Nrf2 as a master regulator of tissue damage control and disease tolerance to infection

Miguel P. Soares*[1] and Ana M. Ribeiro*
*Instituto Gulbenkian de Ciência, Rua da Quinta Grande, 62, 6, 2780-156 Oeiras, Portugal

Abstract

Damage control refers to those actions made towards minimizing damage or loss. Depending on the context, these can range from emergency procedures dealing with the sinking of a ship or to a surgery dealing with severe trauma or even to an imaginary company in Marvel comics, which repairs damaged property arising from conflicts between super heroes and villains. In the context of host microbe interactions, tissue damage control refers to an adaptive response that limits the extent of tissue damage associated with infection. Tissue damage control can limit the severity of infectious diseases without interfering with pathogen burden, conferring disease tolerance to infection. This contrasts with immune-driven resistance mechanisms, which although essential to protect the host from infection, can impose tissue damage to host parenchyma tissues. This damaging effect is countered by stress responses that confer tissue damage control and disease tolerance to infection. Here we discuss how the stress response regulated by the transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) acts in such a manner.

Introduction

Resistance to infection defines a defence strategy that limits host disease severity via immune driven mechanisms that target pathogens for expulsion, containment or killing. Disease tolerance defines a distinct defence strategy that limits host disease severity without however, targeting pathogens [1–3]. Described originally in plants [4], disease tolerance is operational in flies [5–7] and mammals, including in mice [8,9] as well as in humans [10]. The term disease tolerance is used hereby to refer explicitly to the defence strategy defined originally in the plant literature [4,11], which limits host 'damage to functions and structures' [4] imposed by infection, without interfering with host pathogen load [4,11].

Disease tolerance is regulated by a number of evolutionarily conserved stress and/or damage responses. These confer tissue damage control, i.e. prevent 'damage to functions and structures' imposed by infection [4,12]. Presumably, stress and/or damage responses evolved from ancestral forms of life where they provided cellular adaptation to environmental changes [13]. Much like resistance mechanisms, these adaptive responses evolved, most probably, under the selective pressure imposed by host microbe interactions.

Resistance mechanisms can elicit, *per se*, varying levels of cellular stress and damage to the host parenchyma, as illustrated for innate immune responses associated with the production of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). This is coupled to a countervailing oxidative stress response regulated by nuclear factor-erythroid 2-related factor 2 (Nrf2), a member of the cap'n'collar basic leucine zipper family transcription factor characterized structurally by the presence of Nrf2–ECH homology domains [14]. Other members of this family include NF–E2 p45, Nrf1 and Nrf3 [14].

Mechanisms regulating Nrf2 activation in the context of infection

Engagement of pattern recognition receptors (PRRs) by pathogen-associated molecular patterns (PAMP) activates Nrf2 in innate immune cells such as monocytes/macrophages (Mø). For example, lipopolysaccharide (LPS) recognition by toll-like receptor 4 (TLR4) triggers the transcription/expression of the inducible form of nitric oxide synthase (iNOS/NOS2), via a mechanism involving the adaptor molecule Myd88 (myeloid differentiation primary response gene 88) and the transcription factor nuclear factor kappa B (NF-κB) [15]. The TLR4–MyD88–NF-κB signal transduction pathway also triggers the transcription/expression of the phagocytic NADPH oxidase (NOX2/gp91^{phox}) [16], which generates intracellular superoxide ($O_2^{\bullet -}$). The NO generated by iNOS reacts with $O_2^{\bullet -}$ and produces peroxinitrate ($ONNO^-$) anions, which targets several thiol-based (S-H) redox systems, including reactive cysteines in the Kelch-like ECH-associated protein 1 (Keap1) [13,17,18] (Figure 1). Keap1 is an adaptor for the cullin (Cul)3–RING (really interesting new gene)-box protein (Rbx)1 ubiquitin ligase complex, which targets Nrf2 constitutively for proteolytic degradation by the 26s proteasome [13]. Under oxidative stress, some of the reactive cysteines of

Key words: disease tolerance, infection, Nrf2, oxidative stress, tissue damage control.

Abbreviations: ATF3, activating transcription factor 3; Cul, cullin; FtH, Ferritin H chain; GSK, glycogen synthase kinase; Hrd1, HMG-coA reductase degradation 1; IL, interleukin; iNOS/NOS2, inducible form of nitric oxide synthase; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; Mø, macrophages; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor-erythroid 2-related factor 2; $ONNO^-$, peroxinitrate; Rbx, RING box protein; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCF, Skp1–Cul1–F-box; $SCF^{\beta\text{-}TrCP}$, SCF–β-TrCP complex; sMaf, small musculoaponeurotic fibrosarcoma; TLR4, toll-like receptor 4; β-TrCP, β-transducin repeats-containing protein.

