Biomedicine & Pharmacotherapy 143 (2021) 112237

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Emerging role of carbon monoxide in intestinal transplantation

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ARTICLE INFO

Keywords:
Carbon monoxide (CO)
Carbon monoxide-releasing molecules (CO-RMs)
Intestinal transplantation
Cold ischemia-reperfusion injury (IRI)
Static cold storage (SCS)

ABSTRACT

Intestinal transplantation has become an established therapeutic option that provides improved quality of life to patients with end-stage intestinal failure when total parenteral nutrition fails. Whereas this challenging life-saving intervention has shown exceptional growth over the past decade, illustrating the evolution of this complex and technical procedure from its preclinical origin in the mid-20th century to become a routine clinical practice today with several recent innovations, its success is hampered by multiple hurdles including technical challenges such as surgical manipulation during intestinal graft procurement, graft preservation and reperfusion damage, resulting in poor graft quality, graft rejection, post-operative infectious complications, and ultimately negatively impacting long-term recipient survival. Therefore, strategies to improve current intestinal transplantation protocol may have a significant impact on post-transplant outcomes. Carbon monoxide (CO), previously considered solely as a toxic gas, has recently been shown to be a physiological signaling molecule at low physiological concentrations with therapeutic potentials that could overcome some of the challenges in intestinal transplantation. This review discusses recent knowledge about CO in intestinal transplantation, the underlying molecular mechanisms of protection during intestinal graft procurement, preservation, transplantation and post-transplant periods. A section of the review also discusses clinical translation of CO and its challenges in the field of solid organ transplantation.

1. Introduction

Intestinal transplantation is solely reserved for patients with intestinal failure or those with underlying gastrointestinal disease, and depend permanently on total parenteral nutrition due to their inability to maintain normal nutritional support [1,2]. It is the latest on the list of clinical transplantation operations, requiring appropriate graft selection, procurement and preservation to ensure optimal graft function and recipient survival after transplantation. Immediately after procurement of the intestinal graft from donation after brain death (DBD) or donation after cardiac death (DCD), it is cold-stored at 4 °C in clinically standard solutions such as University of Wisconsin (UW) solution, Celsior solution, hystidine-tryptophan-ketoglutarate (HTK) solution or Euro-Collins solution to reduce its metabolic demand [3,4]. These preservation solutions contain impermeant agents and other important pharmacological supplements to sustain the low metabolic demand of the graft, prevent cold ischemic/hypoxic injury and improve histocompatibity matches prior to transplantation and prevent delayed graft function following transplantation [5,6]. Such a method of cold preservation, called static cold storage (SCS), which is the preferred method of hypothermic preservation and considered the current gold standard, is followed by reperfusion of the graft, during which warm oxygenated blood is restored in the graft.

Although advances made in intestinal transplantation have so far improved patient outcomes significantly, illustrating the evolution of this complex and technical procedure from its experimental origin in the mid-20th century to become a routine clinical practice today, SCS and reperfusion contribute to graft injury in a paradoxical phenomenon referred to as cold ischemia-reperfusion injury (IRI) [4,7]. Thus, cold IRI, which is unavoidable in intestinal transplantation, limits the success of this complex and life-saving procedure, and causes poor intestinal graft quality together with compromised barrier function [8–11] (Fig. 1). The compromised barrier function of the intestinal graft, for example, activates inflammatory and apoptotic pathways and increases bacterial translocation, which ultimately leads post-transplant infectious complications, graft rejection, delayed graft function and

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https://doi.org/10.1016/j.biopha.2021.112237
Received 31 August 2021; Received in revised form 17 September 2021; Accepted 21 September 2021
Available online 25 September 2021

