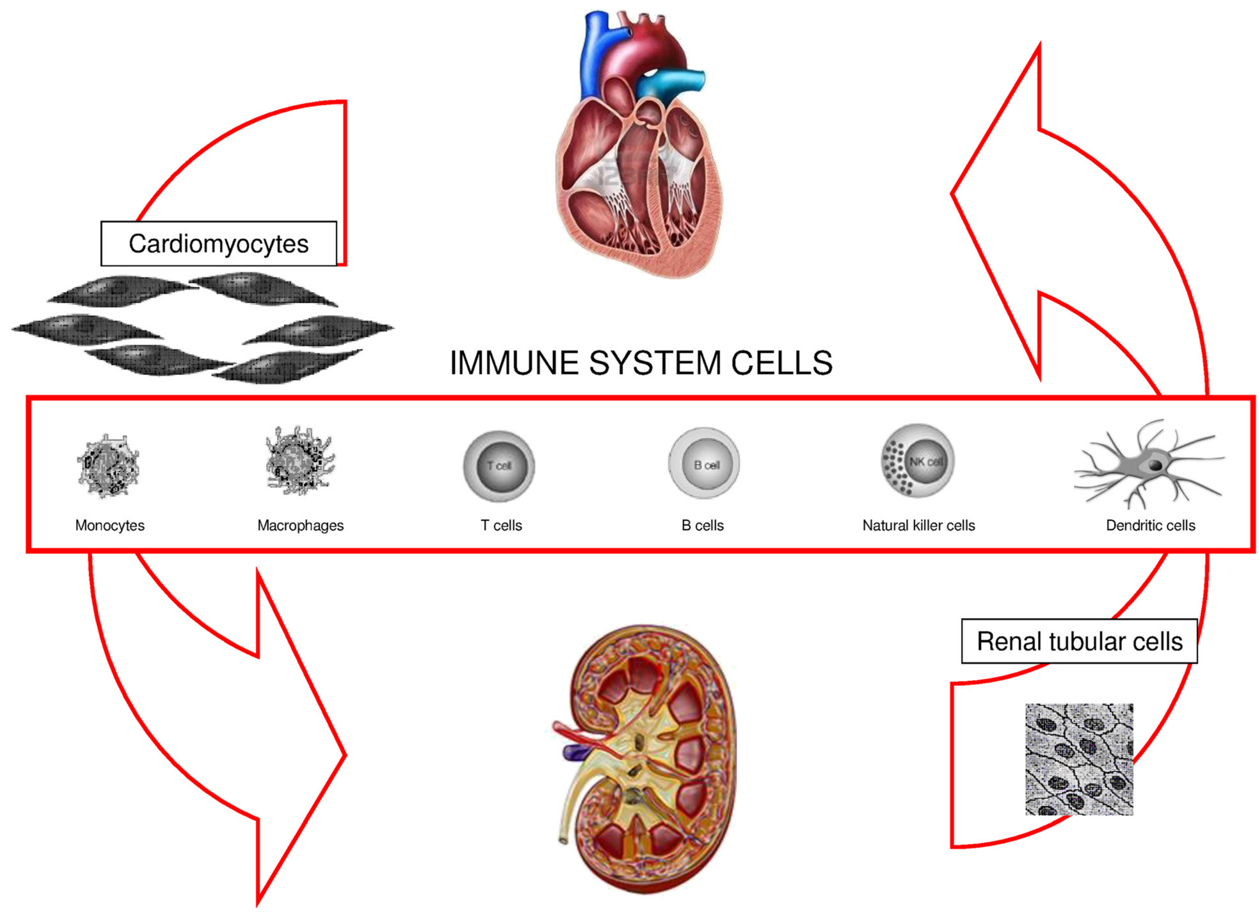

Figure 2 Cellular types involved in heart–kidney crosstalk.

the expression of adhesion molecules in endothelial cells, which leads to the deposition of immune complexes and vascular stiffening in kidney disease [15,73,74]. Either following antigen activation or in the presence of chemokines and ROS/reactive nitrogen species, T cells undergo early activation and function as a bridge between adaptive and innate immune systems. This specific immune response in AKI facilitates and enhances distant heart–kidney crosstalk.

