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Molecular mechanisms of sepsis-associated acute kidney injury

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Abstract

Sepsis-associated acute kidney injury (AKI) is a complex pathological state driven by dynamic interactions between the host and microbes. The rapid progression and the absence of a molecular clock that stages the disease timeline make precise therapeutic interventions highly challenging. In this Review, we aim to refine the timeline of sepsis-associated AKI by dissecting key molecular events that drive disease progression and may inform therapeutic strategies. AKI, initiated by microbes or infection mimicry, involves the rapid and simultaneous activation of inflammatory and anti-inflammatory pathways. This energy-intensive response is further fueled by the loss of distinction between self and non-self, leading to excessive antiviral responses mediated by self-derived nucleic acids. The resulting metabolic burden overwhelms cellular functions, triggering the integrated stress response and profound translation shutdown. While this shutdown response may be necessary for energy preservation and for priming endogenous recovery mechanisms, prolonged inhibition of translation represents a maladaptive feature of septic AKI. Despite these challenges, the kidney exhibits remarkable resilience. Recovery relies on metabolic flexibility and stress-adaptive mechanisms, such as enhanced polyamine biosynthesis and RNA editing. Meanwhile, microbes also demonstrate metabolic adaptability, enabling them to evade host defenses and exploit the host environment. Understanding this dynamic interplay along the timeline of septic AKI is essential for developing rational therapeutic strategies.

Introduction

By 2050, infectious diseases are projected to be the world's leading cause of death due to the emergence of antimicrobial resistance.[1, 2] The combination of microbial invasion and overwhelming host immune responses often leads to sepsis syndrome and multi-organ failure. The kidney's role in homeostasis depends on a rich blood supply and a dense network of trafficking immune cells that constantly communicate systemic cues.[3] While these characteristics are vital for total body homeostasis, they also render the kidney susceptible to systemic infections.[4, 5] Indeed, acute kidney injury (AKI) is a very common complication in patients with sepsis and is an independent risk factor for mortality.[6]

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The underlying pathobiology of sepsis-associated AKI remains poorly understood due to complex host-microbial interactions occurring within tissue niches that are difficult to capture.[7, 8] Since kidney biopsy is rarely performed during active infection, even basic histopathological characterization is largely absent from the literature. Although potential therapeutic targets have been identified and tested in clinical trials, none have proven effective.[9–11] This underscores the complexity of sepsis pathobiology, in which the molecular arms race between the host and pathogen has blurred the boundaries between therapeutic advantages and disadvantages.[12–14] However, despite the current grim prospects of sepsis and sepsis-associated AKI, effective therapeutics may be on the horizon as our understanding of the molecular unfolding of the disease becomes more refined.

The human body can exhibit immense plasticity and resilience to overcome a variety of adverse conditions when stress responses are well-coordinated. Conversely, disease progression occurs when tissue responses become maladaptive, including the overproduction of defense molecules and the persistent shutdown of cellular metabolism. Identifying strategies to balance stress responses and elicit desired endogenous recovery mechanisms is a critical aspect of therapy development. In this Review, we highlight several key cellular and molecular pathways essential for controlling stress responses and promoting tissue recovery, with a particular emphasis on the timeline of disease progression.

Timeline of sepsis-associated AKI

Acute inflammatory phase

Sepsis-associated AKI is a complex pathological state that progresses at a fast pace.[15] The rapid progression of the disease poses a major challenge to implementing stage-specific therapeutics at the bedside (Figure 1). For example, in an animal model of endotoxemia, the surge of classic NFκB-mediated inflammatory molecules is extremely short-lived (a few hours).[16] While the duration of such outburst is likely longer in human sepsis, it is still estimated to occur mostly prior to the time the patient arrives for care.[12] This fast and elusive early inflammatory phase may explain the failure of dozens of clinical trials targeting upstream receptors and cytokines.[17–21]

The initial inflammatory response is accompanied by a marked increase in global transcription and translation rates (Figure 2).[16] This process is energetically costly but necessary to meet the demand for defense molecule production and immune system activation. Even under normal conditions, maintaining transcription and translation is energetically expensive and involves multiple layers of regulation. For example, the transcription cycle consists of four distinct steps: initiation, promoter-proximal pausing, elongation, and termination. The majority of initiated transcription events (~80%) are prematurely terminated at the pausing step, particularly in genes from stress-responsive pathways.[22, 23] While seemingly wasteful, this energy-demanding system is nevertheless essential for enabling a rapid response to stress and the large-scale production of defense molecules.