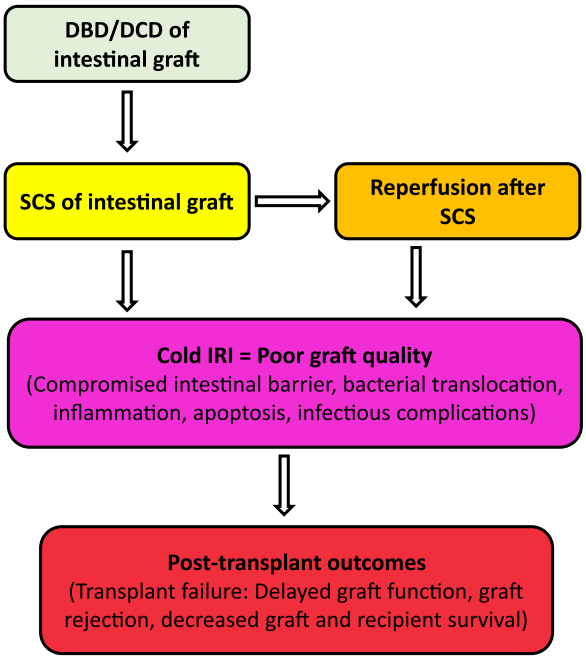

Fig. 1. Simplistic view of intestinal graft transplantation protocol in relation to post-transplant outcome. Intestinal graft procured from donation after brain death (DBD) or donation after cardiac death (DCD) is subjected to static cold storage (SCS) and subsequent reperfusion during which the graft suffers cold ischemia-reperfusion injury (IRI). Cold IRI causes poor intestinal graft quality together with compromised barrier function, which activates inflammatory and apoptotic pathways and enhances bacterial translocation, and ultimately leads post-transplant infectious complications, graft rejection, delayed graft function and decreased graft and recipient survival.

decreased graft and recipient survival (Fig. 1). Also, the intestine is known to be extremely sensitive to SCS [7,12] and aggravates cold IRI, and thereby rendering the outcome of intestinal transplantation inferior compared to transplantation of other solid organ grafts. Moreover, the preservation solutions for SCS of intestinal grafts were developed to effectively protect kidney, pancreas and other organ grafts but less sufficiently protects intestinal grafts [13–15], notwithstanding the good preclinical and clinical preservation data for these organ grafts. The lack of ideal preservation solution and strategy for intestinal graft allows only a short SCS time (6–10 h) in this these suboptimal preservation solutions, and induces various degrees of intestinal injury [16], thereby hampering the success of intestinal transplantation. Hence, improvement in intestinal transplantation protocol to include modification of graft procurement procedure, preservation and reperfusion techniques is a "holy grail" to improve the outcomes of intestinal transplantation.

Carbon monoxide (CO), a gas that was previously considered solely to be as a toxic and an environmental hazard, has recently been shown to be a physiological signaling molecule with therapeutic potentials [17–21] that could overcome the inevitable obstacle of cold IRI in intestinal transplantation. This review discusses recent knowledge about CO in intestinal transplantation, the underlying molecular mechanisms of protection during intestinal graft procurement, preservation, transplantation and post-transplant periods. A section of the review also discusses clinical translation of CO in the field of solid organ transplantation along with current challenges in this translation.

2. Endogenous and exogenous sources of carbon monoxide

CO is endogenously produced in the body by heme oxygenase (HO) enzyme during heme degradation [22,23]. There are two main isoforms of HO: HO-1 and HO-2. HO-1 is the inducible isoform that is activated under pathological conditions [24] while HO-2 is the constitutively expressed isoform [25]. Emerging evidence indicates that at low physiological concentrations, CO modulates several molecular pathways that are beneficial in intestinal transplantation – protecting intestinal grafts against cold IRI and improving post-transplant outcomes [26–28]. Indeed low physiological concentrations of CO have been shown to activate the heme-containing protein, soluble guanylate cyclase (sGC), an enzyme that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which mediates vascular effects of CO, with vasodilation being the downstream effects [29–32]. Such a downstream effect is very crucial during reperfusion phase of intestinal transplantation. There is also evidence that treatment of vascular smooth muscle cells with CO produces cGMP, leading to increased tissue perfusion and cytoprotection during hypoxia and IRI [29–32], which is also very important in intestinal graft protection during transplantation. Furthermore, CO has been found to possess potent anti-inflammatory, anti-apoptotic, anti-proliferative, anti-fibrotic, anti-thrombotic and antioxidant properties [17–21]. These properties make CO an ideal candidate molecule to prevent or limit cold IRI in intestinal transplantation.

