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Pros and cons of NRF2 activation as adjunctive therapy in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease with an important inflammatory component accompanied by deregulated redox-dependent signaling pathways that are feeding back into inflammation. In this context, we bring into focus the transcription factor NRF2, a master redox regulator that exerts exquisite antioxidant and anti-inflammatory effects. The review does not intend to be exhaustive, but to point out arguments sustaining the rationale for applying an NRF2-directed co-treatment in RA as well as its potential limitations. The involvement of NRF2 in RA is emphasized through an analysis of publicly available transcriptomic data on NRF2 target genes and the findings from NRF2-knockout mice. The impact of NRF2 on concurrent pathologic mechanisms in RA is explained by its crosstalk with major redox-sensitive inflammatory and cell death-related pathways, in the context of the increased survival of pathologic cells in RA. The proposed adjunctive therapy targeted to NRF2 is further sustained by the existence of promising NRF2 activators that are in various stages of drug development. The interference of NRF2 with conventional anti-rheumatic therapies is discussed, including the cytoprotective effects of NRF2 for alleviating drug toxicity. From another perspective, the review presents how NRF2 activation would be decreasing the efficacy of synthetic anti-rheumatic drugs by increasing drug efflux. Future perspectives regarding pharmacologic NRF2 activation in RA are finally proposed.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune joint disease with a marked inflammatory component that affects cartilages and bones, leading to a progressive decline in physical function and quality of life as well as cumulative comorbid risk, putting therefore a huge burden on patients, healthcare systems and society. As reviewed by Smolen et al. [1], RA has an elusive autoimmune component involving autoantibodies like rheumatoid factors against the Fc portion of IgG as well as anti-citrullinated protein antibodies (ACPAs) against many citrullinated proteins such as fibrinogen, α-enolase, vimentin, collagen type II and fibronectin [2]. ACPAs, which appear before disease onset and correlate well with disease progression, are used as diagnostic tool early in the course of the disease [3]. In addition to autoantibodies, there is a genetic risk related to HLA-DRB1 polymorphisms that are strongly implicated in self-peptide binding and antigen presentation to autoreactive T cells [4].

Unlike other autoimmune diseases, the triggering autoantigen in RA still remains a mystery. Instead, a wealth of evidence has been brought for the self-sustaining inflammatory processes that drive RA progression. Pro-inflammatory cytokines such as TNFα, IL-1β, IL-6 and IL-17 have a key role in regulating the immunological 'prodrome' that precedes clinically manifested arthritis, underlines synovitis and perpetuates

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chronic inflammation in RA [5]. Indeed, the success of anti-cytokine therapies was a huge step forward in the treatment of RA [6], albeit the fact that methotrexate (MTX), an antifolate drug, still remains the first-line medication [7]. The dynamic cytokine storm in RA [8] brings in the forefront that cytokines act in a tightly controlled network whose components are not independent entities, as they are for the moment considered in the current anti-cytokine therapies [9].

A plethora of immune and non-immune cells are cooperating for defining the self-sustaining inflammatory microenvironment in RA (Fig. 1). The synovial tissue can be considered as ectopic lymphoid structure [10] where both innate and adaptive immune responses occur, mainly involving cytokine production and polarization of T cells [11] as well as of macrophages [12] towards pro-inflammatory phenotypes [13]. The current perspective in RA brings into focus stromal FLS within the synovial niche, not only as responders to the RA-specific cues, but also as active participants in the generation of the pathologic synovial niche. It has been shown that FLS themselves release pro-inflammatory factors in response to TNFα, as for instance IL-6 that mediates the crosstalk with other immune cells in the synovium, especially with macrophage-like synovial cells that are thus driven to a pro-inflammatory M1-phenotype [14,15], and further propagate inflammatory signals. In addition, the pro-inflammatory and hypoxic synovial environment triggers a shift from oxidative phosphorylation to glycolytic ATP production in FLS, that sustains increased FLS survival, recruitment of myeloid cells to the synovial lining layers, production of inflammatory factors and tissue-degrading enzymes, ultimately leading to cartilage damage and bone erosion [16,17].

While current biologic therapies in RA are mainly designed to address inflammation mediated by cytokines, other pathologic processes such as the enhanced production of reactive oxygen species (ROS) and the consequent oxidative stress and alteration of redox-sensitive signaling pathways that accompany inflammation in RA have to be taken into account. In the inflammatory, oxidative and hypoxic synovial niche characterizing RA (Fig. 1), we bring into focus the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) which regulates a large panel of cytoprotective genes, including genes involved in redox control. The disturbance of the NRF2 signaling pathway has been evidenced in many chronic diseases and cancer, making this pathway a valuable therapeutic target in pathologies underlined by chronic low-grade redox alterations and inflammation [18]. Pharmacologic NRF2 activation might be a reliable alternative to conventional antioxidant supplements that has been shown to work in acute but not in chronic diseases, and may even have deleterious effects in the long run [19,20].

Several reviews have lately addressed the NRF2 pathway as a promising therapeutic target in RA, mainly focusing on NRF2 and its pharmacological activators that are in various stages of development [21,22]. Besides updating the information related to the role of NRF2 in RA, the current review brings into the forefront the sophisticated crosstalk of NRF2 with other redox-sensitive transcription factors and inflammasomes that have a critical role in the self-sustaining inflammatory processes characterizing RA. Although a plethora of cells are involved in RA, special emphasis is given in this review to FLS as drivers and executioners of the pathologic processes characterizing this complex disease. The survival advantage of pathologic inflammatory cells in RA is commented. The potential benefits of therapeutically targeting NRF2 in RA are discussed in terms of redox modulation for controlling inflammation, and cytoprotection for alleviating the toxicity of several synthetic anti-rheumatic drugs. The NRF2 interference with the action mechanism of these drugs is discussed.

2. Inflammation - redox crosstalk in RA

2.1. Enhanced oxidative activity in RA

In close crosstalk with inflammation, significant redox disturbances were evidenced at local and systemic level in RA [23]. A meta-analysis evaluating clinical trials that address oxidative biomarkers in RA found a positive correlation between the DAS28 disease score and lipid peroxidation in serum. Authors concluded that additional investigations in large cohorts of RA patients with well-characterized disease variants are highly needed for implementing redox biomarkers in the clinical practice [24].

The increased ROS levels in RA are induced by pro-inflammatory cytokines, danger-associated molecular patterns (DAMPs) and hypoxia in various types of resident synovial cells and blood leukocytes recruited in the inflamed joint [25] (Fig. 1). Through a feed-forward loop, ROS can amplify the production of pro-inflammatory cytokines by activating redox-sensitive transcription factors [26]. Uncontrolled production of ROS “in the wrong place and at the wrong time”, paralleled by the inability of the endogenous antioxidant system to detoxify chronic ROS bursts and to repair oxidative damages, lead to local and systemic cellular dysfunctions in many pathologies, including RA [27].

Excessive ROS in RA derive from increased generation of superoxide resulting from NADPH-oxidases activation [28] and mitochondrial disturbances [25]. TNFα, a critical pro-inflammatory cytokine in RA, has been shown to trigger increased ROS production *via* activation of the NOX1 and NOX2 isoforms of the NADPH-oxidase family through the interaction of the cytosolic domain of the TNF receptor 1 with the

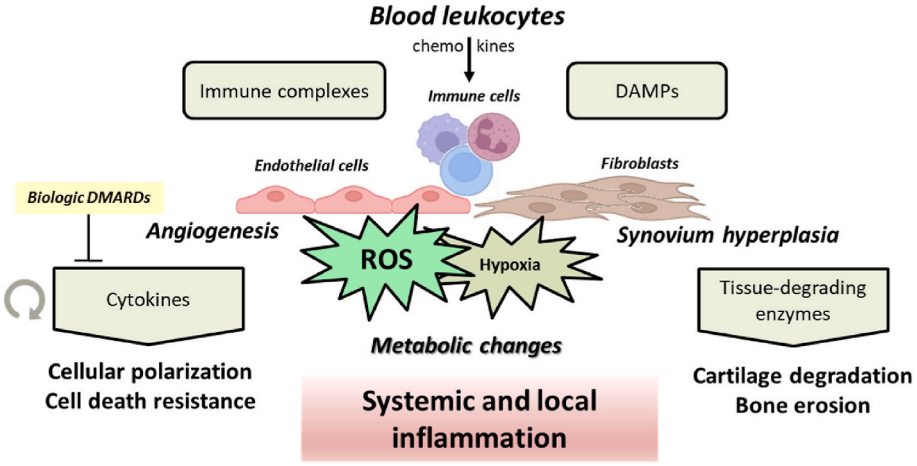

Fig. 1. The synovial niche. Immune cells, resident or newly recruited from the blood stream, along with fibroblast-like synoviocytes and endothelial cells cooperate for maintaining an inflammatory, oxidative and hypoxic microenvironment that finally results in cartilage degradation and bone erosion. Disease-modifying anti-rheumatic drugs (DMARDs) addressing inflammatory cytokines proved to greatly improve the disease course. DAMPs = Danger-Associated Molecular Patterns.

riboflavin kinase and the NADPH-oxidase component $p22^{phox}$ [29]. Moreover, TNFα induces mitochondrial ROS production through a mechanism involving the activation of caspase 8, ROS modulator 1 and B-cell lymphoma-extra-large in the outer mitochondrial membrane [30]. In turn, TNFα-mediated activation of NFκB detoxifies ROS by up-regulating catalase and superoxide dismutase, but also induces increased TNFα production and NOX2 expression that are feeding back into ROS generation [30].

