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5-Aminolevulinic acid regulates the inflammatory response and alloimmune reaction

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ABSTRACT

5-Aminolevulinic acid (5-ALA) is a naturally occurring amino acid and precursor of heme and protoporphyrin IX (PpIX). Exogenously administrated 5-ALA increases the accumulation of PpIX in tumor cells specifically due to the compromised metabolism of 5-ALA to heme in mitochondria. PpIX emits red fluorescence by the irradiation of blue light and the formation of reactive oxygen species and singlet oxygen. Thus, performing a photodynamic diagnosis (PDD) and photodynamic therapy (PDT) using 5-ALA have given rise to a new strategy for tumor diagnosis and therapy. In addition to the field of tumor therapy, 5-ALA has been implicated in the treatment of inflammatory disease, autoimmune disease and transplantation due to the anti-inflammation and immunoregulation properties that are elicited with the expression of heme oxygenase (HO)-1, an inducible enzyme that catalyzes the rate-limiting step in the oxidative degradation of heme to free iron, biliverdin and carbon monoxide (CO), in combination with sodium ferrous citrate (SFC), because an inhibitor of HO-1 abolishes the effects of 5-ALA. Furthermore, NF-E2-related factor 2 (Nrf2), mitogen-activated protein kinase (MAPK), and heme are involved in the HO-1 expression. Biliverdin and CO are also known to have anti-apoptotic, anti-inflammatory and immunoregulatory functions. We herein review the current use of 5-ALA in inflammatory diseases, transplantation medicine, and tumor therapy.

1. Introduction

5-Aminolevulinic acid (5-ALA) as described in detail in Table 1, a naturally occurring amino acid, is synthesized through the condensation of glycine and succinyl-CoA by the catalytic effect of 5-ALA synthase. In the cytosol, 5-ALA sequentially generates porphobilinogen, hydroxymethylbilane, uroporphyrinogen III and finally coproporphyrinogen III. In the mitochondrion, coproporphyrinogen III is metabolized to coproporphyrinogen III, protoporphyrinogen IX and protoporphyrin IX, into which iron is inserted via a ferrochelatase-catalyzed reaction, the latter resulting in the formation of heme [1–3]. 5-ALA is utilized as a precursor of a photosensitizer for performing a photodynamic diagnosis (PDD) and photodynamic therapy (PDT) to confirm and kill tumor cells [1,4]. Due to the substance's short half-life, the toxicity of 5-ALA is very low. The half-life of 5-ALA by 5-ALA administration (20 mg/kg) is 55.2 min in human (our unpublished data), 45 min in human (100 mg) [5], and 40.7 min in dog (7.29 mg/kg) [6]. As a result, clinically relevant photosensitivity is negligible. In addition to the utilization of PDD and PDT, 5-ALA has been undertaken to treat inflammatory disease, autoimmune disease and transplantation due to the anti-inflammation and immunoregulation properties by upregulation of heme oxygenase (HO)-1 expression and release of heme metabolites.

2. Tumor therapy

2.1. Tumor cells and PpIX accumulation

Several factors, although the preferential mechanisms are unknown, have been demonstrated to be involved in the accumulation of PpIX. The expression level of peptide transporter 1 (PEPT1)/solute carrier family 15 member 1 (SLC15A1), ATP-binding cassette sub-family G member 2 (ABCG2) [7,8], SLC6A6 and SLC6A13 [9], which are responsible for the import of 5-ALA and export of PpIX, and the activity of ferrochelatase [10,11] are key regulators of PpIX accumulation. Heme biosynthesis and the iron metabolism are also involved in PpIX accumulation. Inner mitochondrial membrane proteins (mitoferrin-1, which is mainly expressed in erythroid cells, and mitoferrin-2, which is expressed in various cells) are dependent on the transport of iron into mitochondria [12]. In the last step of heme biosynthesis, frataxin-mediated iron delivery to ferrochelatase occurs [13]. Ohgari et al. showed that the overexpression of mitoferrin-2 decreased PpIX

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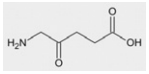
Table 1
Property of 5-aminolevulinic acid hydrochloride.

