An Essential MIF-CD74 Signaling Axis in Kidney Tubular Regeneration, with Prospects for Precision Medicine and Pharmacologic Augmentation.

Running Title: MIF-2/D-DT in AKI

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Despite increased vigilance and supportive care, acute kidney injury (AKI) remains a significant clinical problem with a very high prevalence in tertiary care hospitals, and affects about one in five patients with emergency admissions. Those patients who survive AKI often fail to recover renal function and require long-term dialysis or renal replacement. Even modest AKI increases hospital length-of-stay and the cost of clinical care, and the annual cost of AKI in the US is estimated to exceed $10 billion. Timely recognition of AKI in at-risk patients also is inadequate and there are no specific therapeutic modalities to forestall injury or promote repair once renal injurious pathways become initiated.

Most cases of AKI are caused by ischemia, which may arise as a consequence of diverse medical conditions, surgery, or iatrogenically. Ischemic AKI can be differentiated from purely pre-renal acute renal failure by significant renal tubular cell injury. If recognized, timely supportive intervention can help to ensure that still functioning tissue does not progress to overt and irreversible injury. Lack of knowledge of the molecular pathways mediating damage and repair nevertheless continues to stymie specific and effective therapeutic approaches (3).

Macrophage migration inhibitory factor (MIF) is the first cytokine activity to be described (1), and when cloned was soon found to be widely expressed in both immune and non-immune cells. Beyond its eponymic function, MIF plays an early and critical orchestrating role in the initial cellular response to tissue invasion or injury. Bacterial toxins, cellular stress, and hypoxia prompt MIF release from pre-formed intracellular pools, ensuring its rapid deployment at sites of threatened tissue injury. MIF induces rapid and sustained downstream cascades that regulate cell survival (2). Notably, the transcriptional regulation of MIF is influenced by a commonly occurring promoter polymorphism. A CATT microsatellite repeat in the MIF promoter exists in five to eight copy variants (CATT\textsuperscript{5–8}). Increasing repeat length is associated with increased MIF transcription and MIF plasma expression (9). The transcription factor ICBP90 is essential for CATT\textsuperscript{5–8} dependent MIF transcription in both immune and stromal cells (9) and MIF CATT repeat length has been associated with autoimmune diseases and the inflammatory sequelae of different infections (2).

Most cells in the kidney can synthesize MIF. In an inflammatory injury model of anti-GBM-mediated glomerulonephritis, MIF was expressed in glomerular cells and showed increased abundance in tubular epithelial cells. While an inflammatory role for MIF in renal injury has now been well defined in pre-clinical models of glomerular injury and SLE, MIF also is constitutively expressed in tubular cells, stored in intracellular preformed pools and is released at a low rate (4).

Recently, a second member of the MIF protein superfamily, called D-dopachrome tautomerase (D-DT/ MIF-2) was described. The gene for the protein is closely adjacent to the MIF gene on chromosome 22q11.23 and studies to date suggest that it exhibits a similar
spectrum of activity as MIF (5). Like MIF, MIF-2 is expressed in most tissues and by a variety of
immune cells, circulates in serum at similar concentrations as MIF, and binds with high affinity
to the cognate MIF cell surface receptor CD74 (5). MIF-2 induces similar signaling cascades, but
despite such similarities, recent evidence suggests that MIF-2 may exhibit distinct functional
differences from MIF. MIF-2 is distinct from MIF in lacking a motif necessary for activation of
the CXCR2 chemokine receptor, and it may exert a more selective action than MIF in activating
the tissue protective CD74 signaling pathway. When recombinant MIF-2 was administered in
the isolated Langendorff perfused heart, it improved cardiac function and reduced infarct size
after ischemia-reperfusion by 80% (7). Augmentation of CD74 signaling, either by recombinant
MIF-2 has been proposed as a means to salvage myocardium at risk in acute coronary ischemia.

In the current issue, Ochi et al. provide the first evidence for a specific investigation of
the role of MIF-2 in renal ischemia reperfusion injury (6). Mif−/−, Mif−2−/−, or Cd74−/− mice had
significantly worse tubular injury compared to WT control mice and the treatment with MIF-
2/D-DT significantly improved the recovery of injured epithelial cells. Moreover, Ochi et al.
showed that MIF-2/D-DT stimulated the expression of the secretory leukocyte proteinase
inhibitor (SLPI) and cyclin D1 in IR kidney tissue and proximal tubule cells with hypoxic injury.
The main physiological function of SLPI is to buffer extracellular protease-mediated effects by
inflammatory cells, but it has also shown to have a role in stimulating tumor cell proliferation
through enhanced cyclin D1 expression (10). It may be an important mediator of MIF-2/D-DT-
dependent cell proliferation after hypoxic injury (Figure 1).

MIF-2/D-DT simulation also induced activation eukaryotic translation initiation factor (eIF2α)
and activating transcription factor 4 (ATF4), two transcription factors involved in the integrated
stress response (ISR). The ISR is a signaling pathway activated by extrinsic cell stress such as
hypoxia (8). Activation of eIF2α causes reduction in global protein synthesis and induces
specific gene transcripts, such as ATF4. Since CHOP, one of the known downstream targets of
ATF4, was not activated in MIF-2/D-DT treated cells, the main effect of ATF4 in hypoxic
proximal tubule cells could be stimulating the cell regeneration response rather than apoptosis.
In addition, MIF-2/D-DT also inhibited apoptosis and induced autophagy in hypoxia treated
mouse proximal tubular cells (6).

These results suggest that MIF-2/D-DT is an important factor in tubular cell regeneration. The
results suggest that MIF-2/D-DT initiates an integrated stress response by activation of eIF2α,
followed by stimulation of ATF4 and induction of autophagy. At a later time-point (24-48 hours)
MIF enhances cell proliferation through SLPI-dependent cyclin D expression, which enhances
proliferation of surviving proximal tubule cells, especially in the S3 segment of the outer
medulla. The respective role of CD74 and CD44 in proximal tubule regeneration is still unclear.
In the study by Ochi et al, MIF-2/D-DT treatment ameliorated ischemic tubular injury in CD74-
/ mice. Their RNAseq data showed significant decrease in CD44 in MIF-/- mice, which improved significantly when the animals were treated with MIF-2/D-DT. Their data suggest an important role by both CD44 and CD74 interaction, which are important in mediating the tubular cell regenerative effect of MIF-2/D-DT.

This study has important clinical implications and may be of therapeutic utility as a regenerative agent in the clinical setting of ischemic acute kidney injury. If further validated in clinical studies, the present findings supporting the functional role of MIF/MIF-2/D-DT-dependent autophagy in kidney injury thus may open potential therapeutic approaches for autophagy regulation by MIF/MIF-2/D-DT with relevant clinical implications.

References

Figure 1- A schematic model describing the role of MIF-2 in renal ischemia reperfusion injury.