The main ROS producers in the RA synovium are infiltrating neutrophils endowed with the NOX2 isoform of the NADPH-oxidase family [31]. These cells are intensively recruited to the inflamed synovium in response to IL-8, a chemokine produced by various types of activated cells [32]. Recruited neutrophils get primed by TNFα to respond vigorously to various stimuli such as DAMPs acting *via* toll-like receptors (TLRs), produce significant amounts of ROS *via* NOX2 activation [33], and release potent chemoattractants that foster recruitment of leukocytes to the synovium [33], henceforth perpetuating the inflammatory processes. Activated neutrophils develop a plethora of redox-dependent responses that contribute to RA pathogenesis [34]. For instance, increased formation of neutrophil extracellular traps (NETs) through a process depending on NADPH-oxidase activity was evidenced in RA [35]. NETs present citrullinated arthritogenic peptides to B cells that produce auto-antibodies against citrullinated proteins, along with immunostimulatory molecules that contribute to autoimmunity in RA [36]. During NETosis, a form of cell death associated with NETs formation [37], various degradation products are released and trigger inflammation, being therefore promising candidate biomarkers for monitoring disease progression and therapeutic effectiveness in RA [38]. Noteworthy, FLS can internalize NETs through TLR9 [39], evolving consequently to a pro-inflammatory phenotype, as demonstrated by the increased production of IL-6 [36]. Besides NETs, neutrophils synthesize various inflammatory and tissue degrading factors such as TNFα, IL-8, B cell activating factor, matrix metalloproteinases, granular enzymes and the receptor activator of nuclear factor κB ligand (RANKL), all of them amplifying inflammation and tissue damages in the RA joint [40]. The role of neutrophils in RA was recently revised by a transcriptomic study that identified a combination of neutrophil-specific genes having a good predictive power in differentiating responder and non-responder RA patients to anti-TNFα therapy [41]. Moreover, it was found that TNFα-primed neutrophils become more susceptible to the inhibitory effect of anti-rheumatic drugs on chemotaxis [42].

Surprisingly, NOX2 deficiency and the consequently decreased ROS levels can promote autoimmunity as much as oxidative stress does. This has been reported in various transgenic animal models and in patients with chronic granulomatous disease which have dysfunctional NOX2 and show an increased risk to develop autoimmune diseases, besides suffering from recurrent infections [43]. Albeit these extreme situations, NADPH oxidase-generated ROS are critical for maintaining self-tolerance. Unfortunately, a concentration range for intracellular ROS in various tissues has not been provided yet, raising concerns regarding the pharmacological manipulation of ROS levels.

Besides NADPH-oxidases as ROS producers in RA, plasma and synovial myeloperoxidase (MPO) and its products, the highly toxic hypochlorous acid and the associated 3-chlorotyrosine biomarker, are strongly related with RA. Thus, MPO activity was significantly increased in synovial fluid samples from drug-naïve patients, in association with IL-8 and IL-18, but tended to decrease during anti-rheumatic therapy [44]. Moreover, elevated plasma levels of MPO were associated with increased frequency of ANCA-associated vasculitis in RA [45].

Mitochondrial ROS significantly alter redox signaling and shape the inflammatory phenotype of synoviocytes in RA, mitochondria components acting as DAMPs that stimulate immune receptors and the NLRP3 inflammasome [46]. Profound mitochondrial dysfunctions were evidenced in RA. Besides increased ROS production, defects in mitochondrial biogenesis and mitophagy were evidenced, leading to important metabolic and immune reactivity changes in RA [47]. Indeed, the inhibition of mitochondrial fission in a collagen-induced arthritis mouse model reduced disease severity by decreasing ROS and the expression of inflammatory and destructive mediators in the synovial tissue [48].

Increased ROS levels produced in the context of chronic inflammation, hypoxia, low nutrient levels, enhanced lactate production and decreased pH in the synovial niche lead collectively to joint damage and increased accessibility of the immune system to cryptic neoantigens that may initiate autoimmune reactions [49,50]. The local oxidative environment contributes to articular damage through collagen oxidation [23], as well as to pannus formation due to aberrant differentiation, growth and survival of FLS which release pro-inflammatory cytokines and tissue degrading matrix metalloproteinases that perpetuate joint destruction [51]. If ROS levels are above physiological concentrations, but below the cytotoxic threshold, they can provide a survival advantage to RA synoviocytes and can even support the proliferation and differentiation of cells into pathologic variants by impacting redox-sensitive signaling pathways [52]. Such a mechanism has been extensively evidenced in cancer cells, but may also work in connection with synovial hyperplasia in RA [53]. For instance, increased intracellular ROS levels produced in FLS by NOX4 activation in response to TNFα and IL-17 has been shown to enhance FLS migration and invasion, expression of adhesion molecules and angiogenic factors [54,55]. Extracellular ROS deriving from activated leukocytes infiltrating the synovium [56] can also modulate the pathogenic behavior of FLS, especially in the case of RA patients with moderate disease [57].

Altogether, there is extensive evidence of chronically increased oxidative activity that greatly contributes to RA pathogenesis in concert with inflammatory and metabolic disturbances. The involvement of ROS in synovial hyperplasia shapes the perspective that ROS may act in a more subtle way in RA progression, beyond its tissue-degrading action, through persistent disturbance of redox-sensitive signaling pathways.

2.2. Redox-dependent gene transcription in RA

Besides a direct tissue-damaging action, increased ROS levels are decisively impacting the activity of redox-sensitive transcription factors, including NFκB, AP1 and HIF1α. Their increased activity accounts for chronic inflammation in RA due to enhanced production of a broad array of cytokines, polarization of the immune response towards an inflammatory phenotype and dysregulation of autoreactive lymphocytes [58]. ROS can also exert immunosuppressive effects, as demonstrated by the inhibition of dendritic cells function and T cell activation [59] as well as by the increased immunosuppressive potential of T regulatory cells under oxidative conditions [60].

Generally, ROS modulate redox-sensitive signaling pathways by inhibiting through oxidation critical enzymes that contain cysteines in their catalytic center. While the initial oxidation of cysteines and formation of sulfenic acid can be reversed by endogenous antioxidants, further oxidation to sulfinic and then to sulfonic acid results in irreversible ROS-mediated inactivation of enzymes [61,62]. Of particular interest are phosphatases that represent a bridge between redox and phosphorylation signaling events. It has been demonstrated that prolonged phosphorylation and subsequent activation of kinases can occur aberrantly even in the absence of a triggering stimulus due to the defective phosphatase control in oxidative environments [63].

We will present below NFκB as a prototype of redox-sensitive transcription factors. The NFκB transcription factor shapes cellular responses under stressful conditions, aiming to cope with the threat through an inflammatory response for “wound” healing and elimination of microbial pathogens in healthy organisms [64].

Early studies emphasized increased expression of the NFκB components p50 and p65 in RA synovial intimal lining cells compared to normal synovium [65], as well as increased NFκB activity that was partly due to inappropriate TLR signaling triggered by host-derived ligands. NFκB activation is associated with RA severity in terms of bone erosion and decreased response of patients to anti-TNFα therapy [66].

NFκB can generally exert both pro-survival and death-inducing actions, depending on the context. It appears that NFκB sustains the survival and inflammatory functions of synoviocytes in RA. Thus, RA FLS show only rare morphological signs of apoptosis, despite the relatively high frequency of DNA breaks [67]. This may be due to increased NFκB-mediated transcription of anti-apoptotic factors and/or p53 inhibition through the Tax-NFκB p65/RelA pathway [68].

NFκB is an inducible transcription factor that is expressed both in immune and non-immune cells [13]. It responds to various stimuli playing a critical role in RA, including cytokines (TNF α and IL-1β), DAMPs (HMGB1, citrullinated histones and S100 proteins) [69–71], molecules that bind to antigen receptors on T and B lymphocytes, and other factors such as the osteoclast differentiation factor receptor activator of NFκB ligand (RANKL) involved in osteoclast differentiation and bone destruction in RA [72].

Initial activation of NFκB triggers in innate immune cells as well as in FLS the transcription of a multitude of genes encoding cytokines, chemokines, adhesion molecules and other inflammation-promoting mediators. Thus, through a feed-forward loop, NFκB can induce either alone or in conjunction with other signaling pathways, the expression of the very same types of pro-inflammatory cytokines (i.e. TNFα and IL-1β) that initially elicited NFκB activation [73]. NFκB also triggers the transcription of additional genes encoding pro-inflammatory cytokines such as IL-6 involved in systemic bone loss and structural bone damage in RA [74]. Moreover, NFκB contributes to the activation of the NLRP3 inflammasome by triggering the transcriptional expression of NLRP3 to finally generate the mature and biologically-active form of IL-1β [75]. In addition to innate immune cells and FLS, NFκB is also involved in adaptive immunity by inducing the proliferation of B and T lymphocytes, the maturation of dendritic cells and the polarization of the immune response towards a pro-inflammatory phenotype [76]. Non-canonical NFκB activation sustains the survival, differentiation and antibody production in B cells, contributing to autoimmunity and chronic inflammation in RA [77]. Moreover, CD40-mediated signaling was shown to drive increased RANKL expression and subsequent pathologic osteoclast formation [78].

