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REVIEW

Role of heme oxygenase-1 in transplantation

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Summary

Heme oxygenase-1 (HO-1) is the rate-limiting enzyme in heme catabolism that converts heme to Fe++, carbon monoxide and biliverdin. HO-1 acts anti-inflammatory and modulates apoptosis in many pathological conditions. In transplantation, HO-1 is overexpressed in organs during brain death, when undergoing ischemic damage and rejection. However, intentionally induced, it ameliorates pathological processes like ischemia reperfusion injury, allograft, xenograft or islet rejection, facilitates donor specific tolerance and alleviates chronic allograft changes. We herein consistently summarize the huge amount of data on HO-1 and transplantation that have been generated in multiple laboratories during the last 15 years and suggest possible clinical implications and applications for the near future.

Introduction

The problem areas that lead to failure of transplanted organs are frequently divided into the early complications of ischemia reperfusion injury (IRI), acute and chronic rejection. The vast majority of therapeutic effort has been aimed at preventing the T-cell response that leads to acute rejection; a panoply of immunosuppressive agents has been developed to achieve this goal in a more specific and less toxic manner. Neither the problems associated with IRI nor those with chronic rejection have been successfully overcome.

While so far tested virtually only in nonhuman subjects, heme oxygenase-1 (HO-1), appears to be remarkable in the breath of the pathological processes that it can overcome in transplantation. HO-1 not only is a marker of stress/injury but has, similarly as other chaperones (e.g. HSP 60, HSP 70) [1,2] several beneficial modalities associated with it. HO-1 itself is the sole major mechanism by which excess heme is degraded. Eliminating the excess heme suppresses generation of oxidative radicals and thereby limits the damage associated with those radicals. Degradation of heme by HO-1 yields multiple products: carbon monoxide (CO), Fe++ that leads to the very rapid up-regulation of ferritin, and biliverdin, which is rapidly converted to bilirubin by biliverdin reductase [3]. Each of these products of heme degradation has their own actions. In aggregate, HO-1 and the products of degradation are strongly antioxidant, inhibit cell death, apoptosis, and aberrant proliferation [4–7]. Several groups have addressed the question whether the end products of heme catabolism would, at least in part, account for the effects of HO-1 induction; they do, with respect to IRI, acute and chronic rejection [8–23]. We hypothesize that it is by these multiple differing therapeutic actions that HO-1 in toto can productively interfere with the many pathological processes that are involved in transplantation.

We emphasize in this brief review the enormous activity that is ongoing in multiple laboratories studying the expression and/or induction of HO-1 in different stages of transplantation, including brain death, IRI, acute rejection and chronic allograft changes (Fig. 1). Furthermore, human data on gene polymorphisms and the role of HO-1 in islet transplantation, xenotransplantation and graft versus host disease (GVHD) (that involve different pathomechanisms) will be reviewed. Finally, strategies

how to apply the enormous knowledge on HO-1 in transplantation (that was generated experimentally) to humans are discussed.

Brain death

The majority of organs transplanted are derived from brain dead organ donors. Brain death is associated with upregulation of cytokines, adhesion molecules, endothelial antigens, and leukocyte infiltration [24] and its consequences are critical for the quality of organs [25]. Experimentally, an early increase in HO-1 expression is observed in rat kidneys during brain death [26] that is further promoted in marginal donors [27]. HO-1 mRNA expression (assessed before organ harvest) is threefold higher in kidneys from brain dead human donors when compared with living donor kidneys, which usually do have favorable outcome with respect to early and late graft function [27,28]. Under the circumstances of brain death, HO-1 upregulation seems to be a part of the ''stress response'' (oxyradicals, cytokine storm and unspecific immune response). However, when HO-1 intentionally is induced in brain dead donors with cobalt protoporphyrin (CoPP), survival of rat kidney allografts is significantly increased whereas zinc protoporphyrin (ZnPP), an inhibitor of HO-1 activity, decreases survival rates [29]. In humans, an approach to reduce inflammation in the brain dead donor via HO-1 induction may be promising but has not been tested yet.

Several experimental approaches have been made to induce HO-1 in the (nonbrain dead) donor to improve outcome with respect to early and long-term graft function. Induction of HO-1 in the donor is beneficial, ameliorating IRI [30–46], reducing chronic allograft changes [47] and inducing tolerance to islet allografts [19].

Ischemia and reperfusion

Hypoxia and the lack of nutrients resulting form ischemia is a limiting factor for organ function after transplantation. Damage is paradoxically aggravated upon reperfusion. Deteriorated early graft function is the consequence, caused by oxidative stress, apoptosis and a nonspecific immune response that (in an allogenic setting) subsequently activates the specific immune system [48]. Prevention and treatment of IRI in solid organ transplantation is among the most important issues to address to improve short- and long-term outcomes. HO-1 does have a dual function in this context (i) by preventing oxidative stress because of its antioxidant and antiapoptotic properties and (ii) via suppression of the immune response through anti-inflammatory mechanisms.

Cold ischemia

One would assume, that during cold ischemia time (CIT), defined as the time period from cold perfusion at the harvest until reperfusion in the recipient, no dramatic changes on a RNA/protein level could be expected, as organs are constantly kept at 4 °C to slow down metabolism. However, some interesting facts with respect to HO-1 expression during CIT have been reported.

In human cadaveric kidney grafts, high HO-1 protein expression at the end of CIT is associated with inferior outcome [49]. Similar observations were made in human livers derived from deceased donors: high levels of HO-1 RNA at the end of CIT were associated with inferior outcome. [50]. Whether this increase in HO-1 expression has occurred already in the (brain dead) donor or during CIT has not been studied. HO-1 expression at the end of CIT definitely is an indicator of the severity of organ damage.

Currently, after harvest during CIT organs are either preserved at 4 °C with preservations solutions or, more recently, subjected to continuous hypothermic perfusion [51]. This interval may be used to manipulate the graft pharmacologically or via gene transfer. Experimentally, *ex vivo* HO-1 gene transfer during CIT to kidneys [52] and livers [13] ameliorates IRI and prevents allograft rejection [14].

Reperfusion

As described above, organs expressing high levels of HO-1 at the end of CIT do have inferior outcome, but upregulation during reperfusion seems beneficial [50].

During reperfusion, an oxidative burst is mediated via oxyradicals, cytokines, adhesion molecules and an early, unspecific immune response [48]. As mentioned above, donor treatment by the means of pharmacological HO-1 induction or gene transfer improves IRI in various models [30–46]. Further evidence indicates a prominent role of HO-1 in transplant associated IRI: intragraft IL-13 overexpression leads to minimization of IRI in rat livers, what is reversed by suppression HO-1 activity using tin-protoporphyrin (SnPP), an inhibitor of HO-1 activation [53]. Amelioration of hepatic IRI via co-stimulation blockade with anti-CD154 mAb correlates with HO-1 expression. The effect on IRI seems to be dependent on HO-1 as CD154 KO mice (that do barely develop evidence for IRI) have increased hepatic HO-1 expression, however, when these mice are treated with SnPP, the protective effect is abolished [54]. Two mechanisms have been identified and have to be separated in the context of IRI: (i) improvement of early graft viability because of a decrease in tissue damage and/or (ii) suppression of the innate immune response.

