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Commentary

A Remote Role for Renalase

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Remote preconditioning (RPC) occurs when short periods of induced ischemia of an organ or limb confer protective effects to other distant organs and tissues (Heusch et al., 2015). RPC has shown promise in clinical trials as a strategy to protect against potentially injurious exposures, including the prevention of radiographic contrast-induced kidney damage, a serious clinical problem (Hu et al., 2016). Though an intriguing phenomenon, the mechanisms mediating RPC are not well-understood. In this issue of *EBioMedicine*, Wang et al. report that the 37 kDa protein renalase mediates RPC-induced protection against contrast-induced nephropathy (CIN) in a rat model, and that siRNA knockdown of renalase expression in the kidney abolishes this protection (Wang et al., 2016). The authors find that renalase expression in the kidney is upregulated by RPC, and present evidence that this is mediated by circulating TNFα released into the bloodstream during RPC.

These data add to a growing number of studies showing that renalase has a powerful cytoprotective function, including recent studies showing that this function of renalase is exploited by malignant cells as a survival strategy (Hollander et al., 2016; Guo et al., 2016; Wu et al., 2011). Renalase, named for its discovery as a protein secreted by the kidney, exhibits fascinating biology (Xu et al., 2005). It is an intracellular and extracellular flavoprotein, circulates in blood at a concentration of approximately 5 μg/ml, and functions both as a flavoenzyme and as a cytokine. Its intracellular role has remained unclear, although it has been assumed that its enzyme function is likely important there. Recently an enzymatic role in converting dihydro forms of ßNAD(P)H to metabolically available ßNAD(P)H was described, and it is postulated that intracellular renalase has a metabolic role (Beaupre et al., 2015). Whether this role relates specifically to renalase cytoprotective effects remains unknown, and indeed the relative contributions of intracellular versus extracellular renalase to its cytoprotective function are also unclear.

Extracellular renalase does, however, confer marked cytoprotection, and it has now been established in multiple studies that specific short renalase-derived peptides, devoid of enzyme activity, can confer the same cytoprotection as does full-length renalase (Guo et al., 2016; Hollander et al., 2016; Wang et al., 2014). Strong evidence links this to the ability of renalase, and specific renalase-derived peptides, to activate outside-in signal transduction pathways, including STAT3, MAPK, and AKT. Recently, the plasma membrane Ca^{2+}-ATPase PMCA4b was defined as a receptor for renalase and for the bioactive renalase-derived peptides (Wang et al., 2015). PMCA4b is a low-capacity calcium pump thought to function primarily as part of a signaling complex. Genetic knockdown of PMCA4b, or specific pharmacological inhibition, abolishes renalase and renalase peptide-induced signaling and concomitantly their cytoprotective effects, thus establishing a crucial role of PMCA4b in a receptor-mediated extracellular renalase function.

In the study by Wang et al., RPC-induced renalase expression in the kidney was attributed to NFkB signaling induced by TNFα, and was blocked by a TNFα inhibitor. This is of significant interest in that a role for renalase in modulation of inflammation and immune surveillance has been postulated, potentially as a mechanism whereby tumors escape the immune system (Hollander et al., 2016). Indeed, Wang et al. show that RPC reduced MCP-1 expression and macrophage infiltration of the kidney after contrast exposure, and that siRNA knockdown of renalase abolished this anti-inflammatory effect of RPC. The regulation of renalase expression is an area of active investigation, and it has been shown that STAT3 induces renalase transcription. As such, a role for extracellular renalase, signaling via STAT3, in upregulating intracellular renalase expression in a positive feedback manner has been postulated, and fits with data demonstrating that intracellular renalase levels vary in the same direction as extracellular renalase (Hollander et al., 2016). Whether extracellular renalase acting via receptor-mediated signaling alters other aspects of intracellular renalase biology, influencing post-translational modifications, enzyme activity, cellular location, or even secretion, is also unknown and of significant interest.

In the study by Wang et al., siRNA knockdown of renalase in the kidney abolished the RPC effect. This would at first glance appear attributable to decreased intracellular renalase, as this is where the siRNA works, but it is also possible that siRNA knockdown significantly decreased extracellular renalase levels and interrupted local paracrine or autocrine loops. Further, the kidney is a major source of circulating renalase, and it is possible siRNA knockdown of renalase expression in the kidney led to a significant decrease in circulating renalase, although

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serum renalase levels were not reported. Interestingly, this group has previously reported that administration of recombinant renalase also protects against CIN, and it has been shown in other models of renal injury that recombinant renalase and the renalase-derived peptides are both highly protective, all supporting a crucial role of extracellular renalase-mediated signal transduction in renal protection following insult (Wang et al., 2014). However, this effect is attenuated in renalase deficient mice, suggesting an important role of intracellular renalase in mediating the ultimate cytoprotective effects of extracellular renalase.

This current study adds substantively to a growing literature documenting a powerful cytoprotective function of renalase, establishes for the first time a vital role of renalase in RPC in the kidney, and establishes a previously unknown mechanism whereby induced peripheral ischemia leads to the release of TNFα which then induces RPC in the kidney by a NFκB-mediated upregulation of renalase expression. Whether this is a shared mechanism mediating RPC in other organs will require further investigation, but this study stands as a significant contribution to our further understanding of what remains a somewhat enigmatic but biologically powerful protein.

Conflicts of Interest

G Desir is a named inventor on several issued patents related to the discovery and therapeutic use of renalase. Renalase is licensed to Bessor Pharma, and G Desir holds an equity position in Bessor and its subsidiary Personal Therapeutics.

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