In addition to numerous regulatory mechanisms, ROS were shown to have a key contribution in controlling NFκB activity under physiological conditions, in terms of transient activation of the response against pathogens and final resolution of the elicited inflammatory response when pathogens are eliminated. Considering that NFκB has a pro-survival action in physiologic conditions [64], and that ROS are a powerful weapon for non-specifically destroying microorganisms, it is obvious that NFκB activation by ROS is physiologically designed for protecting "normal" tissues against the deleterious action of ROS. In turn, chronic sterile inflammation persistently increases ROS at levels below the cytotoxicity threshold in pathologic conditions, hence triggering vicious inflammation-oxidation cycles that perpetuate disease.

The role of ROS in regulating NFκB starts at the level of upstream redox-sensitive kinases that activate the NFκB pathway in the cytoplasm. It has been recently demonstrated that the NFκB essential modulator (NEMO) component of the inhibitor of κB (IκB) kinase (IKK) complex requires inter-molecular covalent linkage through disulfide bonds formed by Cys54 and Cys347 in the presence of mitochondrial ROS, resulting in IKK activation and subsequent signaling [79]. In turn, ROS may also inhibit particular IKKs. For instance, IKKβ oxidation at Cys179 and its subsequent S-glutathionylation inactivates kinase activity, leading to a reduction in NFκB signaling [80]. Going downstream, enhanced NFκB activation was registered under oxidative conditions or hypoxia due to changes in the phosphorylation pattern of IkBα, the NFκB repressor in the cytoplasm. IkBα phosphorylation at Tyr42 induces p50 and p65 release and their translocation towards the nucleus, irrespective of the regular Ser32 and Ser36 phosphorylation of IkBα by IKKs [81]. The required activation of protein tyrosine kinases for phosphorylating tyrosine residues can be triggered by ROS-mediated inactivation of tyrosine phosphatases. This mechanism is highlighted by the up-regulation of the NFκB pathway in the absence of proteasomal degradation of IkBα following the treatment of cells with a phosphatase inhibitor [82].

Another redox checkpoint in the NFκB activation pathway in the cytoplasm derives from the crosstalk of NFκB with the redox-sensitive phosphatidylinositol 3-kinase (PI3K)/AKT. Increased PI3K/AKT activity was reported in RA FLS, accounting for their increased NFκB-mediated survival and decreased susceptibility to Fas-induced apoptosis [83]. A potential mechanism relies on the increased ROS levels registered in RA, that inhibit critical phosphatases such as PTEN (phosphatase and tensin homolog deleted on chromosome 10), the main suppressor of the PI3K/AKT pathway. Additionally, ROS can directly inactivate AKT through ROS-mediated disulfide bond formation between Cys297 and Cys311 [84]. Through a feed-forward loop, PI3K/AKT signaling can induce increased ROS production by triggering the assembly and activation of NADPH-oxidases, as demonstrated by the suppression of NOX activity following the treatment of pulmonary microvascular endothelial cells with a PI3K inhibitor or through AKT1 knockout [85].

While increased ROS levels sustain NFκB activation in the cytoplasm, reductive conditions are needed in the nucleus for an appropriate transcriptional program. For instance, the antioxidant thioredoxin (TRX) blocks IkB degradation in the cytoplasm, hence impeding NFκB activation. When NFκB dimers translocate in the nucleus in response to TNFα [86], TRX maintains a local reductive microenvironment, and enhances the transcriptional activity of NFκB by increasing the ability of its functional subunits to bind to DNA and to start the transcriptional program [87]. It is hypothesized that low doses of ROS would trigger NFκB activation, while high levels may adversely affect the NFκB-mediated transcriptional program. Thus, p50 is oxidized at the level of Cys62 in the Rel homology domain, and is retained in the cytosol under basal conditions. In turn, in high oxidative conditions such as those elicited by NOX2 activation in neutrophils, the oxidation and subsequent S-glutathionylation of p50 and p65 diminish their binding to the promoter region of target genes, resulting in decreased expression of the inducible form of cyclooxygenase and lower bactericidal activity [88]. Upon NFκB activation, Cys62 in p50 is reduced in the nucleus through a mechanism mediated by APE1 (Ref-1). APE1 [89] is a nuclear enzyme that reduces critical cysteines in several transcription factors translocated in the nucleus, such as NFκB, AP1, CREB/ATF, p53 and HIF1α, all having a critical role in RA. In addition, by acting as a nuclear chaperone, APE1 facilitates local interaction of transcription factors with antioxidant molecules such as glutathione or TRX for generating a reductive microenvironment in the nucleus. Similar to TRX, APE1 has a pro-inflammatory role in the nucleus, but, once it reaches the extracellular space through exosomes, it mediates anti-inflammatory effects that are dependent on the redox status of its cysteine residue [90]. In this context, the elevated serum levels of APE1 evidenced in RA patients [91] is an inflammation or damage-associated biomarker, but may have also a contribution in lowering the levels of the pro-inflammatory TNFα, IL-1β and IL-6 cytokines [92].

Altogether, the sophisticated transcriptional program of NFκB is influenced by redox- and phosphorylation-mediated changes, as well as by dynamic protein-protein interactions that are still far from being unraveled.

3. The NRF2 transcription factor – a new player in RA

The increased ROS levels that generally accompany inflammation would most likely induce the activation of the cytoprotective KEAP1/NRF2 pathway. This response should lead to enhanced production of endogenous antioxidant defenses and subsequent decrease of elevated ROS levels and their pathologic consequences in RA. However, it seems that the physiological response is not always sufficient to provide full protection, and for this reason a pharmacological strategy is suggested herein.

NRF2 is a ubiquitous basic leucine zipper (bZIP) protein that makes

heterodimers in the nucleus with several other bZIP proteins, of which Small Musculoaponeurotic Fibrosarcoma (MAF) isoforms K, G and F are the best characterized. The heterodimer binds a specific enhancer termed Antioxidant Response Element (ARE) that has been found in around 250 genes. The first identified ARE-genes participate in phase 2 detoxification and biotransformation reactions involved in the elimination of xenobiotic compounds. It became soon evident that many ARE-genes participate in glutathione, TRX, peroxiredoxin, glutaredoxin and sulfiredoxin metabolism, and NRF2 is now recognized as the master regulator of redox homeostasis (Fig. 2A and B). Additional functions of ARE-genes include metabolic reprogramming towards generation of NADPH which is crucial in supporting redox reactions. Other cytoprotective NRF2 target genes participate in proteostasis by regulating the expression of several proteasome and autophagy genes. A role of NRF2 has also been reported in the activation of several anti-inflammatory genes and in the inhibition of pro-inflammatory cytokines expression. A list with some of the best-characterized ARE-genes is reported by Hayes and Dinkova-Kostova [93] (Fig. 2B). The relevance of these cytoprotective pathways will be discussed next in the context of RA.

NRF2 is controlled through a complex transcriptional and post-translational network that sustains prompt responses to oxidative, inflammatory and metabolic perturbations. The most relevant and best characterized mechanism of NRF2 regulation is at the level of protein stability. NRF2 has a short half-life time of about 15–40 min depending on the cell type [94]. It contains seven phylogenetically conserved regions known as NRF2-ECH homology (Neh) domains [95]. Among them, the N-terminus Neh2 domain contains two motifs, DLG and ETGE, that bind with low and high affinity to the main NRF2 regulator, the E3 ubiquitin ligase adapter KEAP1 (Kelch-like ECH-associated protein 1) [96]. KEAP1 belongs to the BTB-Kelch family of proteins that assembles with Cullin 3 (CUL3) and RBX1 to form multi-subunit Cullin-RING ligases (CRLs) for protein ubiquitylation [97]. Under basal conditions, KEAP1 binds to NRF2 at both DLG and ETGE motifs, and presents it to the CUL3/RBX1 complex for ubiquitination and subsequent degradation by the 26S proteasome [98]. KEAP1 contains several highly reactive cysteine residues (e.g. Cys151 in the BTB domain, Cys226, Cys273 and Cys288 in the IVR domain or Cys613 at the Kelch domain) that act as redox sensors [99,100]. Under oxidative stress or in the presence of electrophilic compounds, modification of these cysteines induces a conformational change that prevents a productive presentation of NRF2 to Culin3/RBX1 for ubiquitination. It has been suggested that NRF2 saturates KEAP1 and the newly synthesized NRF2 escapes from degradation and translocates to the nucleus [96] (Fig. 2A).).

