



Stem Cells to Modulate IR: a Regenerative Medicine-Based Approach to Organ Preservation

Rashida Lathan¹ · Ryan Ghita² · Marc J. Clancy²

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Abstract

Purpose of Review Solid organ transplantation is limited by lack of suitable donor organs. Older and comorbid organs are frequently discarded on the basis that they will not withstand the overall process—principally the degree of ischemia reperfusion injury associated with preservation and transplantation. Interventions to prevent injury and promote regeneration are badly needed. Recent stem cells of multiple types including mesenchymal stem cells (MSCs) and adipose-derived regenerative cells (ADRCs) have been demonstrated to protect against tissue injury in multiple models relevant to transplantation.

Recent Findings Recent studies have improved our understanding of the multiple mechanisms underlying these beneficial effects including immunomodulatory and anti-inflammatory actions. Evidence suggests extracellular vesicular transfer of therapeutic factors, such as Sox9, cytokines, IL-17A, CCR2, and S1P has a key role in these effects.

Summary Several novel approaches such as stress treatments, culture techniques, and exogenous chemical manipulation show significant promise in improving the efficacy of stem cell populations in preventing tissue injury. There is even the possibility to harness the body's own sources of such cells through interventions such as point-of-care fat modulation or mobilization of endogenous bone marrow-derived cells. The many unanswered questions and barriers to translating this promising technology to clinical transplantation are discussed.

Keywords Transplantation · Ischemia reperfusion · Stem cells · Preservation · Regeneration

Introduction

Solid organ transplantation has revolutionized the treatment of organ failure. Immunological barriers have progressively reduced, but the challenge of inadequate donor organ supply has grown with increasing demand [1]. This has led to escalating use of older/comorbid donor organs [2]. Aside from intrinsic increased cellular senescence [3], such organs do not tolerate the injurious processes associated with removal, storage, and transplantation as well as traditionally used organs from younger donors [4] particularly, ischemia reperfusion injury (IRI) [5].

Regenerative medicine approaches to organ transplantation have initially focused on the generation of functioning neo-tissue, highlighted widely as the main potential benefit of pluripotent stem cells. This approach spans artificial organ construction, the engineering of bioactive, organ-like tissue [6], and the use of infused stem cells [7]. Examples of such tissue successfully generated for clinical use do exist [8] for relatively simpler tubular structures but translation to therapy fields currently served by solid organ transplantation has been slow and frequently remains at the preclinical stage [9].

This has led to a switch in focus to addressing the regenerative capacity of organs already available—including those currently declined for solid organ transplantation because of predicted poor function post-transplantation. This approach focuses on protecting organs from peri-transplantation injury (principally IRI) and enhancing tissue regeneration after transplantation. Stem cells provide a promising source of protective and regenerative properties; however, there are many different forms of “stem cells” and accurate characterization and functionality can be complex. Pluripotency, multipotency, or oligopotency are clearly essential to form functioning neo-

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✉ Marc J. Clancy
Marc.clancy@ggc.scot.nhs.uk; marcclancy@hotmail.com

¹ Institute of Cardiovascular Medicine and Sciences, University of Glasgow, Glasgow, UK

² Transplant Unit, Queen Elizabeth University Hospital, Glasgow, UK

tissue but such characteristics may be less critical to the ability to influence other tissue to survive injury and regenerate. The wide variety of stem cell subtypes currently used in organ regeneration is illustrated in Table 1. A complex yet promising regenerative tool advances have been made in longevity and efficacy of infused stem cell therapy as well as an increased understanding of signaling pathways and secreted factors associated with stem cell-induced transplantation repair. These and new approaches to mobilizing endogenous stem cells in transplant recipients are emerging and are described in this review.

Stem Cell Administration Protects Against IRI

The efficacy of infused mesenchymal stem cells (MSCs) of various origins in limiting IRI across multiple preclinical models is well established. Several such models have demonstrated this effect in rodent kidney [10–12] and a multicellular suspension of adipose-derived regenerative cells (ADRCs) with a substantial MSC component has exhibited similar properties [13]. Analogous observations have been described in liver models [14] and while less relevant to transplantation, similar cell types have been widely applied to the inhibition of ischemia reperfusion in myocardial infarction [15] and stroke [16]. This work builds on the identification of a key pathway which appears conserved across IRI pathways in different organs—the accumulation of succinate under conditions of ischemia followed by oxygen-free-radical-mediated inflammatory damage on reperfusion [17•]. Harnessing this efficacy and translating it to clinical transplantation is a key challenge.