AKI is involved in the functional abnormalities in immune cell responsiveness and alterations such as leukocyte trafficking, adhesion and tissue extravasation both locally in the kidney and in distal organs such as the heart in CRS type 3. In ischemia animal models, morphological and functional changes in vascular endothelial cells and in tubular epithelium have been extensively confirmed [29,46,75,76]. Leukocyte activation and trafficking play a critical role in heart injury during AKI. Neutrophils, macrophages, natural killers and lymphocytes infiltrate into the injured kidneys. The injury prompts the activation of inflammatory pathways by tubular and endothelial cells recruiting leukocytes into the kidneys [29,46]. In particular, in IRI models, after adherence and chemotaxis, neutrophils release ROS, proteases, and myeloperoxidase, and other cardiorenal mediators directly damage the tissue with local and systemic effects including upregulation of proinflammatory cytokines and chemokines, both critical players in heart failure (HF) [77,78]. During AKI, chemokines recruit inflammatory cells with a consecutive neutrophil infiltration into the heart tissue and this is a causal factor of myocyte apoptosis [29,30], typical of CRS type 3.

The dominant resident leukocyte types present in the kidney are resident intrarenal DCs, suggesting a crucial role in renal immunity and inflammation. In fact, in the normal mouse CD11c^{+} major histocompatibility complex class II^{+} DCs are the most abundant leukocyte subset in the kidney, suggesting an important role in renal immunity and inflammation [29]. Furthermore, intrarenal DCs are an important link between innate and adaptive immunity; unfortunately, the individual contribution of intrarenal DCs to the pathophysiology of AKI is not completely understood. These cells are located in the interstitial extracellular compartment of the whole kidney and are tactically positioned to interact with many different factors [79-81]. Within this compartment, DCs are close to epithelial cells, macrophages, and fibroblasts, and they respond to endogenous molecules released from resident and/or infiltrating cells [80-82]. DCs are a heterogeneous population with different functions. Upon stimulation, DCs can convert to a mature cell type characterized by high levels of class II major histocompatibility complex and co-stimulatory molecules and low phagocytic capacity. Mature DCs are specialized in T-cell activation. However, DCs are also important in the innate immune response by releasing proinflammatory factors, such as TNF, IL-6, IL-12, monocyte chemoattractant protein-1 and RANTES, and interacting with natural killer T cells via CD40–CD40L [29,83]. Recent studies have shown that DCs can improve or prevent injury to the kidney depending on the nature of stimulus. For example, depletion of DCs prior to IRI reduces consequent reperfusion injury and related renal dysfunction [84]. Conversely, depletion of DCs prior to cisplatin exposure resulted in worse renal dysfunction and stronger inflammation [85]. DCs have a central role in orchestrating the immune response in AKI; additional studies are needed to understand the detailed functions of these cells in the CRS and in the heart–kidney crosstalk.

Role of inflammation, cytokines and chemokines

The unbalancing of the cytokine and chemokine networks in inflammation accelerates the deposition of atherosclerotic plaques, mediates insulin resistance, stimulates tumor growth and causes increases in adhesion molecule expression and vascular permeability. Nonresolving and persistent exposure to proinflammatory factors, such as TNFα, IL-1, IL-4, IL-6, IL-13, and IL-17, damages tissue, impairs organ function and is lethal in the critical care setting. The cytokines, chemokines, and eicosanoids mediate cellular responses and interact with genome-encoded receptors expressed on monocytes, macrophages, mast cells, astrocytes, and other cells of the innate immune system [86]. Upregulation of humoral factors by injured cells leads to activation of the toll/IL-1 superfamily. Members of this superfamily signal in a similar manner using a conserved domain that actives nuclear factor-κB, which translocates the nucleus resulting in changes in gene expression. TLR pathways, activated via nuclear factor-κB, result in both intracellular and extracellular upregulaton of inflammatory cytokine expression [87,88].

Over the past 30 years there has been growing evidence for the role played by activation of the inflammatory response in the pathogenesis of acute events of HF at various levels in these patients [89,90]. Further support for the inflammatory etiology of HF came from the evidence that cytokines may also be produced by cardiomyocytes, following ischemic or mechanical stimuli, but also by innate immune response [91-93]. These findings suggest that an immune dysregulation may occur in HF; cytokines not only could provoke distant organ damage such as AKI and CRS type 1, but they may also play a role in concomitant damaging myocytes. In the Program to Improve Care in Acute Renal Disease, a prospective multicenter cohort study, TNFα, IL-1β, IL-6, IL-8 and C-reactive protein were increased in critically ill patients with acute renal failure [94]. These results provide evidence that an inflammatory systemic response is stimulated and maintained in critically ill patients with AKI that probably contributes to distant organ dysfunction, and in particular cardiac dysfunction.

Studies of CRS type 3 have expanded the understanding of heart–kidney crosstalk by demonstrating induction of cardiac damage by inflammatory mediators, oxidative stress and upregulation of neuroendocrine systems early following AKI [13,30,95].