Structural formula	$C_5H_9NO_3 \cdot HCl$ 
Synonym	5-Amino-4-oxopentanoic acid hydrochloride
CAS no.	No. 5451–09-2
Molecular weight	167.6
Color	White to off-white
Melting point (°C)	144–147 (degradation)
pH (1 mol/L)	1.7
Water solubility	Very soluble

accumulation [14]. Furthermore, Sawamoto et al. showed that frataxin overexpressing cells had decreased the amount of intracellular PpIX accumulation [15].

2.2. 5-ALA and PDD

As shown in Fig. 1 (left), 5-ALA is incorporated into cells by exogenous administration and converted into PpIX, which is a fluorescent and has photoactivity. Specific irradiation at 375–475 nm wavelength excites PpIX and generates red fluorescence. PpIX has another property, which is its accumulation in tumor cells, and augmented red fluorescence results in the identification of tumor cells. Its emission of red fluorescence and accumulation in tumor cells are fundamental for PDD [16–18].

2.3. 5-ALA and PDT

PDT has become one of the standard procedures of cancer therapy, which is achieved by the generation of reactive oxygen species (ROS) and singlet oxygen by porphyrin derivatives through the irradiation of visible light [19–21]. PpIX metabolized from 5-ALA is one of the most efficacious photosensitizing agents for PDT [22,23]. The tumor-preferential accumulation of PpIX allows tumor therapy by 5-ALA-mediated PDT (Fig. 1 left).

3. 5-ALA and anti-inflammatory and immunoregulatory properties

3.1. HO-1

5-ALA has been demonstrated to induce the upregulation of heme oxygenase (HO)-1 mRNA levels [24,25]. In heme catabolism, HO functions as a rate-limiting enzyme. As shown in Fig. 1 (right), HO catalyzes heme degradation, thereby producing biliverdin, carbon monoxide (CO) and iron. HO-1 is the inducible isoform of HO [26] and the expression of HO-1 is induced by a range of stress stimuli [27–34], including heme [30,35] and other metalloporphyrins [36,37], in a number of cell types. Endotoxin exposure to mice with HO-1 deficiency results in a higher mortality from endotoxic shock, the upregulation of splenic proinflammatory cytokine secretion and increased hepatocellular necrosis compared with wild-type mice [38]. A study on individuals with HO-1-deficiency has strengthened the above finding and HO-1 has been shown to act as an important cytoprotective factor in counteracting the detrimental increase in oxidative injury and inflammation [39]. Similarly, an in vitro study confirmed that there is a reduction of stress resistance in HO-1-deficient cells [40].

3.2. HO-1 and signal transduction pathway

The signaling mechanisms that activate the transcription of HO-1 remain insufficiently elucidated. Many studies have focused on the activation of mitogen-activated protein kinases (MAPKs) related to cell growth and the stress response. The pathway of p38, c-Jun. N-terminal kinase (JNK) and extracellular signal regulated kinase (ERK) appear to participate to some degree in the upregulation of the HO-1 expression in response to various stimuli [41–43]. MAPK signaling leads to the translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) to the nucleus [43]. Nrf2 is a basic leucine zipper (bZip) transcription factor [44]. Under basal conditions, Bach1, which is also a bZip transcription factor [45], forms heterodimers with musculoaponeurotic fibrosarcoma oncogene homolog K (MafK), and these heterodimers