The rapid upregulation of defense systems comes at the cost of restricting normal metabolic function. Excessive production of proinflammatory cytokines and chemokines also causes

collateral tissue damage through multiple mechanisms, including activation of the cell death pathways, hemodynamic collapse resulting in hypoxia, and en masse recruitment of immune cells, which disrupts normal tissue architecture. To mitigate self-inflicted damage, the host deploys multiple regulatory mechanisms simultaneously—rather than sequentially—from the earliest stages of infection.[24, 25] These modulatory systems include the expression of inhibitory molecules (e.g., NFκB Inhibitor-α, which prevents nuclear localization of the NFκB complex, and TNF-α Induced Protein 3, which terminates NFκB activation via proteasomal degradation of cell death mediators) as well as the upregulation of mRNA decay machinery (e.g., AU-rich element binding proteins and endonucleases).[16] Collectively, the early stages of sepsis are characterized by the vigorous and simultaneous activation of both proinflammatory and anti-inflammatory pathways. This “left foot braking” technique used by our genome enables the drastic overexpression of proinflammatory genes, followed by their rapid downregulation within a matter of hours. In an animal model of endotoxemia, the synthesis of classic NFκB-mediated inflammatory molecules returns to near baseline levels within 4 hours.[16]

Many other layers of regulatory systems are also required for maintaining cellular homeostasis and enabling rapid adaptation to various perturbations. For instance, transcription occurs in bursts, a phenomenon known as transcriptional bursting,[26] which enables the brisk production of nascent transcripts. Concomitantly, multiple mechanisms counteract this pulsatile nature of gene expression. These mechanisms include transcript and protein compartmentalization (e.g., the formation of stress granules to sequester transcripts and the conversion of membrane-bound proteins into soluble decoy receptors to abort signaling), translational regulation (e.g., the use of upstream open reading frames and initiation blocks to modulate translation kinetics), and splicing (e.g., generation of stress-induced isoforms targeted for nonsense-mediated decay to shorten their half-lives), among other mechanisms.[27] Each of these molecular mechanisms contributes to the cell’s ability to mount dynamic and regulated stress responses, and are potential targets for precision therapeutics in sepsis.

Self-amplification phase (Antiviral response)

Despite the multitude of fine-tuning regulatory mechanisms, severe infections and infection mimicry alike can quickly overwhelm the host metabolic system due to self-amplifying stress responses. In contrast to the early inflammatory phase, which is mediated by a variety of innate ligand-receptor interactions, the self-amplifying phase of sepsis follows a conserved pathway common to most pathogens, including bacteria and viruses (Figure 2).[28] Critical factors in this pathway include non-self and self RNA and DNA, which can exacerbate sepsis pathobiology.[29] Pathogen-derived nucleic acids and their unchecked amplification pose a major threat to the host. Consequently, non-self nucleic acids are continuously monitored by potent pattern recognition receptors, such as Protein Kinase R (PKR/eIF2ak2), RIG-I (DDX58), and Melanoma Differentiation-Associated Protein 5 (MDA5/IFIT1) for cytosolic RNA, as well as cyclic GMP-AMP synthase (cGAS) for cytosolic DNA sensing.[30] Although distinct molecular signatures allow for the differentiation of host- and pathogen-derived nucleic acids (e.g., RIG-I preferentially recognizes 5’-triphosphorylated RNA, indicative of viral-derived RNA), these sensors

primarily rely on broad, less discriminatory features such as nucleotide length, conformation (double-stranded or single-stranded), localization, and accessibility. For instance, the double-stranded RNA (dsRNA) sensors PKR and MDA5 preferentially bind to long stretches of dsRNA (longer than 33 bp and 40 bp, respectively), a feature commonly associated with viral replication.[31] Conversely, the accessibility of host-derived RNA is partially masked by host RNA-binding proteins and nucleotide modifications (e.g., pseudouridine). However, these distinguishing features are not absolute, creating the risk of triggering self-amplifying inflammatory responses.