Similar to CoPP, hyperthermia preconditioned kidney (and liver) grafts are protected from IRI by upregulation of heat shock proteins, such as HO-1, via suppression of apoptosis [2,55,56]. Preconditioning in several experimental settings has been efficient in ameliorating IRI, still it is not conclusive, whether this may be applicable for humans as well [57,58]. The mechanism is not fully understood, however, expression of ''protective'' genes such as HO-1 because of a stress response seems to be relevant for the preconditioning effect [59]. An easy approach to precondition, an organ for transplantation would be heating the donor up to 43 °C. Heat shock preconditioning by subjecting rats after cardiac death to whole body hyperthermia dramatically improved isograft survival in a model of kidney transplantation, presumably via induction of HO-1 (amongst other heat shock proteins) [2], as in an isogeneic liver transplantation model in rats, tin protoporphyrin, an inhibitor of HO-1 activation, the heat-preconditioning effect was abolished [60]. However, in clinical reality it seems more suitable to precondition by applying a brief period of ischemia prior to cold perfusion [61]. Ischemic preconditioning improves outcome in a rat model of reduced size orthotopic liver transplantation, also attributed to the induction of HO-1 [62].

Acute rejection and tolerance

The first report describing expression of HO-1 in allografts showed increased mRNA levels of HO-1 and HO-1 protein, mainly in infiltrating macrophages, in rat kidneys that were rejected [63]. Microarray analysis, comparing syngeneic with allogeneic rat heart transplants revealed specific gene expression profiles, HO-1 being upregulated 23-fold when compared with the nonrejecting controls [64]. HO-1 mRNA levels and protein expression are also markedly induced in an allogeneic rat model of lung transplantation (later confirmed in humans) [65–67], what also has been observed in human kidneys and hearts being rejected [68,69]. HO-1 expression was not only found in organs being rejected but also in organs that were tolerized indefinitely, as observed in a mouse model of tolerance induction using donor specific transfusions (DST) and co-stimulation blockade [70]. Moreover, HO-1 serves as a marker of (T-cell mediated) injury as well as an indicator of beneficial effects.

With respect to the immune response to alloantigens two functions of HO-1 induction should be separated. (i) HO-1 induction affects the recipient's cellular response. (ii) HO-1 induction protects the graft itself.

(i) In pregnant mice, upregulation of HO-1 inhibits induced abortion [71]. These effects have been attributed to the generation of regulatory T cells [72]. In allogenic rodent transplant models, HO-1 induction prolongs allograft survival modifying the host's immune response by inhibition of T-cell-mediated cytotoxicity and NK-cell activity [73], reducing the amount of donor derived dendritic cells in the graft and the lymph nodes, accompanied by reduced frequencies of allospecific CD4+ T cells and a decreased infiltrate of macrophages [74]. In a murine heart transplant model, HO-1 induction combined with DST promotes donor specific tolerance to allografts via generation of Tregs [75]. In a model of allograft tolerance using co-stimulatory blockade plus DST, it seems that it is mainly the promotion of Treg generation in the recipient, as HO-1 KO donor derived allografts transplanted to wild-type recipients were tolerized in the same manner as their wild-type controls. By contrast, when wild-type hearts were transplanted to HO-1 KO mice, tolerance induction was not possible. [75]. Which mechanisms make it impossible, in this setting, to become tolerant to alloantigens is still not known, presumably not the lack of regulatory T cells, as Treg development, maintenance and function are not affected in HO-1 deficient mice [76]. It has recently been shown in HO-1 null mice that the lack of HO-1 in antigen presenting cells is responsible for the lack of Treg-mediated suppression of the allospecific immune response [77]. Finally, the application of myeloid derived suppressor cells affects T-cell responses in allotransplantation and prolongs skin allograft survival producing large amounts of IL-10 and HO-1. When HO-1 is blocked, T-cell suppression and IL-10 production is abolished [78].

(ii) The observations that led to the identification of HO-1 as an important gene in transplantation were mainly made in organs that were tolerized, thus the hypothesis that HO-1 protects the graft itself was born. In a model of allogenic thyroid graft transplantation under anti-CD4-mAb treatment, overexpression of HO-1 was found in the nonrejected grafts, however, when HO-1 was inhibited by ZnPP, the thyroid glands were rejected [79]. Adenovirus-mediated transfer of HO-1 to rat liver allografts alone resulted in decreased rejection via an increase in IL-4, IL-10 and a decrease in IL-2 and IFN-γ expression [13,80]. Administration of AdHO-1 to cardiac allografts or to the recipient mediates prolongation of allograft survival [81].

Some studies have suggested that HO-1-mediated effect(s) are not solely ''organ protecting'' effects or effects on the host's immune response, but both. When HO-1 deficient mice are used either as a donor or recipient, acute allograft rejection of tracheal transplants is much more pronounced [82]. Using HO-1 transgenic mice, local and systemic (recipient) overexpression of HO-1 determine the fate of an organ in an allogeneic setting [83].

Chronic rejection

Chronic allograft dysfunction is the limiting factor in long-term allograft survival. Structural changes caused by acute organ damage and chronic immunological stimuli (e.g. neointimal hyperplasia and glomerular changes) are responsible for organ loss. In human heart allografts, increased HO-1 mRNA expression 1 week after transplantation was associated with the development of (chronic) transplant coronary artery disease (TCAD), whereas no difference was found comparing pretransplant samples from hearts developing TCAD to non-TCAD hearts [84].

Donor HO-1 adenoviral transfection or recipient treatment during the perioperative period with CoPP or hemin mediates protection from transplant arteriosclerosis in a mouse model of heart transplantation [47,70] with lower levels of TGF-β, TNF and macrophage migration inhibitory factor [85]. AdHO-1 gene transfer to rat aortas results in amelioration of chronic rejection by a significant reduction in leukocyte infiltration and a decreasing number of vascular smooth muscle cells in the (neo-)intima [14,86], minimizes apoptosis and reduces NF-κB levels [87]. In a rat model of chronic renal allograft rejection even with only a short treatment of CoPP in the perioperative period cortical scarring, vascular hyalinization, intimal hyperplasia, and glomerular sclerosis is decreased [88]. So far, no study has answered the question, whether it is the reduction of IRI alone (via HO-1 induction during the perioperative period) that protects from chronic allograft changes or long-term HO-1 induction (gene transfer, pharmacological HO-1 induction for a longer time period) is additive, clearly this issue has to be addressed.

Gene polymorphisms

Expression of the HO-1 gene is modulated by two functional polymorphisms in the promotor: a $(GT)_n$ length polymorphism and a single nucleotide polymorphism (SNP). The HO-1 $(GT)_n$ repeat resides in a regulatory sequence with a short $(GT)_n$ allele (S-allele) associated with enhanced transcriptional activity [89]. Additionally, the A(−413)T SNP has been identified as a variation with higher promotor activity of the A-allele [90].

