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Review

Regulation of innate immunity by Nrf2

D van der Horst[1], ME Carter-Timofte[1], J van Grevenynghe[2], N Laguette[3], AT Dinkova-Kostova[4,5] and D Olagnier[1]

The transcription factor Nuclear factor erythroid 2-related factor 2 (Nrf2) has been mainly investigated as a regulator of redox homeostasis. However, research over the past years has implicated Nrf2 as an important regulator of innate immunity. Here, we discuss the role of Nrf2 in the innate immune response, highlighting the interaction between Nrf2 and major components of the innate immune system. Indeed, Nrf2 has been shown to widely control the immune response by interacting directly or indirectly with important innate immune components, including the toll-like receptors–Nuclear factor kappa B (NF-kB) pathway, inflammasome signaling, and the type-I interferon response. This indicates an essential role for Nrf2 in diseases related to microbial infections, inflammation, and cancer. Yet, further studies are required to determine the exact mechanism underpinning the interactions between Nrf2 and innate immune players in order to allow a better understanding of these diseases and leverage new therapeutic strategies.

Addresses
[1] Dept. of Biomedicine, Aarhus University, Aarhus, Denmark
[2] Institut National de la Recherche Scientifique (INRS)-Centre Armand-Frappier Santé Biotechnologie, Laval, Quebec, Canada
[3] Institut de Génétique Humaine, Université de Montpellier, CNRS, Montpellier, France
[4] Jacqui Wood Cancer Centre, Division of Cellular Medicine, School of Medicine, University of Dundee, Dundee, UK
[5] Department of Pharmacology and Molecular Sciences and Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA

Corresponding author: D Olagnier (olagnier@biomed.au.dk)

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Introduction

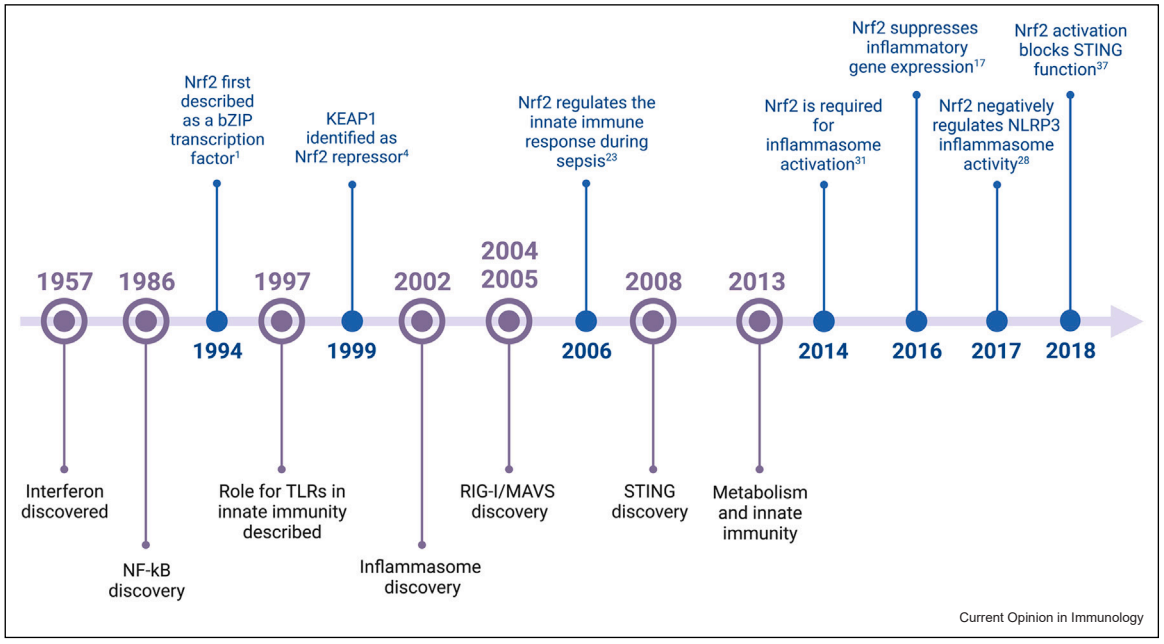
Nuclear factor erythroid 2-related factor 2 (Nrf2) is the transcriptional master regulator of detoxifying and antioxidative responses [1,2]. Under basal conditions, Nrf2 is kept inactive by its repressor Kelch-like-enoyl-CoA hydratase(ECH)-associated protein 1 (Keap1), which serves as a substrate for the Cul3–E3 ligase complex that targets Nrf2 for ubiquitination and proteasomal degradation [3,4]. However, electrophile agents and reactive oxygen species (ROS) can induce Keap1 modifications that consequently inhibit the ubiquitination of Nrf2, thereby saturating Keap1 with Nrf2 and preventing Nrf2 degradation [5–8]. Therefore, due to insufficient availability of Keap1, the newly synthesized Nrf2 accumulates and translocates to the nucleus, where it binds to the antioxidant-response element (ARE) and initiates the expression of cytoprotective genes and detoxifying genes to control redox homeostasis [5–7].