Indeed, due to the sheer volume of host nascent RNA synthesis during the early stages of infection, self-derived RNA stress, in particular self-derived dsRNA stress, does occur.[32] This is because a significant portion of self-transcripts harbor repeat elements, particularly in the 3' untranslated region, which serve as a source of dsRNA through inter- and intramolecular base pairing. Repeat elements such as long terminal repeats (LTRs) and non-LTR retrotransposons (SINEs and LINEs) are also commonly found in the intronic and intergenic regions. Under basal conditions, the activity of transposable elements in the intergenic regions is suppressed through multiple epigenetic mechanisms, including DNA methylation and DNA-binding molecules.[33, 34] For example, heat-shock protein 90 forms a complex with the nuclear corepressor protein KRAB-associated protein 1, which binds to endogenous retrovirus loci and represses their expression. In contrast, under stress conditions, heat-shock protein 90 is relocated, leading to the reactivation of endogenous retroviruses.[35] Finally, mitochondrially-derived transcripts, which increase during early sepsis, are also prone to forming dsRNA structures due to the bidirectional transcription of the mitochondrial genome. Under normal circumstances, such dsRNA is kept in check by the mitochondrial degradosome. However, if the degradation system is overwhelmed, mitochondrial dsRNA could translocate to the cytosol and contribute to dsRNA stress.[36] Similarly, the activation of cytosolic DNA sensing pathway due to mitochondrial damage has been implicated in various disease conditions in the kidney.[37–47]

These host-derived amplifying processes converge on the activation of the antiviral pathway, irrespective of the initiating microbes.[48] The antiviral pathway is characterized by various interferon-mediated responses and culminate in the integrated stress response, marked by the phosphorylation of eIF2α (Eukaryotic Translation Initiation Factor 2 subunit α). For example, the dsRNA sensor PKR autoactivates upon binding to dsRNA. Once activated, PKR phosphorylates eIF2α. Phosphorylated eIF2α in turn stalls nearly all translation initiation events by inhibiting the GTP/GDP exchange reaction required for eIF2 recycling between successive rounds of translation initiation.[49] As a potent translation-inhibitory signal, eIF2α phosphorylation limits pathogen replication, but leads to host global translation shutdown.[50]

Therefore, the antiviral phase in sepsis-associated AKI, which resulted from a massive upregulation of transcription and translation, is terminated by the activation of the integrated stress response, leading to translation shutdown. In an animal model of endotoxemia, this antiviral phase lasts between 8 to 16 hours, depending on the severity, cell type, and experimental model.[51]

Shutdown phase

Among the phases of sepsis-associated AKI, global translation shutdown is the most pronounced and consequential. This shutdown is preceded by a series of inflammatory and antiviral responses that occur in each cell type but are not fully synchronized (e.g., endothelial and stromal cells exhibit antiviral responses first, followed by renal epithelial cells).[52] In contrast, translation shutdown occurs globally across all cell types at a distinct time point. This phase is characterized by the loss of cell-cell communication, dedifferentiation of cell identity, and downregulation of physiological functions, best exemplified in a reversible model of endotoxemia (Figure 2).

Despite the apparent organ paralysis, this shutdown phase is far from a dormant state. Rather, it represents a critical transition period where genome-wide reprogramming takes place to facilitate recovery.[52] For example, SOX9, a key transcription factor involved in renal repair,[53–55] is induced during this period. Notably, a subset of genes are highly resistant to translation shutdown. Shutdown-resistant genes are enriched in pathways related to mRNA processing and RNA splicing.[16] RNA splicing and the resulting isoforms enable rapid diversification of transcript repertoires, driving alterations in cellular phenotypes. Thus, RNA splicing may play a role in recovery programs, allowing cells to simultaneously downregulate stress-induced genes while upregulating genes essential for recovery.

Stress-induced metabolic shutdown is a critical inflection point. In the face of severe stress, transient inhibition of global metabolism is likely beneficial, as it reduces energy consumption and allows for resource reallocation. However, prolonged suppression of global protein synthesis is clearly detrimental.[56] Indeed, both pharmacologic and genetic reversal of translation shutdown promotes renal recovery. For example, ISRIB, a small molecule that enhances GTP/GDP exchange reaction on the eIF2 complex,[57] rescues translation and improves kidney function.[16] Similarly, overexpression of the eIF2α phosphatase GADD34 (PPP1R15A) reverses translation shutdown and promotes recovery.[58] These examples indicate that this shutdown phase is not fully adaptive but rather a component of AKI pathophysiology. The balance between excessive and appropriate shutdown is context-dependent, underscoring the need for strategies to quantitate and calibrate this critical phase.