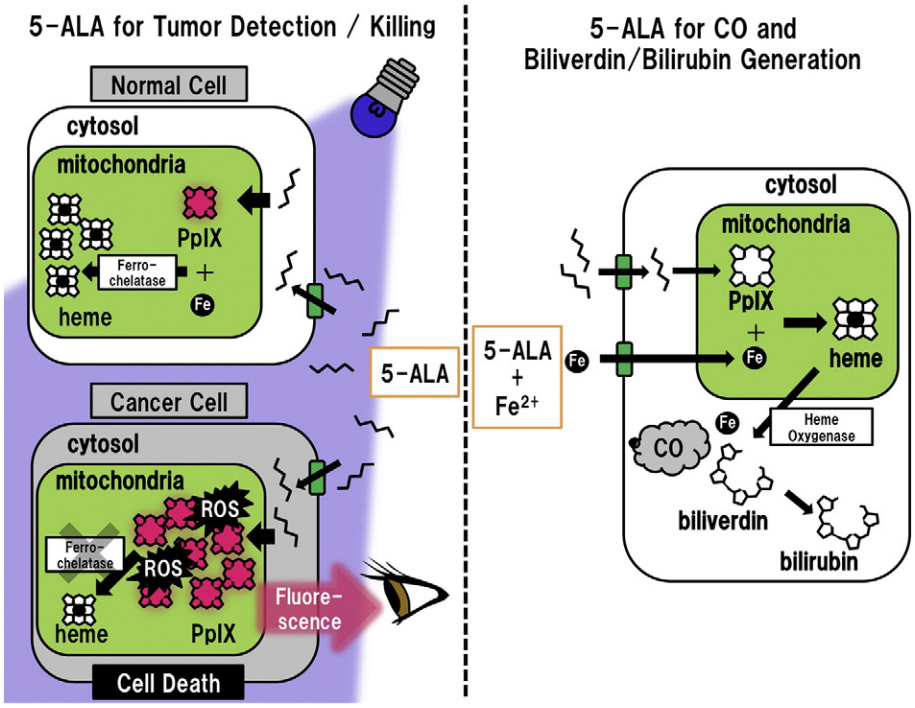


Fig. 1. PDD, PDT and anti-inflammatory/immunoregulatory structure and property of 5-ALA. In normal cell, 5-ALA produces PpIX, then heme is produced by aiding in the insertion of iron by ferrochelatase. In contrast, less ferrochelatase expression in cancer cell gives rise to accumulation of PpIX. 5-ALA with SFC produces heme and upregulates the expression of HO-1, which catalyzes heme to CO, Fe and biliverdin.

repress the transcription of HO-1 gene by binding to the sequence of the Maf recognition element (MARE) in the HO-1 promoter [46].

3.3. HO-1 and Nrf2

In response to various stimuli, Nrf2 translocates to the nucleus, which is followed by the subsequent induction of the HO-1 expression [27,47]. Nrf2 heterodimerizes with small Maf proteins (sMaf) in the induction of HO-1 through binding to MARE [45,46,48–50]. sMaf, which include MafF, MafG and MafK, possess a characteristic bZip domain that mediates DNA binding and dimerization with other bZip proteins such as Nrf2 [51]. Nrf2 resides in the cytosol bound to Keap1, a known negative regulator of Nrf2, in the cytoplasm [52,53]. Upon activation, Nrf2 is released from Keap1 and enters the nucleus, where it heterodimerizes with sMaf and binds to the MARE in the promoters of various target genes [49,52]. Hemin evokes the nuclear translocation of Nrf2 and Nrf2-specific siRNA suppresses the induction of HO-1 by hemin in human monocytes [54]. Other metalloporphyrins were also confirmed to cause the nuclear localization of Nrf2 followed by Nrf2-mediated HO-1 induction [36,37]. Moreover, HO-1 induction by lipopolysaccharide (LPS) was also inhibited by Nrf2 downregulation [27].

3.4. Heme

Heme controls the HO-1 expression [30,35,41,54]. The transcription factor Bach1 heterodimerizes with Maf proteins and binds to MAREs, thereby repressing MARE-dependent transcription, including the transcription of HO-1. In contrast, the DNA binding activity of Bach1 is negatively regulated by heme binding [55]. In the presence of higher concentrations of heme, increased binding of heme to Bach1 leads to a conformational change and a decrease in DNA binding activity [55,56]. This derepression permits Nrf2–sMaf and other activating heterodimers to occupy the MARE regions in the HO-1 promoter, and thus leads to increased transcription and upregulation of the gene expression.