Donor and recipient HO-1 $(GT)_n$ polymorphism may have an influence on long-term graft function: kidneys retrieved from organ donors that were carriers of one or two S-alleles (greater up-regulation of HO-1) had significantly lower serum creatinine at 1, 2 and 3 years after transplantation and better survival when compared with kidneys from donors without a S-allele [91–93], further recipients carrying at least one S-allele had better long-term results [93]. By contrast, no such beneficial effects were seen in two different studies [94,95]. In human heart transplantation, recipients of an (at least one)

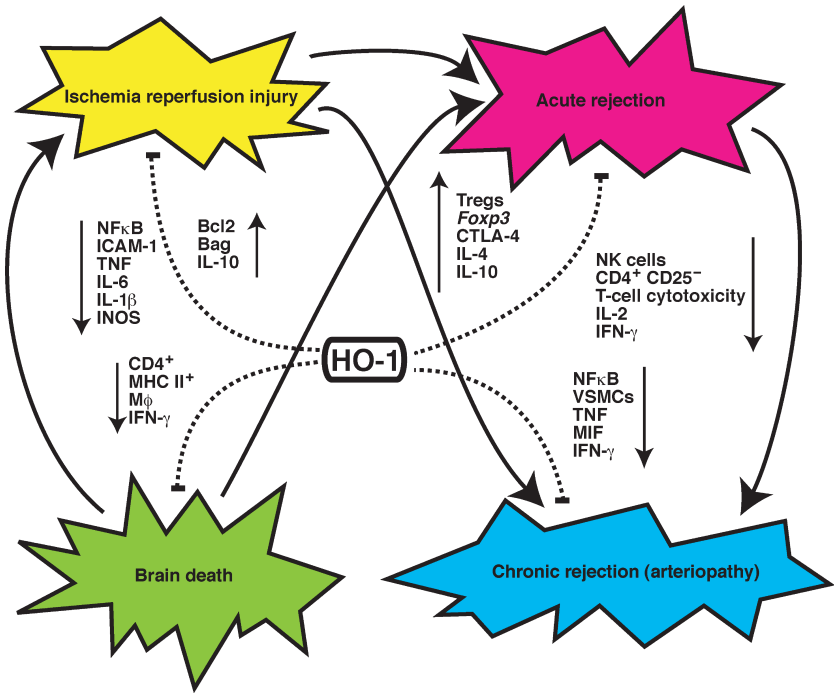

Figure 1 The four crucial (and interconnected) problems to overcome in organ/tissue transplantation and their relation to heme oxygenase-1 (HO-1): inflammation/organ activation caused by brain death, ischemia reperfusion injury, acute and chronic rejection. HO-1 is overexpressed under these conditions, however, when HO-1 is intentionally induced, all four pathologies are ameliorated via two major mechanisms: (i) anti-inflammatory/tolerogenic by affecting the immune system directly and (ii) ''organ-protecting'' by alleviating symptoms of organ damage via antioxidant and antiapoptotic properties.

S-allele carrying donor allograft showed a similar incidence of chronic allograft vasculopathy as recipients of a non-S-allele carrying graft [96].

Single nucleotide polymorphism analysis in liver transplantation revealed that graft survival at 1 and 5 years after transplantation is significantly better in recipients receiving a liver from an A-allele (with a higher HO-1 promotor activity) carrying graft. Those grafts showed higher RNA expression when compared with grafts carrying a T (and thus low promotor activity) allele. In this study, HO-1 $(GT)_n$ polymorphism did not have any influence on outcome [97]. No such correlation of donor SNP and delayed graft function was found in a large cohort of renal transplantation [98].

These data provide additional evidence that HO-1 is crucially involved in the complex pathologies of organ transplantation, but also raise new questions: Is it necessary to adapt immunosuppression in recipients of low HO-1 expressing organs? Is an organ from a low HO-1 expressing donor a bad organ? Clearly studies with higher numbers patients have to be conducted. Additionally, the correlation of HO-1 gene polymorphisms and the efficacy of immunosuppressants has to be studied, especially as mammalian target of rapamycin-inhibitors or co-stimulatory blockade may require HO-1 [54,75,99], one has to take into account that there could be a difference in efficacy among low and high HO-1 expressing recipients.

Islet transplantation

Attempts to transplant allogenic Langerhans islets into patients with Type I diabetes are being conducted since decades. Outcomes of whole organ transplantation are still superior and the biggest challenge besides suppressing the alloimmune response is to better protect the islets from damage because of harvest, isolation, hypoxia, and reoxygenation [100].

HO-1 induction in Langerhans islet cells protects from apoptosis *in vitro* and improves function *in vivo* in a model of marginal mass islet transplantation in rodents [101]. Transfection of islet cells with TAT/PTD-HO-1 does not interfere with cell function and increases cell viability in culture [102]. Induction of HO-1 in the donor only enhances survival of allogeneic islet grafts in a mouse model [19,103,104]. Furthermore, induction of HO-1 in the recipient as well as in the islet grafts only prior to transplantation leads to donor specific hyporesponsiveness and increased graft survival [105]. In allogeneic islet transplantation, a protocol combining ''conventional'' cyclosporine A immunosuppression, HO-1 induction and surface modification of the islets with polyethylene glycol resulted in indefinite graft survival [106]. This article is of special interest, as it shows that HO-1-mediated tolerogenic effects may not be hampered by a calcineurin inhibitor-based immunosuppression.

Xenotransplantation

Xenotransplantation is the field in which the important role in immunomodulation of HO-1 was discovered *in vivo*. HO-1 was shown in various models to be highly expressed in the endothelium and smooth muscle cells of accommodated heart xenografts suggesting that HO-1 (amongst others) acts as a protective gene promoting xenograft survival [107–111]. This has not only been shown for the heart but also the lung [112]. Using the decapeptide RDP1258 as HO-1 inducer in combination with cobra venom factor rat xenograft survival was prolonged [113]. In a mouse to rat heart transplant model, treatment with cobra venom factor and cyclosporine A resulted in more than 50-day survival of the xenografts, which highly expressed HO-1. When SnPP, a known inhibitor of HO-1 activity, was added to the treatment protocol, the tolerogenic effect was abrogated [114]. Adenovirus-mediated overexpression of HO-1 protects endothelial cells from xenoserum-mediated destruction [115]. Induction of HO-1 with hemin significantly prolongs cardiac xenograft survival, attenuates serum levels of xenoantibody and mitigates CD40 ligand transcription in the xenograft [116]. Novel concepts of alpha-Gal silencing are more effective when combined with HO-1 upregulation [117].

Clearly, xenotransplantation, because of the fear of virus infections, is far from clinical application, but if feasible, probably HO-1 induction protocols may be used to alleviate xenograft rejection.

Graft versus host disease

Graft versus host disease is frequently seen after bone marrow transplantation but also in recipients of solid organs, treatment thereof is challenging and outcomes are poor [118]. Induction with CoPP increased survival in a mouse model of GVHD whereas treatment with ZnPP accelerated GVHD development [119]. The protective effects of CoPP-mediated HO-1 induction on survival and GVHD involve a reduction in the proinflammatory cytokine milieu rather than affecting allospecific T-cell stimulation [120].

