



Organ crosstalk: the potent roles of inflammation and fibrotic changes in the course of organ interactions

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Abstract

Background Organ crosstalk can be defined as the complex and mutual biological communication between distant organs mediated by signaling factors. Normally, crosstalk helps to coordinate and maintain homeostasis, but sudden or chronic dysfunction in any organ causes dysregulation in another organ. Many signal molecules, including cytokines and growth factors, are involved in the metabolic dysregulation, and excessive or inappropriate release of these molecules leads to organ dysfunction or disease (e.g., obesity, type 2 diabetes).

Aim and method The aim of this review is to reveal the impact of organ crosstalk on the pathogenesis of diseases associated with organ interactions and the role of inflammatory and fibrotic changes in the organ dysfunction. After searching in MEDLINE, PubMed and Google Scholar databases using ‘organ crosstalk’ as a keyword, studies related to organ crosstalk and organ interaction were compiled and examined.

Conclusion The organ crosstalk and the functional integration of organ systems are exceedingly complex processes. Organ crosstalk contributes to metabolic homeostasis and affects the inflammatory response, related pathways and fibrotic changes. As in the case of interactions between adipose tissue and intestine, stimulation of inflammatory mechanisms plays an active role in the development of diseases including insulin resistance, obesity, type 2 diabetes and hepatic steatosis. The increased level of knowledge about the ‘crosstalk’ between any organ and distant organs will facilitate the early diagnosis of the disease as well as the management of the treatment practices in the short- and long-term organ dysfunction.

Keywords Organ crosstalk · Organ dysfunction · Inflammation · Inflammatory mediators · Fibrosis

List of abbreviations

AGEs	Advanced glycation end products	ECM	Extracellular matrix
AKI	Acute kidney injury	EMT	Epithelial–mesenchymal transition
ALI	Acute lung injury	ER	Endoplasmic reticulum
ANP	Atrial natriuretic peptide	EVs	Extracellular vesicles
AP-1	Activator protein 1	FFA	Free fatty acids
BNP	B-type natriuretic peptide	FGF	Fibroblast growth factor
CKD	Chronic kidney disease	FXR	Farnesoid × receptor
COX-2	Cyclooxygenase-2	HFD	High fat diet
CVD	Cardiovascular disease	HIF-1	Hypoxia-inducible factor 1
CRP	C-reactive protein	IFN-γ	Interferon gamma
DAMPs	Damage-associated molecular patterns	IR	Insulin resistance
DM	Diabetes mellitus	IRI	Ischemia/reperfusion injury
		IL	Interleukin
		iNOS	Inducible nitric oxide synthase
		JNK	c-Jun N-terminal kinase
		KIM-1	Kidney injury molecule 1
		L-FABP	Liver-type fatty acid-binding protein
		LPS	Lipopolysaccharides
		MAPK	Mitogen-activated protein kinase
		MYD88	Myeloid differentiation factor 88

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NASH	Non-alcoholic steatohepatitis
NAFLD	Non-alcoholic fatty liver disease
NF- κ B	Nuclear factor kappa B
NGAL	Neutrophil gelatinase associated lipocalin
NLRP3	Nucleotide-binding domain 3
NO	Nitric oxide
NRF2	Nuclear factor erythroid 2-related factor 2
NT-proBNP	N-terminal pro-B-type natriuretic peptide
MIF	Macrophage migration inhibitory factor
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
PAI-1	Plasminogen activator inhibitor-1
PAMPs	Pathogen-associated molecular patterns
PNPLA3	Patatin-like phospholipase domain-containing 3
PI3	Phosphatidylinositol 3-kinase
PPAR- γ	Peroxisome proliferator-activated receptor- γ
ROS	Reactive oxygen species
SCFAs	Short chain fatty acids
SIRS	Systemic inflammatory response syndrome
sST2	Soluble suppressor of tumorigenicity 2
STAT3	Signal transducer and activator of transcription 3
TECs	Tubular epithelial cells
TGF- β	Transforming growth factor
TLR	Toll-like receptor
TNF- α	Tumor necrosis factor alpha
TNF-RII	Tumor necrosis factor receptor II

Introduction

Definition of organ crosstalk

Vital organs generally function in coordination and harmony. The term ‘organ crosstalk’ refers to the complex biological communications and feedback in different organs, mediated via cellular, soluble and neurohormonal actions. Although crosstalk is essential to keep up body homeostasis, pathological states in one or more organs can lead to functional and structural dysfunctions in other organs [1]. Lane et al. [2] have proposed to describe the effect of an improperly functioning organ on another’s function as ‘organ crosstalk’ for a critical illness. Most physiological functions originate with the communication between organs. If we exclude the nervous system and brain, it can be argued that there are seven pillars for the organ crosstalk. In addition to the four main organs of the heart, liver, lungs and kidneys, the intestines, adipose tissue and skeletal muscle are of secondary importance [3]. Pancreas, spleen and bone tissue as well immune and hematological system are also associated. Literature data show that there has been a notable increase in publications on organ crosstalk over the last decade (Fig. 1).

As seen in Table 1, a large number of interactions between organs have been identified, and the crosstalk between the two organs is expressed as the ‘axis’ in some publications [4]. Some systems, such as nervous and hematological system, are also associated with organ crosstalk. Vital organs generally function in coordination and harmony. But, sudden or chronic dysfunction of one of these organs causes disorder in another organ. For example, kidney can deleteriously affect the hematological system and uremia during acute kidney injury can lead to a hemato-renal syndrome. Similarly, AKI negatively impacts the immune system through immuno-renal crosstalk [5]. As it is known, an excessive metabolic challenge or chronic disorder in any organ leads to the initiation of inflammation and, in turn, to fibrosis [6]. Both inflammation and fibrosis are major components of dysfunction for many organs. In addition, other mechanisms including inappropriate cell signaling, abnormal neurohormonal activation, oxidative stress, adverse functional and structural changes also play an active role in organ injury [1]. Chronic tissue injury with fibrosis results in the disruption of tissue architecture, organ dysfunction and eventual organ failure.

