Ischemic renal failure and organ damage: A new mouse model holds the key

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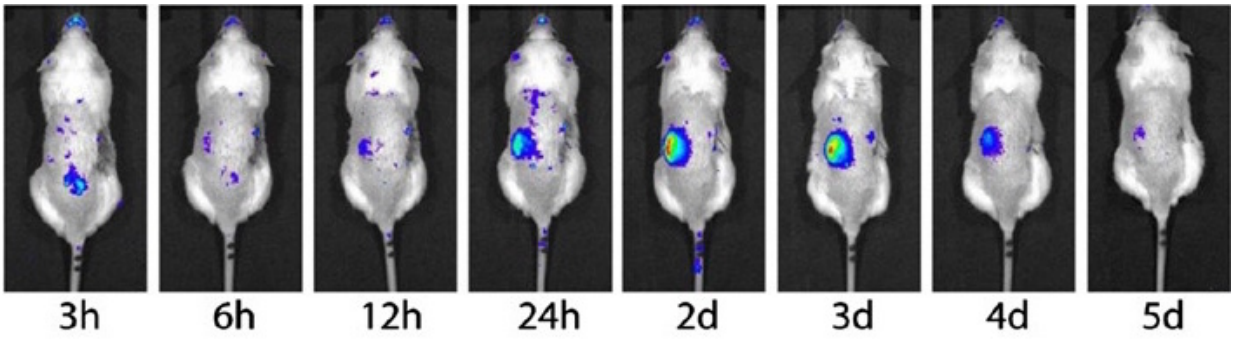

The activation of NF-kB over time is depicted in a rainbow colour scheme. 2-3 days after ischemia it reaches a maximum, then the reversible kidney failure regresses. Credit: Dr L. Markó

Every year acute renal failure affects over 13 million people and leads to 1.7 million deaths across the globe.It often develops when an insufficient supply of oxygen reaches the kidneys, a condition called ischemia. Working with their colleagues from the MDC, the Charité, FMP in Berlin and Hannover Medical School, Dr Lajos Markó and Emilia Vigolo have traced one of the causes of ischemia-related renal failure to a signaling molecule called NF-kappaB and a specific type of tissue: tubular epithelial cells. Suppressing NF-kappaB signaling in these renal cells almost entirely eliminates the fatal tissue damage and inflammatory responses that accompany the disease.

Sometimes a lack of oxygen in the kidneys leads to renal failure—as seen in some heart conditions, or in the aftermath of massive bleeding or treatment with particular drugs. The team of scientists have now used in-vivo imaging techniques to show that a cellular signaling protein called NF-kappaB becomes activated inappropriately in the kidneys after ischemia. NF-kappaB is a transcription factor: a molecule that activates genes, and in other tissues those genes are associated with functions such as programmed cell death, inflammations and immune responses. Because it has so many important tasks in the body, simply targeting the protein with drugs is usually not an option for treatment.

But the scientists' work has now brought the molecule back into play. "We developed a unique mouse model in which we deactivated the NF-kappaB molecule very specifically in renal tubular epithelial cells," says Dr Markó. Following an artificially induced case of ischemia, these mice experienced considerably less tissue damage and necrosis, and had far fewer sites of inflammation than control animals. The loss of NF-kappaB reduced the activity of its normal target genes in the kidneys. And in laboratory cultures of tubular cells, suppressing the signaling pathway allowed more cells to survive while reducing the release of inflammatory factors.

The scientists hope that tracing ischemia's effects to NF-kappaB activity in a specific type of cell might be a first step toward developing a future therapy tailor-made to target it. And the strain of mouse developed for the project can be used to study the activity of other proteins in tubular cells, providing a way to study other kidney diseases that affect them.

More information: dx.doi.org/10.1681/ASN.2015070748

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