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Forum Review

Solar Ultraviolet A Radiation: An Oxidizing Skin Carcinogen that Activates Heme Oxygenase-1

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ABSTRACT

Ultraviolet A (UVA: 320–380 nm) radiation is an oxidizing carcinogen that has proved an ideal agent for demonstrating the oxidant inducibility of the mammalian heme oxygenase-1 (HO-1) gene. The UVA response in cultured human skin fibroblasts and other cell types is mediated by singlet oxygen and is strongly influenced by cellular reducing equivalents. Free heme, an entity that can be generated by UVA irradiation of cells, also appears to be a critical intermediate that can directly influence both the transcriptional activation and repression of the HO-1 gene. Heme release is likely to be of central importance to the inflammatory response in skin and its abrogation by HO. *Antioxid. Redox Signal.* 6, 835–840.

INTRODUCTION

THE ULTRAVIOLET COMPONENT OF SOLAR RADIATION is conveniently divided into the UVB (290–320 nm) wavelengths that are primarily DNA-damaging and the UVA (320–380 nm) wavelengths that generate a strong oxidative stress in cells (32). Although UVB radiation appears responsible for most of the initial events involved in photocarcinogenesis, UVA is also a carcinogen and may play a crucial role in the cancer-promoting properties of sunlight.

The antioxidant potential of cells is a crucial factor in preventing UVA damage, so that it was a logical step to attempt to link the observation that this component of sunlight could induce (see below) the well characterized heme-catabolizing enzyme heme oxygenase (HO) (22, 31) with the properties of this enzyme as a crucial component of cellular adaptation to oxidative stress. The resulting observations form an integral part of our understanding of the role of this fascinating enzyme.

THE IDENTIFICATION OF HO AS AN OXIDANT-INDUCIBLE GENE

In the spring of 1987, we reported the strong induction of a major 32-kDa stress protein by specific UVA (334 nm, 365 nm) and near-visible (405 nm) wavelength radiation and other oxidants in cultured human skin fibroblasts (16). Importantly, the protein was only minimally induced by the shorter UVB wavelengths. Experiments published the previous year (8, 14, 29) and earlier (21) demonstrated that sulfhydryl reagents, heavy metals, and tumor promoters were also able to induce a 32-kDa protein in rodent and human cells, and we speculated that this could be the same protein. As peptide mapping had determined that the proteins induced by arsenite, peroxide, and UVA were identical (16), we went on to isolate specific cDNA clones that hybridized to mRNA, which could in turn generate p32 proteins by *in vitro* translation that were identical (by peptide mapping, etc.) to the UVA-induced protein (17). The availability of 5′ sequence enabled us to

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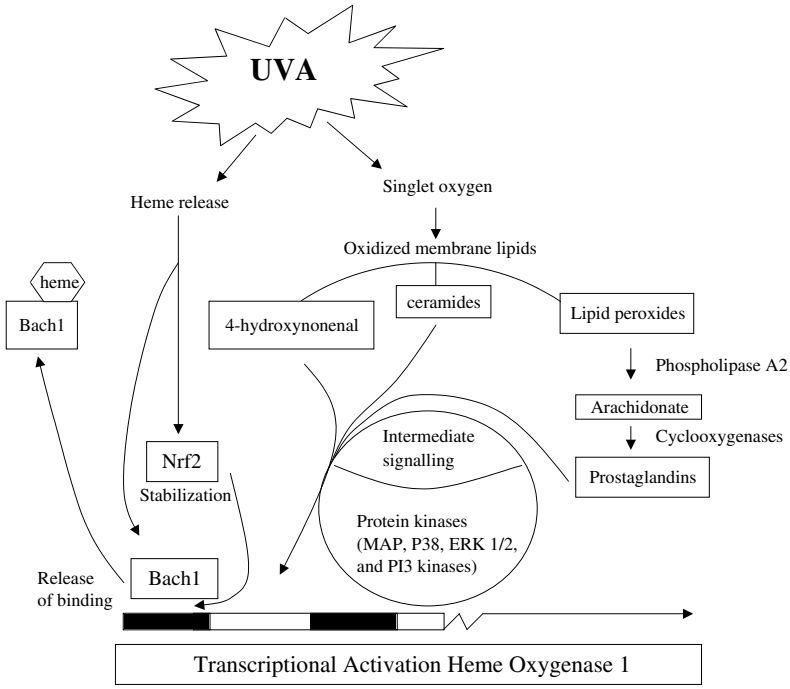