3.5. CO

HO-1 catalyzes the conversion of heme to CO and biliverdin/bilirubin with the concurrent release of iron (Fe^{2+}). Exogenously added CO and biliverdin/bilirubin show a robust effect in antioxidation and protection against renal ischemia reperfusion injury (IRI) [57]. CO Exposure to the recipients improved the functions of the renal graft, the maintenance of internal cellular architecture, less frequent vacuolization, preservation of foot processes, and an ultrastructural improvement according to transmission electron microscopy of viable podocytes in a rat model of transplant-induced IRI [58]. Furthermore, the inhalation of CO reduced programmed tubular epithelial cell death and a decline in nitrite/nitrate formation and the expressions of interleukin (IL)-6, IL-1β, intercellular adhesion molecule (ICAM)-1 and inducible nitric oxide synthase (iNOS) [58]. In addition, previous reports indicated that CO inhibited not only acute and chronic allograft rejection, but also xenograft rejection in the field of transplantation [59–63]. Kidney IRI causes a profound problem that influences the outcome of renal transplantation [64]. Ten to 500 ppm concentrations of CO demonstrated both pharmacological and biological effects which prevented the onset of ischemic injury [62]. CO can confer the beneficial effects of anti-inflammatory and anti-cell death in IRI [65]. In a rat kidney transplantation model, inhalation of low concentration CO was shown to protect against cold IRI [66]. On the other hand, a theoretical risk of impaired O_2 delivery to organs and tissues by increasing carboxyhemoglobin has been reported in the context of endogenous CO administration [67,68]. Heme degradation through the activity of HO-1 generates CO during IRI and the administration of CO upregulates HO-1 expression, with the subsequent suppression of mouse-to-rat cardiac xenograft rejection [63].

3.6. Bilirubin/biliverdin

The treatment of bilirubin improved the mitochondrial integrity, tubular function, glomerular filtration rate, urine output and renal vascular resistance in IRI [69]. In renal transplant recipients, CO gas or biliverdin treatment alone could not recover proteinuria or a decreased creatinine clearance, whereas the concurrent administration of CO gas and biliverdin normalize all these parameters [70]. Furthermore, the extravasation of inflammatory infiltrates and upregulation of proinflammatory mediators in IRI were significantly low with combination treatment compared with untreated controls [70]. Previous reports assessing the effect of biliverdin/bilirubin and CO in IRI have suggested that biliverdin/bilirubin and CO presumably have an effect via different mechanisms according to the results of the above-mentioned report [70] and because the simultaneous administration of the two compounds showed additive protection [71].

3.7. HO-1 and regulatory dendritic cells (RegDC)

HO-1 has been identified as a potential regulator of DC maturation [72,73]. Al-Huseini et al. [74] demonstrated that the treatment of SnPP-IX, an inhibitor of HO-1, resulted in the mature phenotype of DC with impaired phagocytic and endocytic capacity and an enhanced ability to stimulate antigen-specific T cell proliferation.

4. Application of 5-ALA in inflammatory diseases and transplantation

4.1. Cardiomyocyte hypertrophy

Cardiac hypertrophy is a complex inflammatory disease that develops via the dysregulation of various signal transduction pathways and oxidative stress and excess ROS production and plays a definitive role in the pathogenicity of cardiac hypertrophy [75–77]. Using HL-1 cells, a murine cardiomyocyte cell line that maintains phenotypic characteristics of adult cardiomyocytes [78], and a well-established in vitro model of oxidant-induced cardiomyocyte hypertrophy [79], we evaluated the protective effect of 5-ALA/SFC on cardiac hypertrophy (unpublished data). Numerous studies have indicated that intrinsic antioxidants, including superoxide dismutase and vitamin E, can remit hypertrophy through the reduction of ROS generation [77,80,81]. Additionally, simvastatin, a reductase inhibitor, can function as an antioxidant and inhibit hypertrophy via the inhibition of ROS production [82]. A ubiquitous thiol oxidoreductase thioredoxin has also been demonstrated to prevent oxidative stress by direct scavenging of ROS [83]. H_2O_2 treatment induced planar morphometry, ^{3}H-leucine incorporation, and ROS production in HL-1 cells, and the expression of hypertrophy-related genes, including β-myosin heavy chain (β-MHC), atrial natriuretic factor (ANF), brain natriuretic peptides (BNP), and atrial natriuretic peptide (ANP), while 5-ALA/SFC significantly reduced these effects by H_2O_2. 5-ALA/SFC treatment elevated the expression of Nrf2 and HO-1 in dose- and time-dependent manners and Nrf2 knockdown decreased this 5-ALA/SFC-dependent effect. p38, ERK1/2, and JNK/stress-activated protein kinase (SAPK) were activated in HL-1 cells pretreated with 5-ALA/SFC, which was inhibited by pharmacological inhibitors of these kinases. [84].