Improving the Efficacy and Survival of Stem Cells in IRI Therapy

The lifespan of mesenchymal stem cells is short when administered to models of IRI, typically <4% detectable by day 4 post-administration [18], potentially due to the harsh micro-environment created by ischemia reperfusion (IR) [19]. Improving stem cell resilience and survival could improve the efficacy and potency of the administered cells, perhaps reducing side effects related to cell dosage. Current techniques to fortify stem cells for clinical use include culture preconditioning and stem cell genetic transduction.

A recently devised method to precondition MSCs utilizes heat shock. Qiao et al. heated MSCs in a 42 °C water bath 2 h before treating rats suffering from hepatic IRI. They found that heat shock pre-treated MSCs experienced less apoptosis than non-treated MSCs and further discovered that pre-treated MSCs coped in a high oxidative stress environment of hydrogen peroxide by increasing levels of autophagy. Furthermore, the authors demonstrated that an increase in autophagy was via the p38MAPK/mTOR signaling pathway, since a p38MAPK inhibitor removed the effect. Finally, it was demonstrated that MSCs pre-treated with heat shock before administration to hepatic IR rats improved liver function, histological scores, and increased levels of proliferating cells compared to treatment with non-preconditioned MSCs, highlighting the importance of MSC resilience in the IRI microenvironment [20].

3D (versus 2D) cultured stem cells have also been found to enhance stem cell survival and efficacy in IR models of both hepatic and renal injury. 3D cultured cells exhibit an increased

Table 1 Stem cell diversity

Class of stem cell	Potency	Clinical administration
Tissue-specific stem cells (Somatic-derived)		
Blood-derived stem cells	multipotent	Cultured expansion necessary
Adipose derived regenerative cells	pluripotent	Directly transplantable
Bone marrow derived cells	pluripotent	Cultured expansion necessary
Endometrial regenerative cells	pluripotent	Directly transplantable
Induced pluripotent stem cells (Somatic-engineered)	pluripotent	Cultured expansion necessary
Mesenchymal stem cells (Stroma-derived)		
Bone marrow derived mesenchymal stem cells	multipotent	Cultured expansion necessary
Adipose derived mesenchymal stem cells	multipotent	Cultured expansion necessary
Endothelial stem cells	multipotent	Cultured expansion necessary
Dental pulp stem cells	multipotent	Cultured expansion necessary
Embryonic stem cells (Embryo-derived)		
Morula derived stem cells	totipotent	Cultured expansion necessary
Blastocyst derived stem cells	pluripotent	Cultured expansion necessary
Umbilical derived stem cells	pluripotent	Cultured expansion necessary
Extraembryonic stem cells	multipotent	Cultured expansion necessary

anti-inflammatory phenotype and exhibit a higher expression of angiogenesis genes. This anti-inflammatory effect may be explained by upregulated levels of ZC3H12A RNase, which destabilizes mRNAs of pro-inflammatory cytokines and chemokines like IL-6, CXCL1, CXCL2, and CXCL3 [21]. In addition, MSCs from a 3D culture were smaller in size which may allow them better penetration through the microvasculature of the lungs when administered intravenously, and in effect lower doses to be administered. In addition, multiple publications have documented improved angiogenic and anti-apoptotic effects of 3D versus 2D cultured cells and have demonstrated enhanced survival supporting the claim that they are less susceptible to the harsh IR environment [21, 22].