FIG. 1. UVA radiation generation of intermediates that lead to transcriptional activation of the HO-1 gene. Singlet oxygen generated by UVA can create a series of membrane lipids all shown to be involved in transcriptional activation of the gene. UVA-induced heme release from heme-containing proteins may influence the status of the transcriptional activator (Nrf2) and transcriptional repressor (Bach1) proteins (see also Fig. 2). ERK, extracellular signal-regulated kinase; MAP, mitogen-activated protein; PI3 kinase, phosphatidylinositol 3-kinase.

identify the original protein as HO-1 by the high homology of our cDNA to the cDNA corresponding to the rat gene in the EMBL database. This in turn led us to confirm the 100% homology with the published sequence for human HO-1 (37). A similar, but entirely independent, study published while our report was under review confirmed that the 32-kDa protein induced in rat fibroblasts by heat shock, metal salts, and tumor promoters was the rodent form of HO-1 (15). Using a wide range of cell lines (2), we determined that the induction of HO was a general response to oxidant stress in mammals. These studies and others established HO as a major stress protein induced by a variety of agents in addition to oxidants. However, it is misleading to refer to the human protein as a heat shock protein (*e.g.,* HSP32) because, although the rodent gene is clearly strongly induced by heat shock, the human protein is induced at most to low levels by a variety of heat shock treatments (16, 17).

OXIDANT INDUCIBILITY OF HO-1 AND THE INTERMEDIATES INVOLVED

Although both UVA radiation and hydrogen peroxide strongly induce HO-1 in human cells, it is likely that they do so through independent pathways. UVA can generate hydrogen peroxide in cells (32), and in initial experiments with strong iron chelators (18), we concluded that hydroxyl radical generated via Fenton chemistry was an important intermediate in UVA-induced gene activation. However, it is now evident that strong iron chelators such as desferrioxamine strongly induce hypoxia-inducible factor (9) and that mild iron chelators, which also effectively remove labile iron (9), do not modify the UVA-mediated up-regulation of the HO-1 gene (this laboratory, unpublished observations). This implies that free iron is not involved in generating the species that leads to UVA up-regulation, whereas it clearly is involved in the up-regulation by peroxide.

There is very strong evidence that singlet oxygen generated via the interaction of UVA with an as yet unidentified chromophore is the primary intermediate in UVA activation of the gene (6; see Fig. 1). Indeed, this work provided the first example of singlet oxygen as an early messenger molecule in signal transduction. The lack of free iron involvement in UVA activation of HO-1 (see above) strongly implies that the lipid peroxides generated by the lipid peroxidation chain reaction (which will be accelerated by iron) are not involved. However, there is indirect evidence that the initiation of peroxidation of intracellular membranes by UVA radiation can trigger phospholipase activation and release of arachidonic acid, which in turn will be metabolized by cyclooxygenase to prostaglandin intermediates involved in downstream signal transduction (7). In further support of this hypothesis is the observation that indomethacin (a cyclooxygenase inhibitor) completely abrogates the strong activation of HO-1 mRNA accumulation by UVA radiation. Studies in several laboratories have shown that various prostaglandins can activate HO-1 (11, 27). However, nonenzymatic pathways may also be important in UVA activation of HO-1 because it has been shown that the lipid peroxidation product, 4-hydroxynonenal, is an extremely powerful activator of HO-1 in human skin fibroblasts (7). Ceramide generation (12) has also been implicated in UVA activation of genes. The role of lipid oxidation in HO-1 activation is particularly pertinent because it is known that the enzyme mediates an adaptive response involving protection against oxidant-mediated membrane damage (34).