Depending on the cell type and the specific stressful conditions to which cells are subjected, NRF2 may have distinctive signatures that are greatly impacting the elicited cytoprotective mechanisms. Besides the competition with the repressor BACH1-MAFK complex for binding to AREs and the assembly of an active transcriptional machinery, the specific NRF2 fingerprint seems to be highly dependent on the number of ARE sequences and their polymorphisms within the promoter of each of the putative NRF2 target genes [101]. Thus, it has been shown that NRF2 has a high affinity for the C-containing alleles of ARE, but a significant decrease is registered when C is replaced by A in the core TG [A/C]CTCAGC consensus sequence of ARE [102]. As we will describe below in Chapter 4, things are even more complicated due to the array of transcription factors that partially overlap with the transcriptional program of NRF2 for mounting a proper cellular response in inflammatory and oxidative environments.

3.1. NRF2 and antioxidant activity

NRF2 controls the transcription of several antioxidant genes, having therefore a critical role in pathologies underlined by chronic oxidative stress, including RA [93]. Notably, NRF2 is critically involved in glutathione biosynthesis by inducing the expression of the *GCLC*, *GCLM*, *GSS* and *xCT* genes that encode the glutamate-cysteine ligase catalytic and modifier subunits, glutathione synthetase and the SLC7A11 antiporter that transports cystine in exchange for glutamate, respectively [103]. Furthermore, reduced glutathione recycling through the action of glutathione reductase (GSR) is also regulated at transcriptional level by NRF2 [104]. In addition, by inducing the expression of several glutathione-S-transferases, NRF2 controls protein glutathionylation for protecting critical thiols against irreversible oxidation, preserves the glutathione pool for future oxidative challenges and regulates protein functions through post-transcriptional changes [105]. NRF2 is also involved in controlling the thiol status by inducing the expression of TRX as well as of the thioredoxin reductase TRXRD1 that recycles reduced TRX at the expense of NADPH [106]. The production of NADPH required for reducing oxidized glutathione and TRX is impacted by NRF2 through the transcriptional control of several enzymes involved in the pentose phosphate pathway (PPP) such as glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase [107]. Furthermore, NRF2 reduces the levels of hydrogen peroxide and organic hydroperoxides by inducing the transcription of critical antioxidant genes encoding catalase and several glutathione peroxidases [108].

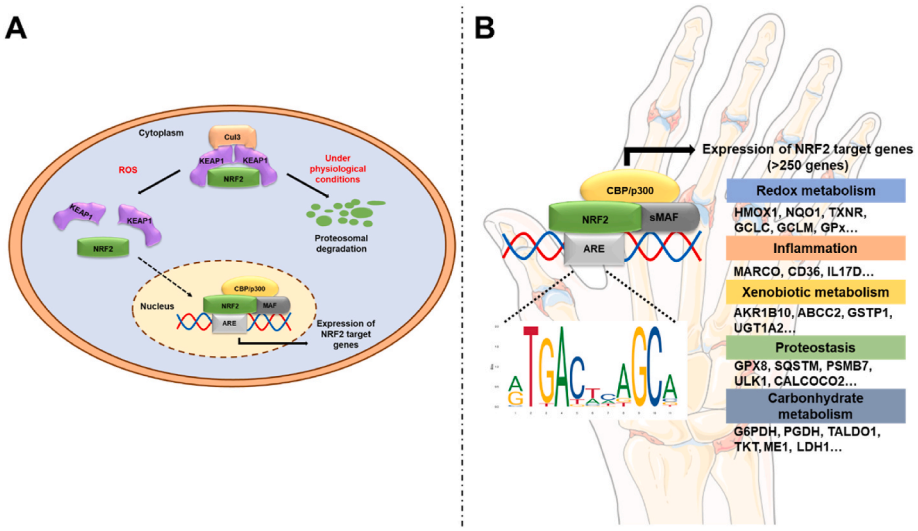

Fig. 2. The NRF2-KEAP1 pathway under physiological and stressful conditions. **(A)** ROS-dependent NRF2 activation, (**B**) cytoprotective NRF2-targeted genes. The Figure was partly generated using Servier Medical Art provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

3.2. NRF2 and cellular metabolism

The transcriptional activity of NRF2 greatly impacts cellular metabolism. Using the SICyLIA mass-spectrometry-based proteomic method to profile thiols oxidation at whole proteome level, it has been recently shown that both acute and chronic oxidative stress cause local metabolic adaptation through direct oxidation of critical metabolic and mitochondrial proteins [109].

A byproduct of the tricarboxylic acid (TCA) cycle, itaconate, links mitochondrial metabolism with the KEAP1/NRF2 response. Itaconate is produced by the catalytic conversion of *cis*-aconitate by the immune-responsive gene 1 (*IRG1*) which is highly expressed in macrophages [110]. Itaconate is an anti-inflammatory metabolite that activates NRF2 *via* alkylation at the cysteine residues 151, 257, 288, 273 and 297 on KEAP1. The initiation of the NRF2 transcriptional program further sustains the anti-inflammatory effects exerted by itaconate for counteracting the action of succinate [111]. In fact, itaconate appears to reduce through NRF2 activation the type I interferon response [112] whose signature was evidenced in RA, among other pathologies, and was shown to correlate with ACPA [113].

NRF2 controls the expression of genes that are critically involved in the PPP as well as the malic enzyme and isocitrate dehydrogenase. Altogether, NRF2 exerts full control over NADPH generation which is critically required for redox reactions. It has been shown that NRF2 deficiency results in decreased oxidative phosphorylation efficiency [114], accompanied by an impairment in complex I activity due to substrates limitation, leading to increased mitochondrial ROS production. Instead, glycolysis is enhanced [115]. Indeed, up-regulation of glucose metabolism and an intrinsic ability to use glycolysis under metabolic stress were evidenced in RA FLS [116]. These cells have to adapt to inflammatory and hypoxic conditions, and to meet increased energetic and biosynthetic demands for proliferation and survival. Accordingly, glucose deprivation or treatment with glycolytic inhibitors impair the generation of pro-inflammatory cytokines, resulting in decreased FLS proliferation and migration. Additional evidence is coming from a functional study using NRF2 siRNA that confirms the role of NRF2 on purine biosynthesis and the metabolism of folate and glutamine, particularly in rapidly proliferating cells like cancer cells and FLS [107]. It was indeed demonstrated that NRF2 expression in the RA synovial tissues was up-regulated by TNFα and increased ROS levels, and both NRF2 knockdown by siRNA or NRF2 inhibition with ML385 promoted proliferation and invasion of RA FLS as well as the generation of tissue-degrading matrix metalloproteinases [117]. This study also evidenced that NRF2 activation with the NRF2 activator sulforaphane (SFN) had a marked inhibitory effect, indicating that therapeutic electrophiles might be able to control synovitis in RA. Not only proliferating FLS, but also activated immune cells (macrophages, dendritic cells, monocytes and expanding effector T cells) exhibit an up-regulated glycolytic metabolism that sustains many of their pro-inflammatory functions [47]. Accordingly, the aberrant immunometabolism of synovial cells in RA could be restored by pharmacologic NRF2 activation. In turn, hyperactive NRF2 in cancer cells is known to induce the expression of the glucose transporter GLUT1 that facilitates an increased glucose import into the glycolytic flux. Further on, NRF2 can increase the expression of several key glycolytic enzymes, including hexokinase 1 and 2, glucose phosphate isomerase 1, 6-phosphofructo-2-kinase, fructose-bisphosphate aldolase A, enolase 1 and pyruvate kinase muscle isoform 2, hence augmenting the glycolytic flow and the pool of associated intermediates required for anabolic reactions [118].

The role of NRF2 in the switch from oxidative phosphorylation to glycolysis, which is dependent on the cell type under particular stressful conditions, raises questions on the outcome of a persistent pharmacological activation of NRF2 that may sustain synovitis in particular circumstances [117]. It has been shown that excessive NRF2 activity can have deleterious effects, as KEAP1-null mice with constitutive NRF2 activation exhibit post-natal death that can be reversed by NRF2 down-regulation, and a decrease in KEAP1 levels to less than 50% results in increased mortality, probably due to malnutrition resulting from hyperkeratosis in the esophagus and forestomach [119]. These findings suggest that constitutive NRF2 activation beyond a certain threshold is rather disadvantageous in terms of survival [120]. Nevertheless, the findings on the biologic consequences of persistent NRF2 activation due to genetic defects might not be translated to chronic treatment with pharmacologic NRF2 activators.