Initially, Nrf2 was solely considered as a regulator of the oxidative-stress response. Interestingly, over the past years, studies have implicated Nrf2 in the regulation of immune and inflammatory responses [9]. The innate immune response is the first line of defense, which relies on dedicated receptors to detect danger signals such as microbial infection and tissue damage and initiate the induction of antimicrobial molecules and inflammatory gene expression [10]. Nrf2 regulates the immune response by interacting directly or indirectly with one or more of the major innate immune signaling components that maintains cellular homeostasis. In this short review article, we give a chronological summary of the past and more recent findings on the interactions between Nrf2 and some of the major components of the innate immune system (Figure 1).

Nuclear factor erythroid 2-related factor 2 and toll-like receptors signaling

Toll-like receptors (TLR), which trigger inflammatory signaling cascades in response to structurally conserved microbial patterns or host danger molecules, and Nrf2 have been shown to interconnect in different ways to regulate the innate immune response [11,12]. TLR signaling can induce Nrf2 activation, and this is primarily found to be through autophagy-mediated degradation of Keap1 [13]. Briefly, TLR signaling induces expression of autophagy adapter protein p62, essential for modulating Keap1 degradation, thereby promoting activation of the Nrf2 pathway [13]. The Nrf2 gene product heme oxygenase-1 was also shown to be upregulated following

Figure 1



Timeline of the main discoveries in innate immunity and the most relevant achievements in the field of Nrf2–immuno interactions. Figure was created using BioRender.com.

Nrf2 nuclear translocation and protein kinase C activation after lipopolysaccharide (LPS) stimulation and TLR4 engagement [14]. Other TLR agonists, such as peptidoglycan (TLR2), polyinosinic–polycytidylic acid (TLR3), and resiquimod (TLR7), have been highlighted to trigger Nrf2-mediated transcription of antioxidant genes, hence stimulating cell survival [13,15]. Thus, TLR agonists may be considered as stimuli that induce Nrf2 to reduce stress and inflammation, linking the immune and antioxidant pathways.

Conversely, Nrf2 activation may restrain TLR-mediated inflammatory response through induction of antioxidant proteins and inhibition of pro-inflammatory cytokines [16]. In addition, Nrf2 induction inhibits LPS-mediated activation of pro-inflammatory cytokines in macrophages [17] (Figure 2). Whereas Nrf2 has been generally accepted to control inflammation through the antioxidant response, these authors report transcriptional repression of pro-inflammatory cytokines, independently of the ARE motif and of ROS levels [17]. Moreover, Nrf2 may also directly control TLR expression as TLR4 and Nrf2 protein levels are inversely correlated [18].