Controversial data

While there is a huge amount of data supporting the hypothesis that HO-1 is one of the most crucial genes that might help us to defend organs from IRI, acute rejection and chronic changes, one has to be aware that

data demonstrating that HO-1 might not be involved in the effects mentioned above have also been published. Transgenic rats overexpressing HO-1 in various organs did not show any alteration in their immune response nor were they prone to allograft rejection [121]. In a rat model of lung allotransplantation HO-1 induction affected signs of IRI but did not alter signs of acute rejection [122]. Additionally, for most of the studies described above, one has to take into account that the effects of upregulation of HO-1 are not formally proven but rather an association of expression with a given effect and in some cases, inhibition of HO-1 with SnPP or ZnPP may represent fairly direct proof to the extent that these substances are specific.

How will we induce HO-1 in humans?

Many effects of the various treatments in experimental transplantation (which, in part, are used in humans as well) are probably mediated via of HO-1, e.g. dopamine [123], glutamine [124], FK352, an adenosine receptor antagonist and FK409, an NO releasing molecule [125,126], co-stimulation blockade [54,75], IL-10 [127] and IL-13 [53,128] gene transfer, decapeptides RDP1257, B2702 and RDP1258 [129–131] somatostatin [132], ginkgo balboa [133], diannexin [134], curcumin [135], PSGL-1 [136], D4-F, an apoA-1 mimetic peptide [137] and stem cell transfer [138], other inducers of HO-1 may follow, which induce HO-1 more specifically.

Two central aspects of HO-1 induction in human transplantation have to be addressed: (i) whom and when to treat, the donor, the organ or the recipient; no study so far has investigated whether there are differences between certain organs. The vast majority of experimental studies on IRI suggest donor treatment, promoting HO-1 expression in the graft reducing immunogenicity; to target the host's immune system, systemic treatment of the recipient seems inevitable. (ii) How to induce HO-1 safely: There has been only one published study on the attempt of specifically inducing HO-1 in humans in allotransplantation [139], using two potent inducers of HO-1, curcumin and quercetin [140,141]. CoPP is used to induce HO-1 in most rodent models; however, its use in humans is hampered by the potential side-effects of porphyrins [142]. The major goal in the near future should be to identify potent specific pharmacological inducers of HO-1 that can be used safely in the organ donor as well as in the recipient, and further serious attempts to safely use HO-1 gene transfer in humans have to be made. Recently, stable transfection of rat liver allografts with adenoviral transfer for 3 months has been demonstrated [143]. A novel approach to use the therapeutic potential of HO-1 induction involves the administration of cell penetrating protein transduction systems. Recombinant HO-1 containing a modified transduction domain applied during cold preservation protects grafts from IRI in a rat model of heart transplantation [144]. Similarly, a HO-1-TAT fusion protein has been efficiently transduced to livers during cold ischemia and reduced apoptosis [145].

Finally, the end products of heme catabolism, CO and biliverdin/bilirubin have to be considered seriously for clinical application [5,6].

Conclusion

A considerable amount of data on the protective gene HO-1 in transplantation has been obtained during the last 15 years. HO-1 is being overexpressed under conditions of transplant related pathologies, namely IRI, acute and chronic rejection, brain death, islet transplantation and xenotransplantation. Treatment thereof by inducing/overexpressing HO-1 and applying the end products of heme catabolism has been successful in many experimental models while it is not yet clear how these findings can be applied to humans and whether we should treat the donor, the graft or the recipient. HO-1 induction, CO or bilirubin/biliverdin treatment (i) of the organ donor to prevent IRI to reduce the immunogenicity of the graft and to be able to use ''more marginal'' grafts and (ii) of the allograft recipient to prevent symptoms of chronic rejection and to facilitate allograft tolerance have to be considered seriously for our patients.

References

1. Luna E, Postol E, Caldas C, *et al.* Treatment with encapsulated Hsp60 peptide (p277) prolongs skin graft survival in a murine model of minor antigen disparity. *Scand J Immunol* 2007; **66**: 62.
2. Redaelli CA, Wagner M, Kulli C, *et al.* Hyperthermia-induced HSP expression correlates with improved rat renal isograft viability and survival in kidneys harvested from non-heart-beating donors. *Transpl Int* 2001; **14**: 351.
3. Tenhunen R, Marver HS, Schmid R. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. *Proc Natl Acad Sci USA* 1968; **61**: 748.
4. Ollinger R, Yamashita K, Bilban M, *et al.* Bilirubin and biliverdin treatment of atherosclerotic diseases. *Cell Cycle* 2007; **6**: 39.
5. Ollinger R, Wang H, Yamashita K, *et al.* Therapeutic applications of bilirubin and biliverdin in transplantation. *Antioxid Redox Signal* 2007; **9**: 2175.
6. Otterbein LE. The evolution of carbon monoxide into medicine. *Respir Care* 2009; **54**: 925.