Reduced glutathione (GSH) provides the major source of reducing equivalents in most cell types and is present constitutively at 3–5 m*M* in cultured skin cells. Depleting cellular GSH leads to a dramatic further increase in both UVA- and

hydrogen peroxide-induced HO-1 mRNA accumulation (20). GSH depletion and conjugation had been shown previously to enhance induction of a 32-kDa stress protein, presumably HO-1 (10, 29). Both UVA and peroxide cause a depletion in cellular GSH and an enhancement in oxidized glutathione (GSSG). It appears likely that the enhanced gene activation in GSH-depleted cells results from the diminished potential of these cells to reduce/detoxify active intermediates, and such data strongly support the concept of HO-1 as an oxidant-inducible gene. It is also possible that lowered GSH levels lead to modification of critical signaling intermediates that enhance gene expression, and there are now several examples of redox regulation of critical protein factors. Sulfhydryl reactive agents all appear to induce HO-1. Interestingly, depletion of GSH alone leads to a fivefold enhancement of HO-1 mRNA accumulation in cultured skin fibroblasts, indicating either an altered reduction state of a critical signaling intermediate/transcription factor or that cellular metabolic activity alone generates sufficient active intermediates to modulate gene expression. It is therefore pertinent to note that the unnatural oxygen tensions in standard cell culture may generate levels of basal gene expression of oxidant-inducible genes higher than those occurring in the normal tissue environment. Very low levels of HO-1 protein are present in lymphocytes and monocytes isolated from freshly drawn blood, but these are enhanced by *ex vivo* hyberbaric oxygen (28) or hydrogen peroxide treatment (23).

HEME AS AN INTERMEDIATE IN HO-1 ACTIVATION

There is now a wealth of evidence demonstrating cytoprotective, antiapoptotic, and antiinflammatory effects of HO (for a recent review, see 36). The mechanism by which these effects are mediated is still far from clear, although much is now known about the potential role of the heme catabolic products carbon monoxide, biliverdin, and iron, and each may have a role according to the biological/pathological events being considered. The catabolism and removal of heme itself, the primary function of HO, could be a critical factor because heme and heme proteins are toxic when present in excess and/or released from their normal compartments (5, 24).

Heme appears central to the UVA response. The compound is a strong UVA chromophore such that many heme proteins, including catalase, are rapidly degraded by UVA radiation. Protoporphyrin IX, the immediate precursor to heme (lacking iron in the heme macrocycle), is a potent photosensitizer that generates singlet oxygen when irradiated with UVA and, as a consequence, strongly activates HO-1. Microsomal heme proteins are found to be immediately degraded in human skin fibroblasts following relatively low doses of UVA radiation with the consequent release of free heme (19). Interestingly, it is possible to establish a correlation between the levels of free heme released by various agents and the levels of HO-1 mRNA accumulation induced, consistent with the notion that heme is a key factor in the up-regulation of the gene. Hydrogen peroxide, the other classical oxidant used in HO studies, also leads to a release of heme from heme-containing proteins. It is therefore pertinent to note that heme has been intimately linked to various aspects of the transcriptional activation/repression of the HO-1 gene (Fig. 2; see also Alam *et al.,* 2004, this issue and reference 30). Transcriptional activation by several HO-1 inducers has been shown to involve binding of an NF-E2-related factor (Nrf2)/small musculoaponeurotic fibrosarcoma (Maf) protein heterodimer complex to the Maf recognition element (MARE) sites that occur in two distinct regions of the mouse and human HO-1 promoter. Nrf2 is normally held in the cytoplasm by the Keap-1 protein, but is released under stress conditions. It is then subject to degradation, but heme itself enhances the stability of the Nrf2 protein by an order of magnitude, strongly increasing the probability of occupation of the MARE sites by the Nrf2 complex (Fig. 2B). There is evidence that a Bach1/small Maf protein heterodimer complex can compete for Nrf2 complexes on the MARE site and lead to transcriptional suppression. Apparently, Bach1 has a heme binding site and when bound to heme, the DNA-binding capacity is lost and the complex dis-