4.2. Renal IRI

Reperfusion subsequent to ischemia generates ROS, mitochondrial failure, endothelial dysfunction, and sterile inflammation. Thus, IRI is a complex pathophysiological process involving oxidant damage and programmed cell death (PCD) that leads to acute renal failure (ARF). Approximately 50–70% of the mortality occurs in ARF patients in intensive care who require dialysis and among postoperative patients, 25–100% of them suffer from ARF. Regarding renal transplantation, renal IRI may elicit acute posttransplant tubular necrosis [85–88]

and delayed graft function [89,90]. Reperfusion provokes inflammation by the activation of enzymes and chemical mediators, such as prostaglandins, leukotrienes, lysozymes, phospholipase A2, and ROS, in renal IRI.

Significant cellular damage also induces the activation of macrophages and other parenchymal cells and the secretion of numerous inflammatory mediators, such as tumor necrosis factor (TNF)-α and IL-1β, which subsequently elicits extravasation of neutrophils, macrophages, and T lymphocytes to the interstitial space [91–94]. In our previous study [25], IRI in mice resulted in an exacerbated kidney function, as exhibited by increased serum levels of creatinine and blood urea nitrogen (BUN), and a decreased survival rate 24 h after IRI; in contrast, 5-ALA/SFC treatment prevented these events in a dose-dependent manner. Moreover, 5-ALA/SFC treatment prevented tubular vacuolization, congestion, necrosis, swelling and dilation by IRI. Furthermore, 5-ALA/SFC treatment inhibited PCD and the accumulation of macrophages in the kidneys compared with the no 5-ALA/SFC group after IRI. 5-ALA/SFC also inhibited the rise of thiobarbituric acid reactive substance (TBARS), a lipid peroxidation marker which is universally utilized to assess cellular injury as well as oxidative stress, following IRI. In 5-ALA/SFC-treated mice, CO in the kidney was significantly elevated and ZnPPIX, an inhibitor of HO-1, prevented CO production in the kidney. In addition, IRI and 5-ALA/SFC treatment increased the HO-1 expression in the kidney. These results suggested that 5-ALA/SFC can safeguard the kidneys against IRI by reducing renal cell apoptosis and macrophage invasion through CO generation.

4.3. Cardiac allograft

Organ transplantation is the optimal treatment for end-stage organ failure, while allografts are generally rejected by the recipient's immune system attacks. The exploitation of immunosuppressants and the refinement of surgical techniques have led to improvements in the short-term outcomes of organ transplantation. However, recipients have to remain on immunosuppressant therapy for their lifetime; hence, there is a risk of adverse effects that can cause infectious disease and carcinogenesis. Therefore, novel immunosuppressants with known independent mechanisms are required. We previously demonstrated [95] that 5-ALA/SFC treatment for the donor (C57BL/10; B10) and recipient (CBA/N; CBA) of cardiac allograft, but not 5-ALA or SFC alone, induced permanent acceptance of fully major histocompatibility complex (MHC)-mismatched cardiac allografts in a dose-dependent manner. 5-ALA/SFC prevented graft structure, $CD8^+$ T cell infiltration and obliterative vasculopathy, a characteristic of chronic graft rejection. Responder cells from 5-ALA/SFC-treated mice exhibited a reduced mixed lymphocyte reaction (MLR). A flow-cytometric (FCM) analysis of graft-infiltrating lymphocyte (GIL) and splenocytes from the recipients demonstrated that 5-ALA/SFC treatment increased the population of $CD4^+CD25^+FoxP3^+$ Tregs. The expression of immunomodulatory cytokines (HO-1, transforming growth factor (TGF)-β, IL-10) and transcript molecule transcription (Foxp3) in the grafts were upregulated by 5-ALA/SFC treatment. Furthermore, a GIL analysis showed that 5-ALA/SFC treatment increased the number of RegDCs in the graft and related mRNA expression (indoleamine 2,3-dioxygenase (IDO), iNOS and HO-1). The secondary CBA allograft recipients treated with adoptive transfer of splenocytes from 5-ALA/SFC-treated primary CBA recipients exhibited a significantly prolonged survival of the B10 hearts, but not BALB/c (third party) hearts. Furthermore, DCs from 5-ALA/SFC-treated recipient mice demonstrated a decline in the MLR, number of B10 stimulator cells and number of CBA responder cells as regulatory cells. The immunomodulatory effects of 5-ALA/SFC were abrogated by a HO-1 inhibitor.