Since MSC-induced expansion of regulatory immune cells in IRI is believed to be an important component of their pro-regenerative effect, group Bai et al. pre-treated cultured MSCs in a regulatory cell attractant, cytokine IL-17A, before injection in a mouse model of renal IRI, demonstrating significantly reduced renal damage compared to non-treated MSC controls [23••]. The increase in splenic and renal T-regs demonstrated, occurred through a cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2)-dependent pathway, as blockage of COX-2 reversed the protective effect and reduced levels of T-regs. The involvement of COX-2 and of PGE2, (a hormone upregulated by COX-2) in T-reg production is likely due to the PGE2 effect of inducing differentiation of T cells to regulatory T cells [24]. A particularly interesting observation about IL-17A pre-treatment, not evident for other cytokine MSC pre-treatments such as IFN γ [25•] is that IL-17A enhanced downstream immunosuppressive effectors without inducing upregulation of histocompatibility molecules (MHC I and MHC II) and maintained normal MSC morphology—both of which could potentiate immunogenicity and harmful MSC properties.

Genetic modification of pluripotent stem cells in humans has been possible and progressively refined since the 1990s [26]. More recently, this approach has been applied to improve stem cells' ability to ameliorate IRI. Administration of amniotic fluid stem cells expressing upregulated vascular endothelial growth factor (VEGF), via a lentiviral vector expressing VEGF, reduced tubular cell necrosis and improved renal function compared to treatment with non-transduced stem cells in a rat IRI model. Additionally, transduced stem cells had a mitogenic effect on tubular cells, increased the levels of T-regs and decreased pro-inflammatory M1 macrophage infiltration [27]. Similarly, bone marrow MSCs transduced to increase anti-oxidant, heme-oxygenase-1 expression, were more resilient to the IR environment surviving longer, decreasing the number of tubular epithelial cells in the G0/G1 (resting/interphase) stage, and significantly increasing proliferating cells [28]. However, although gene modulation appears to be an attractive tool, safety issues remain a fundamental issue.

Advances in Understanding Organ Stem Cell Therapeutic Mechanisms

While efficacy against IRI has been known for more than 10 years, the mechanism of stem cell action remains poorly understood [29, 30]. A consistent theme in recent studies suggests that stem cells exert a paracrine effect transferring cytokines and extracellular vesicles (EVs) to neighboring cells, and in the context of IRI, initiate repair through the limitation of fibrotic progenitors, inhibition of cell death, and the reduction of inflammation. Zhu and colleagues show that injected EVs, exosomes, extracted from adipose-derived stem cells (ADRCs) in a renal IRI mouse model improved renal outcome by tubular epithelial cell activation of transcription factor, SRY (sex determining region Y)-box 9 (Sox9) [31••]. Sox9 as a reparative factor is consistent with evidence that shows Sox9 promotion of tubular epithelial cell proliferation during embryonic development; and supports Zhu et al.'s additional studies which indicated an abrogation of tubular epithelial cell proliferation after administration of Sox9 inhibitors in the IRI model. ADRC exosomal activation of Sox9 may also reduce progression to chronic kidney disease through simultaneous upregulation of Sox9 and downregulation of transforming growth factor (TGF)- β 1 potentially avoiding upregulation of genes involved in building extracellular matrix and developing fibrosis [32]. Sox9 may be a key regenerative mechanism in other organs as Sox9-dependant processes are also present during liver repair [33]. However, whether the Sox9 gene can be administered as a therapeutic remains unclear, as a high Sox9 expression is correlated with glomerulosclerosis and liver fibrosis [34]. Mesenchymal stem cells (MSCs) were also associated with elevated levels of transcription factors, AP-1, STAT3, and NF- κ B. These factors may serve a reparative role by priming resident cells to enter the cell cycle, promoting proliferation and ultimately regeneration of injured tissue [35] (Fig. 1).

Stem cell extracellular vesicle transfer of specificity protein 1 (SP1) and its downstream regulators of necroptosis have been shown to be another paracrine mechanism in IRI inhibition. Necroptosis, like apoptosis, is a form of regulated cell death; however, unlike apoptosis, necroptosis is initiated by inflammation-related cellular damage that externally stimulates TNF receptors in the absence of active caspases [36, 37]. SP1 is a transcription factor that upregulates sphingosine kinase-1 (SK1) which enzymatically catalyzes the formation of sphingosine-1-phosphate (S1P). S1P is a bioactive sphingolipid metabolite that promotes cell growth and survival by acting on several G protein-coupled S1P receptors which upregulate anabolic and survival pathways [38, 39]. Delivering SP1-containing extracellular vesicles derived from human-induced pluripotent stem cell-derived MSCs (hiPSC-MSCs) to a rat IR model improved renal function, histological features, and reduced kidney necroptosis as established by annexin V/PI positivity tests [40••]. Co-administration of