In addition to its endogenous production, CO can also be administered exogenously in its gaseous form and also *via* compounds referred to as CO-releasing molecules (CO-RMs) to augment endogenous levels. CO-RMs are chemical compounds that form carbonyl complexes with central transition metals such as iron, manganese, ruthenium, and are designed to ensure controlled release of CO and keep carboxyhemoglobin levels stable in blood [33,34], and thereby preventing any potential danger associated with CO gas inhalation protocols. The formation of CO-RMs with these transition metals generates various types of CO-RMs such iron-containing CO-RMs (*e.g.* CORM-307, CORM-308, CORM-314, CORM-319), manganese-containing CO-RMs (*e.g.* CORM-1 and CORM-401) and ruthenium-containing CO-RMs (*e.g.* CORM-2 and CORM-3) [35–39]. There are also non-metallic CO-RMs such as CORM-A1, which release CO at a slower rate than some metallic CO-RMs [40,41]. CO-RMs such as CORM-A1 and CORM-3 exhibit anti-thrombotic effect characterized by decreased platelet activation and aggregation and fibrin generation in rats [82,83] while other CO-RMs such as CORM-2 exhibit prothrombotic effect through interaction with key coagulation and fibrinolytic processes, and thereby enhancing plasmatic coagulation and attenuating fibrinolysis in human, rabbit and dog plasma [84–88]. Burgeoning laboratory evidence shows that administration of CO-RMs attenuates IRI in various intestinal conditions [42–45], and could be applied in intestinal transplantation to improve graft quality and post-transplant outcomes.

3. Carbon monoxide in intestinal transplantation

3.1. Carbon monoxide gas in intestinal transplantation

In a rat model of orthotopic syngeneic small intestinal transplantation, 6 h of SCS of entire small intestinal grafts in 4 °C UW solution bubbled with 5% compressed CO gas resulted in marked improvement in intestinal barrier function (gut permeability) with less mucosal denudation, which correlated with significant downregulation in the expression of pro-inflammatory genes (tumor necrosis factor-alpha [TNF-α], inducible nitric oxide synthase [iNOS], interleukin-1beta [IL-1β], IL-6, cyclooxygenase-2 [COX-2] and intercellular adhesion molecule-1 [ICAM-1]), and upregulation of the anti-inflammatory gene IL-10 and simultaneously preventing coagulation through inhibition of the clot-promoting factor, plasminogen activator inhibitor-1 (PAI-1), compared to control grafts preserved in UW without CO supplementation [26] (Fig. 2). The improvement in the intestinal barrier function by CO implies that cold IRI altered important factors such as absorptive surface area, epithelial enzyme function, intraluminar milieu, and humoral factors (autocrine, paracrine, and juxtacrine effectors), and that CO preserved these factors which are necessary to facilitate absorption and ultimately prolonged transplant recipient