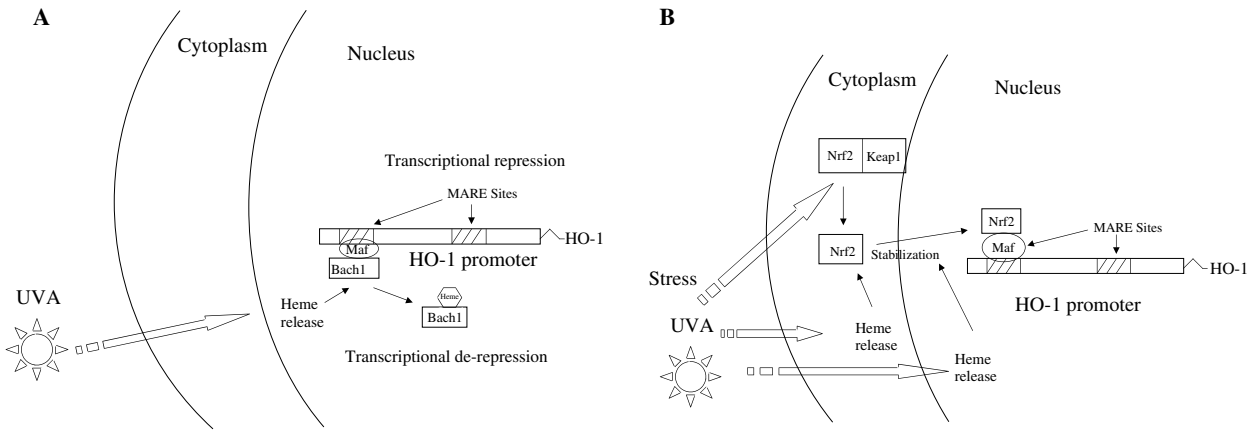

FIG. 2. A tentative model for transcriptional activation of the HO-1 gene. Heme released by UVA radiation will bind to the Bach1 repressor protein and relieve binding of the Bach1/Maf complex to the MARE sites of the HO-1 promoter (**A**). In addition, the heme may contribute to the stabilization of the Nrf-2 newly released from its cytoplasmic anchor (Keap1) by UVA stress and thereby enhance binding of this activator protein to the MARE sites (**B**).

sociates from the MARE site (Fig. 2A) to allow occupation by the Nrf2 activation complex (Fig. 2B). Although *in vivo* proof of this mechanism for UVA regulation of HO-1 transcription is not complete, the observations to date are consistent with the conclusion that free heme can both enhance stabilization of the activation complex and lead to reduced binding of the suppressor complex, thus strongly contributing to transcriptional activation of the HO-1 gene.

As Bach1 protein itself can bind to heme, it is likely that Bach1/heme complexes will be present *in vivo* and these will present a chromophore/target for UVA radiation. The photochemical destruction of such complexes may itself signal *de novo* synthesis of the protein. Indeed we have evidence (Raval, Basu-Modak, and Tyrrell, unpublished observations) that UVA radiation strongly stimulates Bach1 mRNA synthesis. This may eventually lead to an overexpression of Bach1 and could explain the total refractoriness to reinduction of HO-1 that develops slowly during the 48 h following an initial UVA treatment (25).

HO IN THE SKIN

The UVA component of sunlight strongly activates HO-1 in cultured skin fibroblasts. A similar induction is seen in human skin-derived melanocytes (Applegate and Tyrrell, this laboratory, unpublished observations). However, no UVA induction of HO-1 is seen in keratinocytes cultured from human foreskin explants (3). Interestingly, HO-2 is constitutively present in keratinocytes, and HO activity in these cells matches those found after maximum UVA induction in fibroblasts. Ferritin, the iron storage protein, appears to mediate part of the protective role provided by HOs (4, 33) and, consistent with observations of HO activity, basal levels of ferritin in keratinocytes match those induced by UVA radiation in fibroblasts.