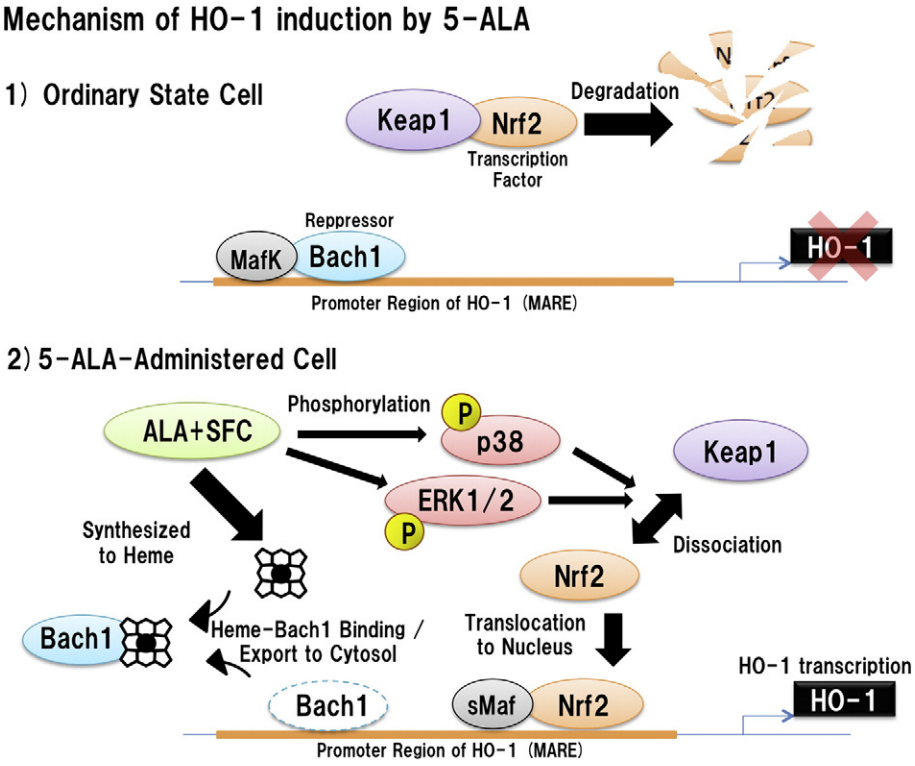


Fig. 2. Mechanism of HO-1 induction by 5-ALA. 5-ALA induced HO-1 expression through MAPK signal transduction and synthesized to heme. In the HO-1 induction based on our observations, treatment with 5-ALA combined with SFC (5-ALA/SFC) induces the phosphorylation of ERK and p38 MAPK. These activated MAPKs lead to HO-1 expression through their effects on post-transcriptional factors, such as Nrf2. In this pathway, 5-ALA/SFC indirectly regulated HO-1 expression. On the other hand, exposure to 5-ALA/SFC increases the intracellular levels of heme. Under conditions with a higher concentration of heme, the HO-1 repressor, Bach1, is inactivated by direct binding to heme to Bach1, which allows for increased expression of HO-1. In this pathway, 5-ALA/SFC directly regulated HO-1 expression (modified from Ref. [103]).

Table 2
Pleiotropic effects of ALA on immune-related diseases and transplantation.