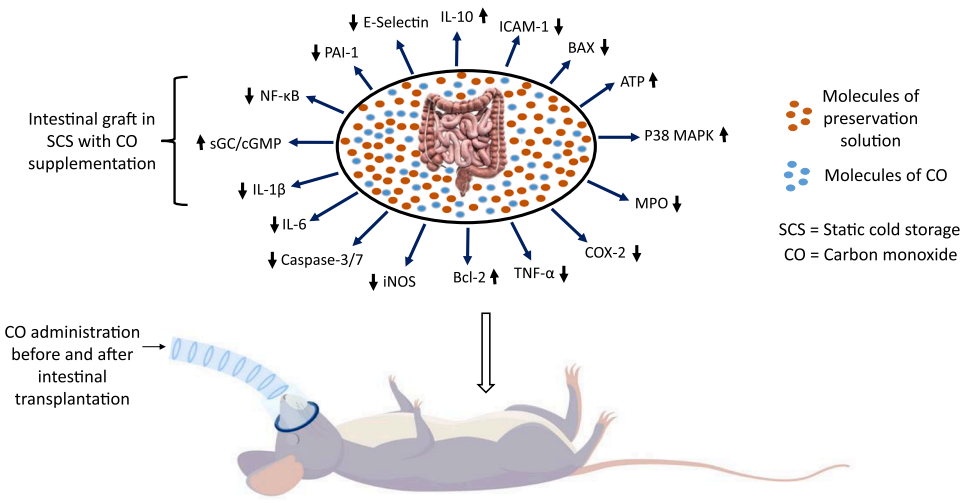

Fig. 2. Supplementation of cold preservation solution with carbon monoxide (CO) or administration to transplant recipients before and after transplantation minimizes cold intestinal ischemia-reperfusion injury (IRI) by modulating several molecular mechanisms. TNF-α: Tumor necrosis factor-alpha, iNOS: Inducible nitric oxide synthase, IL-1β: Interleukin-1beta, IL-6: Interleukin-6, IL-10: Interleukin-10, COX-2: Cyclooxygenase 2, ICAM-1: Intercellular adhesion molecule-1, PAI-1: Plasminogen activator inhibitor-1, ATP: Adenosine triphosphate, sGC/cGMP: Soluble guanylate cyclase/cyclic guanosine monophosphate, p38 MAPK: p38 mitogen-activated protein kinase, Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma-2, NF-κB: Nuclear factor-kappaB; MPO: Myeloperoxidase and Caspase-3/7: Cysteine-aspartic acid proteases-3/7.

survival. In addition, CO drastically reduced vascular resistance and improved intestinal blood flow 1 h after transplantation and ultimately prolonged survival of recipient rats in comparison with control group [26]. It is important to note that the intestinal mucosa is highly vulnerable to ischemic injury [46,47]. Therefore, the improved intestinal flow soon after transplantation strongly suggests involvement of the vasodilation property of CO, contributing to graft protection. To mimic transplant-induced cold IRI, the authors performed in vitro experiment with murine vascular endothelial cell line MS1, in which they subjected the MS1 cells to 24 h of cold storage at 4 °C in UW solution with or without 5% CO supplementation followed by reoxygenation at 37 °C. As was expected, MS1 cell viability markedly decreased by 30% with reduced adenosine triphosphate (ATP) levels after reoxygenation compared to UW + CO-preserved cells [26]. The 5% CO in the UW solution used in both *ex vivo* and *in vitro* studies was similar to low-dose CO (250 ppm) inhalation in other models of intestinal transplantation [27,28]. However, it is yet to be investigated whether a higher CO concentration will provide superior graft protection. Such a higher concentration could be obtained with the same 5% CO but with a longer period of SCS or higher calculated CO concentration in UW solution with the same or shorter SCS period.