3.3. The NRF2 transcriptional signature in RA

We analyzed the microarray datasets deposited in the Gene Expression Omnibus (GEO) database for investigating the following issues: (1) the differentially expressed genes (DEGs) in synovial tissue from rheumatoid arthritis (RA) patients *vs* osteoarthritis (OA) patients as control group; (2) the DEGs in whole blood from RA patients and healthy controls (HC); (3) the DEGs in synovial tissue and whole blood of RA patients after anti-TNFα or MTX treatment; (4) the DEGs in synovial tissue and whole blood in RA patients that were responders and non-responders to anti-TNFα therapies. GSE153015, GSE140036, GSE93777, GSE68689, GSE100191, GSE78068, GSE77298, GSE58795, GSE55457, GSE55235, GSE35455, GSE45867, GSE39340, GSE36700, GSE33377, GSE17755, GSE20690, GSE12051, GSE15258, GSE8350, GSE7669, GSE7524, GSE3698, GSE3592, GSE2053 and GSE1919 were downloaded from GEO and were analyzed using GEO2R. The Benjamini and Hochberg false discovery rate was applied. Genes with a fold change (FC) > 1.5 and adjusted (adj.) p-value < 0.05 were considered statistically significant. Among the significant genes we selected well-known NRF2-regulated genes, listed and reviewed in several studies.

The analysis showed that the *TXN*, *NQO1* and *SLC3A2* genes were dysregulated. We detected the up-regulation of the *TXN* gene encoding TRX1 in the blood of RA patients as compared to controls without joint diseases in two large datasets, GSE1775 and GSE93777, that compared the transcriptomic profile of 112 RA *vs* 53 HC (FC $= 1.58$, adj. $p < 0.0001$) and 232 RA *vs* 43 HC (FC $= 1.80$, adj. $p < 0.0001$), respectively. These findings are supported by previous studies investigating TRX1 at protein level in plasma, synovial fluid and synovial tissues. Elevated TRX1 levels in plasma from RA patients were observed, with higher plasma levels in patients with active disease. TRX levels in plasma significantly decreased during anti-rheumatic treatment, together with serum C-reactive protein (CRP) values. In the same study, it has been shown that TRX levels were significantly higher in RA than in OA patients in the synovial fluid [121], and that thioredoxin receptor (TRXR) levels in plasma and synovial fluid were positively correlated with disease severity. Moreover, using an anti-TRX monoclonal antibody, the authors performed an immunohistochemical analysis of synovial tissue from two RA and two OA patients, finding that TRX was mainly expressed on the surface of the synovial lining layer in RA patients, whilst having only a low expression in the OA counterpart [121]. Results evidencing the up-regulation of the TRX system are indicative of an increased systemic oxidative activity in the blood of RA patients, that the endogenous antioxidant mechanisms elicited by NRF2 aim to counteract. The TRX system maintains the thiol status in cells, both in the cytoplasm through the action of TRX1 and TRXR1, and in mitochondria through TRX2 and TRXR2. *TXN*, whose gene promoter contains ARE sequences targeted by NRF2, can regulate the redox status and activity of specific proteins involved in cellular defense against oxidative stress, cell death by apoptosis and redox regulation of signaling pathways and gene transcription. Therefore, the TRX system is of high interest and relevance for the design of targeted therapies in RA as well as in other inflammatory diseases underlined by oxidative stress [122].

The analysis on the GSE39340 dataset revealed the impairment of the NRF2 target gene encoding NAD(P)H:quinone oxidoreductase (*NQO1*) in the synovial tissue from ten RA patients *vs* seven OA patients, with down-regulation of this gene in the synovial tissue of RA patients (FC $= -1.85$, adj. $p = 0.0057$). In turn, other studies reported the

activation of NQO1 in synovial fibroblasts from RA patients after treatment with calycosin which activated NRF2 by potentiating the accumulation of p62 and consequent non-canonical activation of NRF2 [123]. The up-regulation of NQO1 at protein and mRNA levels was also observed in the synovial tissue in a rat model of RA treated with dihydromyricetin (DMY). In this model, DMY up-regulated the abnormally decreased mRNA and protein levels of the NRF2 targets heme oxygenase 1 (HO-1) and NQO1 in the RA synovial tissue [124]. Altogether, results point out a dysfunction of the KEAP1/NRF2/ARE system in the RA synovium that can be restored, at least at the level of NQO1, by treatment with NRF2 activators.

A less investigated gene in RA is the solute carrier SLC3A2, which is under the transcriptional control of NRF2 [125]. SLC3A2 is a member of the xc-cystine/glutamate antiporter that imports cystine, the oxidized form of cysteine, in exchange with glutamate in a sodium-independent and chloride-dependent manner. Inside cells, cystine is reduced to cysteine by TrxR1 or glutathione. Cysteine is the rate-limiting substrate for glutathione biosynthesis in the presence of glutamate, providing the most powerful intracellular antioxidant buffer. Moreover, cysteine and cystine also form a key redox couple on their own [126,127]. In our analysis, *SLC3A2* transcripts were found up-regulated in the blood of 112 RA patients *vs* 53 controls (GSE17755) (FC = 1.72, adj. $p < 0.0001$), but down-regulated in the blood of 58 RA patients after MTX treatment (GSE35455) (FC = −1.57, adj. $p < 0.0001$). It has been shown that the cystine/glutamate antiporter is inhibited by sulfasalazine, a first-line treatment in RA [128]. Moreover, the disturbed expression of *SLC3A2* tended to normalize after MTX or sulfasalazine treatments, in the analyzed GEO dataset reporting the GEx changes in the blood induced by anti-TNFα biologicals after 14 and 22 weeks of treatment in responder patients (GSE8350). These data indicate that SLC3A2 is not only involved in RA, but it is also responsive to particular anti-rheumatic treatments, being therefore a potential blood biomarker and therapeutic target.

According to our analysis, the NRF2 signature in RA appears to be relatively modest, indicating a potential NRF2 deficiency that may account for the increased oxidative stress evidenced in RA at local and systemic levels. Nevertheless, a more detailed classification of patients is expected to provide additional information on the groups of patients that would most benefit from an adjunctive NRF2-targeted therapy.

3.4. Lessons from NRF2-knockout models in RA

The role of NRF2 in RA was emphasized in NRF2-knockout mice with antibody-induced arthritis where severe joint damages comprising synovial hyperplasia, pannus formation and invasion, cartilage erosion and increased number of spontaneously fractured bones, accompanied by prominent oxidative changes in lipids were reported [129]. In another study, serum transfer from K/BxN transgenic mice to NRF2-knockout mice was performed, resulting in exacerbated autoimmune and inflammatory responses mediated by IgG1 autoantibodies mimicking the effector phase of RA [130]. In this model, it has been shown that NRF2 deficiency and consequent down-regulation of HO-1 accelerated arthritis incidence. NRF2-knockout animals exhibited a widespread disease affecting both front and hind paws, characterized by enhanced infiltration of leukocytes and joint destruction. The inflammatory response was evidenced by increased production of TNFα, IL-6 and CXCL1 in the joint, as well as by higher expression levels of cyclooxygenase-2, inducible nitric oxide synthase and peroxynitrite. Altogether, considering that NRF2 is activated in the synovial membrane of RA patients and arthritic mice [129], NRF2 may exert a protective role against RA-related inflammation and oxidative stress, and NRF2 deficiency may precede or accompany disease onset.

As NRF2-knockout mice or cells represent extreme models, these findings only testify on a role of NRF2 in RA, but do not bring evidence on the level of NRF2 activation that would significantly slow disease progression. Such information was provided by preclinical studies using various NRF2 activators. These compounds are electrophiles that target not only specific cysteines in KEAP1 but also in several other proteins. Therefore, due to possible off-target effects of NRF2 activators, these results are informative but not conclusive. New insights may be brought by the use of KEAP1-knockdown mice where the NRF2 pathway is systemically activated [120], but for the moment this animal model has not been used in the context of RA.

4. The crosstalk of NRF2 with pro-inflammatory transcription factors

Besides decreasing the levels of ROS and secondary oxidants produced in inflammatory conditions, NRF2 interferes at various levels with several transcription factors that play a critical role in inducing and maintaining chronic inflammation in RA (Fig. 3).

4.1. The NRF2-NFκB crosstalk

Recent results using the systems biology approach confirmed the involvement of NFκB signaling pathway and its interaction with ROS/antioxidant mechanisms and NRF2 in RA [131]. A recent study using single-cell RNA-seq and ATAC-seq (https://www.biorxiv.org/content/10.1101/2021.08.27.457747v1) evidenced in both mouse and human datasets particular gene regulatory networks and open chromatin regions in RA FLS, and identified unique patterns of transcriptional activity in FLS populations that drive RA pathogenesis. It was shown that the NFκB pathway components NFκB1/2, RelA and RelB are critically involved in the RA-specific type of inflammation, with IKK2 kinase acting as dual modulator of arthritis that can address both inflammatory and death responses. In addition, the NRF2-encoding gene *Nfe2l2* was found over-expressed during disease, along with the regulatory factors BACH1 and FOSL1, indicating a network related to extensive oxidative stress in TNFα-mediated arthritis.