In IRI animal models, AKI has been highlighted to elicit a systemic immune response characterized by a dose–response increase in circulating proinflammatory and anti-inflammatory factors. Likewise, AKI may be associated with physiologic derangements, alterations to coronary vasoreactivity, ventricular remodeling and fibrosis that indirectly strengthens negative effects on cardiomyocytes and causes cardiac dysfunction [96-98]. Several inflammatory mediators, such as TNFα, IL-1β and IL-6, have been implicated in cardiodepressant effects, and cytokines can impact myocardial function due to both impaired myocyte contractility and extracellular matrix interaction [95,98,99]. In general, cytokine-mediated contractile dysfunction is reversible over an extended time period of several days following exposure [95].

Apoptosis

TLR activation of cell-mediated, humoral, and inflammatory responses can lead to changes in cell fate, or in the worst case to continued heightened activation apoptotic induction. TLR induction of caspase-mediated apoptosis is a key pathogenic feature in kidney disease whereby renal tubular epithelial cells cease to proliferate and embark upon terminal differentiation. Apoptosis is a controlled and physiological mechanism of regulation of cell populations in an endogenously programmed pattern, and it plays a very important role especially in the immune system, during development of lymphocytes as in antigen recognition [100]. A loss of immune cells by apoptosis is associated with physiologic changes that occur in several diseases, and the host response requires a fine equilibrium between recruitment and death of immunocompetent cells [100].

Experimental evidence supports a pathogenic role for apoptosis in AKI and in the development of HF [101]. Two main intracellular pathways for apoptosis have been recognized: ligation of plasma membrane death receptors (extrinsic pathway), and perturbation of the intracellular homeostasis (intrinsic pathway). The two pathways are linked, and molecules in one pathway can influence the other [102]. In the extrinsic pathway, the Fas/Fas-ligand system transmits apoptotic signals from the surrounding environment into the cell; the binding of Fas ligand with Fas initiates receptor oligomerization, which recruits Fas-associated death domain and the activators caspase-8 and caspase-10 [103-105]. These caspases are activated upon oligomerization and then cleave protein substrates to activate downstream effector caspases. The intrinsic pathway involves intracellular organelles, the most important being mitochondria [106-108]. The permeabilization of the outer mitochondrial membrane and the release of proapoptotic factors such as cytochrome c promote caspase-dependent and caspase-independent apoptosis [106]. Caspases are widely expressed in an inactive proenzyme form in most cells and once activated can often activate other pro-caspases, allowing initiation of a protease cascade. This proteolytic cascade, in which one caspase can activate other caspases, amplifies the apoptotic signaling pathway and thus leads to rapid cell death [109,110]. Over the last few years, many studies have demonstrated that survival factors and anti-cytokine strategies can prevent apoptosis *in vivo* [111-114]; better characterization of the molecular pathways activated at each stage of apoptosis and an understanding of the time frames will be crucial to developing new sensible therapeutic strategies.

The multiple factors involved in the development of AKI during HF describe a pathogenesis of AKI accounting for multiple pathways. Evidence suggests that an immune-mediated mechanism has been implicated in CRS type 1 pathogenesis [115,116]. CRS type 1 plasma-induced apoptosis with caspase cascade and IL-6 were recently shown to be significantly higher in CRS type 1 patients when compared with healthy subjects and with HF patients without kidney impairment [115,116]. Limited data are available about cardiac-specific cellular responses associated with AKI, including the role of mitochondrial dysfunction, apoptosis, cardiac remodeling and fibrosis. Some experimental models have explained the role of apoptosis in AKI setting. Prolonged ischemia followed by reperfusion triggers apoptosis and inflammation, leading to tissue damage and organ dysfunction [117-119]. Cardiac myocyte apoptosis and neutrophil infiltration/activation are key contributors to the pathophysiology of myocardiac infarction during AKI, and transgenic rat models have shown that even apoptosis can lead to tissue damage and lethal heart dysfunction [30]. In particular, Kelly demonstrated that kidney IRI but not uremia is fundamental to trigger apoptosis in myocardial tissue [30]. Another experimental rat model of cisplatin-induced AKI showed significant increased levels of myocardial apoptosis by terminal deoxynucleotidyl transferase dUTP nick end-labeling assay [120]. Proinflammatory cytokine TNFα contributes directly to *in vitro* cardiomyocyte apoptosis depression of contractility, and to downregulation of sarcomeric proteins [121-123]. Furthermore, attenuation of apoptosis following administration of anti-TNFα antibodies was demonstrated and clearance of TNFα as a novel therapeutic strategy was hoped to improve HF [30].