Recovery

Finding ways to balance stress responses and elicit desired endogenous recovery mechanisms remains a major challenge. Experimentally, despite significant injury processes, the kidney can ultimately adopt a recovery phenotype, leading to the restoration of renal function and normalization of gene expression in most cell types (Figure 2).[52] Similarly, even though sepsis-associated AKI is a serious clinical problem, a significant proportion of patients recover kidney function.[59] This highlights the remarkable plasticity and resilience of biological systems.

Nature provides many examples of resilience that has been optimized by evolution. Resilience takes many forms and exists across biological scales, from whole organismal levels to specific molecular pathways. For example, metabolic flexibility is a form of resilience in which robust toggling between distinct metabolic routes (or quiescent vs.

active states) enables rapid adaptation to environmental changes (e.g., arousal of hibernating bears and acute renal recovery).[60, 61] In the context of infection, resilience can manifest as efficient microbial killing (disease resistance).[62, 63] Alternatively, disease tolerance —mitigating self-inflicted cytokine damage while permitting microbial cohabitation—is another form of resilience (e.g., bats serving as viral reservoirs).[64, 65] More generally, a wide range of work demonstrates the importance of regulated stress as a fitness strategy against otherwise lethal challenges (e.g., phenomenon of preconditioning).[66–69] Collectively, the natural world illuminates multiple paths to harnessing powerful protective pathways and serves as a blueprint for unlocking the potential of survival mechanisms.

To delineate the link between the initial inflammatory response and endogenous recovery mechanisms, here we highlight the role of polyamines in the kidney as a prime example. Polyamines, namely putrescine, spermidine and spermine, are involved in a variety of fundamental biological processes such as transcription, translation, differentiation, and DNA repair.[70–72] As a crucial metabolic pathway, altered polyamine metabolism has been reported as a unifying feature across more than 10 different kidney injury models in mice, as well as in the context of post-kidney transplantation in humans.[73–75]

The rate-limiting step in polyamine biosynthesis is the conversion of the polyamine precursor ornithine to putrescine. Notably, Antizyme Inhibitor 1 (AZIN1), the master activator of this conversion process, can exist in two distinct protein isoforms.[76] One is derived from a canonical AZIN1 transcript, and another is produced through post-transcriptional RNA editing of the canonical AZIN1, where adenosine is converted to inosine at a specific locus (A-to-I RNA editing). The edited AZIN1 exhibits a gain-of-function phenotype, thus promoting polyamine biosynthesis. This RNA editing has been shown to play a key role in enhancing stemness in cancer cells and promoting the differentiation of hematopoietic stem cells.[76–80]

Under stress conditions in the kidney, AZIN1 A-to-I editing confers an advantage over the unedited state by upregulating the polyamine pathway and co-opting glycolysis and nicotinamide biosynthesis, culminating in a metabolically robust phenotype.[32] Importantly, this AZIN1 A-to-I editing is mediated by RNA-specific Adenosine deaminase (ADAR), specifically in response to interferon signaling and dsRNA stress.[81, 82] Therefore, the initial inflammatory stress not only causes translation shutdown but also primes the kidney to activate the subsequent endogenous recovery programs by boosting polyamine biosynthesis through A-to-I editing.

More broadly, these findings suggest a general model in which inflammation and resultant RNA editing function as an autonomous feedback system, protecting against sustained metabolic shutdown and signaling tissue recovery. Fundamentally, A-to-I editing represents a form of gene pool diversification under basal condition and in response to infections and various environmental factors. This mechanism is exploited by a variety of species to enhance survival fitness (e.g., temperature-dependent A-to-I editing in octopus).[83]

Excitingly, ADAR-based RNA-editing technology has advanced to clinical trials,[84, 85] and the first positive results were announced recently (for alpha-1 antitrypsin deficiency).[86]

This modular technology, which harnesses endogenous ADAR, could be a promising strategy for treating septic AKI at specific timepoints. Additionally, A-to-I RNA editing at various gene loci has been linked to genetic traits of common inflammatory diseases.[87] Therefore, identifying editable sites across the genome and understanding when and in what context editing occurs in the kidney could pave the way for novel RNA-editing therapeutic strategies.