Aim of this article and method

The main aim of this review is to provide a comprehensive and up-to-date knowledge from the physiopathological importance of organ crosstalk in diseases to potential diagnosis and treatment options for these diseases. In addition, we evaluated and discussed organ crosstalk more in terms of inflammatory and fibrotic changes. For this purpose, scientific studies from 2003 to 2019 Jan were searched using MEDLINE, PubMed and Google Scholar. In the related web searches, mostly the terms ‘crosstalk’ and ‘organ interactions’ were used; also, additional keywords such as

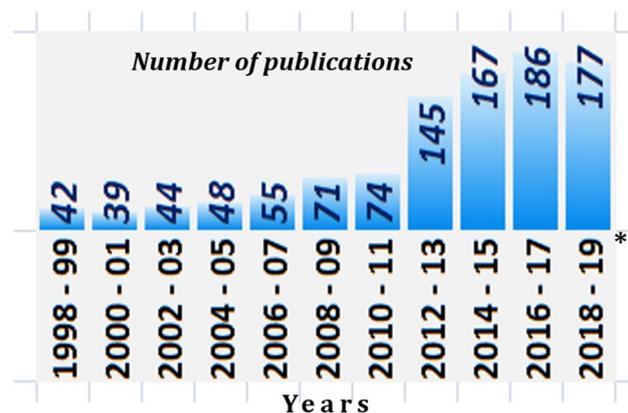


Fig. 1 Estimated number of publications on organ crosstalk in the last two decades as gauged by Pubmed database search (* The first half of 2019)

Table 1 Examples of uni- or bidirectional organ crosstalk between two or multiple organs (a); The disorder and diseases associated with organ interactions which are known and more frequently discussed in recent years (b)

a Type of organ crosstalk/interaction	Related references
Cardio–pulmonary–renal interactions	[1, 3, 58]
Hepato–renal (kidney–liver) crosstalk	[2, 3, 34, 38, 40]
Heart–kidney crosstalk	[38–40, 58, 109]
Kidney–brain crosstalk	[3, 38]
Kidney–gut crosstalk	[3, 38, 40, 79, 88]
Kidney–lung crosstalk	[5, 38, 40, 41, 50, 51, 58, 94]
Cardio–renal axis	[11, 35, 57, 67]
Gut–liver axis	[4, 10, 25, 26, 80]
Lung–gut–heart crosstalk	[77, 78, 89]
Liver–adipose tissue interactions	[10, 24, 27]
Adipose tissue–kidney crosstalk	[6, 24, 75]
Heart–adipose tissue crosstalk	[11, 72]
Liver–brain and liver–lung interactions	[10]
Adipose tissue–gut crosstalk	[81]
Heart–spleen, heart–muscle crosstalk	[11]
Kidney–bone crosstalk	[38]
Gut–brain crosstalk	[78]
Muscle–bone and muscle–kidney crosstalk	[90, 102, 112]
Pancreas (β -cell)–the other organ crosstalk (adipose tissue, liver, brain, bone or muscle)	[27, 29, 69]
b Some examples of disease or disorder related to organ crosstalk	
Hepato–renal syndrome	[2, 34]
Cardio–renal syndrome (type 1–5)	[35, 39, 70, 109]
Goodpasture disease and Wegener’s granulomatosis	[5]
Alcoholic liver disease	[10]
Non-alcoholic fatty livers disease	[4, 23, 25, 26, 74, 80]
Metabolic syndrome or Type 2 Diabetes	[27, 29, 69, 78]
Ischemia–reperfusion injury	[58, 95]
Sepsis/SIRS	[93, 96, 97]
Multiple organ dysfunction syndrome	[85, 96]

‘inflammation’, ‘inflammatory mediators’ and ‘fibrosis’ were combined with these two keywords.

The old and new players associated with organ crosstalk

It is known that hormones, cytokines and growth factors use a variety of signaling mechanisms to facilitate cellular adaptive responses. At the cellular level, the term crosstalk is referred to mutual interactions of signals generated from different pathways such as between various inflammatory cells, cytokines and intracellular signaling pathways. Also, the other circulating factors such as interleukins and chemokines are known to play crucial roles in the communication of organs [7, 8]. A physiologic inter-organ communication network is necessary to maintain the regular homeostasis and the normal functioning of the human body. During disease states, the damaged organ can induce structural and

functional dysfunction in the other organs [8]. In addition, there are many components in this network which are peptides, proteins, and metabolites that act between organs to coordinate cellular processes under homeostasis and stress [9]. Recent publications show that new players are involved in this complex traffic. There are several mechanisms by which cells in an organ can communicate by long distance with the cells of another tissue. For example, inflammation and NLRP3 inflammasome are likely to have a central role in mediating crosstalk with other organs [10, 11]. Among the new players of organ interaction are molecular “hazard signals” such as PAMPS and DAMPS, as well as EVs, nutrients. Also, it is suggested that exosomal cargo components are new important players for metabolic organ crosstalk [10]. These cargo components include EVs as well as miRNAs, exosomes, and apoptotic microbodies. Released by almost all cells these EVs represent an important mode of inter-cellular communication by serving as vehicles for transfer between membrane of cell and cytosolic lipids, proteins,

RNA and miRNAs [12]. Also, exosomes are small EVs transporting proteins and nucleic acids that can be transferred to nearby cells or distant organs in the active form. For example, exosomes released by brown adipose tissue carry miRNAs that can inhibit the expression of target genes in the liver. On the other hand, EVs are considered as new potential biomarkers for the diagnosis and prognosis of diseases in the recently published studies [8, 13]. Extracellular vesicles, which play a central role in cell-to-cell communication, are also an important vehicle for organ crosstalk. Similarly, novel chemokines have also been identified, which have expanded our knowledge on the previously unknown functions of many specific tissues and organs. Proteins secreted from metabolic organs (e.g., adipokines, myokines, hepatokines and cardiokines) are known to play important roles in inter-organ communication leading to fine-tuning and maintenance of glucose and energy homeostasis in the body [8, 10].

Organ crosstalk in terms of inflammation and fibrotic changes

Recent data show that there is a highly complex crosstalk between the various cytokines and their signaling effectors as in the central signaling pathways. Mutual influences of signals generated from different pathways are referred to as crosstalk. This crosstalk occurs between intracellular signaling pathways, as well as between different inflammatory cells and cytokines [7]. The inflammatory process is also characterized by the co-ordinated release of many different cytokines, and its molecular components are now well established. Signal transduction of inflammatory cytokines includes cytosolic and nuclear signaling mechanisms resulting in the activation of NF- κ B, JNK, p38 MAPK, STAT3, and PI3 kinase pathways [7, 14]. Chronic inflammation is also known as persistent, low-grade inflammation; this type of systemic inflammation may contribute to the development of the many disease including obesity, as well as metabolic, cardiovascular and neurodegenerative diseases [15]. According to a recent publication, playing a central role in the metaflammation (known as inflammation accompanying metabolic diseases) gut microbiota releases inflammatory products, and contribute to signaling pathways and crosstalk with other organs [16]. It is known that ‘inflammasome’ is a multi-protein complex which acts as a sensor of cellular damage and is another mediator for inflammation. Activation of inflammasomes leads to the secretion of IL-1 β and IL-18, both of which have been implicated in chronic inflammation and fibrogenesis [7, 17]. Unlike other inflammasomes, the NLRP3 inflammasome is also activated by diverse stimuli such as ROS and mitochondrial dysfunction. As intracellular ROS production regulates inflammasome activity,