[1] **To whom correspondence should be addressed (email mpsoares@igc.gulbenkian.pt).**

Biochem. Soc. Trans. (2015) 43, 663–668; doi:10.1042/BST20150054

Figure 1 | Control of Nrf2 activation by different E3 ubiquitin ligase complexes

Acronyms are defined throughout the text. When no longer targeted for degradation by E3 ubiquitin ligase complexes, Nrf2 activity is controlled mainly by its rate of transcription, with newly transcribed Nrf2 regulating gene expression. It is the Keap1–Cul3–Rbx1, Hrd1 E3 ubiquitin ligase and SCF$^{\beta\text{-TrCP}}$ complexes, however that underlie the stress responsive nature of Nrf2 activity.

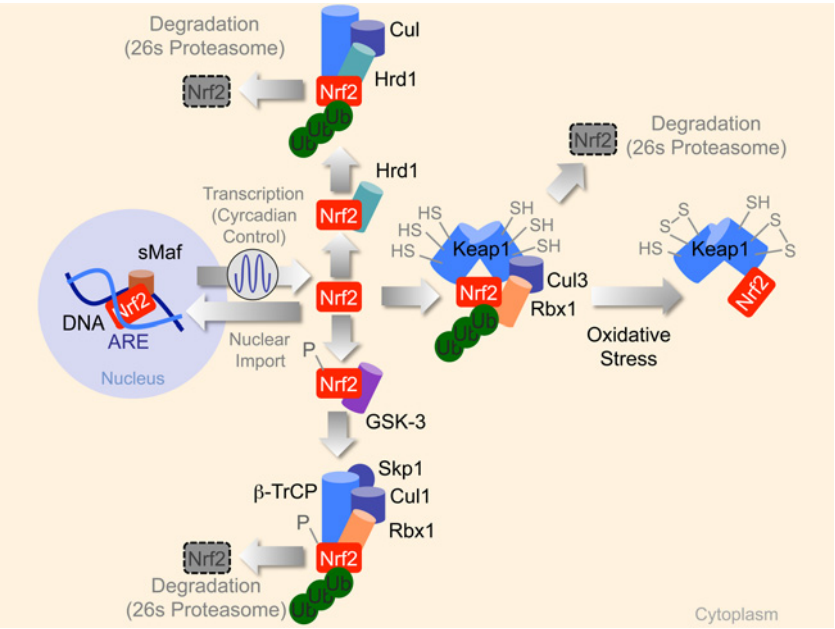
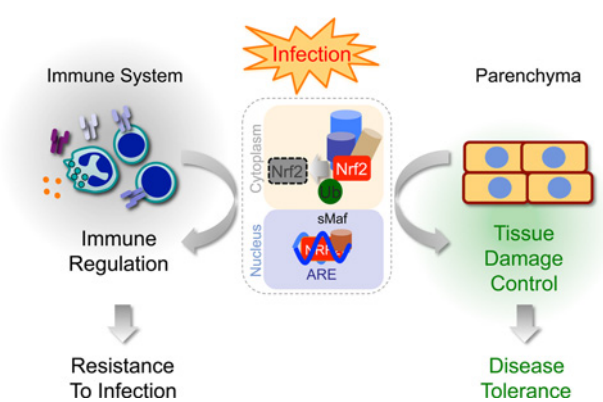


Figure 2 | Outcomes of Nrf2 activation

Upon infection, activation of Nrf2 in different cellular components of the immune system acts in an immunoregulatory manner, which modulates resistance to infection. Activation of Nrf2 in parenchyma tissues provides tissue damage control and disease tolerance to infection. Control of Nrf2 activation is illustrated in the context of a generic E3 ubiquitin ligase complex, detailed under Figure 2.



Keap1, i.e. Cys^{151} are targeted by $ONNO^-$, generating thiol oxidation products and ultimately forming disulfide bonds [19]. These alter the tertiary structure of Keap1, inhibiting its ubiquitin ligase activity and Nrf2 degradation [13,17,18]. The newly transcribed Nrf2 undergoes nuclear translocation and binds to small musculoaponeurotic fibrosarcoma (sMaf) transcription factors, including MafF, MafG and MafK [14], driving the transcription of Nrf2-responsive genes containing DNA antioxidant responsive elements (AREs) in their promoter [13] (Figure 1). In addition, NF-κB also acts directly on the Nrf2 promoter to induce Nrf2 transcription [13], presumably required to sustain Nrf2-dependent gene expression (Figure 2).