Nuclear factor erythroid 2-related factor 2 and the NF-κB pathway

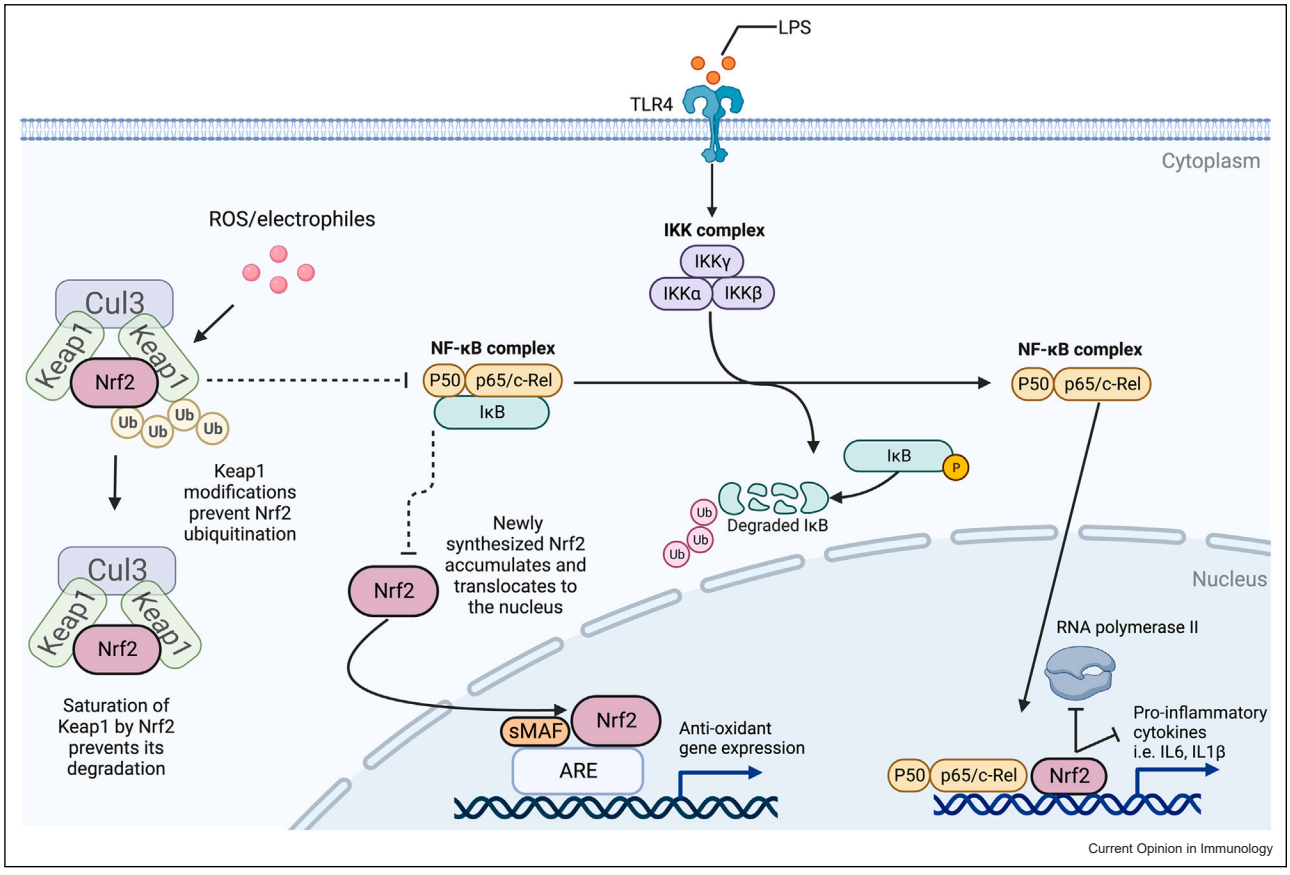
The NF-κB transcription factor is an important transcriptional regulator of the innate immune response upon pathogen infection or tissue damage [19]. The interactions between TLR and Nrf2 signaling may arise from NF-κB pathway activation downstream of TLR signaling. Indeed, NF-κB factor is known to be sensitive to redox-status changes [20]. In this regard, Nrf2 has an indirect capacity to negatively regulate NF-κB through induction of the antioxidant response [21]. Furthermore, Keap1 suppresses NF-κB signaling by inducing IκB kinase-β proteasomal degradation [22]. In addition, Nrf2-deficient mice present increased NF-κB activity upon LPS stimulation, supporting that Nrf2 can regulate the innate immune response by suppressing NF-κB activation [23].