Diseases	Main results	Articles
Cardiomyocyte hypertrophy	5-ALA + SFC alleviate the H_2O_2-induced hypertrophy-like symptoms in HL2 cardiomyocyte cell line.	Zhao et al. 2015 [84]
Renal ischemia reperfusion injury	5-ALA + SFC alleviate renal injury induced by Ischemia reperfusion through CO generation.	Hou et al. 2013 [25]
Heart transplantation	In cardiac allograft transplantation model, administration of 5-ALA + SFC to donor and recipient induces permanent acceptance of the graft. The number of regulatory T cells and regulatory dendritic cells is increased in this model.	Hou et al. 2014 [95]
-	HO-1 protein is induced by 5-ALA + SFC administration to macrophage cell line RAW264 via MAPK phosphorylation and negative regulation of Bach1.	Nishio et al. 2014 [103]
Graft versus host disease/systemic sclerosis	In graft versus host disease/systemic sclerosis model (allogenic bone marrow transplantation to the immunodeficient mice), 5-ALA + SFC ameliorate skin fibrosis, vascular damage, and macrophage infiltration.	Unpublished
Chronic cyclosporine nephropathy	5-ALA + SFC ameliorate cyclosporine A-induced inflammation and fibrosis in kidneys of mice.	Unpublished

4.4. Systemic sclerosis (SSc)

Alloreactive immune reactions from donor-derived immune cells to host cell populations induce graft-versus-host disease (GvHD). Transplantation of bone marrow and splenocytes from B10.D2 mice into BALB/c Rag2$^{-/-}$ recipients is a well-known animal model for human sclerodermatous chronic GvHD and SSc, which exhibit many clinical similarities [96]. Histologically, the invasion of mononuclear cells into the dermis concomitant with an increase in collagen synthesis has been shown in the early stages of SSc and sclerodermatous chronic GvHD in mice. In our experiment (unpublished data), treatment of 5-ALA/SFC ameliorated the decline in body weight in the murine sclerodermatous chronic GvHD model and inhibited the severity and fibrosis and vascular damage in SSc. Furthermore, treatment of 5-ALA/SFC also prevented collagen-1 overproduction and the infiltration of CD4$^+$ T cells and macrophages into the skin. Moreover, 5-ALA/SFC treatment diminished the expression of mRNA related inflammation and SSc, including TGF-β, iNOS, interferon (IFN)-γ, TNF-α, IL-6, and RANTES in the skin.

4.5. Chronic cyclosporine nephropathy

Cyclosporine (CsA), an inhibitor of calcineurin, was clinically approved for use in the early 1980s and has revolutionized transplant medicine. CsA remains an attractive agent for immunosuppression in various solid organ transplantations. Despite the remarkable improvement in the rejection rates and graft survival, side effects were found with the early stage of its use. One of the most serious adverse reactions is nephrotoxicity due to long-term CsA usage. In mice, the administration of CsA (30 mg/kg/day s.c.) with a low salt diet for 4 weeks increases the BUN and serum creatinine levels and decreases the glomerular filtration rate (GFR) along with morphological changes, resulting in renal endothelial dysfunction, arteriolar injury, tubular atrophy and interstitial fibrosis. Bing et al. [97] demonstrated that nephropathy induced by CsA appears to involve the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, renin angiotensin system, and the overexpression of TGF-β and IL-6 in endothelial cells. In our experiment, treatment with 5-ALA/SFC significantly reduced progressive inflammation and fibrosis in the kidney. The elevated