It is now clear that other E3 ubiquitin ligase complexes contribute to integrate Nrf2 activation within different forms of cellular stress [13]. These include the Skp1 (S-phase kinase-associated protein 1)–Cul1–F-box (SCF)–β-transducin repeats-containing proteins (β-TrCP) complex (SCF$^{\beta\text{-TrCP}}$) [20], which recognizes the Neh6 (Nrf2-ECH homology 6) domain of Nrf2 when phophorylated by the

glycogen synthase kinase 3 (GSK3) [20]. Presumably, Nrf2 phosphorylation at the Neh6 domain allows for coupling of different forms of stress sensed by GSK3 with Nrf2 ubiquitination by the $SCF^{\beta\text{-TrCP}}$ complex and its degradation by the 26s proteasome [13,20] (Figure 1). The HMG (high mobility group)-coA reductase degradation 1 (Hrd1) E3 ubiquitin–protein ligase involved in endoplasmic reticulum-associated protein degradation (ERAD) also controls Nrf2 activation [21]. Hrd1 targets the Nhe4–5 domain of Nrf2 for ubiquitination and degradation by the 26s proteasome [21] (Figure 1). How Hrd1 acts in the context of other components of the endoplasmic reticulum stress response, such as the protein kinase RNA-like ER kinase 1 (PERK1) [22], to regulate Nrf2 is not clear.

It is worth noting that Nrf2 activity is controlled to a large extent by its rate of transcription/expression (Figure 1). This is regulated by several transcription factors including NF-κB and Nrf2 itself, as well as clock components that impose a circadian control to Nrf2 activity [23] (Figure 1).

Nrf2 and resistance to infection

Perhaps the best demonstration that Nrf2 modulates host resistance to infection is provided by the observation that deletion of the *Nrf2* allele in mice enhances resistance to Marburg virus infection [24]. This effect is mediated by the Marburg virus encoded VP24 protein, which binds the Kelch domain of Keap1 and inhibits the ubiquitin ligase activity of the Keap1–Cul3–Rbx1 complex, hence inducing Nrf2 activation [24,25]. Several other observations are consistent with the notion that viruses induce host Nrf2 activation *in vitro*, as suggested for Kaposi's sarcoma-associated herpes virus [26], as well as for Influenza [27,28] and dengue [29] viruses. However, the pathophysiologic relevance of these observations remains to be elucidated. Conversely, other viruses such as hepatitis C virus, down-regulate Nrf2 activation via a mechanism impairing its nuclear import through delocalization of sMaf proteins [30]. The impact of this phenomenon to the outcome of hepatitis C virus infection is also not clear.

Intracellular bacteria also modulate Nrf2 activation, as demonstrated for *Salmonella typhimurium* infection in Mø [31]. Activation of Nrf2 enforces the transcription/expression of Ferroportin-1, an iron exporter that decreases iron cellular content [31]. This limits *Salmonella* access to iron, restraining the proliferation of this intracellular pathogen [31]. Whether Nrf2 acts under pathophysiologic conditions to promote resistance to *Salmonella* infection is likely, but this remains to be formally demonstrated [31]. Pharmacologic activation of Nrf2 by sulforaphane promotes resistance to *Pseudomonas aeruginosa* [32] as well as to *Plasmodium* infection in mice [33].

Nrf2 in tissue damage control and disease tolerance

The Nrf2 signal transduction pathway also confers tissue damage control and disease tolerance to systemic infections. One of the mechanisms via which this occurs involves the establishment of a functional cross-talk between the gasotransmitters NO and CO, as illustrated for *Plasmodium* infection [34,35]. When applied pharmacologically, both NO [35–37] and CO [34,38,39] can suppress the development of experimental cerebral malaria in mice, a lethal form of severe malaria that resembles, in many aspects, human cerebral malaria [40]. This protective effect acts via Nrf2 activation by NO [41], presumably through a mechanism targeting Keap1 at Cys^{151} [13,42], but this has not been established experimentally. Nrf2 activation induces HO-1 (heme oxygenase-1) expression and the production of CO, via haeme catabolism by HO-1, which acts ultimately as the gasotransmitter suppressing the onset of experimental cerebral malaria [41]. This occurs via a mechanism involving the binding of CO to the prosthetic haeme group of cell free haemoglobin generated during the blood stage of *Plasmodium* infection, thus preventing haeme from participating in the pathogenesis of experimental cerebral malaria [34,38,39,41]. The protective effect exerted by the NO->Nrf2->HO-1->CO signal transduction pathway is not associated with modulation of host pathogen load, suggesting that the cross-talk established between these two gasotransmitters confers disease tolerance to *Plasmodium* infection via a mechanism regulated by Nrf2 [11,41].

Presumably, the mechanism via which Nrf2 confers tissue damage control and disease tolerance to malaria also involves the expression of Nrf2-responsive genes regulating haeme/iron metabolism [43]. These include the iron storage protein Ferritin H chain (FtH) [44,45], which can confer *per se* tissue damage control and disease tolerance to malaria in mice [10].