interestingly, the activity of NLRP3 inflammasomes may also induce ROS production [18]. NF- κ B plays a role in regulating the activation of inflammasomes by stimulating the expression of pro-inflammatory genes. Therefore, it is well accepted that NF- κ B serves as a central inflammatory mediator that responds to a large variety of immune receptors contributing to the initiation and development of various inflammatory diseases [14, 19]. During inflammation, the extent of crosstalk is not known, especially among vital organs. Inflammation of the organ-specific epithelial surface, caused by disease or tissue damage, represents a large area of cell injury inflammation as well as local ECM dysregulation. Moreover, it is known that epithelial cells can acquire fibroblastic phenotype via epithelial–mesenchymal transition and contribute to fibrogenesis in tissues such as liver and kidney [20]. Chronic tissue injury with fibrosis results in the disruption of tissue architecture, organ dysfunction and eventual organ failure. Namely, fibrosis is the end result of a complex series of events that follow tissue damage and inflammation. The repair process of damaged tissue involves the coordinated activities of inflammatory cells and resident stem cells in response to local and systemic signals and to restore tissue homeostasis [21, 22]. Thanks to its wide distribution in different tissues and organs, the inflammatory pathways act a crucial signaling mechanism that facilitates organ crosstalk and local injury in tissues targeted by metabolic damage. Although fibrosis is a pathological process distinct from inflammation, it is often linked with inflammatory pathways, and it is a critical stage of many chronic diseases that lead to organ dysfunction. Therefore, in this article, the organ crosstalk is reviewed and discussed especially in terms of inflammation and fibrotic changes.

The role and relationships of the liver in the organ interactions

Recent evidences suggest that continuous and dynamic inter-organ crosstalk is associated with several processes involved in the pathogenesis of many diseases. Some organs play a key role in the crosstalk, including the heart, liver, kidney, adipose tissue and pancreas, and their roles in the control of energy metabolism. Also there is a functional association between the function of liver and the other organs; therefore, dysfunction of one of these organs causes deterioration of the other one [2, 4]. Especially, liver is an ideal candidate for organ crosstalk, because of there is a need for efficient gut–liver and adipose tissue–liver communications to control energy metabolism and maintain homeostasis [4, 10]. Being a major organ for energy storage, a key role in the glucose and lipid metabolism, liver is also directly involved in development of insulin resistance, type 2 DM and obesity. Research indicates that obesity-induced dysfunctions

within these crosstalks can lead to imbalances in energy metabolism and contribute to the pathogenesis of metabolic diseases such as non-alcoholic fatty liver disease [4, 23]. Recently, there has been a remarkable increase in the studies to understand the mechanisms behind organ crosstalk relationships in obesity and NAFLD (Table 1). It is proposed that excessive lipid accumulation caused by imbalances in gut–liver and adipose tissue–liver crosstalk can initiate a cycle of damaging liver inflammation and lead to NAFLD. Also, dietary factors that alter gut microbiota and intestinal barrier function may contribute to the development of obesity and obesity-related fatty liver disease by promoting metabolic endotoxemia and low-grade inflammation [24, 25]. The altered gut microbiota affects the metabolism by producing microbial metabolites that play a key role in NAFLD development as well as affecting energy balance [4]. As in the case of obesity, lipodystrophy or IR, adipocytes play an active role in the pathogenesis of NAFLD, leading to the release of proinflammatory cytokines, such as IL-6 and TNF- α , as well as adipokines such as leptin, adiponectin and resistin [10, 26]. Additionally, recent evidence suggests that changed intestinal permeability affects circulating levels of LPS, FFA, and bile acid. In addition to the release of pro-inflammatory cytokines, the regulation of Farnesoid X and toll-like receptors also affects NAFLD development and progression. Obesity and inflammation are highly integrated processes in the pathogenesis of IR, type 2 DM, and NAFLD. In liver with NAFLD, Kupffer cells, liver-derived macrophages of the reticuloendothelial system, play a similar role to M1 macrophage and, therefore, secrete inflammatory cytokines that contribute to local or systemic inflammation and, accordingly, worsening of metabolic homeostasis [27]. In a recent paper, Ma et al. [28] alleged that some ncRNAs (miRNAs and lncRNAs) may participate in the pathological process of NAFLD by changing body fat homeostasis and they could regulate the activity of hepatic stellate cells, thereby affecting the progression of inflammation and fibrosis in the course of NAFLD.

Chronic inflammation has been observed in adipose tissue, liver, vascular endothelial cells, circulating leukocytes as well as in pancreatic islets of obese and diabetic subjects [29]. In the relation of gut microbiota and glucose metabolism, many factors including increased intestinal permeability, low-grade endotoxemia, changes in the production of SCFAs, alterations in bile acid metabolism and effects on the secretion of gut hormones may contribute to metabolic dysfunction. For instance, FGF-19 has metabolic effects on the FXR in the pancreatic β -cell and liver [30]. Additionally, liver with NAFLD plays a critical role in the progression of β -cell failure by augmenting β -cell workload and modulating islet inflammation [27]. It is also claimed that under obesity conditions, the release of exosomes by the adipose tissue promotes the inflammatory state associated

with the development of IR [8]. In the liver, impaired lipid metabolism and imbalance of lipid stream cause lipotoxicity, mitochondrial dysfunction, overproduction of ROS and ER stress as well as the consequent activation of inflammatory responses. This pathologic process, which is common in IR, obesity and type 2 DM, also affects the risk of NAFLD progressing to NASH and fibrosis development [26]. Liver fibrosis is the result of a complex multicellular response to hepatic injury and it may also be influenced by other organs such as intestine, muscle and adipose tissue [31]. For example, the intestinal microbiota may contribute to hepatic fibrosis by stimulating the profibrotic pathways associated with TLR-9 in hepatic Kupffer cells [32]. There is a functional association between the function of liver and lungs, as well as kidneys and liver; therefore, dysfunction of one of these organs causes deterioration of the other one. In terms of any other interaction, Patterson et al. [33] suggested that perfusate from injured lungs caused a robust inflammatory response in cultured hepatic sinusoidal endothelial cells, and lung-derived mediators may contribute to liver inflammation. According to their model, inflammation initiated in the lung releases inflammatory mediators which then translocate to the liver. Liver amplifies the inflammatory signal, through an NF- κ B-dependent pathway, leading to a further release of inflammatory mediators, which then travel back to the lung or other organs where the signal is further propagated in a feed-forward mechanism of acute inflammation. On the other hand, hepatic and renal failure is often closely related and, multiple pathophysiological processes such as endothelial damage are involved in the induction and progression of organ damage [34]. Also in a recent study, it was pointed out that chronic liver diseases were among the causes of acute and chronic (type 5) cardiorenal syndrome [35] (Table 1; Figs. 2, 3).