7. Ollinger R, Kogler P, Troppmair J, *et al.* Bilirubin inhibits tumor cell growth via activation of ERK. *Cell Cycle* 2007; **6**: 3078.
8. Yamashita K, McDaid J, Ollinger R, *et al.* Biliverdin, a natural product of heme catabolism, induces tolerance to cardiac allografts. *FASEB J* 2004; **18**: 765.
9. Ollinger R, Bilban M, Erat A, *et al.* Bilirubin: a natural inhibitor of vascular smooth muscle cell proliferation. *Circulation* 2005; **112**: 1030.
10. Nakao A, Otterbein LE, Overhaus M, *et al.* Biliverdin protects the functional integrity of a transplanted syngeneic small bowel. *Gastroenterology* 2004; **127**: 595.
11. Wang H, Lee SS, Dell'Agnello C, *et al.* Bilirubin can induce tolerance to islet allografts. *Endocrinology* 2006; **147**: 762.
12. Amersi F, Shen X-D, Anselmo D, *et al. Ex vivo* exposure to carbon monoxide prevents hepatic ischemia/reperfusion injury through p38 MAP kinase pathway. *Hepatology* 2002; **35**: 815.
13. Ke B, Buelow R, Shen X-D, *et al.* Heme oxygenase 1 gene transfer prevents CD95/Fas ligand-mediated apoptosis and improves liver allograft survival via carbon monoxide signaling pathway. *Hum Gene Ther* 2002; **13**: 1189.
14. Chauveau C, Bouchet D, Roussel J-C, *et al.* Gene transfer of heme oxygenase-1 and carbon monoxide delivery inhibit chronic rejection. *Am J Transplant* 2002; **2**: 581.
15. Nakao A, Moore BA, Murase N, *et al.* Immunomodulatory effects of inhaled carbon monoxide on rat syngeneic small bowel graft motility. *Gut* 2003; **52**: 1278.
16. Akamatsu Y, Haga M, Tyagi S, *et al.* Heme oxygenase-1-derived carbon monoxide protects hearts from transplant associated ischemia reperfusion injury. *FASEB J* 2004; **18**: 771.
17. Neto JS, Nakao A, Kimizuka K, *et al.* Protection of transplant-induced renal ischemia-reperfusion injury with carbon monoxide. *Am J Physiol Renal Physiol* 2004; **287**: F979.
18. Martins PNA, Reuzel-Selke A, Jurisch A, *et al.* Induction of carbon monoxide in the donor reduces graft immunogenicity and chronic graft deterioration. *Transplant Proc* 2005; **37**: 379.
19. Wang H, Lee SS, Gao W, *et al.* Donor treatment with carbon monoxide can yield islet allograft survival and tolerance. *Diabetes* 2005; **54**: 1400.
20. Goldberg A, Parolini M, Chin BY, *et al.* Toll-like receptor 4 suppression leads to islet allograft survival. *FASEB J* 2007; **21**: 2840.
21. Chen B, Guo L, Fan C, *et al.* Carbon monoxide rescues heme oxygenase-1-deficient mice from arterial thrombosis in allogeneic aortic transplantation. *Am J Pathol* 2009; **175**: 422.
22. Lee SS, Gao W, Mazzola S, *et al.* Heme oxygenase-1, carbon monoxide, and bilirubin induce tolerance in recipients toward islet allografts by modulating T regulatory cells. *FASEB J* 2007; **21**: 3450.
23. Berberat PO, Katori M, Kaczmarek E, *et al.* Heavy chain ferritin acts as an antiapoptotic gene that protects livers from ischemia reperfusion injury. *FASEB J* 2003; **17**: 1724.
24. Weiss S, Kotsch K, Francuski M, *et al.* Brain death activates donor organs and is associated with a worse I/R injury after liver transplantation. *Am J Transplant* 2007; **7**: 1584.
25. Pratschke J, Neuhaus P, Tullius SG. What can be learned from brain-death models? *Transpl Int* 2005; **18**: 15.
26. Schuurs TA, Morariu AM, Ottens PJ, *et al.* Time-dependent changes in donor brain death related processes. *Am J Transplant* 2006; **6**: 2903.
27. Nijboer WN, Schuurs TA, van der Hoeven JAB, *et al.* Effect of brain death on gene expression and tissue activation in human donor kidneys. *Transplantation* 2004; **78**: 978.
28. Nijboer WN, Schuurs TA, van der Hoeven JAB, *et al.* Effects of brain death on stress and inflammatory response in the human donor kidney. *Transplant Proc* 2005; **37**: 367.
29. Kotsch K, Francuski M, Pascher A, *et al.* Improved long-term graft survival after HO-1 induction in brain-dead donors. *Am J Transplant* 2006; **6**: 477.
30. Amersi F, Buelow R, Kato H, *et al.* Upregulation of heme oxygenase-1 protects genetically fat Zucker rat livers from ischemia/reperfusion injury. *J Clin Invest* 1999; **104**: 1631.
31. Coito AJ, Buelow R, Shen X-D, *et al.* Heme oxygenase-1 gene transfer inhibits inducible nitric oxide synthase expression and protects genetically fat Zucker rat livers from ischemia-reperfusion injury. *Transplantation* 2002; **74**: 96.
32. Tullius SG, Nieminen-Kelhä M, Bachmann U, *et al.* Induction of heme-oxygenase-1 prevents ischemia/reperfusion injury and improves long-term graft outcome in rat renal allografts. *Transplant Proc* 2001; **33**: 1286.
33. Tullius SG, Nieminen-Kelhä M, Reutzel-Selke A, *et al.* Improvement of long-term function in renal allografts from 'marginal donors' following the induction of heme-oxygenase-1. *Transplant Proc* 2001; **33**: 1160.
34. Tullius SG, Nieminen-Kelhä M, Buelow R, *et al.* Inhibition of ischemia/reperfusion injury and chronic graft deterioration by a single-donor treatment with cobalt-protoporphyrin for the induction of heme oxygenase-1. *Transplantation* 2002; **74**: 591.
35. Kato H, Amersi F, Buelow R, *et al.* Heme oxygenase-1 overexpression protects rat livers from ischemia/reperfusion injury with extended cold preservation. *Am J Transplant* 2001; **1**: 121.
36. Tsuchihashi S, Tamaki T, Tanaka M, *et al.* Pyrrolidine dithiocarbamate provides protection against hypothermic preservation and transplantation injury in the rat liver: the role of heme oxygenase-1. *Surgery* 2003; **133**: 556.
37. Uchida Y, Tamaki T, Tanaka M, *et al.* Induction of specific stress response increases resistance of rat liver