Cardiorenal syndrome type 5

A brief part of this review is focused on CRS type 5, in which the heart and the kidney are both targets of a strong systemic inflammatory reaction [124]. CRS type 5 reflects concomitant cardiac and renal dysfunction in the setting of a wide spectrum of systemic disorders, such as diabetes mellitus, systemic lupus erythematosus and sepsis [1,125,126]. In CRS type 5, cardiac dysfunction and renal dysfunction are often observed and are part of the clinical picture of severe sepsis, septic shock and multiple organ failure [1,127]. Following the RIFLE criteria, AKI ranges from minor alterations in renal function to indication for RRT in critically ill patients [128]. AKI is a common complication in septic patients and carries a poor prognosis. AKI occurs in 20% of critically ill patients, and in 51% of patients with septic shock and positive blood cultures [129]. Cardiac dysfunction in sepsis is characterized by decreased contractility, impaired ventricular response to fluid therapy, progressive ventricular dilatation and myocardial depression [124,127]. CRS type 5 is characterized by generalized inflammatory response and by activation of coagulation and the fibrinolytic system, and induces cellular and molecular changes in the heart and kidneys [125,126,130]. This inflammatory reaction is particularly relevant for sepsis in which the majority of mechanisms of immune-mediated heart and kidney tissue injury have been described in detail [131-134]. In particular, several studies have shown in critically ill patients that inflammatory mediators, release of nitric oxide and increased production of peroxynitrite are able to alter organ function and cause abnormal cell signaling, cell cycle arrest, and mitochondria dysfunction, and can induce direct proapoptotic and proinflammatory effects on cardiomyocytes and kidney resident cells such as podocytes, endothelial cells, mesangial cells and particularly tubular epithelial cells [3,124,135-140]. Recently, apoptosis was put forward as a major player in septic AKI [141]. Lerolle and colleagues studied kidney biopsies from 19 patients who died from septic shock and compared them with postmortem biopsies taken from eight trauma patients and from nine patients with nonseptic AKI. Acute tubular apoptosis was demonstrated by different techniques in septic AKI whereas almost no apoptosis was detected in the nonseptic AKI patients [141]. Indeed, inflammatory mediators, activation and induction of cytokines, leukocytes and toll receptors play a key role in the pathogenesis of renal and cardiac dysfunction during sepsis [125,142]. Inflammatory cytokines such as TNFα and IL-6 trigger apoptosis in tubular epithelial cells, probably playing a role in tissue damage, and TNFα and IL-1 are the principal culprits in the pathogenesis of cardiac dysfunction during sepsis [137,143-146].

Conclusions

Immune response orchestrates healing and tissue generation, and eradication of pathogens, yet the danger of uncontrolled inflammation is a core homeostatic phenomenon in human disease and distant organ damage. Dysregulation of crosstalk between the heart and kidney is probably a therapeutic option, which currently includes cytokines, chemokines, and growth factors known to initiate intercellular and intracellular changes. Signaling pathways from damaged cells in either the heart or the kidney promote innate immune activation and strengthen adaptive immunity. Other targets may include serine/threonine kinases such as Akt capable of apoptotic cycle inhibition and repairing stimulation pathways in response to damage resulting from extracellular stimuli to control regulation of nutrient metabolism and survival [147]. Rapid characterization of cellular and subcellular research in human and animal models continues to elucidate the complex crosstalk as well as putative epigenetic changes resulting from brief or chronic states of immune–inflammatory changes in gene expression.

Heart–kidney crosstalk has significant clinical relevance, and the current review highlights the humoral mechanism involved in multiorgan failure. In particular, the management of acute CRS subtypes is challenging because of the multitude and complexity of pathophysiological interactions between the heart and the kidney and the possible progression from acute to chronic injury in these organs. In critical illness, the complete characterization of cellular and subcellular orchestration in heart–kidney crosstalk and the early recognition of disease by new biomarkers could allow choice of the best therapeutic options, prevention of the necessity for RRT, shorten the AKI duration, limit multiple organ injury and improve survival. The combination of clinical status and new functional and damage biomarkers provides a novel set of tools for the clinician to manage patients with CRS. Present and future studies on pathogenetic mechanisms involved in cardiorenal crosstalk will allow the development not only of better directed but also more appropriately timed therapeutic strategies to improve outcome in these patients.

Abbreviations

AKI: Acute kidney injury; CD40L: CD40 ligand; CRS: Cardiorenal syndrome; DC: Dendritic cell; HF: Heart failure; IL: Interleukin; IRI: Ischemia/reperfusion injury; RANTES: Regulated upon activation normal T-cell expressed and secreted; ROS: Reactive oxygen species; RRT: Renal replacement therapy; TLR: Toll-like receptor; TNF: Tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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