From a mechanistic perspective, the levels of cGMP in intestinal grafts preserved in UW solution without CO supplementation decreased significantly after 1 h of reperfusion compared to CO-treated grafts. Also, preservation of intestinal grafts in cold UW solution supplemented with 50 μM of ODQ (a selective inhibitor of sGC) together with 5% CO gas completely reversed the protective effect of CO. As CO is a known activator of sGC (a heme-containing protein) in vascular smooth muscle cells with cytoprotection against hypoxia and IRI [29–32], it is likely that CO in the UW solution binds to the heme motif of sGC during SCS of the intestinal graft, generating cGMP in the intestinal vascular smooth muscle cells with vasodilation as the downstream effect. In addition, SCS of intestinal grafts in CO-supplemented solution activated p38 MAPK (mitogen-activated protein kinase; a mediator of cell survival or cell death) at the end of the 6-hour preservation and at 1 h after reperfusion [26]. The involvement of p38 MAPK in the intestinal graft protection was later confirmed in *in vivo* experiments in which intraperitoneal administration of 250 ppm of CO significantly reduced apoptotic and inflammatory mediators and increased intestinal antioxidant capacity *via* the activation of p38 MAPK in a rat model of intestinal injury induced by lipopolysaccharide (LPS; a potent inducer of inflammation) [48–50]. Interestingly, a study by Otterbein et al. [51] suggests that cGMP interacts with and activates p38 MAPK, leading to protection against vascular injury (atherosclerosis lesion) after aorta transplantation. Although this interactive mechanism between cGMP and p38 MAPK has not been investigated in transplantation of the intestinal and other solid organ grafts, it is possible that the same interaction accounts for the CO-mediated intestinal graft protection. However, such but it remains unclear whether it is involved in the effects observed in this model. These observations suggest that activation of sGC/cGMP and p38 MAPK signaling pathways and other mechanisms derived from CO contribute to preservation of intestinal vascular architecture and early intestinal graft protection. Thus, supplementation of UW solution with CO could represent a simple and innovative pharmacological intervention to prevent or minimize transplant-induced cold IRI and improve the outcomes of intestinal transplantation (Fig. 2).

Apart from CO delivery into preservation solution, there are studies also showing that exposure of transplant recipients to CO gas before and after transplantation is another innovative technique that provides intestinal graft protection with improved transplantation outcomes. In a rat model of syngeneic orthotopic small intestinal transplantation, 6 h of SCS of intestinal grafts in 4 °C UW solution followed by transplantation into recipient rats exposed to 250 ppm of CO gas 1 h before and 24 h after transplantation prevented intestinal hemorrhage, preserved intestinal ultrastructure and cellular integrity, attenuated intestinal tissue injury (loss of intestinal epithelial cells) and improved instestinal blood flow with intact HO-1 activity and prolonged recipient survival compared to air-treated control grafts [27]. The authors further reported significant downregulation of mRNA levels for inflammatory mediators such as IL-6, COX-2, iNOS, ICAM-1 and reduced inflammatory infiltrates with intact intestinal epithelial cells in grafts transplanted into CO-exposed recipients compared to those of air-exposed recipients [27] (Fig. 2). This finding supports the observation from the study in which intestinal grafts were cold-stored in UW-CO preservation [26]. It is also in agreement with another study by the same research team in which intestinal grafts transplanted into CO-exposed recipient rats inhibited inflammation and apoptosis (Bax) and upregulated the expression of anti-apoptotic gene Bcl-2 *via* activation of sGC/cGMP system [28] (Fig. 2). Taken together, supplementation of conventional preservation solution with CO gas during SCS of intestinal grafts and administration to the graft recipient before and after transplantation is a unique pharmacological approach to prevent or mitigate cold intestinal IRI, improve graft quality and minimize transplant-associated complications.

3.2. *Carbon monoxide-releasing molecules in intestinal IRI for transplantation*

While administration of CO gas has been shown to be protective in intestinal grafts against cold IRI and improve graft quality and post-transplant outcome, there is currently no data on the use of CO-RMs