Nrf2 and NF-κB display an antagonistic relationship. The NF-κB subunit p65 has been shown to negatively regulate Nrf2 transcriptional activation through deprivation of CREB-binding protein from Nrf2 and recruitment of histone deacetylase 3 to the ARE region, thereby directly repressing Nrf2 transcriptional signaling [24]. Furthermore, p65 has also been shown to inhibit Nrf2 transcriptional activation through interaction with Keap1 [25] (Figure 2). Overall, this antagonistic interaction is crucial for maintaining cellular processes such as innate immune signaling, although this interplay mostly relies on second messengers or occurs through indirect transcriptional regulation.

Nuclear factor erythroid 2-related factor 2 and the NLRP3 inflammasome

Inflammasomes are cytoplasmic multimeric complexes formed in response to a variety of physiological and

Figure 2



Direct regulation of pro-inflammatory gene expression by Nrf2. Keap1 modification by electrophilic agents or ROS, prevents Nrf2 ubiquitination and degradation, hence allowing the newly synthesized Nrf2 to translocate to the nucleus, where it can initiate cytoprotective gene expression and establish redox control by binding to ARE regions. Following LPS stimulation, the NF-kB pathway is engaged to initiate a host of pro-inflammatory responses, such as IL-6 and interleukin 1 beta (IL-1β) gene expression. Nrf2 was shown to bind the proximity of these genes, thereby blocking the recruitment of RNA polymerase II to the IL-6 and IL-1β loci. The anti-inflammatory properties of Nrf2 were shown to be independent of its redox activity. The transcription factors Nrf2 and the NF-κB display an antagonistic relationship. NF-κB subunit p65 negatively regulates Nrf2 transcriptional activation directly and indirectly by interacting with Keap1. Figure was created using BioRender.com.

pathogenic stimuli [26]. Inflammasome activation is an essential component of the innate immune response and is critical for the clearance of pathogens or damaged cells through pro-inflammatory cytokine secretion and/or cell-death induction [26]. The interaction between Nrf2 and inflammasomes has been extensively reviewed elsewhere [27]. Yet, it is worth mentioning that while Nrf2 activation is in general associated with an anti-inflammatory state, the literature on this topic is more contrasted. Indeed, during the last few years, a crosstalk and inverse correlation of both pathways in regulating inflammation became apparent. While ROS are natural inducers of the NLR Family Pyrin Domain Containing 3 (NLR= NOD-like receptor) (NLRP3) inflammasome, Nrf2 can counteract the action of ROS through its anti-oxidant activity, and it is reasonable to assume that Nrf2 activation causes NLRP3 inflammasome inhibition [28]. Additionally, NF-κB, which is required to prime the inflammasome cascade by upregulating pro-inflammatory cytokine gene levels, also crosstalks with the Nrf2 pathway as described above. Finally, Nrf2 itself has been suggested to suppress the transcription of NLRP3 and other inflammatory-associated genes such as IL-1β [17,29]. However, Nrf2 has also been reported to be required for optimal NLRP3 inflammasome activity [30,31]. This suggests that more profound mechanistical studies are still needed to decipher the exact involvement of each player in this complex interaction.

Mechanisms of type-I interferon regulation by Nuclear factor erythroid 2-related factor 2

In addition to the induction of pro-inflammatory cytokines through TLR/NF-κB and inflammasome signaling, the type-I interferon (IFN) system constitutes an essential part of innate immunity. Type-I IFNs are produced upon recognition of foreign or self-DNA or

RNA and are best-known for inducing an antiviral state through the induction of interferon-stimulated genes (ISGs) [32]. Therefore, the role of Nrf2 in the type-I IFN response has mainly been investigated in the context of viral infection.