Host-microbial interplay in the kidney

> "It is not the strongest or the most intelligent species that survives, but the one most adaptable to change"
>
> —Leon Megginson/Charles Darwin

From the species level down to individual cells, the ability to adapt to diverse stresses is essential for survival and fitness. For example, host cells dynamically adjust their bioenergetics in response to their environment by modulating the balance between glycolysis and oxidative phosphorylation. Neither glycolysis nor oxidative phosphorylation is inherently superior; the optimal pathway depends on the cellular context. Similarly, invading microbes exhibit metabolic flexibility as they adapt to host ecological niches through genetic drift, adaptive evolution, and transcriptional reprogramming.[88, 89] In fact, lethal bloodstream infection and tissue destruction are evolutionary dead ends for the invading microbe. Therefore, beyond modulating virulence and immune evasion factors, microbes initiate a complex crosstalk with the host that is constantly at play.[90, 91] This poses a formidable challenge in resolving the evolutionary conflict between species over their environmental responses and control.

In this final section, we discuss *Staphylococcus aureus* infection in the kidney, a common cause of AKI,[92–97] particularly Methicillin-resistant *S. aureus* (MRSA), to highlight the complexity of sepsis syndrome and unresolved questions.

Both as a commensal and as a pathogen, MRSA has been highly successful in prevailing in multiple hosts since it was first identified in the 1960s. MRSA can traverse diverse host environments and persist in tissue niches by employing a variety of metabolic adaptation strategies and subverting the host immune system.[88] On the host side, neutrophils are the main defense against MRSA infections.[89] Neutrophils launch various bactericidal arsenals such as degranulation and neutrophil extracellular traps. In turn, MRSA immediately counters by mounting multiple neutralizing molecules. On balance, the molecular arms race between the host and MRSA is currently very close, and the identification of a novel therapeutic strategy is urgently needed.

In murine models of MRSA infection, systemically administered MRSA localizes primarily to the liver during the early stages of infection. The focus of infection then shifts to the kidney later in the course, resulting in renal tissue damage and high mortality.[98–100] Even before the emergence of MRSA, the kidney was known as a major destination for bloodstream *S. aureus* infections in both humans and animals.[101–103] Human autopsies and animal experiments conducted before the era of molecular biology have clearly defined

the aggressive nature of "descending" *S. aureus* infection in the kidney (i.e., hematologic dissemination).[104] However, the molecular mechanisms leading to the spread of *S. aureus* in the kidney are unknown.

The difference between MRSA and MSSA (Methicillin-susceptible *S. aureus*) is not solely based on antibiotic resistance. The largest genomic region that sets MRSA apart from MSSA is the presence of the arginine catabolic mobile element (ACME) in MRSA—specifically, the ACME that contains spermidine acetyltransferase in the USA300 strain (Figure 3).[88, 105, 106] USA300 is the dominant MRSA strain, accounting for almost all community-associated MRSA cases presenting to emergency rooms in the United States,[107, 108] as well as healthcare settings.[109] The ACME encodes arginine deiminase enzymes (arc Operon *arcA*/*arcB*/*arcC*) and spermidine acetyltransferase. The acquisition of ACME by USA300 MRSA coincided with its global spread,[106, 107] suggesting that arginine catabolism (the conversion of arginine to ornithine) confers a significant survival advantage. The byproducts of arginine catabolism in *S. aureus* include ATP and ammonium, which provide energy and contribute to acid resistance.[105] It is possible that the unique kidney microenvironment, such as the inner medulla, could serve as an MRSA reservoir due to its ability to resist acid, hypoxia, and high osmolality.