against cold IRI in intestinal transplantation. However, a number of studies have reported protective effect of CO-RMs against warm intestinal IRI, in which the pathophysiological pathway is the same as cold IRI and applicable in intestinal transplantation. In a mouse model of intestinal IRI to assess the effects and potential mechanisms of CORM-2 in modulating inflammation in small intestine, Katada et al. [42] reported that intravenous administration of 8 mg/kg of CORM-2 immediately before 45 min of superior mesenteric artery occlusion (ischemia) and subsequent reperfusion significantly decreased intestinal tissue levels of TNF-α, E-selectin and ICAM-1 proteins as well as reduced activation of the inflammation-related transcription factor, nuclear factor-kappaB (NF-κB) and myeloperoxidase (MPO) activity compared to sham control group (Fig. 2). Similarly, treatment of cultured intestinal epithelial cells with 100 μM of CORM-2 before stimulation with 50 μg/mL of LPS markedly decreased LPS-induced secretion of the inflammatory cytokines TNF-α and IL-1β, and attenuated LPS-induced reduction of tight junction proteins and increased myosin light chain phosphorylation compared to control group [43]. Additionally, CORM-2 prevented reduction in electron-dense material and disruption of tight junction and desmosomes between apical lateral margins of adjoining cells, an effect which was reversed by inactive variant of CORM-2 (iCORM-2) [43]. The result of this study was confirmed by Zhang et al. [44], in which intravenous administration of 8 mg/kg CORM-2 but not iCORM-2 produced the same salutary effects on LPS-induced intestinal epithelial permeability and provided additional evidence that CORM-2 increases survival in a rat model of cecal ligation and puncture. All these observations show that CORM-2 protects and preserves the barrier function of intestinal epithelial cells from inflammation, which supports the report by Nakao et al. [26] showing that preservation of intestinal grafts in cold CO-supplemented UW solution improves intestinal barrier function and prolongs transplant recipient survival through its anti-inflammatory action.

Whereas these studies were done using a metallic CO-RM, Babu et al. [45] also reported protection of intestinal epithelial cells by the non-metallic CO-RM, CORM-A1. In their *in vitro* mouse model of post-operative ileus (cessation of intestinal peristalsis due to painful obstruction of part of the intestine), they observed that pretreatment of MODE-K cells (intestinal epithelial cell line) with CORM-A1 followed by exposure to different concentrations of TNF-α/cycloheximide (CHX) prevented TNF-α/CHX-induced oxidative stress and apoptosis by inhibiting increased production of intracellular reactive oxygen species (a destructive mediator in tissue injury) and activities of caspases-3/7 (executioner caspases in apoptosis) respectively [45]. In conclusion, the protective effects of CORM-2 and CORM-A1 in these *in vitro* and *in vivo* studies suggest that CO released from these CO-RMs exerts the same effects observed in the intestinal transplant models discussed above, and therefore their beneficial effects (especially protection of the epithelial barrier) and those of other CO-RMs should be studied in the context of intestinal transplantation.

4. Roadblock to the promises to clinical translation and the way forward

The unavoidable challenge of cold IRI of intestinal grafts procured from DBD or DCD together with current transplantation protocol including the lack of adequate preservation solution for SCS negatively impacts intestinal graft quality, post-transplant patient care and transplantation outcomes. This has led to the search for novel techniques to improve current intestinal transplantation protocol. It is now emerging that supplementation of existing preservation solution with CO gas or exposure of transplant recipients to CO gas before and after transplantation is an innovative technique that provides intestinal graft protection and other solid organ grafts with improved transplantation outcomes in experimental setting [80,81]. While the few findings from this novel strategy are very promising at the preclinical stage and has also shown good results in other solid organ grafts so far [52–59], its clinical translation is decades away, with several challenges that need to be addressed. First of all, this new technique of intestinal graft protection, which has been reported by only one research team so far, needs to be studied extensively by other research groups to confirm their results and also determine important factors such as timing of CO delivery into the preservation solution and administration to the graft recipient before and after transplantation. Also, as CO administration to intestinal graft recipients proved beneficial, future studies should investigate whether CO administration to organ donors prior to intestinal graft procurement will provide additional protection to the graft against cold IRI. Such extensive studies by other research groups will also provide a broader insight into the molecular evidence of graft protection such as reperfusion injury salvage kinase pathway, hypoxia-inducible factor/vascular endothelial growth factor system, JNK-ERK1/2-MEK1/2 pathway, heat shock protein family, autophagy pathway, TGF-β/Smad pathway, as well as the impact of CO in the mitochondrial electron transport chain and other heme proteins such as cytochrome P450 and myoglobin in transplantation of the intestine and other transplantable solid organs.