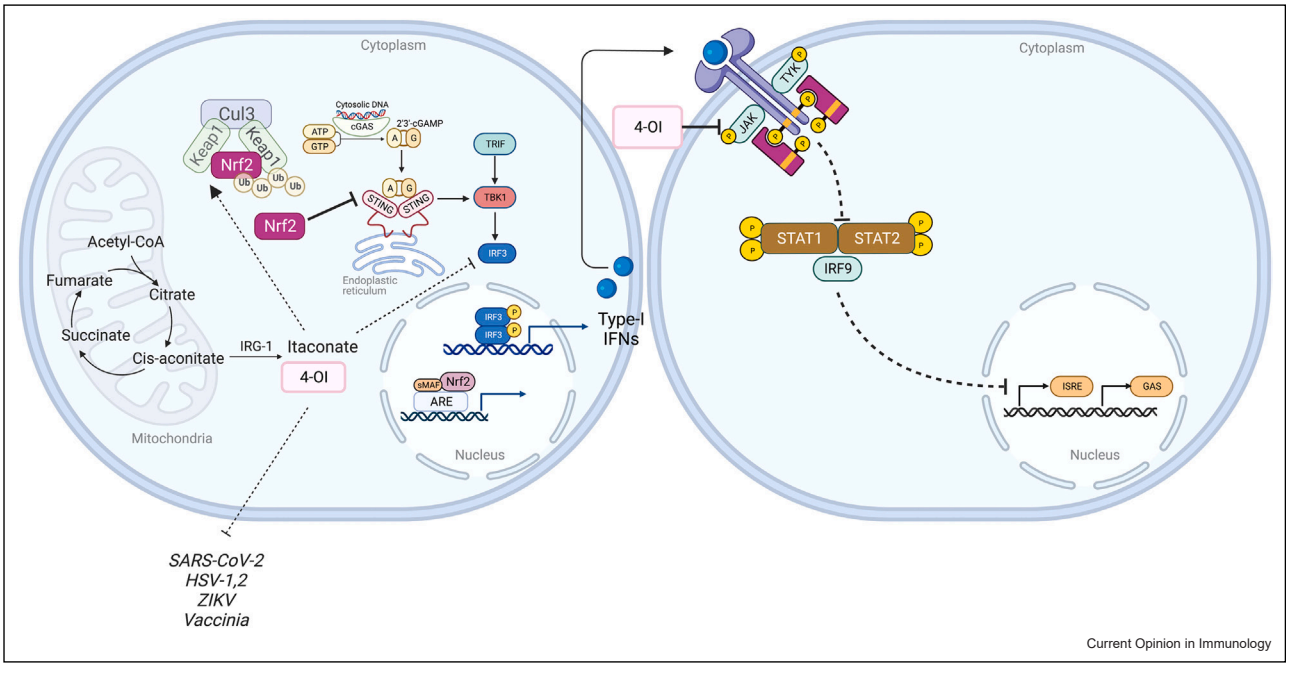
Dengue virus (DENV) infection in Nrf2-silenced monocyte-derived dendritic cells has been shown to trigger higher levels of interferon beta 1 (IFNβ) and ISGs, indicating an important role for Nrf2 in limiting antiviral responses upon DENV infection [33]. Activation of Nrf2 using sulforaphane inhibits vesicular stomatitis virus-induced antiviral response, thereby promoting the oncolytic activity of the virus in cancer cells [34]. More specifically, Nrf2 activation decreased nuclear localization of interferon-regulatory factor 3 (IRF3), induction of IFNβ, and expression of the subsequent ISGs through autophagy engagement [34]. Accordingly, Nrf2 activation suppresses IRF3 dimerization and expression of ISGs in human lung epithelial cells (A549) and human keratinocytes (HaCaTs) in response to a sequence-optimized RNA ligand [35]. Moreover, fibroblasts from Nrf2-deficient mice showed increased activation of IRF3 upon stimulation with LPS and poly-IC [23]. This suggests that Nrf2 represses IRF3-dependent type-I IFN induction.