Given that dermal skin fibroblasts are shielded by the overlying epidermis and stratum corneum, it appears metabolically economic to have an inducible adaptive response to UVA radiation in these cells rather than constitutive defense. On the other hand, the epidermis is in the first living tissue to be encountered by the penetrating UVA radiation component of sunlight and will therefore benefit from a strong constitutive antioxidant defense such as that provided by the HO/ferritin system. The pattern of expression of HO-1 and HO-2 enzymes in cultured skin cells (described above) closely reflects that seen in human skin (Applegate and Tyrrell, unpublished observations). Strong activation of HO-1 is seen in the dermis, whereas HO-1 expression in the epidermis is weak except in the cells lining the hair follicles. However, it has recently been reported that HO-1 mRNA and protein are higher in the skin derived from patients with the inflammatory skin disease, psoriasis, with the highest levels being found in the hyperproliferative epidermis (13) so that HO-1 expression may be associated with rapid proliferation in keratinocytes. In addition to the observations in skin from psoriatic patients, HO-1 expression has been observed in the epidermis and infiltrated leukocytes of a patient suffering from chronic inflammation (35).

Activation of HO also appears to be strongly implicated in wound healing in rodent skin (13, 35). Although one study (35) attributed most of the increased expression of HO-1 to newly recruited fibroblasts and macrophages in the wounded area, a previous study (13) concluded that part of the response originated from keratinocytes in the hyperproliferative epithelium. The precise origin of the HO-1 observed requires further clarification, but it is clear from the studies in human inflammatory skin conditions (*e.g.,* psoriasis) and rodent wound healing studies that enhanced HO-1 levels are associated with the proliferating epidermis. In view of the crucial role of heme in HO-1 regulation described above, it is highly relevant that newly released heme may play a major part in the inflammatory response induced by wounding (35) because the concomitant induction of HO-1 may abrogate and thereby regulate the response.

HO has also been implicated in protection against immunosuppression in UVB-irradiated mouse skin (26). UVA radiation abrogates the immunosuppression mediated by the shorter UVB wavelengths, and this can be almost entirely accounted for by UVA induction of HO activity. However, it should be noted that expression of HO-1 in the epidermis of mouse and human appears to be markedly different. Whereas HO-1 levels are low in the epidermis (and dermis) of normal human skin and there is no evidence for UVA induction (13), high levels of the inducible isoform appear to be present in the epidermis of rodent skin (35) and the rodent enzyme appears to be UVA-inducible in mouse epidermis (1). These differences need to be understood and further experiments undertaken in human skin before a full interpretation of rodent experiments can be related to the human skin response.

Although studies with cultured human skin cells and many other cells of mammalian origin first established the stress response involving activation of HO as being oxidant-inducible, it now appears that the release of free heme may be the common factor in the oxidant-mediated response and indeed in the initiation of the inflammatory response abrogated by HO. Heme is directly relevant to the response of skin to oxidizing UVA radiation because heme-containing compounds (such as cytochromes) and precursors (such as protoporphyrin IX) are strong chromophores for UVA radiation. Absorption of UVA by porphyrins and heme-containing proteins is almost certainly responsible for both the generation of singlet oxygen that is a crucial early signaling event in the UVA response and the release of free heme (from heme-containing protein) that appears to play such a central role in regulating the activation of HO-1.

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ABBREVIATIONS

Bach, BTB and CNC homology; GSH, reduced glutathione; GSSG, oxidized glutathione; HO, heme oxygenase; Maf, musculoaponeurotic fibrosarcoma; MARE, Maf recognition element; Nrf2, NF-E2-related factor; UVA, ultraviolet

A (320–380 nm) radiation; UVB, ultraviolet B (290–320 nm) radiation.