allografts to cold ischemia and reperfusion injury. *Transpl Int* 2003; **16**: 396.
38. Zeng Z, Huang HF, Chen MQ, Song F, Zhang YJ. Heme oxygenase-1 protects donor livers from ischemia/reperfusion injury: the role of Kupffer cells. *World J Gastroenterol* 2010; **16**: 1285.
39. Kato Y, Shimazu M, Kondo M, *et al.* Bilirubin rinse: a simple protectant against the rat liver graft injury mimicking heme oxygenase-1 preconditioning. *Hepatology* 2003; **38**: 364.
40. Katori M, Buelow R, Ke B, *et al.* Heme oxygenase-1 overexpression protects rat hearts from cold ischemia/reperfusion injury via an antiapoptotic pathway. *Transplantation* 2002; **73**: 287.
41. Yang ZF, Tsui TY, Ho DW, Tang TC, Fan S-T. Heme oxygenase-1 potentiates the survival of small-for-size liver graft. *Liver Transpl* 2004; **10**: 784.
42. Wang XH, Wang K, Zhang F, *et al.* Alleviating ischemia-reperfusion injury in aged rat liver by induction of heme oxygenase-1. *Transplant Proc* 2004; **36**: 2917.
43. Wang X-H, Wang K, Zhang F, *et al.* Heme oxygenase-1 alleviates ischemia/reperfusion injury in aged liver. *World J Gastroenterol* 2005; **11**: 690.
44. Kotsch K, Martins PNA, Klemz R, *et al.* Heme oxygenase-1 ameliorates ischemia/reperfusion injury by targeting dendritic cell maturation and migration. *Antioxid Redox Signal* 2007; **9**: 2049.
45. Becker T, Zu Vilsendorf AM, Terbish T, Klempnauer J, Jörns A. Induction of heme oxygenase-1 improves the survival of pancreas grafts by prevention of pancreatitis after transplantation. *Transplantation* 2007; **84**: 1644.
46. Hölzen JP, August C, Bahde R, *et al.* Influence of heme oxygenase-1 on microcirculation after kidney transplantation. *J Surg Res* 2008; **148**: 126.
47. Clarke HM, Shrivastava S, Motterlini R, Sawle P, Chen D, Dorling A. Donor HO-1 expression inhibits intimal hyperplasia in unmanipulated graft recipients: a potential role for CD8+ T-cell modulation by carbon monoxide. *Transplantation* 2009; **88**: 653.
48. Boros P, Bromberg JS. New cellular and molecular immune pathways in ischemia/reperfusion injury. *Am J Transplant* 2006; **6**: 652.
49. Ollinger R, Kogler P, Biebl M, *et al.* Protein levels of heme oxygenase-1 during reperfusion in human kidney transplants with delayed graft function. *Clin Transplant* 2008; **22**: 418.
50. Geuken E, Buis CI, Visser DS, *et al.* Expression of heme oxygenase-1 in human livers before transplantation correlates with graft injury and function after transplantation. *Am J Transplant* 2005; **5**: 1875.
51. Moers C, Smits JM, Maathuis MH, *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; **360**: 7.
52. Blydt-Hansen TD, Katori M, Lassman C, *et al.* Gene transfer-induced local heme oxygenase-1 overexpression protects rat kidney transplants from ischemia/reperfusion injury. *J Am Soc Nephrol* 2003; **14**: 745.
53. Ke B, Shen X-D, Lassman CR, Gao F, Busuttil RW, Kupiec-Weglinski JW. Cytoprotective and antiapoptotic effects of IL-13 in hepatic cold ischemia/reperfusion injury are heme oxygenase-1 dependent. *Am J Transplant* 2003; **3**: 1076.
54. Shen X-D, Ke B, Zhai Y, *et al.* CD154-CD40 T-cell costimulation pathway is required in the mechanism of hepatic ischemia/reperfusion injury, and its blockade facilitates and depends on heme oxygenase-1 mediated cytoprotection. *Transplantation* 2002; **74**: 315.
55. Wagner M, Cadetg P, Ruf R, Mazzucchelli L, Ferrari P, Redaelli CA. Heme oxygenase-1 attenuates ischemia/reperfusion-induced apoptosis and improves survival in rat renal allografts. *Kidney Int* 2003; **63**: 1564.
56. Mokuno Y, Berthiaume F, Tompkins RG, Balis UJ, Yarmush ML. Technique for expanding the donor liver pool: heat shock preconditioning in a rat fatty liver model. *Liver Transpl* 2004; **10**: 264.
57. Ambros JT, Herrero-Fresneda I, Borau OG, Boira JM. Ischemic preconditioning in solid organ transplantation: from experimental to clinics. *Transpl Int* 2007; **20**: 219.
58. de Rougemont O, Lehmann K, Clavien PA. Preconditioning, organ preservation, and postconditioning to prevent ischemia-reperfusion injury to the liver. *Liver Transpl* 2009; **15**: 1172.
59. Patel A, van de Poll MCG, Greve JWM, *et al.* Early stress protein gene expression in a human model of ischemic preconditioning. *Transplantation* 2004; **78**: 1479.
60. Redaelli CA, Tian Y-H, Schaffner T, Ledermann M, Baer HU, Dufour J-F. Extended preservation of rat liver graft by induction of heme oxygenase-1. *Hepatology* 2002; **35**: 1082.
61. Dufour J-F, Redaelli C. Survival pathways and preconditioning in liver transplantation. *Transpl Immunol* 2002; **9**: 239.
62. Franco-Gou R, Roselló-Catafau J, Casillas-Ramirez A, *et al.* How ischaemic preconditioning protects small liver grafts. *J Pathol* 2006; **208**: 62.
63. Agarwal A, Kim Y, Matas AJ, Alam J, Nath KA. Gas-generating systems in acute renal allograft rejection in the rat. Co-induction of heme oxygenase and nitric oxide synthase. *Transplantation* 1996; **61**: 93.
64. Edemir B, Kurian SM, Eisenacher M, *et al.* Activation of counter-regulatory mechanisms in a rat renal acute rejection model. *BMC Genomics* 2008; **9**: 71.
65. Song R, Kubo M, Morse D, *et al.* Carbon monoxide induces cytoprotection in rat orthotopic lung transplantation via anti-inflammatory and anti-apoptotic effects. *Am J Pathol* 2003; **163**: 231.
66. Jiang K, Cheng L, Wang J, Li J, Nie J. Heme oxygenase-1 expression in rats with acute lung rejection and implication. *J Huazhong Univ Sci Technol Med Sci* 2009; **29**: 84.

67. Lu F, Zander DS, Visner GA. Increased expression of heme oxygenase-1 in human lung transplantation. *J Heart Lung Transplant* 2002; **21**: 1120.
68. Avihingsanon Y, Ma N, Csizmadia E, *et al.* Expression of protective genes in human renal allografts: a regulatory response to injury associated with graft rejection. *Transplantation* 2002; **73**: 1079.
69. Souza AID, Felkin LE, McCormack AM, *et al.* Sequential expression of three known protective genes in cardiac biopsies after transplantation. *Transplantation* 2005; **79**: 584.
70. Hancock WW, Buelow R, Sayegh MH, Turka LA. Antibody-induced transplant arteriosclerosis is prevented by graft expression of anti-oxidant and anti-apoptotic genes. *Nat Med* 1998; **4**: 1392.
71. Sollwedel A, Bertoja AZ, Zenclussen ML, *et al.* Protection from abortion by heme oxygenase-1 up-regulation is associated with increased levels of Bag-1 and neuropilin-1 at the fetal-maternal interface. *J Immunol* 2005; **175**: 4875.
72. Zenclussen AC, Schumacher A, Zenclussen ML, Wafula P, Volk H-D. Immunology of pregnancy: cellular mechanisms allowing fetal survival within the maternal uterus. *Expert Rev Mol Med* 2007; **9**: 1.
73. Woo J, Iyer S, Cornejo MC, *et al.* Stress protein-induced immunosuppression: inhibition of cellular immune effector functions following overexpression of haem oxygenase (HSP 32). *Transpl Immunol* 1998; **6**: 84.
74. Martins PNA, Kessler H, Jurisch A, *et al.* Induction of heme oxygenase-1 in the donor reduces graft immunogenicity. *Transplant Proc* 2005; **37**: 384.
75. Yamashita K, Ollinger R, McDaid J, *et al.* Heme oxygenase-1 is essential for and promotes tolerance to transplanted organs. *FASEB J* 2006; **20**: 776.
76. Zelenay S, Chora A, Soares MP, Demengeot J. Heme oxygenase-1 is not required for mouse regulatory T cell development and function. *Int Immunol* 2007; **19**: 11.
77. George JF, Braun A, Brusko TM, *et al.* Suppression by CD4+ CD25+ regulatory T cells is dependent on expression of heme oxygenase-1 in antigen-presenting cells. *Am J Pathol* 2008; **173**: 154.
78. De Wilde V, Van Rompaey N, Hill M, *et al.* Endotoxin-induced myeloid-derived suppressor cells inhibit alloimmune responses via heme oxygenase-1. *Am J Transplant* 2009; **9**: 2034.
79. Niimi M, Takashina M, Takami H, *et al.* Overexpression of heme oxygenase-1 protects allogeneic thyroid grafts from rejection in naive mice. *Surgery* 2000; **128**: 910.
80. Ke B, Shen XD, Melinek J, *et al.* Heme oxygenase-1 gene therapy: a novel immunomodulatory approach in liver allograft recipients? *Transplant Proc* 2001; **33**: 581.
81. Braudeau C, Bouchet D, Tesson L, *et al.* Induction of long-term cardiac allograft survival by heme oxygenase-1 gene transfer. *Gene Ther* 2004; **11**: 701.
82. Visner GA, Lu F, Zhou H, Latham C, Agarwal A, Zander DS. Graft protective effects of heme oxygenase 1 in mouse tracheal transplant-related obliterative bronchiolitis. *Transplantation* 2003; **76**: 650.
83. Araujo JA, Meng L, Tward AD, *et al.* Systemic rather than local heme oxygenase-1 overexpression improves cardiac allograft outcomes in a new transgenic mouse. *J Immunol* 2003; **171**: 1572.
84. Holweg CTJ, Balk AHMM, Snaathorst J, *et al.* Intragraft heme oxygenase-1 and coronary artery disease after heart transplantation. *Transpl Immunol* 2004; **13**: 265.
85. Tsui T-Y, Wu X, Lau C-K, *et al.* Prevention of chronic deterioration of heart allograft by recombinant adeno-associated virus-mediated heme oxygenase-1 gene transfer. *Circulation* 2003; **107**: 2623.
86. Bouche D, Chauveau C, Roussel JC, *et al.* Inhibition of graft arteriosclerosis development in rat aortas following heme oxygenase-1 gene transfer. *Transpl Immunol* 2002; **9**: 235.
87. Du D, Chang S, Chen B, Zhou H, Chen ZK. Adenovirus-mediated heme oxygenase transfer inhibits graft arteriosclerosis in rat aortic transplants. *Transplant Proc* 2007; **39**: 3446.
88. Bédard ELR, Jiang J, Parry N, *et al.* Peritransplant treatment with cobalt protoporphyrin attenuates chronic renal allograft rejection. *Transpl Int* 2005; **18**: 341.
89. Okinaga S, Takahashi K, Takeda K, *et al.* Regulation of human heme oxygenase-1 gene expression under thermal stress. *Blood* 1996; **87**: 5074.
90. Ono K, Goto Y, Takagi S, *et al.* A promoter variant of the heme oxygenase-1 gene may reduce the incidence of ischemic heart disease in Japanese. *Atherosclerosis* 2004; **173**: 315.
91. Exner M, Böhmig GA, Schillinger M, *et al.* Donor heme oxygenase-1 genotype is associated with renal allograft function. *Transplantation* 2004; **77**: 538.
92. Baan C, Peeters A, Lemos F, *et al.* Fundamental role for HO-1 in the self-protection of renal allografts. *Am J Transplant* 2004; **4**: 811.
93. Ozaki KS, Marques GM, Nogueira E, *et al.* Improved renal function after kidney transplantation is associated with heme oxygenase-1 polymorphism. *Clin Transplant* 2008; **22**: 609.
94. Courtney AE, McNamee PT, Middleton D, Heggarty S, Patterson CC, Maxwell AP. Association of functional heme oxygenase-1 gene promoter polymorphism with renal transplantation outcomes. *Am J Transplant* 2007; **7**: 908.
95. Turpeinen H, Kyllönen LE, Parkkinen J, Laine J, Salmela KT, Partanen J. Heme oxygenase 1 gene polymorphisms and outcome of renal transplantation. *Int J Immunogenet* 2007; **34**: 253.
96. Ullrich R, Exner M, Schillinger M, *et al.* Microsatellite polymorphism in the heme oxygenase-1 gene promoter and cardiac allograft vasculopathy. *J Heart Lung Transplant* 2005; **24**: 1600.