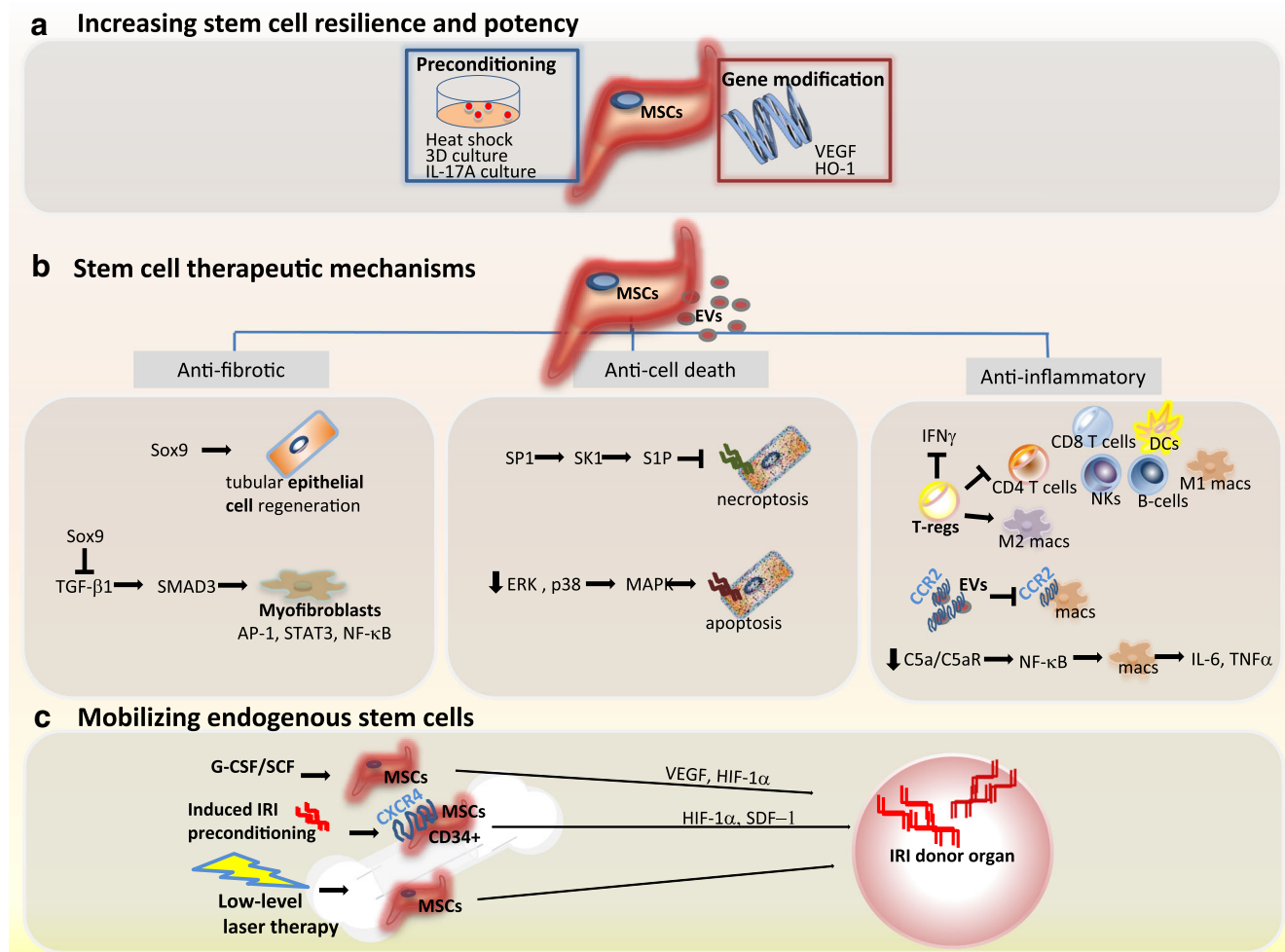


Fig 1 New concepts in stem cell therapy of organ graft IRI repair. Summary of recent advances in stem cell IRI organ therapy includes a progress in increasing cell resilience through culture techniques which incorporates mechanical stimulation of heat shock and 3D culturing as well as through stimulation with cytokine IL-17A. In addition, benefits are being made to increase stem cell therapeutic potency in an IR environment by gene transduction with VEGF and heme-oxygenase-1 (HO-1). **b** Recent advances in therapeutic stem cell mechanisms have spanned signaling pathways that reduce fibrosis, necroptosis/apoptosis, and inflammation. Notably, developmental gene, Sox9, specificity

protein 1 (SP1), part of the necroptosis pathway, and regulatory T-cells (T-regs) play significant roles in stem cell IR amelioration. **c** An alternative to exogenous administration of stem cells, which has potential side-effects, methods have progressed to mobilize endogenous mesenchymal stem cells (MSCs) from transplant recipient's own regenerative tissue (bone marrow-derived). Mobilization methods include mechanical stimulation such as low-level laser therapy as well as administration of stem cell proliferative factors, growth colony-stimulating factor (G-CSF)

SP1 or SK1 inhibitors increased necroptosis and abolished the renoprotective effects in the animal model. Analogously, SK and S1P-dependant inhibition of necroptosis is also a demonstrated MSC mechanism in liver IRI treatment [41].

In addition to inhibiting necroptosis, stem cells may also discourage cell death by inhibiting apoptosis. Stem cell promotion of mitogen-activated protein kinases (MAPK), which potentiate downstream signaling leading to apoptosis has been proposed as a potential stem cell induced pathway, especially given that bone marrow-derived stem cells have been shown to reduce the phosphorylation of ERK and p38, both vital signaling proteins in MAPK transduction [42]. However, further studies confirming stem cell downstream effects in inhibiting cell death, either through apoptosis or necroptosis are required.