REFERENCES

1. Allanson M and Reeve VE. Immunoprotective UVA (320–400 nm) irradiation upregulates heme oxygenase-1 in the dermis and epidermis of hairless mouse skin. *J Invest Dermatol* 122: 1030–1036, 2004.
2. Applegate LA, Lüscher P, and Tyrrell RM. Induction of heme oxygenase: a general response to oxidant stress in cultured mammalian cells. *Cancer Res* 51: 974–978, 1991.
3. Applegate LA, Noël A, Vile GF, Frenk E, and Tyrrell RM. Two genes contribute to different extents to the heme oxygenase enzyme activity measured in cultured human skin fibroblasts and keratinocytes: implications for protection against oxidant stress. *Photochem Photobiol* 61: 285–291, 1995.
4. Balla G, Jacob HS, Balla J, Rosenberg M, Nath K, Apple F, Eaton JW, and Vercellotti GM. Ferritin: a cytoprotective antioxidant stratagem of endothelium. *J Biol Chem* 267: 18148–18153, 1992.
5. Balla J, Vercellotti GM, Nath K, Yachie A, Nagy E, Eaton JW, and Balla G. Haem, haem oxygenase and ferritin in vascular endothelial cell injury. *Nephrol Dial Transplant* 18: v8–v12, 2003.
6. Basu-Modak S and Tyrrell RM. Singlet oxygen. A primary effector in the UVA/near visible light induction of the human heme oxygenase gene. *Cancer Res* 53: 4505–4510, 1993.
7. Basu-Modak S, Lüscher P, and Tyrrell RM. Lipid metabolite involvement in the activation of the human heme oxygenase-1 gene. *Free Radic Biol Med* 20: 887–897, 1996.
8. Caltabiano MM, Koestler TP, Poste G, and Grieg RG. Induction of 32- and 34-kDa stress proteins by sodium arsenite, heavy metals, and thiol-reactive agents. *J Biol Chem* 261: 13381–13386, 1986.
9. Creighton-Gutteridge MG and Tyrrell RM. A novel iron chelator that does not induce HIF-1 activity. *Free Radic Biol Med* 33: 356–363, 2002.
10. Freeman ML and Meredith MJ. Glutathione conjugation and induction of a 32 000 dalton stress protein. *Biochem Pharmacol* 38: 299–304, 1989.
11. Gong P, Stewart D, Hu B, Li N, Cook J, Nel A, and Alam J. Activation of the mouse heme oxygenase-1 gene by 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 is mediated by the stress response elements and transcription factor Nrf2. *Antioxid Redox Signal* 4: 249–257, 2002.
12. Grether-Beck S, Bonizzi G, Schmitt-Brenden H, Felsner I, Timmer AH, Johnson JP, Piette J, and Krutmann J. Non-enzymatic triggering of the ceramide signalling cascade by solar UVA radiation. *EMBO J* 19: 5793–5800, 2000.
13. Hanselmann C, Mauch C, and Werner S. Haem oxygenase-1: a novel player in cutaneous wound repair and psoriasis? *Biochem J* 353: 459–466, 2001.
14. Hiwasa T and Sakiyama S. Increase in the synthesis of a Mr 32,000 protein in BALB/c 3T3 cells after treatment with tumor promoters, chemical carcinogens, metal salts, and heat shock. *Cancer Res* 46: 2474–2481, 1986.
15. Kagayama H, Hiwasa T, Tokunaga K, and Sakiyama S. Isolation and characterization of a complementary DNA clone for a Mr 32,000 protein which is induced with tumor promoters in BALB/c 3T3 cells. *Cancer Res* 48: 4795–4798, 1988.
16. Keyse SM and Tyrrell RM. Both near ultraviolet radiation and the oxidizing agent hydrogen peroxide induce a 32-kDa stress protein in normal human skin fibroblasts. *J Biol Chem* 262: 14821–14825, 1987.
17. Keyse SM and Tyrrell RM. Heme oxygenase is the major 32-kDa stress protein induced in human skin fibroblasts by UVA radiation, hydrogen peroxide and sodium arsenite. *Proc Natl Acad Sci U S A* 86: 99–103, 1989.
18. Keyse SM and Tyrrell RM. Induction of the heme oxygenase gene in human skin fibroblasts by hydrogen peroxide and UVA (365 nm) radiation: evidence for the involvement of the hydroxyl radical. *Carcinogenesis* 11: 787–791, 1990.
19. Kvam E, Noel A, Basu-Modak S, and Tyrrell RM. Cyclooxygenase dependent release of heme from microsomal heme proteins correlates with induction of heme oxygenase 1 transcription in human fibroblasts. *Free Radic Biol Med* 26: 511–517, 1999.
20. Lautier D, Lüscher P, and Tyrrell RM. Endogenous glutathione levels modulate both constitutive and UVA radiation/oxidant-inducible expression of the human heme oxygenase gene. *Carcinogenesis* 13: 227–232, 1992.
21. Levinson W, Oppermann H, and Jackson J. Transition series metals and sulfhydryl reagents induce the synthesis of four proteins in eukaryotic cells. *Biochim Biophys Acta* 606: 170–180, 1980.
22. Maines MD. *Heme Oxygenase: Clinical Implications and Functions*. Boca Raton, FL: CRC Press, 1992.
23. Markovitch D, Thompson D, and Tyrrell RM. Heme oxygenase 1 induction following *ex-vivo* treatment in human lymphocytes and monocytes. *J Physiol* 555P PC74, 2004.
24. Nath KA, Balla G, Vercellotti GM, Balla J, Jacob HS, Levitt MD, and Rosenberg ME. Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *J Clin Invest* 90: 267–270, 1992.
25. Nöel A and Tyrrell RM. Development of refractoriness of induced human heme oxygenase-1 gene expression to reinduction by UVA irradiation and hemin. *Photochem Photobiol* 66: 456–463, 1997.
26. Reeve VE and Tyrrell RM. Heme oxygenase induction mediates the photoimmunoprotective activity of UVA radiation in the mouse. *Proc Natl Acad Sci U S A* 96**:** 9317–9321, 1999.
27. Rossi A and Santoro MG. Induction by prostaglandin A1 of haem oxygenase in myoblastic cells: an effect independent of expression of the 70 kDa heat shock protein. *Biochem J* 308: 455–463, 1995.
28. Rothfuss A, Radermacher P, and Speit G. Involvement of heme oxygenase-1 (HO-1) in the adaptive protection of human lymphocytes after hyperbaric oxygen (HBO) treatment. *Carcinogenesis* 22: 1979–1985, 2001.
29. Shelton KR, Egle PM, and Todd JM. Evidence that glutathione participates in the induction of a stress protein. *Biochem Biophys Res Commun* 134: 492–498, 1986.
30. Sun J, Brand M, Zenke Y, Tashiro S, Groudine M, and Igarashi K. Heme regulates the dynamic exchange of Bach1

