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Ischaemic preconditioning drives expansion of a protective cell population in the renal stroma

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Introduction: Ischaemia-reperfusion-injury-(IRI) drives delayed-graft-function-(DGF) and poor graft-survival in kidney transplantation. Ischaemic-Preconditioning-(IPC) is a brief period of ischaemia, which reduces IRI by unknown mechanisms. Delineating mechanisms by which IPC prevents IRI-associated damage could identify new therapies to prevent/limit IRI-associated damage. Hyaluronan-(HA) is a matrix polysaccharide ordinarily undetectable in the renal-cortex but accumulates in pathological states and correlates with poor renal outcomes and is synthesised by the HA synthases (HAS1/2/3). We use a model of evolving kidney injury to characterise cell populations that drive IPC versus IRI and examine the relationship to HA-expression and metabolism in the kidney.

Methods: A rat-model of bilateral kidney IRI was used: Male-Lewis rats (n=81) were assigned to IRI, Sham or IPC. In IRI, renal-pedicles were clamped for 45mins. IPC groups underwent pulsatile-IPC prior to IRI. Kidneys were retrieved at 48-hours, 7-days, 14-days and 28-days and assessed histologically and by RNA-sequencing.

Results: IRI led to marked histological damage. Key inflammatory and fibrotic mediators significantly increased at acute-(48-hours) and chronic-(28-days) timepoints. IPC led to renoprotection with attenuated inflammatory/fibrotic mediators demonstrated at both timepoints. IRI led to increased HA in the renal cortex from 48hrs through-to 28days; whilst this did not occur in sham/IPC animals. Gene-Set-Enrichment-Analysis demonstrated enrichment of HA genes in IRI compared IPC, however HAS1 expression was enhanced in IPC-groups. HAS1 and HAS2 staining were distinct: HAS2 was prominent in IRI in areas of fibrotic damage, whilst HAS1 was prominent in IPC in distinct areas not associated with damage but associated with markers of renal protection (CD44v7/8, GATA3, MCR1).

Discussion: IPC can protect from both acute and chronic IRI damage potentially limiting both DGF and chronic-allograft-nephropathy. IPC facilitates renoprotection through modulation of HA matrix. HAS1 and HAS2 isoenzymes have distinct and likely conflicting roles in this with HAS2 promoting renal damage, whilst HAS1 prevents renal damage and opens future possibilities for stromal-targeted therapies in IRI.