A mutual transcriptional antagonism between NFκB and NRF2 has been generally documented as homeostatic mechanism. Thus, NFκB activation by lipopolysaccharide (LPS) can stimulate NRF2 activity *via* the Ras-related C3 botulinum toxin substrate 1 (RAC1) small GTPase which promotes β-actin-dependent cytoskeletal rearrangements and oxidative processes. In turn, up-regulated NRF2 activity is able to inhibit RAC1-dependent activation of NFκB, contributing to inflammation resolution [132]. Moreover, NFκB itself can elicit enhanced transcription of *Nfe2l2* that contains several kB-binding sites in the proximal promoter, to which p65 can bind and initiate NRF2 transcription, as demonstrated in acute chronic leukemia in the context of elevated TNFα levels [133]. These mechanisms account for the resolution of oxidative stress and inflammation. Thus, in physiologic conditions, high NRF2 levels were detected in circulating neutrophils, being though insufficient for dampening the oxidative burst developed by phagocytes for killing pathogens, but sufficiently high for protecting normal tissues through a "wound healing" process against the deleterious action of ROS on the host organism [134]. In turn, NFκB and NRF2 have opposing activities in chronic inflammatory conditions such as those characterizing RA, and therefore pharmacologic NRF2 activation is needed for restoring homeostasis.

In the cytoplasm, NRF2 and NFκB negatively interfere at the level of the NRF2 repressor KEAP1 which drives the suppression of NFκB-mediated transcription of inflammation genes in oxidative conditions. An important activator of the NFκB pathway is the IKK complex formed by two serine/threonine protein kinases, IKKα and IKKβ, and the regulatory protein IKKγ. The complex phosphorylates IκBα, the NFκB repressor, leading to its ubiquitin-proteasome degradation and to the release of NFκB. The human IKKβ subunit contains in its kinase domain the ETGE and DLG motifs required for interacting with KEAP1, and it has been suggested that KEAP1 might drive IKKβ to degradation, therefore leading to NFkB activation [135]. However, the ETGE motif of IKKβ is not conserved in rodents, suggesting additional crosstalk mechanisms.

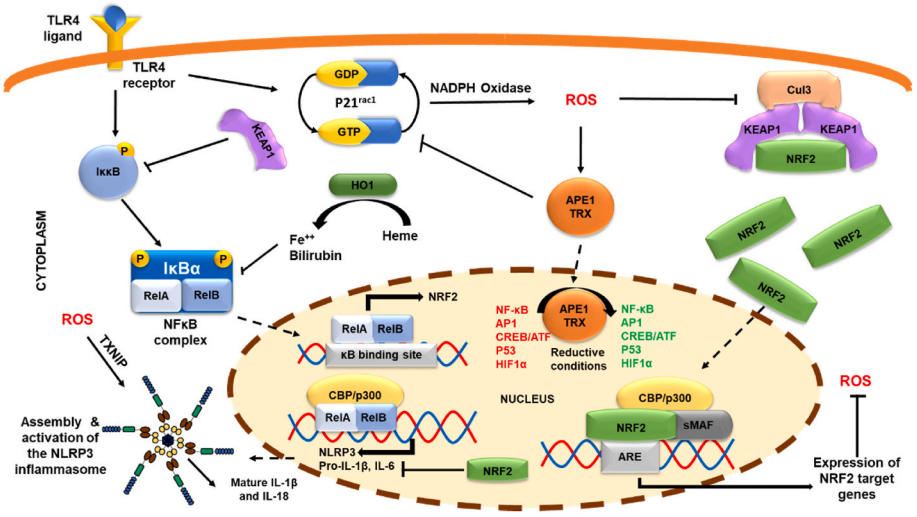

Fig. 3. Inflammation and redox circuits in RA – the role of the transcription factor NRF2. Inflammatory stimuli, such as TLR4 ligands, activate the NFκB signaling pathway and the NLRP3 inflammasome, resulting in a cytokine storm. In addition, increased production of ROS is elicited by the activation of NADPH oxidases through the small GTP-binding protein $p21^{racl}$. Coordinated phosphorylation and redox changes occur in NFκB-related signaling molecules such as IKK, IκBα, RelA and RelB. Noteworthy, oxidative conditions are needed in the cytoplasm for activating the NFκB pathway, while a reductive microenvironment elicited by APE1 in conjunction with TRX sustains the DNA binding of various transcription factors (NFκB, AP1, CREB/ATF, P53, HIF1α). Increased ROS levels trigger the oxidation of critical cysteines in KEAP1, resulting in decreased proteasomal degradation of NRF2 and consequent translocation in the nucleus of newly synthesized NRF2 molecules. Moreover, NFκB itself elicits the transcription of *Nfe2l2*, the gene that encodes NRF2. The transcription of NRF2 target genes is initiated (see Fig. 2B), resulting in the production of potent endogenous antioxidants that lower ROS levels. NRF2 can also exert an anti-inflammatory action through a negative crosstalk with NFκB. Thus, in the cytoplasm, HO-1-dependent bilirubin generation following NRF2 activation inhibits the release of transcriptional dimers from the NFκB complex. Moreover, the available KEAP1 molecules target IKKβ for ubiquitination and consequent proteosomal degradation. In the nucleus, NRF2 and NFκB compete for limited amounts of co-factors (i.e. CBP/p300), hindering therefore each-others activity. NRF2 can also inhibit directly the transcription of the inflammatory genes *IL1B* and *IL6* through the recruitment of transcriptional repressors. Moreover, NRF2 hinders the maturation of IL-1β and IL-18 by inhibiting the NLRP3 inflammasome.

In this regard, KEAP1 prevents the binding of the heat shock protein HSP90 to IKKβ, thus promoting its autophagic degradation [136]. KEAP1 binding also impedes on the TAK1-mediated phosphorylation of IKKβ at S177 and S181 [137], resulting in decreased IKKβ activation. Altogether, when IKKs are perturbed, IKBs are not properly phosphorylated, and NFκB activation is hindered [138]. In turn, in severe oxidative conditions, KEAP1 alkylation becomes irreversible and hinders its interactions with NRF2 and IKKβ [139].

Another common regulatory mechanism for both NRF2 and NFκB in the cytoplasm is mediated by glycogen synthase kinase 3 (GSK3β). This kinase phosphorylates serine residues in the Neh6 domain of NRF2 that is subsequently targeted for proteasomal degradation through ubiquitination by a β-TrCP/Cul1 E3 ligase complex, independently of KEAP1. Both KEAP1- and GSK3β/β-TrCP-dependent regulatory mechanisms act in concert, albeit reflecting differential regulation of NRF2 in various circumstances. It is speculated that, during a significant oxidative or electrophilic attack, KEAP1-mediated degradation mechanisms seem to be active in early phases, while GSK3β-mediated mechanisms are acting in late phases of cellular response. It has also been hypothesized that GSK3β activation occurring before the NRF2-mediated restoration of redox homeostasis would drive cells to death as a result of oxidative stress [140]. In the case of the NFκB pathway, the degradation of the IκB repressor and subsequent NFκB activation involves the action of the SCF/β-TrCP ubiquitin ligase complex following the recognition of the IκB degron resulting from phosphorylation by IKK within minutes after cell stimulation [141]. Moreover, p65 is substrate for GSK3β-mediated phosphorylation that may either activate or inhibit NFκB, depending on the cell type and experimental conditions. GSK3β-related regulatory mechanism seems to be inactive in blood monocytes from RA patients where GSK3β deactivation was emphasized, resulting in hypermetabolic monocytes with enhanced mitochondrial activity and excessive production of tissue-degrading enzymes [142].

As most of the antioxidant effects are mediated by products of NRF2-targeted genes, it is expected that an increased NRF2 transcriptional activity regulates ROS levels and impedes the initiation of redox-sensitive inflammatory pathways in the cytoplasm. The products of particular NRF2-targeted genes have been shown to exert broad cytoprotection, beyond their antioxidant action. Of utmost importance in RA is HO-1 which confers protection against oxidative, inflammatory and hypoxic stress in joint tissues by regulating the activation and metabolism of synovial cells [143]. HO-1 was found up-regulated in the lining and sub-lining layers of the RA synovial tissue [144] as well as in synovial fluid where its concentration correlates well with matrix metalloproteinase 3 and serum C-reactive protein levels [145]. Induction of HO-1 by hemin or ectopic expression of HO-1 in synovial cells inhibited IL-6 and IL-8 production induced *in vitro* by LPS [144]. Part of the anti-inflammatory action of HO-1 is mediated by the inhibition of NFκB in the cytoplasm. HO-1 catalyzes the degradation of the heme group, resulting biliverdin which is converted into bilirubin by the biliverdin reductase, along with carbon monoxide and ferrous iron which is further reduced by NRF2-driven induction of ferritin and the activation of ATPase Fe^{2+}-secreting pump (Fig. 3). As demonstrated in the study of Li et al. [146], bilirubin inhibited the production of TNF-α and IL-6 in LPS-primed macrophages through decreased phosphorylation of IκBα and p65, as well as through caspase 1-dependent IL-1β maturation by NLRP3, AIM2 and NLRC4 inflammasomes. Moreover, bilirubin inhibited *in vivo* IL-1β and TNFα release in mice with LPS-induced sepsis. Elevated levels of HO-1 in RA are predictable as protective response against the deleterious action of ROS, multiple inflammatory factors and hypoxia. Of note is that the transcription of the HO-1 encoding gene, *HMOX1*, is at the crossroad of several pro-inflammatory transcription factors such as NFκB, AP1, members of the heat-shock factor family and hypoxia-inducible factor (HIF)1α, in addition to NRF2. This makes HO-1 a pleiotropic cytoprotective factor in stress responses triggered concomitantly by multiple cues [147]. While several TRE and ARE sequences have been identified within the *HMOX1* gene indicating that NRF2 and AP1 directly induce gene expression, it is debatable if NFκB can directly activate *HMOX1* transcription considering that its promoter does not contain a κB sequence. Most probably, NFκB-mediated activation occurs indirectly by the association of NFκB with other DNA-binding proteins within a larger complex containing various endogenous transcription modulators [148]. With respect to NRF2, it has been found that BACH1 repression is dominant over NRF2-mediated *HMOX1* transcription, and inactivation of BACH1 is a prerequisite for *HMOX1* induction by allowing NRF2 molecules already existent in the nucleus to bind to the gene promoter and elicit *HMOX1* transcription

[149]. It has even been shown that, in particular conditions, the effect of BACH1 on *HMOX1* expression could be independent of NRF2 [150]. This is not true for all NRF2 gene targets. For instance, it has been found that the *TXNRD1* gene encoding TRXR1 is regulated primarily by NRF2 and not by BACH1 [149].