In addition to these challenges in translating this novel pharmacological technique from bench to bedside, other hurdles such as obtaining proper therapeutic doses and duration of CO exposure raise logistical and staff safety concerns in routine use, as it is difficult to ensure an optimal gaseous CO concentration. Moreover, two recent clinical studies showed no beneficial effect of CO in phases I and II clinical trials of low-dose inhaled CO in patients with sepsis-induced acute respiratory distress syndrome and idiopathic pulmonary fibrosis respectively compared to placebo-treated subjects [60,61]. In fact, the latter study reported increased carboxyhemoglobin level, which raises a toxicity concern, as it compromises oxygen-carrying capacity of blood *via* inhibition of cytochrome *c* oxidase (complex IV) of the mitochondrial electron transport chain and cytochrome P450-dependent monooxygenases as well as myoglobin, which ultimately inhibits oxidative phosphorylation, alters energy metabolism with increased production of reactive oxygen species [62–64]. This mechanism has been established to account for the known toxicity of CO gas. Hence, therapeutic gas delivery systems such as membrane-controlled extracorporeal CO-releasing system, therapeutic gas-releasing system intended for quality-improved preservation and perfusion solutions and organ transplant, and oral CO-saturated liquids which will allow self-administration to organ donors prior to organ procurement and to organ recipients before and after transplantation [65–67] without exposing the transplant donor, recipient and transplant team to toxic components of CO, should be developed.

The challenges associated with the use of CO gas protocol was partially overcome following the development of CO-RMs. Although there is currently no studies on the use of CO-RMs in intestinal transplantation, there are studies showing salutary effects of various CO-RMs in experimental transplantation of kidney, heart, lung, liver and pancreatic islets [68–72]. These studies should be expanded to cover the use of CO-RMs in intestinal transplantation. This will help provide a comprehensive understanding of the biology and pharmacokinetics of CO in intestinal transplantation, and will further harness its therapeutic potential. While CO-RMs seem to produce beneficial effects in organ transplantation, it is emerging that metallic CO-RMs produce cytotoxicity due to reactive nature of their central transition metal carbonyl complexes [39]. This could partly explain why CO-RMs were not pushed forward in clinical development of improved transplants since their introduction about two decades ago. Also, newer evidence from experimental studies shows that metallic CO-RMs produce various CO-independent effects, and therefore all the biological effects of CO-RMs including cyto- and organ protection in transplantation cannot be attributed to CO alone [73–76]. In the light of the above findings, developments of transition metal-free CO-RMs and organic CO prodrugs are underway [41,77,78], which could address the potential cytotoxicity concern associated with metallic CO-RMs, and could advance transition from preclinical to clinical development of improved human transplant

in the future. In addition, a technique should be developed in the future to track CO release from CO-RMs, which will help differentiate the biological effects of CO released from CO-RMs and CO-RMs themselves. Despite all these roadblocks to clinical translation, a recent study showed that preservation of human pancreatic islets in CO-supplemented medium and autotransplanted through the portal vein into the liver of chronic pancreatitis patients significantly improved islet quality, and increased insulin independence compared to control human islets preserved in normal medium without CO supplementation [79]. Interestingly, the authors further reported that preservation of the pancreatic islets in CO-supplemented medium did not produce any CO-related adverse events. Compared to existing organ transplantation protocols, this fascinating clinical outcome together with the positive experimental findings suggests that circumvention of the challenges and hurdles in the clinical translation of CO would produce a safer, more effective and inexpensive transplantation protocol to improve the quality and function of intestinal grafts and other transplantable organs, limit post-transplant complications and prolong transplant recipient survival.

Funding

There was no funding received for this article.

CrediT authorship contribution statement

GJD conceived and designed the research. **GJD** drafted the manuscript. **GJD** prepared the figures. **GJD** edited the manuscript. **GJD** approved the final version of the manuscript.

Conflict of interest

None.

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