Reducing regulated cell death may improve residual organ function but being able to modulate the immune systems' response to IRI may provide greater benefits on both retaining residual function and on long-term organ survival by disrupting positive feedback of sensitizing events. Stem cell immunomodulation has been extensively researched, in particular, stem cell-induced expansion of T-regs is proposed as a key therapeutic mechanism [43]. T-regs are known to suppress inflammatory functions of cells such as CD8+ T cells, macrophages, dendritic cells, natural killer cells, and B cells. In the context of renal IRI, it is reported that T-regs downregulate IFN γ production by local T cells, reducing the overall kidney inflammatory insult [44]. In a recently studied IRI mouse model, endometrial regenerative cell treatment resulted in a

significant increase in splenic T-regs which is proposed to have improved the renal IRI outcome by potentiating a decrease in CD4+ T cells, CD8+ T cells, and inflammatory-associated M1 macrophages levels while increasing levels of regulatory M2-type macrophages [45]. Other potential mechanisms through which T-regs support organ preservation in IRI include metabolic interference, cytolysis, and targeting of antigen-presenting cells [46, 47]. Multiple clinical studies modulating T-regs in the context of organ transplantation are on-going and while not the principal end-point, evidence of an improved preservation effect may emerge [46].

Another recent discovery implicating beneficial IRI immunomodulatory effects of stem cells was made by Shen et al. This group uncovered that mesenchymal stem cells and their exosomes contain particularly high levels of chemokine receptor proteins—CCR1 and CCR2 [48•]. These receptors actively bind and reduce the amounts of free CCL2. They went on to demonstrate that the decrease in available CCL2 resulted in reduced migration and activation of macrophages expressing the CCL2 cognate receptor, CCR2. Administration of MSC-derived exosomes rich in CCR2 to a mouse model of IRI conferred protection, and was reversed by a knockdown of CCR2 on MSC-derived exosomes. This study thus provides a potentially novel target for therapeutic studies in IRI and suggests that stem cell-derived exosomes not only mediate cellular transfer of transcription factors and microRNAs but also of protein receptors.