The NFκB-NRF2 interference in the nucleus occurs through additional mechanisms than those acting in the cytoplasm (Fig. 3). In the nucleus, the NFκB component p65, NRF2 and cyclic-AMP Response Element Binding Protein (CREB) compete for the CREB binding protein (CBP), a critical co-activator that is present only in limited amounts in the nucleus. CBP binds to NRF2 at the level of its Neh4 and Neh5 domains [151], while p65-CBP interaction involves the KIX region of CBP, which is the same region responsible for binding the transcriptionally active S133-phosphorylated form of CREB [152]. CBP in conjunction with its p300 paralog acts as scaffold to stabilize the components of transcriptional complexes through their TAZ domains [153]. In addition, through their acetyltransferase activity, CBP and p300 acetylate particular lysine side chains within the positively charged N-terminal tail region of histones, hence locally destabilizing the nucleosome structure through electric charge alterations that enable the transcription complex to access a genetic locus [154]. CPB can modulate gene transcription also through other mechanisms that might be relevant for RA. This is the case of the transcriptional antagonism between NFκB and glucocorticoid receptors (GR). Glucocorticoids trigger immune suppression, partly by decreasing the expression of inflammatory genes that are under the transcriptional control of NFκB [155]. It has been demonstrated that CBP functions in this case as an integrator of the physical interaction between NFκB-p65 and GR at the level of the Rel Homology Domain (RHD), and not as a limiting co-factor for the transcriptional NFκB program [156]. Moreover, in the context of prolonged hypoxia, both CREB, NFκB and the hypoxia-induced factor (HIF) 2 cooperatively induce the expression of the matrix metalloproteinase 1 and subsequent changes in cell shape, migration and invasion, as seen in cancer cells and FLS [157,158]. The combined transcriptional activity of CREB and NFκB suggests that their needs for CBP are in the limit of the existing pool, and/or that they interact with the same CBP molecules that may shift from one transcription factor to another found in close proximity of the promoter region. This behavior shapes the hypothesis that the antagonism of inflammation-triggering transcription factors and NRF2 is evident only when particular stimuli are dominant, such as in the case of RA where the inflammatory challenge is apparently dominant over oxidative stress.

The inhibitory action of NFκB on the transcriptional activity of NRF2 is also supported by the observation that NFκB-p65 enhances the MAFK-associated histone deacetylase activity by facilitating the recruitment of histone deacetylase 3 (HDAC3) to the ARE-enriched enhancers [159]. HDAC3 promotes chromatin condensation and transcriptional repression [160], and also deacetylates CBP, hence abolishing its co-activator activity [159]. Indeed, the *in vitro* inhibition of HDAC3 in RA FLS could suppress inflammatory gene expression, including the production of type I interferons that contribute to RA pathogenesis, and can also predict the patient's response to anti-TNFα therapies [161]. Moreover, p65 can promote HDAC3 association with MAFK, thus preventing heterodimer formation with NRF2 [159]. The availability of MAFK is also controlled by NRF2 considering that NRF2-knockdown results in increased MAFK levels, indicating that nuclear NRF2 is required for maintaining low levels of this protein in order to limit p65 activation by acetylation [162].

4.2. The NRF2-AP1 crosstalk

Activation of particular NFκB-targeted genes may be induced jointly by several transcription factors, since it was demonstrated that the sites of p65 binding to DNA are enriched not only in κB motifs, but also in recognition sites for other transcription factors, especially AP1 which comprises JUN homodimers or JUN/FOS heterodimers [163]. The tight crosstalk of NRF2 with AP1 is based primarily on the fact that both factors are basic leucine zipper (bZip) transcription factors that regulate each other at several levels. Moreover, the NRF2-binding ARE sequence and the AP1-binding site TRE (TGA(C/G)TCA) often overlap, with TRE being embedded into ARE [101].

This particular feature of the TRE and ARE binding sites can drive either a positive or a negative crosstalk between AP1 and NRF2 when working on the same ARE with embedded TRE, and is also responsible for the reciprocal regulation of gene expression in a cell-dependent context. Zolotukhin and Belanova hypothesized [164] that, when JUN proteins stimulate NRF2 expression, the subsequently increased production of TRX promotes JUN binding to DNA by creating a reductive microenvironment. Such a feed-forward loop gives arguments that AP1-driven inflammation can trigger the activation of the NRF2 pathway which, through a feed-forward loop, will further promote inflammation by enhancing the DNA-binding capacity of inflammatory transcription factors. In turn, in cells in which JUN has been shown to suppress NRF2 expression, less TRX is produced, consequently altering the transcriptional activity of AP1 and of other transcription factors such as NFκB. In this case, the negative crosstalk between AP1 and NRF2 is acting as a homeostatic mechanism for controlling inflammation. These positive and negative regulatory circuits connecting AP1 and NRF2 are highly cell-dependent, and are dictated by the numbers of various types of JUN proteins and their dimerizing partners that shape the transcriptional profile. Another possible interference mechanism between NRF2 and AP1 resides in the fact that c-JUN and NRF2 can form transcriptionally active dimers that bind to ARE, whose action depends on the amount of available JUN proteins [101,165]. Thus, it is hypothesized that, in case of relatively high c-JUN levels, c-JUN/NRF2 dimers induce the ARE-dependent transcription of the FTL gene, while its transcription is repressed in the case of low c-JUN levels.

4.3. The NRF2-HIF1α crosstalk

Both fibroblast- and monocyte-derived synoviocytes proliferate extensively in RA and contribute decisively to the inflammatory process. In the latter stages of disease, the synovium becomes a mass of growing tissue that becomes hypoxic and triggers specific responses to low oxygen levels that are mediated by HIFs [166].

HIFs are dimeric transcription factors that regulate the response to hypoxia. They consist of an oxygen-sensitive α subunit, and a proteolytically stable β subunit. As in the case of NRF2, the transcriptional activity of HIF1α is regulated by controlling its stability in the cytosol as well as through its binding to transcriptional co-activators in the nucleus. In normoxia, three isoforms of prolyl hydroxylases (PHD) catalyze the hydroxylation of proline residues in HIF1α, generating a high affinity binding site for the von-Hippel Lindau protein which determines the ubiquitination and proteasomal degradation of HIF1α [167]. Another hydroxylase, the factor inhibiting HIF (FIH), targets an asparagine residue from a transactivating domain in HIF1α, and disrupts the interaction between HIFs and their CBP/p300 co-activator [168]. In hypoxia, the two hydroxylases are inhibited, HIF1α is stabilized and translocates to the nucleus where it binds to hypoxia-responsive elements (HRE) in the promoter region of HIF-dependent genes [169].

Even under normoxic conditions, pro-inflammatory cytokines such as TNFα and IL-1β can increase HIFs expression at mRNA and protein level in FLS through the mitogen-activated protein kinases and the PI3K pathways [170].

HIFs are highly expressed in RA synovium; they are present not only in FLS but also in resident and infiltrating immune cells, as well as chondrocytes and osteoclasts [171]. This high level correlates with an increased synovial vascularization and inflammation [25]. HIFs can regulate RA inflammation through several mechanisms. Over-expression of HIF1α promotes the expansion of inflammatory Th1 and Th17 cells mediated by RA FLS, leading to an increased production of IFNγ and IL-17. Moreover, TLR-stimulated immune responses and

TNFα release also depend on HIF1 function in RA [172].

Although glycolysis is less efficient than oxidative phosphorylation, it is the preferred source of ATP under hypoxic conditions. HIF1α is an inducer of glycolysis, and its expression in RA FLS is linked to their aggressive features related to migration and invasion [173] which are also linked to hypoxia-induced epithelial-to-mesenchymal transition (EMT) through the PI3K/AKT/HIF1 pathway [174].

ROS are key players in cellular responses to hypoxia. They increase HIF1 stability by inhibiting the activity of PHD and FIH [167]. Moreover, ROS can induce the oxidation of Fe (II) which inactivates PHD activity and stabilizes HIF1α [175]. Redox-active molecules can also modulate indirectly HIF1α activity. For instance, ascorbate reduces Fe (III) to Fe (II) and stabilizes it in the PHD active site, while also suppressing the HIF1 transcriptional response through an effect on FIH [176].