Stimulator of interferon genes (STING) plays an essential role in innate immunity by mediating type-I IFN production upon recognition of cytoplasmic DNA or invading pathogens [36]. Nrf2 has also been found to inhibit STING expression, thereby increasing susceptibility to herpes simplex virus (HSV) infection [37] (Figure 3). Interestingly, although Nrf2 does not control STING expression in mice [38], Nrf2-deficient mice exhibit increased basal level of type-I IFN and ISG levels together with decreased susceptibility to HSV-2 infection [38], and the Nrf2 activity was found to be associated with restriction of HSV-1 infection [39]. Moreover, Nrf2-dependent inhibition of STING and ISGs was shown in human melanoma cells, supporting a link between Nrf2 and the innate antiviral immune response [40]. Altogether, Nrf2 has been demonstrated to broadly modulate the type-I IFN response. While Nrf2 interferes with IRF3 activation, STING expression, and type-I IFN signaling, none of these crucial players in innate immunity have been demonstrated to be direct targets of Nrf2.

Nuclear factor erythroid 2-related factor 2 and immunomodulatory metabolites

Over the past decade, studies have identified cell-derived immunomodulatory metabolites as potent Nrf2

Figure 3



Type-I IFN and Nrf2 signaling pathway interactions. Cell-derived metabolites that display immunomodulatory properties include itaconate and its more cell-permeable derivative 4-OI. 4-OI has been shown to inhibit STING signaling and reduce IRF3 dimerization as well as limiting viral replication following SARS-CoV-2, HSV-1/2, Zika, and Vaccinia virus infection. Furthermore, OI also directly inhibits JAK1 phosphorylation and downstream interferon signaling. Figure was created using BioRender.com.

inducers. For example, tricarboxylic acid-cycle derivatives itaconate or fumarate demonstrated anti-inflammatory activity in LPS-stimulated macrophages or virus-infected cells, respectively [41,42].

The immunomodulatory role of the Kreb's cycle derivative itaconate was first described when the immune-responsive gene-1 protein (IRG1) was identified, a mitochondrial enzyme responsible for itaconic acid production [43]. IRG1 and itaconate production were significantly increased in LPS-activated macrophages, promoting antimicrobial activity, and linking metabolism to the immune response [43]. Subsequently, 4-octyl itaconate (4-OI), its more cell-permeable derivative, was shown to activate Nrf2 through alkylation of Keap1 and exhibited anti-inflammatory properties by limiting IL-1β production [41]. However, another study showed that the original itaconate could not activate Nrf2 through Keap1 alkylation, suggesting that this could be attributed to its lower electrophilic properties compared with 4-OI [44]. In agreement, Nrf2 activation by itaconate derivative, dimethyl itaconate (DI), was also demonstrated to rely on its high electrophilic property and glutathione Glutathione Synthetase (GSH) depletion [45,46].

Although stimulation with an RNA ligand enhanced IRG1 and itaconate levels [47], 4-OI inhibits IFN and ISG expression, creating a Nrf2-dependent negative-feedback loop between itaconate and the type-I IFN response [41,48] (Figure 3). In addition, 4-OI, such as Nrf2, was shown to repress STING levels and STING-dependent signaling [37]. 4-OI also restricted viral replication of severe acute respiratory-syndrome coronavirus 2 (SARS-CoV-2), HSV-1, HSV-2, Vaccinia virus, and Zika virus, independently of type-I IFN signaling [35] (Figure 3). This indicates that the antiviral effect of Nrf2 activation by 4-OI may use various pathways to limit viral replication that have not been identified yet [35]. Furthermore, it has recently been demonstrated that 4-OI may also act independently of Nrf2 on the type-I IFN and inflammasome pathways [49,50]. 4-OI and derivatives can directly modify Janus Kinase 1 (JAK1), a tyrosine kinase important in type-I IFN signaling [49] (Figure 3). This is driven by 4-OI-mediated inhibition of JAK1 phosphorylation and decreased downstream Signal Transducer And Activator Of Transcription 1 (STAT1) phosphorylation in IFNβ-stimulated cells [49]. Hence, it is important to consider that Nrf2-activating metabolites may also act as immunomodulators in a Nrf2-independent manner. The same was shown for itaconate and 4-OI in modifying NLRP3 and inhibiting inflammasome activation and IL-1β release in LPS-stimulated macrophages [50].

