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The ten barriers for translation of animal data on AKI to the clinical setting

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It is well established that acute kidney injury (AKI) is a common disease of hospitalized patients associated with significant morbidity and mortality. To date, there are no targeted pharmacotherapies for AKI prevention or treatment, and treatment is entirely supportive, including renal replacement therapy (RRT). Here, we comment on 10 barriers for translation of animal data on AKI to the clinical setting. Because the vast majority of studies have been performed in rodent models of AKI, these are a major focus of our comments.

1. Animals can be pre-treated or treated at the time that AKI occurs; humans usually cannot

With the exceptions of the perioperative setting (coronary artery bypass grafting and high risk vascular surgery, for example) and high-risk medication use (contrast-induced nephropathy), it is generally not possible to pre-treat humans to prevent AKI. Furthermore, in humans, serum creatinine (SCr, our primary biochemical marker of AKI) lags changes in glomerular filtration rate, so by the time AKI is detected, the disease is well-established [1]. While there is an effort among basic scientists to prove efficacy of novel therapeutics by administering the agent after the AKI insult, how this would translate to patients where “time zero” is indeterminate remains challenging.

2. AKI in animals is often due to a single insult; human AKI is usually multifactorial

Animal models typically induce AKI with a single severe insult; in contrast, humans may have several acute insults that culminate in AKI. In addition, the single insult that culminates in AKI in animal models is often ischemia-reperfusion injury (IRI), whereas sepsis is the most common cause of AKI in critically ill humans. Furthermore, not all humans appear to have the same susceptibility to a given insult. Efforts are ongoing to develop models to

address what happens when acute injury occurs on a background of prior injury [2, 3], with the hope that this will address the issue of why some patients develop AKI and others do not, when faced with similar insults.

3. At its core, human AKI is still poorly understood, and human AKI pathophysiology cannot be inferred from rodent ischemia-reperfusion models

Despite advances in disease epidemiology, human AKI remains poorly understood - with very little insight into what changes GFR and when it happens. The scope of AKI in humans (defined by sCr and urine output) is a late injury event, and our understanding of molecular, cellular, and intra-renal hemodynamic events remains poorly defined. In particular, there is a major knowledge gap concerning the pathophysiology of human AKI - our assumptions are largely based on rodent IRI studies, which can be considered the equivalent of using Galen of Pergamon's manual of anatomy based on dissection of monkeys and pigs to define human anatomy. The NIH has recently committed resources to studying human AKI by evaluating research biopsies using a variety of 'omic' approaches [4].

4. Some common insults in humans cannot be replicated in small animals

Although there are number of recent studies focused on models of myocardial infarction-induced[5] and cardiorenal AKI[6] in rodents (which may lead to a better understanding of these conditions), there is no simple rodent model of contrast induced AKI, and no model of multifactorial ICU-AKI. The absence of better preclinical AKI models represents a major barrier to progress.

5. Severe (dialysis-requiring) AKI cannot be replicated in small animal models

When severe AKI is induced in small animal models, there is no way to provide renal support (e.g., RRT) to allow the animals to survive and to better understand determinants of renal recovery. This is a critical clinical problem that cannot be modeled in the laboratory, limiting translation.

6. Small animals are inherently more resistant to sepsis

Unlike humans undergoing surgery, rodents undergoing IRI do not require antibiotics to prevent infection. Along the same lines, rodents exposed to bacterial lipopolysaccharides (LPS) to induce a sepsis-like response require much higher doses than humans [7]. Until recently, many rodent models of sepsis did not include supportive care (e.g. fluids, antibiotics) to mimic the human condition. In fact, acute inflammatory stresses cause a characteristic set of genomic responses in humans, but changes in the expression of the murine orthologs of these human genes are close to random in rodents [8]. Thus, the injury and the host response that lead to AKI in these animal models is inherently different than what occurs in humans.

7. Young animals elderly humans in terms of disease susceptibility

The expense of maintaining animal colonies for extended periods of time and the desire to complete scientific experiments in an efficient manner has led to the establishment of AKI models that use young animals that undergo a severe and homogenous injury – the predictable nature of the injury results in smaller sample sizes and reduced costs. However, in marked contrast, the humans at greatest risk for AKI are elderly individuals with multiple comorbidities who are often treated with multiple medications, some of which may increase the risk of AKI (such as angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers). Furthermore, humans appear to have variable susceptibility to injury.

8. Mice are typically inbred, and humans are not

Along the same lines, variability in animal susceptibility to injury has encouraged the use of inbred animals with similar susceptibility to a given insult. Oftentimes, only male animal “subjects” are used due to differences in susceptibility to injury between male and female animals, which further increases the homogeneity of the population studied. We currently have little understanding of how comorbidities, underlying genetics including gender, and acute illness impact the development of AKI in humans.

9. Time and money are not on our side: rodent models of CKD require months for the animals to age, and old rodents and sheep (best animal models) are expensive

Much work has been done to develop AKI models in older rodents with comorbidities including diabetes (though again the injury that results in diabetes mellitus is more homogeneous than the human disease entity). Along the same lines, elegant work has been done to elucidate renal hemodynamics and histopathology during sepsis in sheep AKI models [9, 10]. However, relatively few investigators have the resources to employ and further develop these types of models because they are so expensive compared to models that use young, inbred rodents.

10. Variable conditions during animal studies have led to low reproducibility even in animals – not surprisingly, the results do not translate to humans

Finally, even animal models that use young, inbred rodents have been subject to inherent variability – due to issues in lack of standardization of models across research groups, inadequate group size, differences in animal housing and chow, as well as seasonal differences [11]. Other challenges to animal studies have included a lack of blinding and power calculations, measures that are standard in human studies. Consequently, even in these models there has been limited reproducibility – so it is again not surprising that results do not translate to humans.

In sum, we have outlined 10 important barriers to translating animal studies to humans. Active efforts are ongoing to improve animal models to better simulate human AKI. Ultimately, however, more effort must be placed on understanding human AKI so that the physiological principles that underlie human AKI can be translated backwards to develop better animal models.

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