The role and relationships of the kidney in the organ interactions

There is a crosstalk between the kidney and the other remote organs in both directions. The heart, lung, brain, liver and gut have all been demonstrated to be intimately involved in the complex mechanisms of crosstalk signals [1]. In the case of both AKI and chronic kidney disease, interactions with other organs occur and the prognosis of the disease is affected. Although AKI is a common complication which ultimately worsens outcomes in critical patients, CKD is a systemic disease that refers to a long-term loss of kidney function [1, 36]. Similarly, the progression of CKD is associated with THE effects on other organs, leading to many extrarenal complications. While well-known consequences of AKI may contribute to the high mortality, evidence from many studies indicates that disruption in the immune

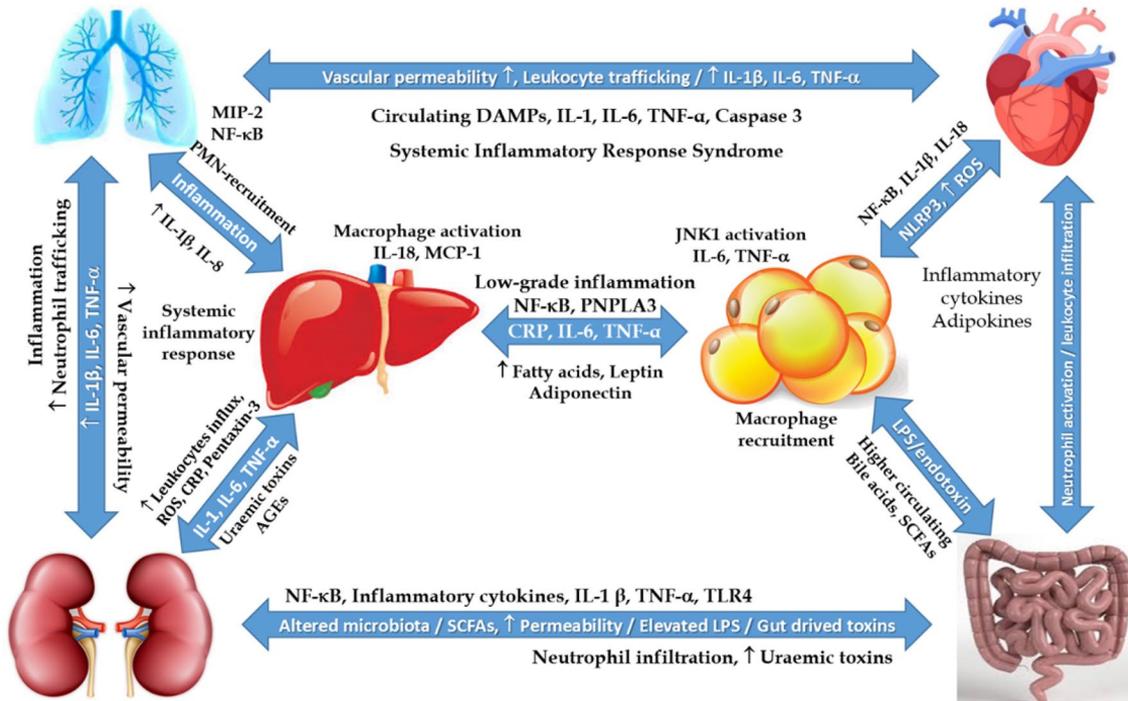


Fig. 2 Schematic representation of organ crosstalk and associated inflammatory processes and its effects on major organ systems in the body. Inflammation, the most common feature of many chronic dis-

eases and complications, also contributes to the development and progression of a lot of diseases in which organ interactions play a role in the pathogenesis

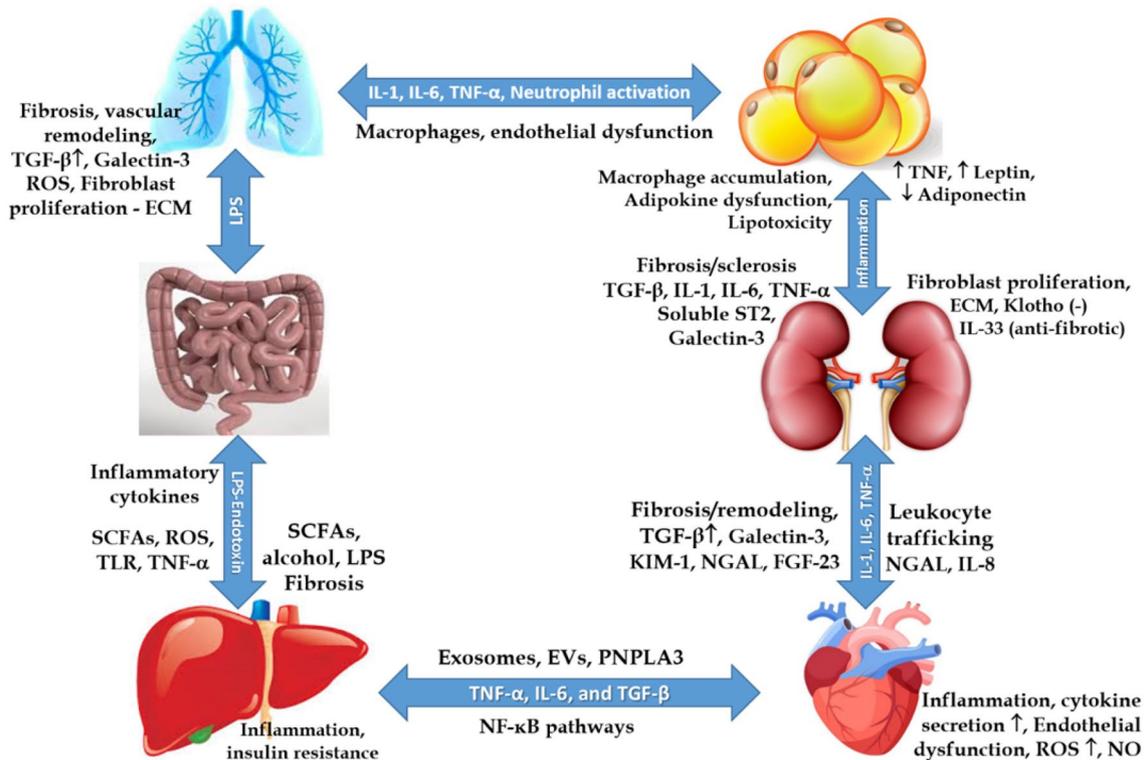


Fig. 3 Organ crosstalk mediates systemic inflammatory responses and fibrotic changes causing target organ damage in the heart, kidney, lung, liver, gut and adipose tissue

balance and soluble inflammatory metabolism mediators may cause important effects through remote organ crosstalk [2]. The majority of the studies associating AKI with distant organ dysfunction have demonstrated the pathophysiological importance of proinflammatory and proapoptotic pathways as well as ROS production, leukocyte activation and infiltration [37]. AKI and hepatic dysfunction is a typical example of the crosstalk between kidney and liver. It is known that AKI induces oxidative stress and promotes apoptosis, tissue damage and inflammatory mediators such as TNF α , IL-1 and IL-6 in the liver [37, 38]. Recent evidences from multiple organ failure suggest that crosstalk occurs between kidney and lungs via bidirectional inflammatory mediators in the each organ [39]. Uncontrolled inflammatory processes involving one organ may cause distant organ damage. Furthermore, prolonged exposure to proinflammatory factors does not only impair the organ function by damaging the tissues, but also lethal in the organ crosstalk [39, 40]. The close proximity and crosstalk between epithelial proximal tubular and endothelial cells leading to the release of cytokines and chemokines result in the progression of inflammation [41]. It is suggested that persistent inflammation leads to chronic myofibroblast activation, and excessive accumulation of ECM which promotes the formation of a permanent fibrotic scar [42].