There is further evidence that argues strongly for a central role of the Nrf2 signal transduction pathway in the establishment of disease tolerance to *Plasmodium* infection. In a similar manner to humans carrying hemizygous sickle mutations in the β-chain of haemoglobin, transgenic sickle haemoglobin mice are protected from cerebral malaria [38]. This protective effect is exerted irrespectively of parasite load, revealing that sickle haemoglobin can confer disease tolerance to *Plasmodium* infection [11,38]. Sickle haemoglobin induces the expression of HO-1 through a mechanism regulated by Nrf2 and leading to the production of CO, which confers tissue damage control and disease tolerance to malaria [38,39]. Whether this mechanism explains how sickle haemoglobin protects humans from malaria remains to be established but is likely to be the case.

It is probable that a similar mechanism underlies the protective effect exerted by other chronic haemolytic conditions against malaria, including haemoglobin C [46,47], glucose 6 phosphate dihydrogenase (G6PD) deficiency in males [48], β- or α-thalassemia [47] as well as mutations underlying red blood cell cytoskeleton or membrane protein defects [49]. Presumably, the protective effect associated with these mutations is mediated via different mechanisms that converge at the level of Nrf2 activation. Therefore it is possible that sickle haemoglobin and probably these

other red blood cell mutations co-evolved with the Nrf2 signal transduction pathway to limit disease severity driven by these mutations while conferring protection against malaria, such as illustrated for the sickle haemoglobin [38].

There is also circumstantial evidence to suggest that Nrf2 confers disease tolerance to systemic infections, other than malaria. Namely, Nrf2 is protective against endotoxic shock [50], severe sepsis triggered by polymicrobial infection [50] and lung injury induced by *Staphylococcus aureus* infection [51] in mice. These salutary effects have been associated mainly with immunoregulation but there is no clear evidence whether Nrf2 modulates pathogen load in these specific experimental settings [50]. Our own data confirms that Nrf2 activation prevents the lethal outcome of polymicrobial sepsis in mice, without however interfering with pathogen load (Weis, S., Ribeiro, A. and Soares, M.P., unpublished observation). This suggests that Nrf2 can confer disease tolerance to infection, presumably acting as an immunoregulatory transcription factor in innate immune cells and/or parenchyma cells to provide tissue damage control, although this remains to be fully established.

Mechanisms underlying the protective effect of Nrf2 against infection

There is a general consensus that Nrf2 is protective against systemic infections, via a mechanism targeting NF-κB and modulating pro-inflammatory gene expression in Mø [50,52] (Figure 2). However, Nrf2 activation is required to sustain interleukin (IL)-1β secretion in Mø, via a mechanism involving NLRP3 (NACHT, LRR and PYD domains-containing protein 3) driven caspase 1 activation, an essential step in the processing of pro-IL-1β towards IL-1β secretion [53]. This would argue that Nrf2 promotes, rather than restrains, inflammation. Moreover, Nrf2 induces the expression of the activating transcription factor 3 (ATF3) in Mø, an IL-6 repressor that is protective against LPS but highly deleterious against bacterial infection [54]. This suggests that Nrf2 can also act in a deleterious manner in the context of systemic bacterial infections (Figure 2).

Oxidative stress can trigger parenchyma cells to undergo regulated necrosis [55], leading to tissue damage and organ dysfunction, eventually compromising disease tolerance to infection [12]. Therefore, host protective mechanisms that prevent parenchyma cells from undergoing regulated necrosis, such as those driven by Nrf2, should enforce tissue damage control and disease tolerance to systemic infections [12] (Figure 2). Presumably, this occurs via the expression of Nrf2 regulated effector genes, such as those controlling glutathione synthesis/conjugation [13,18], haeme metabolism, i.e. HO-1 [56–58], iron metabolism, e.g. FtH [59,60], ferroportin-1 [31] and/or lipid peroxidation, e.g. biliverdin reductase [61]. Other mechanisms underlying the protective effects of Nrf2 were linked to maintenance of mitochondrial function [51].

Trade-off of the stress response driven by Nrf2

Disease tolerance mechanisms do not exert a negative impact on pathogens. As such, stress responses underlying disease tolerance create a situation in which the infected host, although healthy, can transmit the disease. This has probably major consequences on the natural selection of genes regulating stress responses, including Nrf2 [62]. Moreover, stress responses preserve core cellular functions at the expense of 'accessory' ones [63–65] and therefore must be tightly regulated over time [11]. Nrf2 is no exception to this rule as illustrated by the observation that chronic Nrf2 activation promotes tumorigenesis [66].

Conclusion

The stress response regulated by Nrf2 probably plays a major role in conferring disease tolerance to systemic infections, such as those triggered by bacteria infection and leading to severe sepsis or the one triggered by *Plasmodium* infection and leading to severe forms of malaria. Viral infections, on the other hand, appear to thrive on host Nrf2 activation, as illustrated by a number of examples in which induction of Nrf2 activity favours virus proliferation. Given the above, it is not clear to what extent the Nrf2 signal transduction pathway may be targeted to treat infectious diseases.