Notably, *S. aureus* (both MRSA and MSSA) does not synthesize its own polyamines and instead relies solely on external sources. This is highly unusual among living organisms.[105, 106, 110–112] Polyamine biosynthesis was once believed to be conserved across the tree of life (still the case for nearly all archaea and eukaryotes, and the vast majority of bacteria).[113, 114] USA300 MRSA encodes only a single polyamine catabolic gene, spermidine acetyltransferase, whereas MSSA lacks this gene and any other genes related to polyamine metabolism.[110] Spermidine acetyltransferase neutralizes the amine groups on spermidine and spermine, thereby facilitating their export to the extracellular space. This results in differential use of polyamines between MRSA and MSSA. The implications of these characteristics and resulting susceptibility to polyamines, or the advantages polyamines offer to *S. aureus* in the kidney, remain largely unexplored. In response to *S. aureus* infection, host neutrophils and macrophages upregulate arginine catabolism via arginase 2 and arginase 1, respectively (unpublished observation). These innate immune cells also upregulate Spermidine/spermine N1-acetyltransferase 1, an enzyme functionally analogous to Spermidine acetyltransferase in MRSA. This suggests a parallel—competitive or exploitative—dynamic between host and pathogen along the axis of arginine and polyamine catabolism, underscoring the complex ecology of host-microbial interactions.

Beyond direct kidney infection, *S. aureus* remains a vexing problem across the spectrum of clinical practice, ranging from endocarditis and osteomyelitis to dialysis access complications.[115, 116] In addition, the pathobiology of *S. aureus*-associated glomerulonephritis[117, 118] and vancomycin nephrotoxicity[119–121] remains poorly understood, as these conditions are confounded by concomitant bacteremia. Further investigation into the host-microbe interplay will enhance our understanding of disease unfolding and the unique renal microenvironment impacting AKI outcomes in sepsis.

Outlook

> "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that"
>
> —Lewis Carroll/Leigh Van Valen (The Red Queen hypothesis)

To survive sepsis and maintain vital physiological functions, the kidney must dynamically adapt and evolve throughout the course of infection. The constant battle between hosts and microbes renders any therapeutic option irrelevant or even detrimental if the timeline of sepsis is not carefully considered. While we have dissected several key molecular pathways involved in the progression and transition of septic AKI, many other equally important and active pathways remain beyond the scope of this Review.[122–158] In particular, we acknowledge that this Review places less emphasis on cell-specific effects, as we have prioritized defining the overall tissue phenotype and timeline. Although the intense competition between hosts and microbes is a major driver of sepsis, it is likely more than a simple zero-sum game. Complex interactions within and between species may even generate new resources and foster mutualism. A remarkable array of technologically advanced research tools is now available at scale. More than ever, we must re-examine the time-dependent molecular crosstalk between host and pathogens to identify novel therapeutic approaches for improving the outcome of septic AKI.

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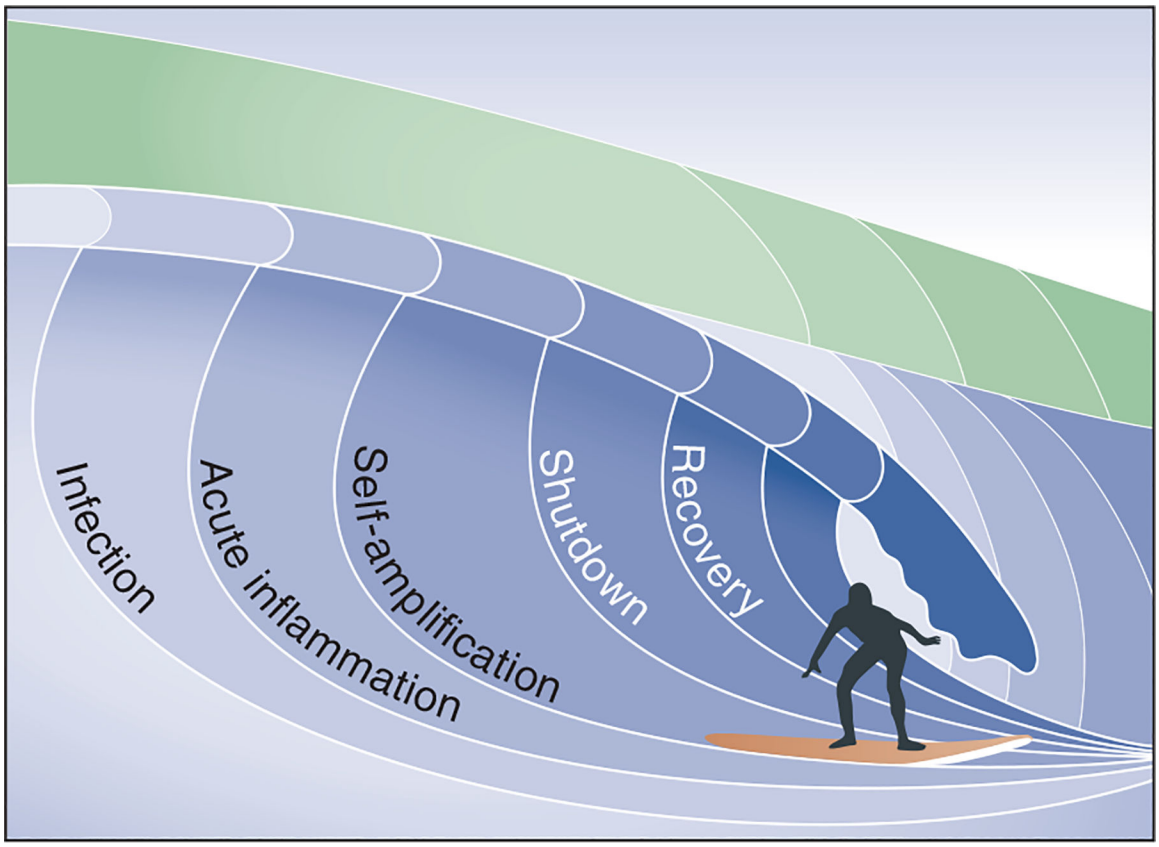