97. Buis CI, van der Steege G, Visser DS, *et al.* Heme oxygenase-1 genotype of the donor is associated with graft survival after liver transplantation. *Am J Transplant* 2008; **8**: 377.
98. Israni AK, Li N, Cizman BB, *et al.* Association of donor inflammation- and apoptosis-related genotypes and delayed allograft function after kidney transplantation. *Am J Kidney Dis* 2008; **52**: 331.
99. Zhou H, Liu H, Porvasnik SL, *et al.* Heme oxygenase-1 mediates the protective effects of rapamycin in monocrotaline-induced pulmonary hypertension. *Lab Invest* 2006; **86**: 62.
100. Cravedi P, van der Meer IM, Cattaneo S, Ruggenenti P, Remuzzi G. Successes and disappointments with clinical islet transplantation. *Adv Exp Med Biol* 2010; **654**: 749.
101. Pileggi A, Molano RD, Berney T, *et al.* Heme oxygenase-1 induction in islet cells results in protection from apoptosis and improved *in vivo* function after transplantation. *Diabetes* 2001; **50**: 1983.
102. Ribeiro MM, Klein D, Pileggi A, *et al.* Heme oxygenase-1 fused to a TAT peptide transduces and protects pancreatic beta-cells. *Biochem Biophys Res Commun* 2003; **305**: 876.
103. Fu S-H, Hsu BR, Juang J-H, Chen S-T, Yang T-Y, Hsu S. Cobalt-protoporphyrin treatment enhances murine isoislets engraftment. *Transplant Proc* 2004; **36**: 2205.
104. Li Y, Li G, Dong W, Chen J, Lu D, Tan J. Transplantation of rat islets transduced with human heme oxygenase-1 gene using adenovirus vector. *Pancreas* 2006; **33**: 280.
105. Pileggi A, Molano RD, Berney T, *et al.* Prolonged allogeneic islet graft survival by protoporphyrins. *Cell Transplant* 2005; **14**: 85.
106. Lee DY, Lee S, Nam JH, Byun Y. Minimization of immunosuppressive therapy after islet transplantation: combined action of heme oxygenase-1 and PEGylation to islet. *Am J Transplant* 2006; **6**: 1820.
107. Bach FH, Ferran C, Hechenleitner P, *et al.* Accommodation of vascularized xenografts: expression of ''protective genes'' by donor endothelial cells in a host Th2 cytokine environment. *Nat Med* 1997; **3**: 196.
108. Koyamada N, Miyatake T, Candinas D, *et al.* Transient complement inhibition plus T-cell immunosuppression induces long-term survival of mouse-to-rat cardiac xenografts. *Transplantation* 1998; **65**: 1210.
109. Miyatake T, Koyamada N, Hancock WW, Soares MP, Bach FH. Survival of accommodated cardiac xenografts upon retransplantation into cyclosporine-treated recipients. *Transplantation* 1998; **65**: 1563.
110. Soares MP, Lin Y, Anrather J, *et al.* Expression of heme oxygenase-1 can determine cardiac xenograft survival. *Nat Med* 1998; **4**: 1073.
111. Lin Y, Soares MP, Sato K, *et al.* Accommodated xenografts survive in the presence of anti-donor antibodies and complement that precipitate rejection of naive xenografts. *J Immunol* 1999; **163**: 2850.
112. Tabata T, de Perrot M, Keshavjee S, Liu M, Downey GP, Waddell TK. Accommodation after lung xenografting from hamster to rat. *Transplantation* 2003; **75**: 607.
113. Brouard S, Cuturi MC, Pignon P, *et al.* Prolongation of heart xenograft survival in a hamster-to-rat model after therapy with a rationally designed immunosuppressive peptide. *Transplantation* 1999; **67**: 1614.
114. Sato K, Balla J, Otterbein L, *et al.* Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse-to-rat cardiac transplants. *J Immunol* 2001; **166**: 4185.
115. Wang N, Lee JM, Tobiasch E, *et al.* Induction of xenograft accommodation by modulation of elicited antibody responses1 2. *Transplantation* 2002; **74**: 334.
116. Zhen-Wei X, Jian-Le S, Qi Q, Wen-Wei Z, Xue-Hong Z, Zi-Li Z. Heme oxygenase-1 improves the survival of discordant cardiac xenograft through its anti-inflammatory and anti-apoptotic effects. *Pediatr Transplant* 2007; **11**: 850.
117. Zhu M, Zhang W, Liu F, *et al.* Resistance to anti-xenogeneic response by combining alpha-Gal silencing with HO-1 upregulation. *Transpl Immunol* 2008; **19**: 202.
118. Kohler S, Pascher A, Junge G, *et al.* Graft versus host disease after liver transplantation – a single center experience and review of literature. *Transpl Int* 2008; **21**: 441.
119. Woo J, Iyer S, Mori N, Buelow R. Alleviation of graft-versus-host disease after conditioning with cobalt-protoporphyrin, an inducer of heme oxygenase-1. *Transplantation* 2000; **69**: 623.
120. Ewing P, Hildebrandt GC, Planke S, Andreesen R, Holler E, Gerbitz A. Cobalt protoporphyrine IX-mediated heme oxygenase-I induction alters the inflammatory cytokine response, but not antigen presentation after experimental allogeneic bone marrow transplantation. *Int J Mol Med* 2007; **20**: 301.
121. Braudeau C, Bouchet D, Toquet C, *et al.* Generation of heme oxygenase-1-transgenic rats. *Exp Biol Med (Maywood)* 2003; **228**: 466.
122. Bonnell MR, Visner GA, Zander DS, *et al.* Heme-oxygenase-1 expression correlates with severity of acute cellular rejection in lung transplantation. *J Am Coll Surg* 2004; **198**: 945.
123. Berger SP, Hünger M, Yard BA, Schnuelle P, van der Woude FJ. Dopamine induces the expression of heme oxygenase-1 by human endothelial cells *in vitro*. *Kidney Int* 2000; **58**: 2314.
124. Tamaki T, Konoeda Y, Yasuhara M, *et al.* Glutamine-induced heme oxygenase-1 protects intestines and hearts from warm ischemic injury. *Transplant Proc* 1999; **31**: 1018.
125. Katori M, Tamaki T, Takahashi T, Tanaka M, Kawamura A, Kakita A. Prior induction of heat shock proteins by a nitric oxide donor attenuates cardiac ischemia/reperfusion injury in the rat. *Transplantation* 2000; **69**: 2530.