Funding

This work was supported by the Fundação para a Ciência e Tecnologia [grant numbers RECI-IMI-IMU-0038-2012, PTDC/SAU-TOX/116627/2010 and HMSP-ICT/0018/2011 (to M.P.S.) and SFRH/BD/51877/2012 (to A.M.R.)]; and the European Research Council [grant number ERC-2011-AdG 294709-DAMAGECONTROL (to M.P.S.)]

References

1 Medzhitov, R., Schneider, D. and Soares, M. (2012) Disease tolerance as a defense strategy. Science **335**, 936–941 CrossRef PubMed
2 Ayres, J.S. and Schneider, D.S. (2012) Tolerance of infections. Annu. Rev. Immunol. **30**, 271–294 CrossRef PubMed
3 Schneider, D.S. and Ayres, J.S. (2008) Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. Nat. Rev. Immunol. **8**, 889–895 CrossRef PubMed
4 Caldwell, R.M., Schafer, J.F., Compton, L.E. and Patterson, F.L. (1958) Tolerance to cereal leaf rusts. Science **128**, 714–715 CrossRef PubMed
5 Ayres, J.S. and Schneider, D.S. (2008) A signaling protease required for melanization in *Drosophila* affects resistance and tolerance of infections. PLoS Biol. **6**, 2764–2773 CrossRef PubMed
6 Ayres, J.S., Freitag, N. and Schneider, D.S. (2008) Identification of *Drosophila* mutants altering defense of and endurance to *Listeria monocytogenes* infection. Genetics **178**, 1807–1815 CrossRef PubMed
7 Teixeira, L., Ferreira, A. and Ashburner, M. (2008) The bacterial symbiont Wolbachia induces resistance to RNA viral infections in *Drosophila melanogaster*. PLoS Biol. **6**, e2 CrossRef PubMed

8 Raberg, L., Sim, D. and Read, A.F. (2007) Disentangling genetic variation for resistance and tolerance to infectious diseases in animals. Science **318**, 812–814 CrossRef PubMed

9 Seixas, E., Gozzelino, R., Chora, A., Ferreira, A., Silva, G., Larsen, R., Rebelo, S., Penido, C., Smith, N.R., Coutinho, A. and Soares, M.P. (2009) Heme oxygenase-1 affords protection against noncerebral forms of severe malaria. Proc. Natl. Acad. Sci. U.S.A. **106**, 15837–15842 CrossRef PubMed

10 Gozzelino, R., Andrade, B.B., Larsen, R., Luz, N.F., Vanoaica, L., Seixas, E., Coutinho, A., Cardoso, S., Rebelo, S., Poli, M. et al. (2012) Metabolic adaptation to tissue iron overload confers tolerance to malaria. Cell Host Microbe **12**, 693–704 CrossRef PubMed

11 Medzhitov, R., Schneider, D.S. and Soares, M.P. (2012) Disease tolerance as a defense strategy. Science **335**, 936–941 CrossRef PubMed

12 Soares, M.P., Gozzelino, R. and Weis, S. (2014) Tissue damage control in disease tolerance. Trends Immunol. **35**, 483–494 CrossRef PubMed

13 Hayes, J.D. and Dinkova-Kostova, A.T. (2014) The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem. Sci. **39**, 199–218 CrossRef PubMed

14 Sykiotis, G.P. and Bohmann, D. (2010) Stress-activated cap'n' collar transcription factors in aging and human disease. Sci. Signal. **3**, re3 CrossRef PubMed

15 Xie, Q.W., Kashiwabara, Y. and Nathan, C. (1994) Role of transcription factor NF-kappa B/Rel in induction of nitric oxide synthase. J. Biol. Chem. **269**, 4705–4708 PubMed

16 Anrather, J., Racchumi, G. and Iadecola, C. (2006) NF-kappaB regulates phagocytic NADPH oxidase by inducing the expression of gp91phox. J. Biol. Chem. **281**, 5657–5667 CrossRef PubMed

17 Itoh, K., Wakabayashi, N., Katoh, Y., Ishii, T., Igarashi, K., Engel, J.D. and Yamamoto, M. (1999) Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Genes Dev. **13**, 76–86 CrossRef PubMed

18 Suzuki, T., Motohashi, H. and Yamamoto, M. (2013) Toward clinical application of the Keap1-Nrf2 pathway. Trends Pharmacol. Sci. **34**, 340–346 CrossRef PubMed

19 Kensler, T.W., Wakabayashi, N. and Biswal, S. (2007) Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu. Rev. Pharmacol. Toxicol. **47**, 89–116 CrossRef PubMed

20 Rada, P., Rojo, A.I., Chowdhry, S., McMahon, M., Hayes, J.D. and Cuadrado, A. (2011) SCF/{beta}-TrCP promotes glycogen synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. Mol. Cell. Biol. **31**, 1121–1133 CrossRef PubMed

