

## COMMENTARY

# Mouse adult renal progenitor cells in combination with erythropoietin or suramin - a potential new strategy for the treatment of acute kidney injury

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### Abstract

Experimental evidence has indicated a role of adult renal progenitor cells in kidney regeneration and a protective role of the kidney by erythropoietin (EPO) and suramin in animal models and in humans after acute kidney injury (AKI). Han and colleagues analyzed different therapeutic effects between mouse renal progenitor cells (MRPCs), MRPC/EPO, or MRPC/suramin on the regeneration and protection of renal function after AKI. Their results revealed that MRPCs in combination with EPO or suramin are able to attenuate renal damage and promote renal recovery after ischemia/reperfusion injury in a mouse model. The researchers concluded that the combined approach with MRPCs and EPO or suramin could be a new therapeutic strategy for AKI.

In the previous issue of *Stem Cell Research & Therapy*, Han and colleagues [1] showed research of how mouse renal progenitor cells (MRPCs) alone – or, in particular, in combination with erythropoietin (EPO) or suramin – are able to attenuate renal damage and promote renal recovery after ischemia/reperfusion (I/R) injury in a mouse model. The researchers revealed that a combination rather than a single therapeutic approach seems to provide better outcomes for acute kidney injury (AKI).

AKI is a syndrome characterized by the rapid loss of the kidney's excretory function [2] and causes progression to advanced chronic kidney disease and a high patient mortality. I/R injury frequently occurs in patients with shock or cardiac surgery or renal transplantation and represents a major cause of acute renal failure.

No specific and effective therapies that can attenuate AKI or expedite recovery have emerged thus far. However, stem cells offer increasing potential to achieve the goal of truly regenerative therapies for AKI. Stem cells have the capacity for self-renewal and differentiate into specialized cell types with specialized functions. Tissue-specific stem cells have attracted much attention. Adult stem cells such as renal progenitor cells have been isolated from the kidney and have been revealed to function by accelerating the repair process and regenerating injured kidney in experimental animal models and in humans [3-5]. The administration of mouse renal stem cells can accelerate renal regeneration and prolong survival after AKI by means of differentiating into renal tubule cells and vascular endothelial cells with the expression of E-cadherin and CD34 [5]. These findings suggest that adult kidney stem cells have important therapeutic effects on renal regeneration. In addition, pharmaceutical management with agents such as EPO and suramin was useful in the recovery of renal I/R injury [6,7].

To compare the effects of MRPCs alone, MRPC/EPO, or MRPC/suramin in the treatment of AKI in a mouse model, Han and colleagues analyzed different therapeutic effects between MRPCs, MRPC/EPO, or MRPC/suramin on kidney regeneration after AKI during the study period. They found that MRPCs alone, MRPC/EPO, or MRPC/suramin could attenuate renal damage in I/R AKI C57BL/6 mice. Protection of renal function was found to be especially effective in mice that received MRPC/EPO or MRPC/suramin.

Why was protection of renal function found to be more effective in mice that received MRPCs in combination with EPO or suramin? What are the cellular and molecular mechanisms that attenuate ischemic cell damage and renal structural and functional recovery after AKI?

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A previous report has shown that MRPCs formed vessels with red blood cells inside their lumen (CD34<sup>+</sup> cells) and some were incorporated into renal tubules (E-cadherin<sup>+</sup> cells) [5]. The result by Han and colleagues revealed that more CD34<sup>+</sup> and E-cadherin<sup>+</sup> cells formed with the fast incorporation into renal tubules and capillaries in MRPC/EPO- or MRPC/suramin-treated groups than MRPCs alone. These results suggest that EPO or suramin or both can promote MRPC proliferative potential, migratory activity, and regenerative capacity.

EPO is a glycoprotein hormone that regulates red blood cell production in the bone marrow, and its role as a general tissue-protective drug to protect kidneys against acute injury has been confirmed by animal studies and clinical application. The potential mechanisms of EPO-mediated protective effects might be related to the anti-apoptotic, anti-oxidative, and anti-inflammatory properties and proangiogenic potential [6]. Suramin, a common drug in the treatment of trypanosomiasis, has recently been found to be useful in accelerating kidney recovery after AKI [7,8]. The result illustrated significantly decreased macrophage infiltration in MRPC/EPO- or MRPC/suramin-treated groups in comparison with MRPCs alone in that research. Han and colleagues suggest that macrophage and T-lymphocyte infiltration had a critical role in the initiation of the immune response to I/R injury in murine kidneys. MRPCs with EPO or suramin provided improved protection of renal function by reducing the post-ischemic inflammatory response, reducing apoptosis and cell death, and promoting MRPC differentiation and regenerative capacity.

As we know, current strategies for AKI focus on cellular and pharmaceutical therapy, specifically stem cell and immune cell therapy [3-5,9]. Despite successes in various animal models, translation to human studies either has failed or has been inconclusive. Many barriers to successful clinical trials in AKI still exist [10]. Promising preclinical human studies using combination therapy for AKI are in progress or are close to starting. Use of MRPCs in combination with EPO or suramin is a potential new strategy for the treatment of AKI.

Han and colleagues as well as others are exploring MRPC transplantation combined with EPO/suramin injection as a feasible approach to AKI. However, many important questions remain. What therapeutic effects would the combination have in human clinical studies? What are the key mechanisms by which MRPC/EPO or MRPC/suramin aids regeneration in injured renal tissue? Does MRPC/EPO or MRPC/suramin play a therapeutic role in protecting kidneys and decreasing the risk of subsequent chronic kidney disease? Further research will be expected to answer these and other questions and lead to improved therapeutic strategies.

#### Abbreviations

AKI: Acute kidney injury; EPO: Erythropoietin; I/R: Ischemia/reperfusion; MRPC: Mouse renal progenitor cell.

#### Competing interests

The author declares that he has no competing interests.

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