126. Katori M, Tamaki T, Tanaka M, *et al.* Cytoprotective role of antioxidant stress protein induced by adenosine A1 receptor antagonist in rat heart ischemic injury. *Transplant Proc* 1999; **31**: 1016.
127. Chen S, Kapturczak MH, Wasserfall C, *et al.* Interleukin 10 attenuates neointimal proliferation and inflammation in aortic allografts by a heme oxygenase-dependent pathway. *Proc Natl Acad Sci USA* 2005; **102**: 7251.
128. Ke B, Shen X-D, Gao F, Busuttil RW, Kupiec-Weglinski JW. Interleukin 13 gene transfer in liver ischemia and reperfusion injury: role of Stat6 and TLR4 pathways in cytoprotection. *Hum Gene Ther* 2004; **15**: 691.
129. Cuturi MC, Christoph F, Woo J, *et al.* RDP1258, a new rationally designed immunosuppressive peptide, prolongs allograft survival in rats: analysis of its mechanism of action. *Mol Med* 1999; **5**: 820.
130. DeBruyne LA, Magee JC, Buelow R, Bromberg JS. Gene transfer of immunomodulatory peptides correlates with heme oxygenase-1 induction and enhanced allograft survival. *Transplantation* 2000; **69**: 120.
131. Magee JC, DeBruyne LA, Buelow R, Bromberg JS. Gene transfer of immunosuppressive peptides B2702 and RDP1257 prolongs allograft survival: evidence suggesting a role for heme oxygenase-I. *Transplant Proc* 1999; **31**: 1194.
132. Xu X, Man K, Zheng SS, *et al.* Attenuation of acute phase shear stress by somatostatin improves small-for-size liver graft survival. *Liver Transpl* 2006; **12**: 621.
133. Huang XS, Liu X, Chen DZ. Effect of ginkgo biloba extract preconditioning on discordant cardiac xenografts. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2006; **26** (Suppl.): 108.
134. Shen X-D, Ke B, Zhai Y, *et al.* Diannexin, a novel annexin V homodimer, protects rat liver transplants against cold ischemia-reperfusion injury. *Am J Transplant* 2007; **7**: 2463.
135. Kanitkar M, Bhonde RR. Curcumin treatment enhances islet recovery by induction of heat shock response proteins, Hsp70 and heme oxygenase-1, during cryopreservation. *Life Sci* 2008; **82**: 182.
136. Coito AJ, Shaw GD, Li J, *et al.* Selectin-mediated interactions regulate cytokine networks and macrophage heme oxygenase-1 induction in cardiac allograft recipients. *Lab Invest* 2002; **82**: 61.
137. Schnickel GT, Hsieh GR, Kachikwu EL, *et al.* Cytoprotective gene HO-1 and chronic rejection in heart transplantation. *Transplant Proc* 2006; **38**: 3259.
138. Chabannes D, Hill M, Merieau E, *et al.* A role for heme oxygenase-1 in the immunosuppressive effect of adult rat and human mesenchymal stem cells. *Blood* 2007; **110**: 3691.
139. Shoskes D, Lapierre C, Cruz-Correa M, *et al.* Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: a randomized placebo controlled trial. *Transplantation* 2005; **80**: 1556.
140. McNally SJ, Harrison EM, Ross JA, Garden OJ, Wigmore SJ. Curcumin induces heme oxygenase-1 in hepatocytes and is protective in simulated cold preservation and warm reperfusion injury. *Transplantation* 2006; **81**: 623.
141. Yao P, Nussler A, Liu L, *et al.* Quercetin protects human hepatocytes from ethanol-derived oxidative stress by inducing heme oxygenase-1 via the MAPK/Nrf2 pathways. *J Hepatol* 2007; **47**: 253.
142. Schmidt R. Cobalt protoporphyrin as a potential therapeutic agent? *FASEB J* 2007; **21**: 2639; author reply 40.
143. Sun L, Qiao HQ, Shi TF, *et al.* Expression of heme oxygenase-1 and GFP gene mediated by recombinant adeno-associated-virus in transplanted liver in rats. *Zhonghua Wai Ke Za Zhi* 2008; **46**: 851.
144. Ma J, Lau CK, Obed A, *et al.* A cell penetrating heme oxygenase protein protects heart graft against ischemia/reperfusion injury. *Gene Ther* 2009; **16**: 320.
145. Yue LH, Zhao YL, Chen J, Lu DR. Effect of fusion protein TAT and heme oxygenase-1 on liver sinusoidal endothelial cells apoptosis during preservation injury. *Chin Med J (Engl)* 2010; **123**: 68.