Figure 1: Renal tissue responses in sepsis

Phases of tissue responses in the kidney following a systemic infection. Surviving sepsis is analogous to navigating all the steps without being ‘wiped out’ by a wave. The magnitude and duration of each phase vary depending on the type of infection, but the sequence of responses remains constant. These phases overlap, each involving a diverse array of molecular pathways and cell types.

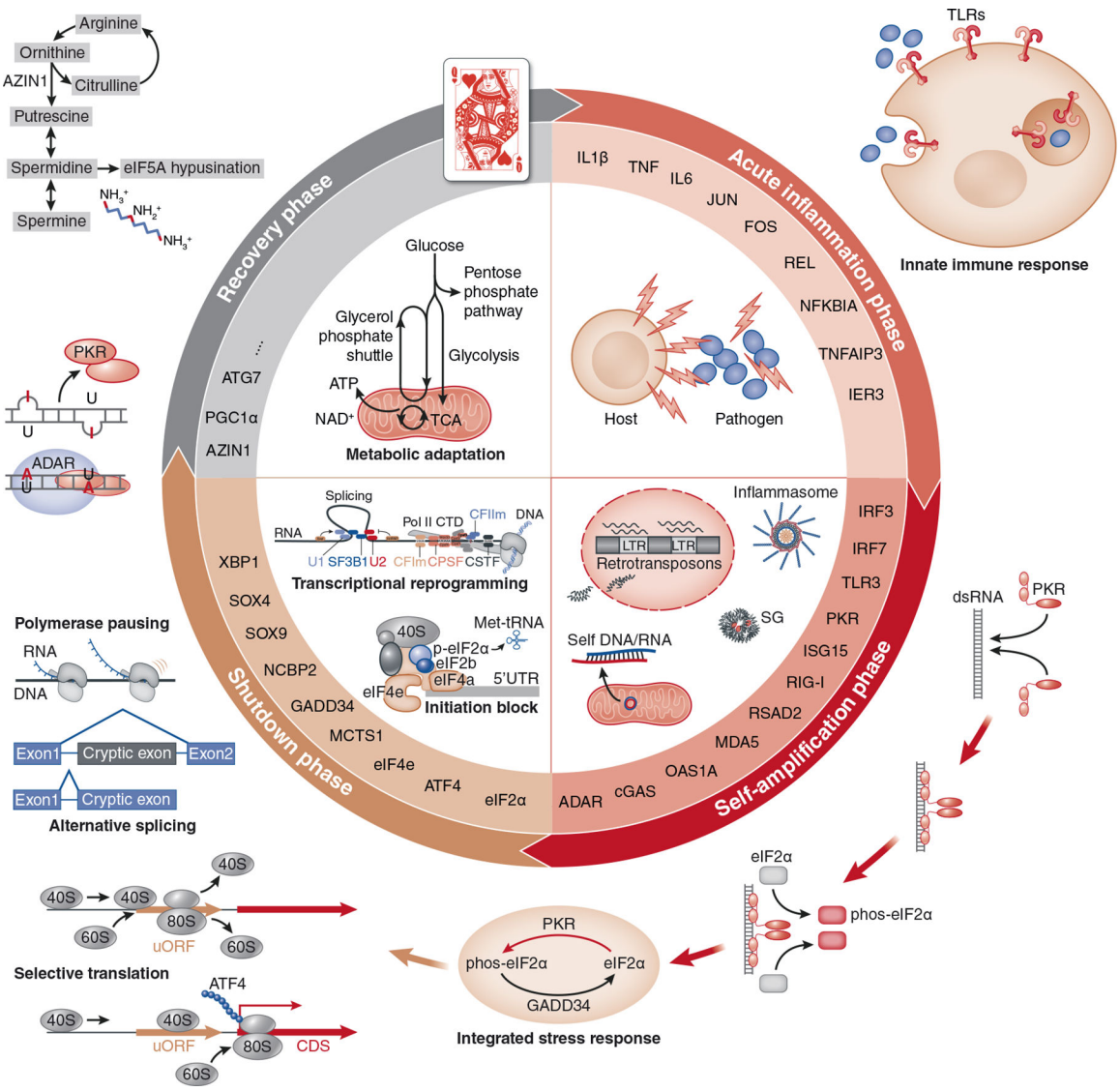

Figure 2. Molecular mechanisms of sepsis-associated AKI

Illustration of representative molecular pathways involved in each phase of sepsis-associated AKI. The inner circle depicts a cadre of mechanisms, while the middle and outer circles highlight select genes and systems active in each phase. The Red Queen card symbolizes concurrent microbial evolution and