Translating Knowledge Into Therapy for Acute Kidney Injury

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Summary: No therapies have been shown to improve outcomes in patients with acute kidney injury (AKI). Given the high morbidity and mortality associated with AKI this represents an important unmet medical need. A common feature of all of the therapeutic development efforts for AKI is that none were driven by target selection or preclinical modeling that was based primarily on human data. This is important when considering a heterogeneous and dynamic condition such as AKI, in which in the absence of more accurate molecular classifications, clinical cohorts are likely to include patients with different types of injury at different stages in the injury and repair continuum. The National Institutes of Health precision medicine initiative offers an opportunity to address this. By creating a molecular tissue atlas of AKI, defining patient subgroups, and identifying critical cells and pathways involved in human AKI, this initiative has the potential to transform our current approach to therapeutic discovery. In this review, we discuss the opportunities and challenges that this initiative presents, with a specific focus on AKI, what additional efforts will be needed to apply these discoveries to therapeutic development, and how we believe this effort might lead to the development of new therapeutics for subsets of patients with AKI.

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No therapies have been shown definitively to improve clinical outcomes in patients with acute kidney injury (AKI).[1–4] Although there are many reasons for this, ranging from the paucity of preclinical models that accurately model the types of patients studied in AKI trials[5] to weaknesses in preclinical and clinical study design,[6,7] a common feature is that none of these discovery efforts primarily were human data-driven. An illustrative example of this comes from one of the more recent clinical studies of a melanocyte-stimulating hormone (MSH) agonist to prevent AKI in patients after cardiac surgery.[8]

A RECENT THERAPEUTIC FAILURE IN AKI

A synthetic α-MSH agonist, ABT-719 (formerly known as AP214), was evaluated for the prevention of AKI in patients undergoing cardiac surgery.[8] This was a phase 2B study that was powered properly to test the hypothesis that there is a dose-dependent protective effect of ABT-719 on the development of AKI in high-risk patients 72 hours after surgery. This study built on promising data from a small, unpublished, single-dose study of ABT-719 in cardiac surgery patients. It also was supported by a body of preclinical evidence indicating that α-MSH and AP214 have potent anti-inflammatory effects in a variety of experimental models, including dermal inflammation, inflammatory bowel disease, and arthritis, as well as models of ischemia reperfusion (IR) injury to the brain and kidney.[9,10] AP214 and α-MSH subsequently were shown to enhance survival and ameliorate AKI in a mouse model of sepsis-associated AKI[11]; in toxin-induced models of AKI in rats and mice[12,13]; and, more recently, in IR-induced AKI in pigs.[14] These effects are thought to be mediated by anti-inflammatory effects of melanocortin receptors (MRs), which are expressed in rodent and human monocytes and neutrophils, and possibly via direct protective effects resulting from activation of MR signaling in renal tubular epithelial cells.[10,15] The required patient enrollment was reached in this large, well-conducted, multicenter clinical study, but unfortunately the study showed no effect of ABT-719 on the primary (early AKI) or secondary end points (90 days >25% reduction in estimated glomerular filtration rate, or urinary or plasma AKI biomarkers).[8] In retrospect, it is notable that despite the strong supportive preclinical data, there were no published data indicating that MRs are expressed in human kidneys, or that there is aberrant activation of MSH/MR signaling in human kidneys after AKI. Another concern is that although published preclinical data in a variety of species from different laboratories have indicated that AP214 and α-MSH are protective

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after IR-induced AKI,[10,16–18] it is not clear that IR injury is the mechanism of AKI after cardiac surgery with modern cardiopulmonary bypass machines.[5] In addition, although approximately 40% of patients in the ABT-719 study had pre-existing chronic kidney disease (CKD), none of the preclinical studies were performed in AKI models with pre-existing CKD at the time the clinical trial was initiated. In this respect, it is notable that a study published after the ABT-719 study was initiated showed that α-MSH had no protective effects in rats with IR AKI subjected to subtotal nephrectomy to induce CKD.[19] Thus, we would suggest that the reason the ABT-719 study failed to show benefit in humans may have been because: (1) although the therapeutic target, the MSH/MR signaling axis, was validated in multiple preclinical models, we are unaware that it has been studied in human AKI; (2) in the absence of data on the effects of MR pathway activity in human AKI, there was no possibility of evaluating whether ABT-719 was in fact activating this pathway in these studies; (3) none of the preclinical models that were used to support the use of ABT-719 modeled the dominant pathobiology of injury that was likely to be occurring in the clinical study population; and (4) before starting the study, no preclinical studies had been performed using animal models with risk factors for AKI that were included in the clinical trial, including CKD.

