A new outlook towards kidney injuries

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COVER LETTER

Dear Reader,

Acute and chronic kidney injuries have reached a problematic scenario due to the disappointing diagnosis and management strategies. The detection of kidney injuries occurs only after the 70 percent irreversible loss of kidney function. The current research is being focused only on the clinical manifestations after the kidney injuries and has no clue towards the cause of the condition. Our paper proposes the involvement of a pathogen in the cases of acute and chronic kidney injuries. Such proposal has not been reported so far in the literature.

Looking towards some of the pathogen based life threatening diseases such as hepatitis or AIDS. Until the discovery of the pathogen and its exact site of location, the precise diagnosis and therapeutic management of the disease had been quite difficult and disappointing. Similarly, in the cases of acute and chronic kidney injuries, occurring irrespective of a genetic or toxicity basis has shown a rapid increase in the onset, raising a number of mysterious questions. Interestingly, we found the presence of a specific pathogen in the cases of kidney injuries. Surprisingly, it was not seen in normal people and in other disease state. We have outlined various facts in this paper, which support our proposal for the involvement of pathogen in the conditions of kidney injury.

You might be well aware that characterization and confirmation for the role of a pathogen in a disease state requires the involvement of various experts from cell biology, immunology, microbiology, genomics, proteomics, and so on. Our idea is at the budding stage and apart from nephrologists, it requires awareness among the diverse experts of the scientific community, to pursue this new possibility for unraveling the pathogen based pathogenesis of the acute and chronic kidney injuries.

Research in this theme possesses a strong possibility in the development of precise diagnostics on advanced platforms. Then, therapeutics development towards the cure of

the condition followed by, the generation of vaccines for prevention of the condition. Unraveling the exact cause would provide better management strategies for the acute and chronic kidney injuries.

Therefore, I look forward to interact with interested researchers and discuss further. I certify that this work is the first report and is completely authentic.

Thanking you,
Best regards

Dr. Abhijeet Satwekar and Dr. Mahesh Satwekar

Abstract

Acute and chronic progression of injury to the kidney leads to the failure of the renal system and has become an increasingly important cause of the morbidity and mortality. Present diagnosis detects the condition only after 70 percent irreversible loss of kidney function. Current research is focused only on the clinical manifestations after the kidney injuries and has no clue towards the exact cause of the condition. Here we propose a new outlook that there is an involvement of a pathogen in the pathogenesis of kidney injuries. Basis for our proposal is by given by the similarity of the pathogenesis events occurring between a classical example of hepatitis and kidney injuries. Furthermore, literature regarding the role of early kidney injury biomarkers in innate immunity indicates the involvement of the pathogen. Research in this theme possesses a strong possibility in the development of therapeutic, preventive and management strategies for the acute and chronic kidney injuries.

Introduction

Kidney injury is a problematic clinical condition which leads to the failure of the renal system. Its occurrence can be manifested through two major processes; acute kidney failure, which is a sudden and rapid deterioration of the kidney function, and chronic kidney disease, which involves the destruction of the kidney tissue over a period of time. Both of these processes lead to the end stage renal disease, with a damaged kidney having less than 10 % of the normal renal activity. The indicators for the diagnosis of kidney injury are based on the serum creatinine and BUN (blood urea nitrogen) levels, which lacks specificity and are insensitive for the early detection of the kidney damage (*1-3*). Other biomarkers based on the filtered high molecular weight proteins or enzymes also suffer from the lack of specificity (*4*). Relying on these traditional diagnosis methods, the detection occurs only after the 70 % irreversible loss of kidney function, and once established, the only effective treatment is dialysis or transplantation. Due to the disappointing diagnostic and management strategies; kidney failure has become an important cause of morbidity and mortality, and despite of technical improvements in the critical care, the onset of kidney failure is increasing at an alarming rate (*5-7*). It has been speculated that the mortality due to kidney failure of the postoperative patients ranges from 24-100 % (*8, 9*), and 50-70% with the patients under dialysis (*8*).

Kidney consists of a highly specialized vascular bed (glomerulus) for the selective ultra filtration of blood plasma to retain essential proteins (*10-12*). The primary structural support for the glomerular tuft is the glomerular basement membrane consisting of terminally differentiated epithelial cells known as podocytes. Podocytes occur as foot

processes like projections and the slit diaphragm bridging the foot processes is the determinant of filtration barrier characterized by distinct charge and size selectivity (*12, 13*). Characteristic feature of the acute and chronic kidney injury is proteinuria, in which the permeability of the glomerular membrane is increased and there is a loss of excessive albumin along with the other plasma macromolecules in the urine (*14*). Researchers have demonstrated that podocytes are vulnerable to immune and non-immune mediated responses leading towards the injury and effacement (*15-17*). This damage to the podocyte eventually results in the spreading of the foot processes along the glomerular membrane with the loss of filtration slits causing proteinuria (*18*). Injury to the podocytes has been observed in human and in experimental glomerular diseases (*19*). Studies have demonstrated that podocyle injury leading to the podocyte foot process effacement and slit diaphragm disruption are reversible (*20, 21*) However, the question remains a mystery as, *why nephropathies of different types lead to end stage renal disease?*