adaptation, which are not detailed in this diagram. Note that the size of the quadrants does not represent actual duration of each phase in sepsis. TLRs, Toll-like receptors; SG, stress granules; Pol II CTD, RNA polymerase II C-terminal domain; uORF, upstream open reading frame; CDS, coding sequence

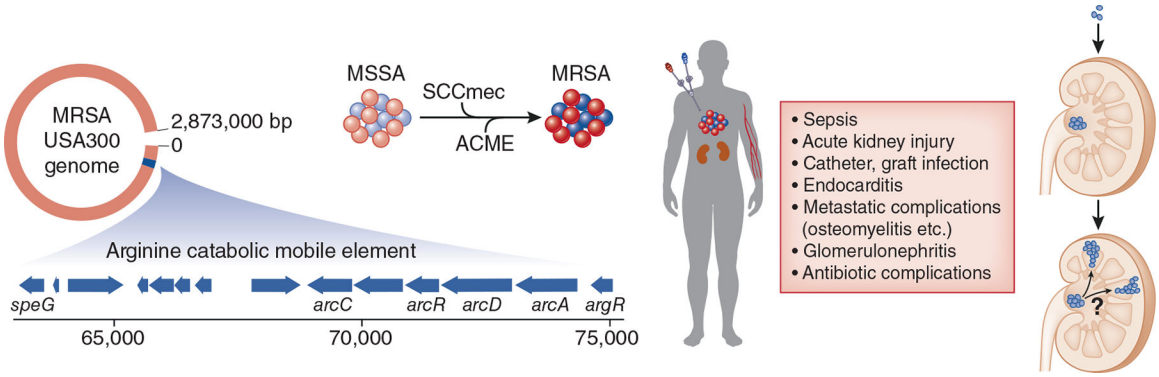

Figure 3. Staphylococcus aureus infection

Left: Genome structure of MRSA USA300. The region corresponding to the arginine catabolic mobile element (ACME) is magnified (blue). SCCmec: *Staphylococcal Cassette Chromosome mec*, which encodes methicillin resistance. *speG*: spermidine acetyltransferase. Middle: Representative clinical challenges encountered by nephrologists. Right: Illustration of hematogenous dissemination of *S. aureus* resulting in acute kidney injury (descending pyelonephritis).