AKI IS A HETEROGENEOUS CLINICAL SYNDROME

One of the challenges for therapeutic development in AKI is that it is classified based on simple measures of renal function that do not distinguish between patients with highly variable responses and pathobiology.[20] There are many different causes of AKI that often occur in combination with other comorbidities, such as CKD, diabetes, old age, and heart failure, all of which may affect the underlying pathobiology and therapeutic responses after AKI.[21,22] In addition, there are marked differences in individual responses to the same injury, with some otherwise indistinguishable patients showing complete functional recovery after AKI, while others have delayed or incomplete recovery.[23] This has implications for therapeutic development because it makes our ability to predict common molecular and cellular mechanisms of AKI nearly impossible. This in turn poses fundamental challenges to the use of modern, largely target-based drug discovery campaigns because these are predicated on a detailed knowledge of the causal cellular and molecular pathways of disease, and creates real challenges for the design of cost-effective clinical trials, because it is difficult to predict clinical outcomes in heterogeneous populations of patients presenting with AKI.[24] Finally, even if we had a better understanding of the underlying mechanisms of disease in more clearly defined subsets of patients, the ill-defined phenotypic heterogeneity of patient with AKI in clinical practice makes it nearly impossible to determine whether individual patients will engage the same primary molecular pathways and will respond to therapy in the same way.

MOLECULAR RECLASSIFICATION OF AKI

Most disease classifications are dependent on clinically observable and easily measurable parameters that do not necessarily reflect common pathogenic mechanisms of disease.[25] One of the goals of the National Institutes of Health (NIH) Precision Medicine Initiative is to reclassify complex diseases into more clearly defined categories that more closely reflect the cellular and molecular mechanisms of disease.[26] AKI is an example of a complex and often multifactorial syndrome that shows a high degree of interindividual variability in responses and outcomes.[21] Despite this, AKI currently is classified by simple measures of renal function that do not take into account its underlying pathophysiological heterogeneity (Fig. 1).[20] In addition, because of concerns about the risks of renal biopsies in patients with AKI,[27] we rarely have the benefit of renal histology to determine whether there are common pathologic responses in these patients. The net result of this is that our current classification system for patients with AKI does not provide any insight into the molecular, cellular, or even basic histologic heterogeneity of this syndrome. As part of the NIH Precision Medicine Initiative, one of the stated goals of the Kidney Precision Medicine Project (KPMP) that recently was launched by the National Institute of Diabetes and Digestive and Kidney Diseases is to "ethically obtain and evaluate human kidney biopsies from participants with AKI to create a kidney tissue atlas, define disease subgroups, and identify critical cells, pathways, and targets for novel therapies."[28] If achieved, this will provide an unprecedented opportunity for the renal community to develop a new

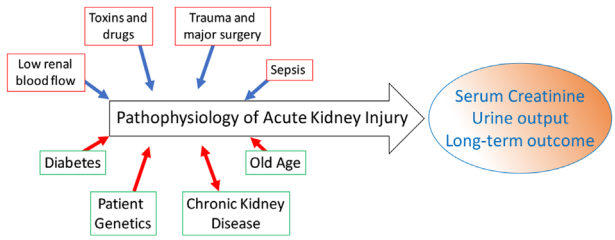

Figure 1. Current classification of AKI. Current clinical classification of AKI relies largely on shared functional responses and outcomes that do not take into account how the varied and often poorly defined causes of injury interact with the patients' own genetic background and relevant comorbidities to define the underlying pathophysiology of injury and repair in an individual patient after AKI.