More recently, newly discovered itaconate derivatives mesaconate and citraconate have also been shown to exhibit immunomodulatory properties [51,52]. Citraconate is the most electrophilic and therefore the strongest Nrf2 agonist [52]. Mesaconate and its precursor itaconate, but not citraconate, are both induced in LPS-stimulated macrophages [51,52]. Both mesaconate and citraconate demonstrate similar immunomodulatory properties by reducing the type-I IFN response [51,52]. While this immunomodulation is reported to be mainly independent of Nrf2 for mesaconate, this has not been investigated for citraconate [51]. Moreover, itaconate, mesaconate, citraconate, and OI decreased STAT1 phosphorylation upon influenza-A virus (IAV) infection in both Tamm-Horsfall Protein 1 (THP1) and A549 cells [52], corresponding to the previously shown effects of 4-OI and DI [35,53]. In IAV-infected cells, citraconate was able to inhibit Interferon Induced Protein With Tetratricopeptide Repeats 1 (IFIT1) and C-X-C Motif Chemokine Ligand 10 (CXCL10) expression [52]. Altogether, these studies on metabolites have expanded and strengthened our knowledge of the role of Nrf2 in innate immunity. However, further research is required to determine to which extent the metabolic immunomodulation is dependent on Nrf2.

Nuclear factor erythroid 2-related factor 2 regulates cytokine release and immune-cell recruitment

The innate immune response is particularly important for recruiting immune cells to the site of infection by producing cytokines [54]. Here, Nrf2 was shown to interfere with the transcriptional activation of pro-inflammatory cytokines IL-6 and IL-1β in LPS-stimulated macrophages by binding in the proximity of their promotor region and preventing RNA polymerase-II recruitment [17] (Figure 2). Whereas Nrf2 was generally thought to repress inflammation through the antioxidant response, this study was the first to show that the anti-inflammatory properties of Nrf2 were independent of redox control [17]. Moreover, Nrf2 was also shown to increase IL-8 mRNA stability [55]. Therefore, Nrf2 can promote cytokine expression at the transcriptional and post-transcriptional level.

Another cytokine controlled by Nrf2 activity is IL-17D. IL-17D is part of the interleukin-17 family of pro-inflammatory cytokines and plays an important role in the antitumor immune response by mediating tumor rejection through NK-cell recruitment [56]. Nrf2 activation by tert-butylhydroquinone was shown to induce IL-17D expression, NK-cell infiltration, and delayed tumor growth in vivo [57]. In contrast, lung adenocarcinoma constitutively active for Nrf2 due to Keap1 mutations displayed a reduced infiltration of dendritic cells, CD4+, and CD8+ T cells [40]. Both Nrf2 and IL-17D expression were increased upon viral infection, indicating a role in antiviral response [57]. Hence, Nrf2- and IL-17D-

deficient mice increased susceptibility to mouse cytomegalovirus (MCMV) infection [58]. Furthermore, innate immune- cell recruitment was shown to be controlled by Nrf2-induced IL-17D expression during MCMV infection in vivo [58]. Overall, Nrf2-mediated IL-17D expression plays an important role in the antitumor as well as the antiviral response through regulation of innate immune- cell recruitment.

Conclusion

Studies over the past decade have indicated Nrf2 as a major player in innate immunity. Nrf2 has been shown to widely control important innate immune components to maintain cellular homeostasis, implying a significant role for Nrf2 in diseases related to microbial infections, inflammation, and cancer. Nonetheless, further mechanistical studies are needed to decipher the exact indirect and/or direct interactions between Nrf2 and innate immune players, which will allow a better understanding of these diseases, and moreover, new possibilities for treatment strategies.

Conflict of interest statement

The authors declare no conflict of interest.

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