Another recent study links stem cell IRI modulation of the complement pathway. C5a is a major regulator in inflammation and can potentiate NF- κ B activation. NF- κ B regulates the transcription of many inflammatory genes and can serve as an upstream activator of macrophages. Bone marrow-derived MSCs administered in a mouse model of renal IRI significantly suppressed C5a in serum and C5aR in kidney tissue. The suppression of the C5a/C5aR-NF- κ B pathway resulted in reduced macrophage activation and reduced secretion of macrophage pro-inflammatory cytokines, TNF- α and IL-6, with significant improvement in renal function [49].

Mechanistic data has paved the way for clinical trials in stem cell therapy in organ preservation and indicates important roles for reducing fibrosis, cell death, and inflammation. However, new discoveries of stem cell-derived regenerative factors and newly discovered stem cell targets of modulation still leaves us well short of understanding the full scope of stem cell's potential beneficial effects including possible synergistic effects between multiple cell types.

Mobilizing Endogenous Stem Cells in Transplant Recipients

Exogenous administration of cells carries the risk of infection, immune-sensitivity, teratogenicity, microvascular thrombosis as well as the possible logistical and cost issues associated

with administration. To address some of these concerns, several groups have investigated methods to increase the production and mobilization of stem cells from one's own resident stem cell populations. Rats treated with stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) in renal models of IRI were found to have increased mobilization of endogenous stem cells, which homed to the injured kidney and ameliorated IR through mechanisms associated with up-regulation of angiogenic factor, VEGF and anti-oxidant factor, hypoxia-inducible factor (HIF)-1 α . Treated rats displayed reduced kidney apoptosis and increased tubular repair [50]. However, as an IRI treatment, there is concern with systemic administration of growth factors related to high bioactive effects which can lead to deleterious side-effects including tumorigenesis [51]. Additionally, evidence indicates that resident stem cells become depleted or dysfunctional with increasing age, limiting this approach in older patients [52]. There may however be potential for this approach if stem cell mobilization therapies can be rendered organ and/or signaling pathway specific.

In a novel attempt to reduce injury from IR by recruitment of endogenous stem cells, Tan et al. investigated postconditioning kidneys with supplementary mechanical injury insult in their rat model [53]. The postconditioning model consisted of 3 cycles of 30 s of ischemia followed by 30 s of reperfusion in a kidney which previously sustained 45 min of ischemia followed by 7 min of reperfusion. Postconditioning markedly reduced features of renal injury including kidney necrosis, neutrophil infiltration, and cellular vacuolization, and significantly reduced creatinine levels compared to non-preconditioned rats [53]. Importantly, the Tan et al. group illustrated that this technique mobilized endogenous stem cells as blood from preconditioned rats had increased levels of CXCR4+ and CD34+ (haemopoietic) bone-derived stem cells. They concluded that preconditioning regulated oxidative stress and increased HIF-1 α levels which then increased stromal cell-derived factor expression, a stem cell attractant, resulting in stem cell migration and homing to ischemic tissues [54, 55]. MacAllister et al. performed a similar preconditioning technique in a trial of 406 live donor kidney transplants. Though there was only mild improvement in glomerular filtration rate when compared to control, the trend of graft functional improvement appeared promising and may be greater in deceased donor transplantation where IRI is more significant [56].

In an innovative attempt to mobilize resident stem cells, Wang et al. used low-level laser therapy (LLT) treatment of bone marrow in rats before renal IRI. By exposing both tibiae to two episodes of 100 s each of LLT they significantly increased bone marrow-derived stem cell infiltrates in the glomerulus and renal tubules but not in the peripheral blood. Interestingly, rats undergoing LLT without IRI had elevated levels of bone marrow-derived stem cells in the peripheral

blood, indicating that injury status affected migration. Notably, LLT-treated rats had significantly improved renal function and kidney histology indicating the potential value of LLT mobilized stem cells as an IRI therapy. They hypothesized that LLT induces proliferation of bone marrow-derived mesenchymal stem cells, which home to injured kidney tissue and elicit repair [57•]. Promising as this seems, further studies are required to understand if sufficient numbers of ameliorative endogenous stem cells can be mobilized to have an effect on larger human organs that have sustained clinically significant tissue injury. There is also a potential limit in elderly or physiologically unfit patients where the capacity of endogenous stem cells to replicate may be significantly impaired.