Inflammation has been widely observed in a variety of CKD biopsy specimens and animal models and has been recognized as crucial for the initiation of renal fibrogenesis [43]. In addition, the pathogenesis of interstitial fibrosis occurring in injured kidneys involves induction of TGF- β 1 expression and the development of inflammation, fibroblast activation, and ECM deposition. Among inflammatory cells affecting the process, the role of monocytes/macrophages is quite evident [43, 44]. Proinflammatory factors secreted by tubular epithelial cells (TECs) can produce cytokines that stimulate EMT of these cells as well as activating different inflammatory cells. Moreover, in the maladaptive repair process, TECs become sources of proinflammatory and profibrotic cytokines, leading to aggravated renal fibrosis [45]. On the other hand, tubular cells directly contribute to systemic inflammation by carrying out immune functions, such as cytokine release and leukocyte recruitment and activation. Also, uremic toxins seem to mediate the increased expression of fibrosis-related genes, inflammatory mediators and chemokines in tubular cells [46]. Systemic inflammation, alongside with the loss of renal function, can damage the resistance of the body to internal and external stressors, by reducing functional and structural tissue reserves and by impairing normal organ crosstalk. Therefore, among the mechanistic causes of kidney injury during sepsis, there is also detrimental organ crosstalk [47, 48]. Ultimately, systemic inflammation is quite relevant in the case of sepsis-associated AKI, and kidney-induced inflammatory reactions

contribute to the remote organ (heart, lung, liver, gut and brain) dysfunction (Figs. 2, 3).

The role and relationship of the lung in the organ interactions

In the any organ failure, primary involvement and course of disease lead to pathophysiological interactions and contributing to the organ crosstalk. The lungs have critical pathophysiological connections with other organs, primarily the heart and kidneys [1]. Due to the extensive capillary network, the lungs are highly susceptible to injury. Multiple dependent pathways in the acute pulmonary disorders elevate the risk of AKI and AKI has been shown to impact lung function [49]. The lung–kidney crosstalk occurs due to the increase in systemic immune mediators that cause inflammatory reactions, oxidative stress, and vascular permeability increase in the lung [50]. Because of the continuity bi-directional interaction between lung and kidney injuries, it is thought that high mortality in the prolonged AKI may be associated with pulmonary inflammation [51]. Circulating factors have been implicated in the pathogenesis of pulmonary inflammation following renal and hepatic IRI [1, 49]. Additionally, enhanced lung and liver injury caused by LPS correspond to particular changes in the pro-inflammatory cytokine (such as TNF- α) expression profiles in the both organs. According to the hypothesis suggested by two different authors claim that TNF- α released from liver into the systemic circulation increases inflammatory ALI [10, 52]. Likewise, IL-6 plays a central role in AKI-induced lung injury and is an important cytokine in the hepatic response to inflammation. Interestingly, patients with a high level of IL-6 had worse lung function and more frequent asthma exacerbations than patients with low IL-6 levels [53]. On the other hand, changes in the alveolar-capillary barrier may induce pulmonary microcirculatory inflammatory cascade and oxidative stress, resulting in alveolar wall injury and/or aggravating lung damage [1]. In addition, pulmonary congestion in chronic heart failure can initiate structural lung remodeling by proliferation of fibroblasts with fibrosis and ECM deposition, resulting in thickening of the alveolar wall [54]. Repeated epithelial injury elicits abnormal wound repair and lung remodeling, often associated with alveolar collapse and edema, leading to focal hypoxia. In the recent new study, Kathiriya et al. [55] reported that hypoxia causes fibrosis by activating lung epithelial cells via galectin-1. Thus, fibrosis in solid organs such as the lung or kidneys suggests that neurohormonal translation to cell signals is a part of the pathogenesis and progression of the disease (Figs. 2, 3).

The role and relationships of the heart in the organ interactions

Inter-organ crosstalk plays a vital role in the physiological homeostasis of the heart and other organs and requires a complex interaction between a host of cellular, molecular, and neural factors. Although not fully understood at first, there is increasing interest in the extent and importance of the bi-directional crosstalk between the heart and other organs. There is a bidirectional and well-documented organ interaction between heart and kidneys [1]. For example, cardiorenal syndrome is defined as a complex pathophysiological disorder of the heart and the kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. Likewise, chronic kidney disease is common in heart failure and vice versa. Heart failure is a pivotal and progressive condition that leads to a cascade sequence of inter-organ crosstalk, including lung and kidney [11, 39]. In the early studies, it is reported that several inflammatory mediators such as TNF- α and IL-6 participate in the pathophysiological process of cardiorenal syndrome and their high blood levels are associated with the development of congestive heart failure [56, 57]. In a more recent study, it has been reported that different pathways such as activation of inflammatory transcription factors, stimulation of inflammatory genes and cytokines may contribute to cardiac damage following renal IRI [58]. Nevertheless, a number of clinical and animal studies suggest that inflammation is a key contributor to adverse myocardial remodeling [59]. In any case, it is claimed that prolonged exposure to inflammatory cytokines may exacerbate adverse remodeling and increase myocardial damage [60]. It is known that proinflammatory cytokines such as interleukin IL-1 β and IL-18 are released from the heart as a result of local adverse effects and IR-induced inflammation on cardiac remodeling. These, and similar cardiokines, can have significant endocrine effects on other tissues, leading to damage in multiple peripheral organs [11]. On the other hand, it has been implicated that oxidative stress is the final common pathway that plays an active role in the damage and injury in various pathological conditions of the heart, lung and kidneys [39]. For instance, myocardial infarction, ischemia or IRI induces cardiomyocytes to release ROS, ATP and mtDNA. In heart failure, activation of NLRP3 inflammation can exacerbate local inflammation; similarly, crosstalk from the heart to other tissues may cause multi-organ damage as a result of ischemia-induced inflammation [39, 61]. In addition to cytokines/chemokines, there are also many mediators, such as Lipocalin-2, NO, and DAMPs that are involved in crosstalk between the heart and peripheral organs [11].

When the heart is under stress or injured, it undergoes structural and functional changes termed cardiac remodeling including hypertrophy, fibrosis, apoptosis and altered metabolism [62]. Cardiac fibrosis is implicated in almost all forms of CVD and commonly plays a major role in myocardial infarction and heart failure [63]. Emerging evidence suggests that cardiac fibrosis is mainly due to complications associated with acute and prolonged inflammation and low-grade persistent inflammation is enough to promote heart fibrosis [63, 64]. In addition, there are many similarities in the cardiac and pulmonary fibrosis involving shared biochemical pathways as well as cellular processes associated with inflammatory cells, fibroblasts and ECM [63]. Furthermore, the increase in soluble and cellular TGF- β 1, which plays a central role in the process of fibrosis/remodeling, is an important indicator of heart–kidney and heart–lung crosstalk [1, 65]. In recent studies, some mediators of kidney and adipose tissue affecting the pathogenesis of heart failure have been as interested as cardiac lipids, exosomes and cardiocines [65, 66]. Also, it is suggested that disturbances of calcium phosphate homeostasis affect the cardiorenal crosstalk and that vitamin D plays a role in the regulation of endothelial and cardiac cell function, inflammatory and fibrotic pathways [67]. According to these results, it is right that cardiac injury related to distant organ disrupts the balance between fibroblasts and cardiomyocytes and creates a state favouring inflammation and fibrosis (Figs. 2, 3).