and NF-E2-related factors in the Maf transcription factor network. *Proc Natl Acad Sci U S A* 101: 1461–1466, 2004.
31. Tenhunen R, Marver HS, and Schmid R. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. *Proc Natl Acad Sci U S A* 61: 748–755, 1968.
32. Tyrrell RM. UVA (320–380 nm) radiation as an oxidative stress. In: *Oxidative Stress: Oxidants and Antioxidants*, edited by Sies H. London: Academic Press, 1991, pp. 57–83.
33. Vile GF and Tyrrell RM. Oxidative stress resulting from ultraviolet A irradiation of human skin fibroblasts leads to a heme oxygenase-dependent increase in ferritin. *J Biol Chem* 268: 14678–14681, 1993.
34. Vile GF, Basu-Modak S, Waltner C, and Tyrrell RM. Heme oxygenase 1 mediates an adaptive response to oxidative stress in human skin fibroblasts. *Proc Natl Acad Sci U S A* 91: 2607–2610, 1994.
35. Wagener FA, van Beurden HE, von den Hoff JW, Adema GJ, and Figdor CG. The heme–heme oxygenase system: a molecular switch in wound healing. *Blood* 102: 521–528, 2003.
36. Wagener FA, Volk HD, Willis D, Abraham NG, Soares MP, Adema GJ, and Figdor CG. Different faces of the heme–heme oxygenase system in inflammation. *Pharmacol Rev* 55: 551–571, 2003.
37. Yoshida T, Biro P, Cohen T, Muller RM, and Shibahara S. Human heme oxygenase cDNA and induction of its mRNA by hemin. *Eur J Biochem* 171: 457–461, 1988.

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