21 Wu, T., Zhao, F., Gao, B., Tan, C., Yagishita, N., Nakajima, T., Wong, P.K., Chapman, E., Fang, D. and Zhang, D.D. (2014) Hrd1 suppresses Nrf2-mediated cellular protection during liver cirrhosis. Genes Dev. **28**, 708–722 CrossRef PubMed

22 Cullinan, S.B., Zhang, D., Hannink, M., Arvisais, E., Kaufman, R.J. and Diehl, J.A. (2003) Nrf2 is a direct PERK substrate and effector of PERK-dependent cell survival. Mol. Cell Biol. **23**, 7198–7209 CrossRef PubMed

23 Pekovic-Vaughan, V., Gibbs, J., Yoshitane, H., Yang, N., Pathiranage, D., Guo, B., Sagami, A., Taguchi, K., Bechtold, D., Loudon, A. et al. (2014) The circadian clock regulates rhythmic activation of the NRF2/glutathione-mediated antioxidant defense pathway to modulate pulmonary fibrosis. Genes Dev. **28**, 548–560 CrossRef PubMed

24 Page, A., Volchkova, V.A., Reid, S.P., Mateo, M., Bagnaud-Baule, A., Nemirov, K., Shurtleff, A.C., Lawrence, P., Reynard, O., Ottmann, M. et al. (2014) Marburgvirus hijacks nrf2-dependent pathway by targeting nrf2-negative regulator keap1. Cell Rep. **6**, 1026–1036 CrossRef PubMed

25 Edwards, M.R., Johnson, B., Mire, C.E., Xu, W., Shabman, R.S., Speller, L.N., Leung, D.W., Geisbert, T.W., Amarasinghe, G.K. and Basler, C.F. (2014) The Marburg virus VP24 protein interacts with Keap1 to activate the cytoprotective antioxidant response pathway. Cell Rep. **6**, 1017–1025 CrossRef PubMed

26 Gjyshi, O., Bottero, V., Veettil, M.V., Dutta, S., Singh, V.V., Chikoti, L. and Chandran, B. (2014) Kaposi's sarcoma-associated herpesvirus induces Nrf2 during de novo infection of endothelial cells to create a microenvironment conducive to infection. PLoS Pathog. **10**, e1004460 CrossRef PubMed

27 Kosmider, B., Messier, E.M., Janssen, W.J., Nahreini, P., Wang, J., Hartshorn, K.L. and Mason, R.J. (2012) Nrf2 protects human alveolar epithelial cells against injury induced by influenza A virus. Respir. Res. **13**, 43 CrossRef PubMed

28 Kesic, M.J., Simmons, S.O., Bauer, R. and Jaspers, I. (2011) Nrf2 expression modifies influenza A entry and replication in nasal epithelial cells. Free Radic. Biol. Med. **51**, 444–453 CrossRef PubMed

29 Olagnier, D., Peri, S., Steel, C., van Montfoort, N., Chiang, C., Beljanski, V., Slifker, M., He, Z., Nichols, C.N., Lin, R. et al. (2014) Cellular oxidative stress response controls the antiviral and apoptotic programs in dengue virus-infected dendritic cells. PLoS Pathog. **10**, e1004566 CrossRef PubMed

30 Carvajal-Yepes, M., Himmelsbach, K., Schaedler, S., Ploen, D., Krause, J., Ludwig, L., Weiss, T., Klingel, K. and Hildt, E. (2011) Hepatitis C virus impairs the induction of cytoprotective Nrf2 target genes by delocalization of small Maf proteins. J. Biol. Chem. **286**, 8941–8951 CrossRef PubMed

31 Nairz, M., Schleicher, U., Schroll, A., Sonnweber, T., Theurl, I., Ludwiczek, S., Talasz, H., Brandacher, G., Moser, P.L., Muckenthaler, M.U. et al. (2013) Nitric oxide-mediated regulation of ferroportin-1 controls macrophage iron homeostasis and immune function in *Salmonella* infection. J. Exp. Med. **210**, 855–873 CrossRef PubMed

32 Harvey, C.J., Thimmulappa, R.K., Sethi, S., Kong, X., Yarmus, L., Brown, R.H., Feller-Kopman, D., Wise, R. and Biswal, S. (2011) Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. Sci. Transl. Med. **3**, 78ra32 CrossRef PubMed

33 Olagnier, D., Lavergne, R.A., Meunier, E., Lefevre, L., Dardenne, C., Aubouy, A., Benoit-Vical, F., Ryffel, B., Coste, A., Berry, A. and Pipy, B. (2011) Nrf2, a PPARgamma alternative pathway to promote CD36 expression on inflammatory macrophages: implication for malaria. PLoS Pathog. **7**, e1002254 CrossRef PubMed

34 Pamplona, A., Ferreira, A., Balla, J., Jeney, V., Balla, G., Epiphanio, S., Chora, A., Rodrigues, C.D., Gregoire, I.P., Cunha-Rodrigues, M. et al. (2007) Heme oxygenase-1 and carbon monoxide suppress the pathogenesis of experimental cerebral malaria. Nat. Med. **13**, 703–710 CrossRef PubMed