The role and relationships of the adipose tissue in organ interactions

Adipose tissue is a true endocrine organ that produces and secretes a large number of mediators that affect important distant organs such as the liver, pancreas, skeleton and heart muscle, as well as the regulation of adipocyte function. In particular, after the discovery of adipokines, it was found that he assumed important roles in the crosstalk network, which mediated the regulation of distant organs and tissues [68]. Adipose tissue dysfunction has a central role in the development of cardiovascular diseases, IR and type 2 diabetes. In metabolic disorders, which are typical examples of obesity, the increased volume of adipocytes causes adipose tissue dysfunction as well as secretion profile changes in the manner of increased pro-inflammatory adipokine release. In other words, obese adipocytes, which become hypertrophic as lipid contents increase, secrete less adiponectin and more leptin and proinflammatory cytokines [68, 69]. Obesity-induced visceral fat inflammation promotes end-organ chronic inflammatory damage. Activation of adipose cell associates an inflammatory milieu characteristic to obesity-related pathologic states. While this inflammatory environment induces production of TNF- α and IL-6, increase in the chronic inflammatory cytokine

production and in the rate of angiotensin II adiponectin leads to a vicious pathological cycle that results in an organ damage [70]. In addition, increasing evidence indicates that a number of diverse and parallel processes contribute to the development of NAFLD and liver inflammation. Sabio et al. [71] pointed to the critical role of the crosstalk between the periphery, particularly adipocytes and adipose-infiltrating macrophages, and the liver to the pathogenesis of NAFLD. In addition, it has been claimed that JNK1 activation in extrahepatic tissues especially via macrophage may contribute to the development of hepatic inflammation [26, 71]. Similarly, there is a well-documented association between obesity and heart failure and adipose tissue is clearly an important contributor to inflammation in this organ failure [11, 72]. On the other hand, visceral obesity is an important predictor of hepatic inflammation and fibrosis [73], while obesity-induced metabolic complications and oxidative stress cause molecular changes in hepatocytes. NAFLD progresses via both metabolic dysfunction and the transformation of adipocytes from healthy small cells to dysfunctional large ones [74]. Adiponectin and leptin are the two key adipokines needed to maintain the crosstalk between adipose tissue and the liver, and the liver occupies a central role in relevant metabolic pathophysiology such as NAFLD and fibrosis development. Also, adiponectin has been proposed as a good predictor of necroinflammatory grade and fibrosis in NAFLD [26]. Interestingly, dyslipidemia complicates renal function and leads to provocative dysfunction in other homeostatic organs. The interactions of adipose tissue with the kidney—referred to as the adipo-renal axis—are important for normal kidney function as well as the response of the kidney to injury. Primarily, Zhao et al. [75] reported that unilateral nephrectomized rats exhibit a progressive loss of white adipose tissue associated with ectopic lipid deposition and IR indicating the adipo-renal crosstalk. As a source of proinflammatory cytokines, adipocytes as well as macrophages can have significant effects on the inflammatory state of the kidney. It is suggested that adiponectin might also be produced locally within the kidney and exert important metabolic functions [76]. Renal dysfunction in the context of CKD is associated with high levels of adipose-derived molecules, such as adiponectin, leptin, angiotensin II, IL-6 and TNF- α as well as dysregulated metabolites. Integration of these factors increases inflammation, oxidative stress and EMT-induced fibrotic changes in the kidney and eventually causes renal injury [48, 76], (Figs. 2, 3).

The role and relationships of the gut in the organ interactions

According to the recent research, intestinal microbiota communicates with peripheral organs in the body and influences processes in health and disease [77]. The gut microbiota converts dietary factors including fiber, cholesterol and

animal-derived saturated lipids and environmental factors such as cold exposure and antibiotics into metabolites that allow communication with peripheral organs and tissues in the host. For instance, the gut microbiota communicates with the brain, and bidirectional gut-brain interactions/axis are involved in the maintenance of homeostasis [78]. Alterations in composition, diversity and metabolites derived from the gut microbiota are associated with diseases affecting different organs of the human body. Notably, emerging data suggest associations between the gut microbiota and cardiovascular diseases including atherosclerotic plaque formation, myocardial infarction, and heart failure [77]. Similar relationships have also been described in patients with chronic kidney disease [79]. Moreover, evidence of the causal role of intestinal bacteria has been found to be more significant in metabolic diseases such as obesity, type 2 diabetes and NAFLD [80]. The gut–liver axis refers to the physical and biological connections between the liver and organs in the gastrointestinal tract; stomach, intestines, and pancreas. It suggests that obesity plays a key role in the dysregulation of both gut–liver crosstalk and adipose tissue–liver crosstalk. Also, studies indicate that obesity can cause interruptions in gut–liver crosstalk by altering the gut microbiota [4, 80]. The gut–liver axis, which induces intestinal barrier and microbiota, plays an important role in energy metabolism and de novo lipogenesis [81].

Several lipid metabolites are shown to coordinate energy metabolism among tissues. There are many gut-derived lipid mediators implicated in the inter-tissue communication including palmitate, palmitoleate, stearate and oleate. Gut microbiota can also produce lipid metabolites that have immunomodulatory activities. Butyrate and glycosphingolipids produced by gut bacteria have been shown to induce colonic regulatory T cells and repress natural killer T cells, respectively, to modulate colonic inflammation [82]. Further, the change in intestinal microbiota due to obesity or high fat diet leads to negative metabolic results such as intestinal permeability and endotoxemia, as well as steatosis, IR and adipose tissue inflammation [77]. The altered gut permeability affects not only the circulating levels of mediators such as LPS, FFA, bile acid, but also the release of pro-inflammatory cytokines by the regulation of TLR and FXR. These repetitive changes that are effective in the development or progression of NAFLD can also lead to fibrotic changes over time [26]. On the other hand, Cianci et al. [83] suggested that gut microbiota may be implicated in the induction and in the maintenance of local and systemic inflammation in autoimmune diseases. It is discovered that the absence of MYD88 in hepatocytes strongly affected glucose and lipid metabolism without affecting energy homeostasis. Everard et al. showed that mice lacking MYD88 in hepatocytes are prone to develop hepatic insulin resistance, inflammation and diabetes [84].