Conclusion

Stem cells from diverse tissue sources have intrinsic therapeutic properties that can be harnessed in organ repair and preservation. Though they impart their therapeutic properties when administered to the harsh environment of IR-inflicted organs, they can be fortified and administered at minimized dosages through preconditioning and genetic modification to extend the persistence and potency of their beneficial effects.

Our understanding of stem cell therapeutic mechanisms remains limited; however, there is a general consensus that they reduce inflammation and encourage repair and growth [58, 59]. Research presented in this review indicates the importance of extracellular vesicular transfer, the importance of therapeutic factors that include signaling transducers, cytokines, chemokine receptors, microRNAs, and RNAses; and clinical studies confirm that stem cell-treated IR organs undergo a considerable reduction of injury as determined by histological parameters and by significant improvement in organ measurements of function.

We believe that for the purpose of organ protection and reconditioning for transplantation, the therapeutic potential of stem cell therapies is great. Two major obstacles to routine clinical use are immunological barriers and the risks of ex vivo culture/expansion. To that end, autologous, point-of-care-derived stem cell therapies, such as adipose-derived regenerative cells (ADRCs) and endometrial regenerative stem cells (women-only) are attractive. In the case of ADRCs, this may be particularly fruitful as cells derived from adipose tissue are characterized as containing > 500 times the levels of MSCs as from cells derived from bone marrow [60–62]. ADRC use, combined with researched preconditioning technologies (such as IL-17A exposure) can potentially improve persistence and efficacy without acquiring deleterious dosage side effects related to teratoma development [63]. However, pre-manipulation of stem cells can pose risks. Mori da Cunha et al. notes that beneficial effects of VEGF-transduced MSCs

were actually reversed and even caused a worsened IR outcome when MSC expressed VEGF at high levels [27].

Since severe IRI leads to fibrosis, the principal driver that decreases critical mass of organ function [64], we also believe stem cell repair mechanisms that reduce the development of healthy tissue into fibrotic tissue should be prioritized. Therefore, recent discoveries which implicate MSC mechanistic pathways that involve the expansion of T-regs seem promising as this regulatory arm of immunity targets early inflammatory events that potentially lead to fibrosis.

In addition, stem cell use as an IR-organ treatment requires comprehensive profiling to understand and minimize potential risks before clinical use. Clinical considerations also include but are not limited to the route, dosage, and timing of administration. Injecting adipose-derived stromal vascular fractions prior to ischemia in a rat model of renal IRI demonstrated more ameliorative properties and significantly reduced tubulointerstitial fibrosis than when injected post-ischemia [65]. However, the clinical nature of transplantation may provide greater freedom in choosing exactly when to administer the regenerative therapy compared to other indications. The route of administration should also not be overlooked, as many studies have shown that MSCs injected into the venous system often become trapped in the microvasculature of the lungs [18, 66]. Compared to systemic arterial or venous injection of stem cell therapies, studies have found that direct MSC injection (in this case into the renal artery in a renal model of IRI) has the most profound effect on the injured organ and also required much lower doses [67]. Direct intraparenchymal or intra/subcapsular routes have also been utilized in stem cell renal IR research as direct renal artery injection can be associated with renal microvasculature occlusion at higher therapeutic doses. The nature of solid organ transplantation, however, may actually allow beneficial flexibility in the choice of administration route since the organs vessels are at least transiently accessible. The topical route of application to the liver in a rat hepatic IRI model was also tested by Lam et al. with promising effects [68]. Lastly, the clinical setting of administration may also be important. MSCs may be altered by commonly used anesthetic agents as highlighted in a recent rat model of hepatic IRI. Intravenously administered dexmedetomidine and midazolam enhanced the protective effects of MSC during liver IRI more effectively than propofol by binding to MSC receptors and regulating a downstream paracrine effect [69•]. Collectively, this is a reminder that other manipulations during organ repair could also have an opposing effect on MSC regenerative properties, thus reducing their potential benefits.

In the future, the increasing accessibility of ex vivo perfusion technologies [70, 71] may provide an ideal setting to address the many remaining questions around stem cell therapy's role in preventing peri-transplant injury and provide the bridge to translating its undoubted potential into real patient benefit.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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