35 Gramaglia, I., Sobolewski, P., Meays, D., Contreras, R., Nolan, J.P., Frangos, J.A., Intaglietta, M. and van der Heyde, H.C. (2006) Low nitric oxide bioavailability contributes to the genesis of experimental cerebral malaria. Nat. Med. **12**, 1417–1422 CrossRef PubMed

36 Cabrales, P., Zanini, G.M., Meays, D., Frangos, J.A. and Carvalho, L.J. (2011) Nitric oxide protection against murine cerebral malaria is associated with improved cerebral microcirculatory physiology. J. Infect. Dis. **203**, 1454–1463 CrossRef PubMed

37 Ong, P.K., Melchior, B., Martins, Y.C., Hofer, A., Orjuela-Sanchez, P., Cabrales, P., Zanini, G.M., Frangos, J.A. and Carvalho, L.J. (2013) Nitric oxide synthase dysfunction contributes to impaired cerebroarteriolar reactivity in experimental cerebral malaria. PLoS Pathog. **9**, e1003444 CrossRef PubMed

38 Ferreira, A., Marguti, I., Bechmann, I., Jeney, V., Chora, A., Palha, N.R., Rebelo, S., Henri, A., Beuzard, Y. and Soares, M.P. (2011) Sickle hemoglobin confers tolerance to plasmodium infection. Cell **145**, 398–409 CrossRef PubMed

39 Ferreira, A., Balla, J., Jeney, V., Balla, G. and Soares, M.P. (2008) A central role for free heme in the pathogenesis of severe malaria: the missing link? J. Mol. Med. **86**, 1097–1111 CrossRef PubMed

40 Newton, C.R. and Warrell, D.A. (1998) Neurological manifestations of falciparum malaria. Ann. Neurol. **43**, 695–702 CrossRef PubMed

41 Jeney, V., Ramos, S., Bergman, M.L., Bechmann, I., Tischer, J., Ferreira, A., Oliveira-Marques, V., Janse, C.J., Rebelo, S., Cardoso, S. and Soares, M.P. (2014) Control of disease tolerance to malaria by nitric oxide and carbon monoxide. Cell Rep. **8**, 126–136 CrossRef PubMed

42 Fourquet, S., Guerois, R., Biard, D. and Toledano, M.B. (2010) Activation of NRF2 by nitrosative agents and H2O2 involves KEAP1 disulfide formation. J. Biol. Chem. **285**, 8463–8471 CrossRef PubMed

43 Gozzelino, R. and Soares, M.P. (2014) Coupling heme and iron metabolism via ferritin H chain. Antioxid. Redox Signal. **20**, 1754–1769 CrossRef PubMed

44 Pietsch, E.C., Chan, J.Y., Torti, F.M. and Torti, S.V. (2003) Nrf2 mediates the induction of ferritin H in response to xenobiotics and cancer chemopreventive dithiolethiones. J. Biol. Chem. **278**, 2361–2369 CrossRef PubMed

45 Iwasaki, K., Mackenzie, E.L., Hailemariam, K., Sakamoto, K. and Tsuji, Y. (2006) Hemin-mediated regulation of an antioxidant-responsive element of the human ferritin H gene and role of Ref-1 during erythroid differentiation of K562 cells. Mol. Cell. Biol. **26**, 2845–2856 CrossRef PubMed

46 Modiano, D., Luoni, G., Sirima, B.S., Simpore, J., Verra, F., Konate, A., Rastrelli, E., Olivieri, A., Calissano, C., Paganotti, G.M. et al. (2001) Haemoglobin C protects against clinical *Plasmodium falciparum* malaria. Nature **414**, 305–308 CrossRef PubMed

47 May, J., Evans, J.A., Timmann, C., Ehmen, C., Busch, W., Thye, T., Agbenyega, T. and Horstmann, R.D. (2007) Hemoglobin variants and disease manifestations in severe falciparum malaria. JAMA **297**, 2220–2226 CrossRef PubMed

48 Guindo, A., Fairhurst, R.M., Doumbo, O.K., Wellems, T.E. and Diallo, D.A. (2007) X-linked G6PD deficiency protects hemizygous males but not heterozygous females against severe malaria. PLoS Med. **4**, e66 CrossRef PubMed

49 Williams, T.N. (2006) Human red blood cell polymorphisms and malaria. Curr. Opin. Microbiol. **9**, 388–394 CrossRef PubMed

50 Thimmulappa, R.K., Lee, H., Rangasamy, T., Reddy, S.P., Yamamoto, M., Kensler, T.W. and Biswal, S. (2006) Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis. J. Clin. Invest. **116**, 984–995 CrossRef PubMed