Briefly, the cause of kidney injuries could be classified into categories based on: a) toxicity by drugs and toxins, which leads into a kidney injury state (*22*), and b) genetic basis, which involves the genes governing the structural features of the glomerular basement membrane (*23*). Indeed, the structural organization of slit diaphragm and the podocyte foot processes constitute the basis of glomerular selectivity (*11-12*), and any change in these features would lead to kidney injury like condition with excessive proteinuria. However, the above discussed causes are incapable to explain the rapidly growing onset of acute and chronic kidney injuries occurring irrespective of any relation towards the toxicity or genetic basis.

The new outlook

Slightly diverting from kidney to liver and taking a close look at the pathogenesis of hepatitis; the observation shows chronic and acute progression of the disease associated with the pathogen. However, for the time being, if the presence of the pathogen is excluded, then it will be observed that the progression of hepatitis occurs by the involvement of the innate immune response, through a sequence of events consisting of an initial local inflammatory response – systematic inflammatory response – compensatory anti-inflammatory response, which finally leads to the liver failure (*24*). Almost 50 % of the acute liver failure patients require liver transplantation and the condition is associated with significant morbidity and mortality.

In case of kidney injuries, a similar chronic and acute progression of the disease is observed. The process of kidney injury initiates by inflammation and occurs through multiple pathways involving the induction of chemokines, complement activation, expression of chemo-attractants, infiltration of macrophages (*25*). These features clearly indicate the involvement of the innate immune system and a basis for the probable presence of the pathogen. Indeed, it is a well established fact that the innate immune system is the first line of non-specific rapid defense against pathogens or foreign bodies (*26*). Therefore, we propose herewith an infectious agent based cause of the acute and chronic kidney injury. The inability of the host to eliminate the pathogen is supposed to be the reason for the persistent chronic inflammatory response leading to fibrosis (very poorly repairable tissue injury) and kidney failure.

Indeed, our assumption for the infectious basis of kidney injury can be surprising, as there are no reports in the literature for the presence or involvement of an infectious

agent in the disease state of the kidney injuries. Interestingly, in the clinical settings, we have evaluated the specific presence of a particular pathogen only in the cases of acute and chronic kidney injuries (unpublished data). We expect that this pathogen might be capable to subvert the host immune response and cause persistent infection, which forms the basis for the unrepairable kidney damage.

Biomarkers and their relevance

The advent of technologies based on the functional genomics and proteomics in the human and animal models of the kidney injury have provided some promising candidates as early kidney injury biomarkers. Among these NGAL, KIM-1, IL-18, L-FABP have gained considerable attention as the biomarkers for early detection (*4*).

Neutrophil gelatinase–associated lipocalin (NGAL) protein is coded by the lipocalin 2 (*lcn2*) gene, which is one of the most up-regulated gene during the kidney injury (*4*). Bacteriostatic role of NGAL in the iron-limiting defense strategy of innate immune system has been well characterized in the literature (*27*). Certain bacteria release siderophores, to chelate and uptake iron, hence NGAL is released at the sites of infection and inflammation. NGAL binds with the bacterial siderophore-iron complexes, thus limiting the iron to the bacteria and provides an anti-bacterial activity. Interleukin-18 (IL-18) is a pro-inflammatory cytokine and the role of IL-18 has been well established in the innate immunity based defense against infection (*28-30*). IL-18 induces the expression of IFN-γ, which is involved in the Th1-immune response for the elimination of the intracellular pathogens (*31, 32*). Indeed, infected cells need to be eliminated by phagocytosis and the occurrence of kidney injury molecule-1 (KIM-1) receptor on the

tubule epithelial cells, confers these cells the property of phagocytosis (*33*). KIM-1 has been reported to have a role in the elimination of the pathogen infected cells and in the tissue repair and development (*33*). Moreover, inflammation is one of the first responses of the immune system to infection and liver fatty acid binding protein (L-FABP) is a chaperon for the lipids, and strongly linked to the inflammatory response (*34*). Interestingly, these facts also indicate the probability for the involvement of an infectious agent in the injured kidney related diseases.

Prospects

The above discussed facts clearly indicate the probability for the involvement of pathogen in the acute and chronic kidney injuries. Further research requires involvement of the interdisciplinary experts to *exactly identify and confirm the pathogen*, understand *the genome and morphology of the pathogen*, then *how the pathogen subverts the host immune system*, and *the study of infection cycle in the host*. These studies would essentially provide the clues to develop rapid diagnosis, therapeutic and management strategies for acute and chronic kidney injuries. Of interest, would be the characterization of the pathogen to identify different strains, which might explain the significance between different nephropathies. The idea has a strong potential towards the cure of the acute and chronic kidney injuries.

Acknowledgements

This research was supported by Prarthana Laboratory (India).

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