High fat diet was shown to promote colonic inflammation through induction of TLR4 on epithelial cells and macrophages. This allows the production of several inflammatory cytokines (TNF- α , IL-6, IL-1 β , iNOS, COX-2 and myeloperoxidase activity, etc.), which promptly mediate vascular changes to promote immune cell recruitment against invading pathogens, initiating the inflammatory state [81]. Both excessive and uncontrolled inflammations are the dominant trigger in the intestines driven by the endothelium. In addition, the gut microbiota has a central role in both metaflammation and inflammaging owing to its ability to release inflammatory products, contribute to crosstalk with other organ and systems by circadian rhythms [16, 85]. Besides, dysfunction of organs such as fat tissue, brain, liver, muscle and pancreas, which are adversely affected by the induction of low-grade inflammation, contributes to IR. Cani et al. [86] reported that a 4-week HFD in mice led to diet-induced obesity and IR. They also observed elevated plasma LPS levels parallel to the increase in the mRNA levels of TNF- α , IL-1 and IL-6 in the liver and adipose tissue, which they thought were associated with a low-grade inflammation. Overgrowth of pathogenic bacteria, the loss of barrier integrity, and the breach in the epithelia barrier lead to endotoxemia. However, circulating endotoxin (LPS) activates the production of inflammatory cytokines, and the endotoxin translocation from the intestine has been suggested as one of the causes of inflammation in CKD [87, 88]. Additionally, increased intestinal concentration of uremic toxins associated with the progression of CKD leads to microbial dysbiosis [88], although separate organs, intestinal and respiratory tracts are part of a shared mucosal immune system termed as gut–lung axis. Changes in microbial composition and function in the respiratory tract and the gut have recently been linked to alterations in immune responses and to disease development in the lungs such as asthma and chronic obstructive pulmonary disease [89]. After all, it is accepted that the intestinal microbiota communicates with peripheral organs in the body directly or indirectly and influences processes in health and disease (Figs. 2, 3).

In addition to the vital organs mentioned in this review article, it is known that there are other organ crosstalk examples such as brain–intestinal, muscle–fat tissue, heart–spleen and muscle–bone interactions [11, 90]. The details of these examples were excluded due to the size limitation. However, in recent publications on organ interactions, the issue of sepsis, sepsis-related MODS or MOF appears to be the focus of interest. Therefore, the issue of sepsis and MODS has also been briefly discussed in the context of inflammatory pathways and fibrosis process, taking into account recent publications.

The organ interactions in the sepsis and multiple organ dysfunction syndrome

Sepsis is a dysregulated immune response to an infection that leads to organ dysfunction. Sepsis-associated organ dysfunction involves multiple responses to inflammation, including endothelial and microvascular dysfunction [91]. Sepsis, also known as a systemic inflammatory response syndrome associated with bacterial infection, tends to trigger excessive production of inflammatory cytokines and other inflammatory molecules and induces multiple organ failure, such as acute lung, acute kidney and inflammatory cardiac injuries [92]. Although a systemic process, pathophysiological events differ from organ to organ as well as blood circulating system. Pro-inflammatory mediators (e.g. TNF- α , IFN- γ and MIF) that are produced locally and released high levels into the circulation can initiate remote organ damage as an effect of organ crosstalk [93]. Although remote to the local inflammatory reactions in the organs exposed to the mechanical injury of the initial stimulus, the inflammatory processes affect all the organs of the body. In the severe inflammation and sepsis, the sequence of “SIRS–severe SIRS–MODS–MOF and death” is typical progress for multiple and deleterious organ crosstalk [3]. On the other hand, lung and kidneys are closely associated with MOF caused by sepsis, shock or trauma, and interplay between these two organs occurs through of dynamic and bidirectional mechanisms as in acute respiratory distress syndrome and renal failure. These organs share several pathophysiologic pathways and have the potential to further harm each other (kidney–lung crosstalk). Inflammatory signals in both directions and volume overload with consecutive edema formation in both organs may play a key role in this crosstalk [94].

Unfortunately, the high mortality rate caused by sepsis is closely related to the development of MODS. Ologunde et al. [95] suggest different mechanisms (and their mutual interactions) involved in the development of MODS. Moreover, complex interactions have been described between organs involved in the process of MODS [96]. The injury to one organ may cause a secondary damage or dysfunction in other organs by activating a vicious cycle and a worsening of MODS. For example, the effect of AKI on distant organs is now well documented [97]. It has proven the presence of a detrimental crosstalk between sepsis, the systemic inflammatory response to infection, and the development of AKI [47]. Lung inflammation increases the alveolar–capillary permeability, affects the kidneys and leads to an increase in circulating levels of IL-6 and PAI-1. Similarly, glomerular damage caused by acute kidney injury maintains lung injury by increasing circulating IL-6, DAMPs, TNF- α and caspase 3 [51].

Sepsis-related AKI mediates a systemic inflammatory response that causes damage not only to the lung, but also to remote organs such as liver, heart, brain, and gut [47, 97]. On the other hand, sepsis represents the main cause of renal dysfunction in mortally patients admitted to the intensive care units and sepsis-mediated organ failure is caused by the effect of over-released inflammatory cytokines (hyperinflammation) during the inflammatory response [98]. Indeed, sepsis mutates the symbiotic intestinal microenvironment into a dysbiotic medium that promotes epithelial cell hyperpermeability and apoptosis, hyperinflammation, and dominance of pathogenic bacteria [99]. Contrary to rapid onset and MOF observed in sepsis, chronic organ injury leads to fibrosis and eventually organ failure. Chronic progressive fibrosis happens in virtually all organs including the lung, kidney, liver and heart and it is commonly a result of excessive, prolonged or repeated injury with associated chronic inflammation [1, 100]. Therefore, the inflammation and fibrosis responses have been suggested as therapeutic targets for the management of fibrotic disorders, such as liver and lung fibrosis.

The relationship of organ crosstalk and aging

Aging is a complex process which progressively manifests itself at multiple levels of structural and functional organization from molecular reactions and cell–cell interactions in tissues to the physiology of the whole organ. It is also associated with a gradual decline in critical cellular processes, signaling pathways, and regulatory mechanisms [101]. Recently, it is suggested that the aging process affecting almost all tissues and organs is also related to crosstalk between multiple physiological systems [90, 102]. Leading to eventual disruption of tissue homeostasis, aging and age-related diseases share some basic mechanistic factors that largely intersect with inflammation. During aging, chronic, sterile, low-grade inflammation (also known as inflammaging) develops, which contributes to the pathogenesis of age-related diseases [16, 103]. As aging is associated with a reduction in the beneficial commensal gut microbes, change in dysbiosis and leakage of microbial products contribute to the inflammaging. According to Franceschi et al. [16], gut microbiota also contributes to circadian rhythms and crosstalk with other organs and systems and also releases inflammatory products. A number of mediators are known to activate inflammatory pathways, leading to chronic diseases on time. Also chronic inflammation is related to the biological aging process. Important inflammatory pathways associated with aging and chronic diseases include NF- κ B, STAT3, AP-1, HIF-1, NRF2, PPAR- γ and Wnt/ β -catenin pathways [104]. For instance, recent emerging evidence