51 Athale, J., Ulrich, A., MacGarvey, N.C., Bartz, R.R., Welty-Wolf, K.E., Suliman, H.B. and Piantadosi, C.A. (2012) Nrf2 promotes alveolar mitochondrial biogenesis and resolution of lung injury in *Staphylococcus aureus* pneumonia in mice. Free Radic. Biol. Med. **53**, 1584–1594 CrossRef PubMed

52 Rushworth, S.A., MacEwan, D.J. and O'Connell, M.A. (2008) Lipopolysaccharide-induced expression of NAD(P)H:quinone oxidoreductase 1 and heme oxygenase-1 protects against excessive inflammatory responses in human monocytes. J. Immunol. **181**, 6730–6737 CrossRef PubMed

53 Zhao, C., Gillette, D.D., Li, X., Zhang, Z. and Wen, H. (2014) Nuclear factor E2-related factor-2 (Nrf2) is required for NLRP3 and AIM2 inflammasome activation. J. Biol. Chem. **289**, 17020–17029 CrossRef PubMed

54 Hoetzenecker, W., Echtenacher, B., Guenova, E., Hoetzenecker, K., Woelbing, F., Bruck, J., Teske, A., Valtcheva, N., Fuchs, K., Kneilling, M. et al. (2012) ROS-induced ATF3 causes susceptibility to secondary infections during sepsis-associated immunosuppression. Nat. Med. **18**, 128–134 CrossRef

55 Vanden Berghe, T., Linkermann, A., Jouan-Lanhouet, S., Walczak, H. and Vandenabeele, P. (2014) Regulated necrosis: the expanding network of non-apoptotic cell death pathways. Nat. Rev. Mol. Cell Biol. **15**, 135–147 CrossRef PubMed

56 Brouard, S., Otterbein, L.E., Anrather, J., Tobiasch, E., Bach, F.H., Choi, A.M. and Soares, M.P. (2000) Carbon monoxide generated by heme oxygenase 1 suppresses endothelial cell apoptosis. J. Exp. Med. **192**, 1015–1026 CrossRef PubMed

57 Brouard, S., Berberat, P.O., Tobiasch, E., Seldon, M.P., Bach, F.H. and Soares, M.P. (2002) Heme oxygenase-1-derived carbon monoxide requires the activation of transcription factor NF-kappa B to protect endothelial cells from tumor necrosis factor-alpha-mediated apoptosis. J. Biol. Chem. **277**, 17950–17961 CrossRef PubMed

58 Vile, G.F., Basumodak, S., Waltner, C. and Tyrrell, R.M. (1994) Heme oxygenase mediates an adaptive response to oxidative stress in human skin fibroblasts. Proc. Natl. Acad. Sci. U.S.A. **91**, 2607–2610 CrossRef PubMed

59 Berberat, P.O., Katori, M., Kaczmarek, E., Anselmo, D., Lassman, C., Ke, B., Shen, X., Busuttil, R.W., Yamashita, K., Csizmadia, E. et al. (2003) Heavy chain ferritin acts as an antiapoptotic gene that protects livers from ischemia reperfusion injury. FASEB J. **17**, 1724–1726 PubMed

60 Pham, C.G., Bubici, C., Zazzeroni, F., Papa, S., Jones, J., Alvarez, K., Jayawardena, S., De Smaele, E., Cong, R., Beaumont, C. et al. (2004) Ferritin heavy chain upregulation by NF-kappaB inhibits TNFalpha-induced apoptosis by suppressing reactive oxygen species. Cell **119**, 529–542 CrossRef PubMed

61 Stocker, R., Yamamoto, Y., McDonagh, A.F., Glazer, A.N. and Ames, B.N. (1987) Bilirubin is an antioxidant of possible physiological importance. Science **235**, 1043–1046 CrossRef PubMed

62 Vale, P.F., Fenton, A. and Brown, S.P. (2014) Limiting damage during infection: lessons from infection tolerance for novel therapeutics. PLoS Biol. **12**, e1001769 CrossRef PubMed

63 Lopez-Maury, L., Marguerat, S. and Bahler, J. (2008) Tuning gene expression to changing environments: from rapid responses to evolutionary adaptation. Nat. Rev. Genet. **9**, 583–593 CrossRef PubMed

64 Kultz, D. (2003) Evolution of the cellular stress proteome: from monophyletic origin to ubiquitous function. J. Exp. Biol. **206**, 3119–3124 CrossRef PubMed

65 Kultz, D. (2005) Molecular and evolutionary basis of the cellular stress response. Annu. Rev. Physiol. **67**, 225–257 CrossRef PubMed

66 DeNicola, G.M., Karreth, F.A., Humpton, T.J., Gopinathan, A., Wei, C., Frese, K., Mangal, D., Yu, K.H., Yeo, C.J., Calhoun, E.S. et al. (2011) Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature **475**, 106–109 CrossRef PubMed

Received 19 February 2015
doi:10.1042/BST20150054