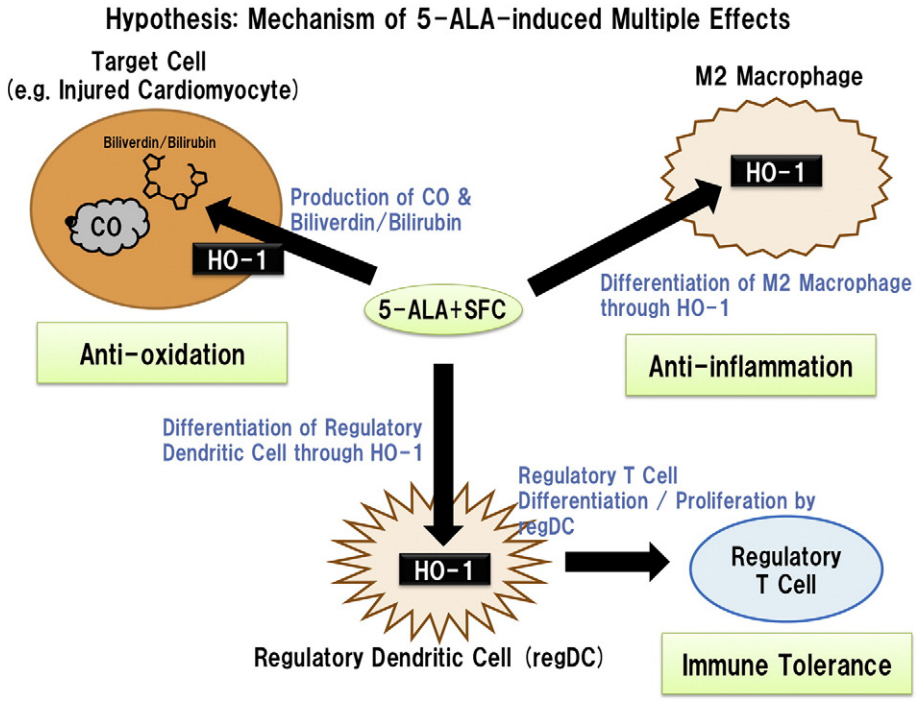


Fig. 3. Hypothetical mechanism of 5-ALA-induced multiple effects. 5-ALA/SFC-incorporated cell induce HO-1 expression and exert the anti-oxidative and/or anti-inflammatory and immune regulatory response.

expression of HO-1 in the mouse kidney was shown in 5-ALA/SFC administration. Further, 5-ALA/SFC was shown to attenuate tubulointerstitial fibrosis and renal apoptosis in chronic cyclosporine nephropathy (unpublished data).

5. HO-1 expression by 5-ALA/SFC in macrophages

Activated macrophages play an important role in inflammatory diseases including IRI, CsA-nephropathy and SSc. The early infiltration of macrophages plays an important pathogenic role in these diseases, presumably by the release of proinflammatory cytokines and chemokines [93]. Furthermore, macrophages have been known to be responsible for allograft rejection and GvHD development [98,99]. The production of inflammatory cytokines, including IL-1, IL-18 and TNF-α, as well as ROS and eicosanoids by macrophages may promote donor allograft rejection [100,101], while the acquisition of the regulatory phenotype in macrophages may attenuate the alloimmune response [101]. Additionally, we found that DCs treated with 5-ALA/SFC showed a regulatory phenotype (unpublished data). Furthermore, Sierra-Filardi et al. [102] demonstrated that HO-1 is important for the anti-inflammatory activities of M2 macrophages. Therefore, we performed an experiment to determine the effect and signal transduction of 5-ALA/SFC in macrophages with a particular focus on the expression of HO-1 [103]. As shown in Fig. 2, the combination of 5-ALA/SFC significantly upregulated the HO-1 expression compared with 5-ALA or SFC alone in a dose- and time-dependent fashion. The ERK and p38 MAPK signaling pathways were upregulated by 5-ALA/SFC and pharmacological inhibitors of these pathways inhibited the upregulated HO-1 expression by 5-ALA/SFC. 5-ALA/SFC induced the translocation of Nrf2 from the cytosol to the nucleus, and Nrf2 knockdown prevented the HO-1 expression by 5-ALA/SFC. 5-ALA/SFC increased the intracellular heme and induced the binding of heme to Bach1. Bach1 knockdown upregulated the HO-1 expression. These data suggested that HO-1 expression by 5-ALA/SFC in macrophages is one of the key factors in the anti-inflammatory effect of 5-ALA/SFC treatment.

6. Conclusion

5-ALA clearly exerts immunological effects that may potentially be used to alter the immune responses in autoimmune pathologies, allografting and GvHD (Table 2). Although the impact of 5-ALA treatment in cancer has been well characterized, the use of 5-ALA for both immunological diseases and allografting requires further investigation (Fig. 3). Specifically, whether or not 5-ALA can be administered in high enough doses to exert an immunosuppressive effect remains unclear, however, this is an interesting new treatment option and further research in the area should be encouraged. Taken together, these results have important implications for the potential use of 5-ALA/SFC in the treatment of sclerodermatous chronic GvHD and SSc in humans.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

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