demonstrates that Wnt signaling may play a fundamental role in the aging process of kidney, intestine, and adipose tissue [102]. Actually, diabetes, dyslipidemia, and hypertension are age-related risk factors for CVD and CKD. However, it is a fact that aging is an independent risk factor by itself. Because the heart and kidney gradually, but significantly, undergo inflammation and subsequent fibrosis, which eventually results in an irreversible decline in organ physiology with advancing age [105]. Both inflammation and fibrosis are major components of renal dysfunction in aging and exacerbate the decline in renal function [106]. Coexistence of systemic inflammation and loss of kidney function can impair the resistance of the body to internal and external stressors by reduced functional and structural tissue reserves and by impairing normal organ crosstalk. Additionally, there is a relationship between uremic inflammation and a premature aging phenotype, as well as potential causes and consequences [48]. In an elderly population study of 2489 people, there was a significant interaction between visceral abdominal fat and CKD with regard to a decrease in renal function [107]. On the other hand, different hallmarks have been defined in aging and dysregulation of the ECM is proposed as an additional hallmark of aging for the lung by Meiners et al. [54]. In the other study, Hamrick [90] suggested that aging is associated with bone loss and muscle atrophy; thus, aging appears to significantly alter leptin-mediated crosstalk among various organs and tissues.

Organ crosstalk and related potential diagnostic biomarkers

As in the example presented in one of the recent publications, there are many organ interactions samples in the metabolic processes and regulation of energy homeostasis. Baskin et al. [108] proposed that factors released from the adipose tissue and liver regulate skeletal and cardiac muscle metabolism, and many factors are released from the heart and muscle that exert feedback on these tissues. Similar to adipokines, mediators secreted by skeletal muscle are defined as myokines (e.g., IL-6) and mediators released from the heart as cardiokines (e.g., ANP). More than 600 adipokines have been identified, and an increasing number of hepatokines and myokines have recently been discovered with mostly unknown physiological impact. The search for new relevant biomarkers to better stratify patients with organ interaction according to the risk of progression, morbidity, and mortality is required. However, since it is difficult to identify markers for organ interaction, interacting organ or disease-associated markers, and sometimes combinations are preferred. There is evidence supporting the prognostic value of various circulating markers of inflammation, particularly CRP, pentraxin 3, TNF- α , IL-1, and IL-6 [109].

Several inflammatory and fibrotic biomarker including CRP, soluble TNF-RII, pentraxin-3, urine IL-18 and TGF- β 1 have been evaluated as potential markers associated with structural and functional changes of kidney in the CKD [110]. In addition, it has been suggested that a biomarker group consisting of troponin I and T, BNP and NT-proBNP, sST2, Galectin3, NGAL, L-FABP and KIM-1 can be used for early diagnosis and evaluation of cardio-pulmonary–renal interactions [1]. Signaling molecules, myokines (e.g., IL-6 and -15), secreted from skeletal muscle cells affect most organs and, thereby, provide a molecular explanation for the crosstalk between skeletal muscles and other tissues [111]. Also, in a recent study, Peng et al. [112] have reported that irisin mediates crosstalk between muscle and kidney tubule cells and myokine-mediated crosstalk can suppress fibrogenesis during kidney disease. On the other hand, the multifunctional protein Klotho regulates phosphate/calcium metabolism and is identified as an important molecule in the aging processes. It is suggested that Klotho may be an intermediate mediator that attenuates acute and chronic injury in the organs including heart, kidney and lung [1]. Consequently, evidences have been occurred that the measurement of circulating some biomarkers may have clinical values for diagnosing and monitoring organ crosstalk-related diseases and dysfunction. Actually, no biomarker can definitely diagnose organ interaction or predict its clinical outcome. Because of its complexity, improvements in the diagnosis of organ crosstalk outcomes are both slow and a systematic and holistic approach is required.

Conclusion

Vital organs generally function in coordination and harmony. Sudden or chronic dysfunction of one of these organs causes disorder in another organ. The inter-organ crosstalk and the functional integration of organ systems are exceedingly complex processes. Crosstalk between the organs is crucial for controlling energy homeostasis. In many diseases, inter-organ communication is significantly disturbed, which contributes to changes in some physiological and metabolic functions. Of all the complex regulatory systems, a lot of communication axes have been proposed as crucial paths that control these metabolic features. Several pathological conditions, such as obesity, type 2 diabetes and NAFLD, are characterised by a loss of excessive inter-organ communication that contributes to the development of disease. For example, when organ interactions are examined in a disease development, dysfunction of adipose tissue in obesity provides a source of excess fat and results in the secretion of multiple factors involved in the pathogenesis of NAFLD. In addition, emerging evidences suggest that an altered gut microbiota can influence the development and progression

of NAFLD, possibly via the gut–liver axis. In the liver, the dysregulation of lipid de novo lipogenesis and imbalance of lipid influx and efflux causes lipotoxicity which may further result in mitochondrial dysfunction and ER stress as well as the consequent activation of inflammatory responses, as observed in obesity and IR.

Also experimental and clinical studies have proven the presence of a detrimental crosstalk between sepsis, the systemic inflammatory response to infection, and the development of organ damages such as lung and kidneys. The detrimental activity of circulating proinflammatory and proapoptotic mediators directly linked to established organ cells affects the pathogenic mechanisms of sepsis and MOF. Indeed, the inflammatory phenomenon is a whole body process, with complex interactions between multiple organs. Integral to this inflammatory response is a well-coordinated system of communication, by neural and endocrine means, involving tissues of all sizes, from individual cells to entire organs. The inflammatory phenomenon is a whole body process, with complex interactions between multiple organs. Integral to this inflammatory response is a well-coordinated system of communication, by neural and endocrine means, involving tissues of all sizes, from individual cells to entire organs. This review article, focusing on inflammation and fibrotic changes among organ relationships, is highlighted the examples of mutual crosstalk between two vital organ such as liver–kidney or gut–adipose tissue. Some cases of combined acute organ dysfunction are reversible and appropriate managing is based on recognizing the underlying mechanisms. An improved knowledge of the pathogenic ‘crosstalk’ between any organ and remote organs will not only help to modulate known risk factors associated with the onset of a disorder and its progression to organ failure but will also provide a vision for the treatment.

Concluding remarks

- Interaction between organs provides physiological homeostasis, while any organ dysfunction causes organ crosstalk-mediated disorder in the other organs.
- The organ crosstalk-mediated inflammatory response that leads to increased inflammatory mediators in the circulation causes harmful effects on other distant organs.
- Increased evidence has shown that adipose tissue and intestinal microbiota are important players in the organ crosstalk and interaction.
- The aging process is adversely affected by organ interactions due to inflammation and inflammation-induced fibrosis.
- To clarify complexity and provide more accurate risk classification and effective interventions, some biomarkers on organ crosstalk are recommended.

- Present and future studies on pathogenetic mechanisms about various organ crosstalk will allow better and timed therapeutic strategies to improve outcome in these patients.

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Compliance with ethical standards

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