There is a crosstalk between HIF1 and NRF2, going beyond the fact that ROS regulate the activity of both transcription factors. NRF2 signaling appears to be involved in the activation and maintenance of the HIF1-mediated response. Several studies demonstrated that NRF2-knockdown decreases HIF1 at post-translational level, suggesting that NRF2 or its downstream targets play a role in PHDs regulation [177]. Oh et al. [178] recently reported that increased expression of the NRF2 target gene *NQO1* enhanced the half-life of HIF1, and its over-expression was sufficient to stabilize HIF1 levels in normoxic conditions. NQO1 binds to HIF1α, inhibiting its degradation by preventing the interaction with PHD.

Stress responses mediated by HIFs and NRF2 can directly and indirectly regulate each other. A recent study, which investigated the metabolic reprogramming from oxidative to glycolytic energy production in induced pluripotent stem cells, found that oxidative phosphorylation and ROS generation led to increased NRF2 activity, which in turn activated HIF1α and promoted the switch to glycolysis [179]. Through a feed-forward loop, HIF1 signaling and vascular endothelial growth factor (VEGF) have been shown to activate the NRF2-ARE pathway [180].

NRF2 and HIF1 pathways do not always cooperate or reinforce each other. For instance, HIF1-mediated downregulation of IL-8 and HO-1 in endothelial cells was associated with lowered NRF2 expression and induction of the nuclear NRF2 repressor BACH1 [181]. It has been demonstrated that HIF1-dependent inhibition of IL-8 expression was caused by NRF2 down-regulation, independent of HO-1. Moreover, treatment with the natural product andrographolide, an NRF2 inducer, was reported to decrease HIF1 expression by increasing PHDs levels, and this was rescued by NRF2-knockdown [182]. Altogether, these studies indicate that the stress responses mediated by HIF1 and NRF2 form a complex and interactive signaling network that is highly dependent on the context.

Noteworthy, most of the above-mentioned *in vitro* studies are performed in air, at oxygen concentrations significantly higher (19.95%) than those found in various body compartments (1–11%), and therefore do not mimic physiologic normoxia or pathologic hypoxia [183,184]. This raises questions about their experimental outcome regarding cellular responses and their underlying mechanisms. Moreover, such experimental settings may provide inaccurate results on the efficacy of therapeutic compounds that generally appear to work very well in cell cultures, but results are not reproducible in animal models or in humans [184].

4.4. The NRF2-p53 crosstalk

Increased DNA damage was evidenced in the RA synovium, both in immune cells and FLS, probably caused by increased oxidative stress [185]. The observation that synovial cells have a survival advantage [186] brings into focus that potent DNA repair mechanisms might be activated in the genotoxic synovial microenvironment specific to RA. Indeed, it has been reported that the wild-type p53 tumor suppressor (p53), with a critical role in repairing DNA damages, is over-expressed in RA FLS [187]. However, somatic mutations in p53 evidenced in the RA synovium [188] confer a prolonged half-time to the mutated protein, and contribute to the increased survival, proliferation and invasion of RA FLS [189]. Additionally, some p53 mutations detected in RA patients impede on the ability of p53 to inhibit directly or indirectly the expression of IL-6. Thus, RT-PCR analysis of micro-dissected synovium indicated that those regions presenting abundant p53 mutations expressed significantly higher amounts of IL-6 mRNA compared with regions containing predominantly wild-type p53 [190].

NRF2 and p53 interfere at the level of the p21/WAF1/CIP1/CDKN1A, transcriptionally regulated by both p53 and NRF2, which arrests the cell cycle between the G1 and S interface for allowing repair mechanisms to rescue damaged DNA. Mutations in p53 or dysfunction of repressors at the level of DNA [191], possibly complemented by low levels of NRF2 activation in RA, may account for the decreased p21 levels found in the synovium [14]. Indeed, p21-deficient collagen antibody-induced arthritis mice are susceptible to RA, exhibiting severe synovitis, increased joint cartilage destruction and infiltration of M1-type macrophages in the synovial layer. The fact that these mice have an increased production of the pro-inflammatory cytokines IL-1β, IL-6 and TNFα indicates a crosstalk of p21 with NFκB [192]. In this respect, it has also been shown that p21 regulates macrophage reprogramming by shifting the balance between transcriptionally active p65-p50 and inhibitory p50-p50 dimers of NFκB. Thus, p21 deficiency reduced the DNA-binding affinity of the p50-p50 homodimer in LPS-primed macrophages, and impaired their ability to polarize towards an M2-like hyporesponsive status [193]. Another study showed that p21 deficiency was partly responsible for the increased invasiveness of RA FLS, independent on cellular proliferation and cell cycle regulation [194].

p21/WAF1/CIP1/CDKN1A is also an activator of NRF2 and, through a feed-forward loop, NRF2 induces increased expression of p21 [195]. Therefore, in the context of the decreased p21 levels in RA, lower NRF2 activation is expected to occur through this alternative pathway, possibly having deleterious consequences in terms of redox control and anti-inflammation in RA. In turn, NRF2 deficiency could beneficially decrease the survival advantage conferred by this transcriptional factor to synovial cells.

Concluding, the sophisticated crosstalk of transcription factors in the cytoplasm occurs through the unifying action of ROS and phosphorylation events, followed by their functional or physical interaction in the nucleus where they compete for co-factors, as well as by the occurrence of multiple chromatin-based strategies for regulating DNA binding.

4.5. ROS-independent anti-inflammatory effects of NRF2

NRF2 can directly inhibit the production of the pro-inflammatory cytokines IL-6 and IL-1β in macrophages treated with LPS [196]. Thus, chromatin immunoprecipitation (ChIP)-seq and ChIP-qPCR revealed that this immunosuppressive effect is not dependent on ROS levels or ARE. It relies factually on NRF2 recruitment in close proximity of cytokines genes through association with other nuclear proteins (p65, C/EBPβ and c-JUN), whose binding to DNA is preserved in inflammatory conditions such as those related to M1-type monocytes. Alternatively, it is possible that the inhibitory effect of NRF2 might be mediated by the recruitment of transcriptional repressors acting in *trans* to the transcription factor complex formed in the proximity of the inflammatory cytokine genes. The presence of NRF2-containing complexes further hinders the recruitment of RNA polymerase II, indicating that a suppressive effect is exerted early, in the initiation phase of transcription. This mechanism of NRF2 action does not extend to all inflammatory genes, but to the selected subset of M1-induced genes comprising IL-6 and IL-1β.

5. The crosstalk of NRF2 with inflammasomes

The crosstalk between pro-inflammatory signaling pathways leads to increased production of cytokines that shape the inflammatory and oxidative environments in RA. A particular case is related to IL-1β and IL-18 that are generated in an inactive form after gene transcription, and need inflammasome activation for being transformed into mature and biologically-active molecules. Indeed, these cytokines play a critical role in RA. For instance, the severity of RA and IL-18 serum levels were shown to positively correlate [197]. Even when there is an enhanced transcription of *IL1B* in RA, the NRF2-mediated down-regulation of the NLRP3 inflammasome would have a therapeutic benefit by impeding the generation of mature cytokines, in addition to the treatment with the recombinant human IL-1 receptor antagonist Anakinra that inhibits IL-1 signaling in RA.

Inflammasomes are cytoplasmic multi-protein complexes that sense pathogen-associated molecular patterns (PAMPs), DAMPs and homeostasis-altering molecular processes (HAMPs) that initiate potent innate immune responses [198]. Inflammasomes comprise a sensor protein from the NLR family or absent in melanoma 2 (AIM2)-like receptors (ALRs), an adaptor protein apoptosis-associated speck-like protein containing a CARD domain (ASC), and an effector caspase protein [199].

5.1. ROS-mediated modulation of the inflammasome

The NLRP3 inflammasome can be activated by canonical and non-canonical pathways [200]. The canonical pathway requires a priming step in the context of low intracellular levels of pro-inflammatory cytokines and NLRP3 that are insufficient to activate the inflammasome complex. The priming step is initiated *via* TLR4 receptors and leads to nuclear translocation of NFκB, resulting in the transcription of pro-inflammatory cytokines genes [201]. In the activation step, sensor proteins such as NLRP3, recognize various danger signals and interact with ASC *via* its PYD domain. The NLRP3-ASC complex gets further activated by recruiting pro-caspase 1 through the CARD domain, and mature caspase 1 cleaves pro-IL-1β, pro-IL-18 and Gasdermin D. The N terminus of Gasdermin D forms plasma membrane pores which cause pyroptotic cell death and release of cytokines [200]. Caspase 11 in mice and its human homologues caspase 4 and caspase 5 contribute to the non-canonical pathway which induces pyroptotic cell death and subsequent canonical inflammasome activation by cleavage of Gasdermin D in LPS-exposed cells [202].

The detailed mechanism of how diverse endogenous and exogenous signals activate the inflammasome remains unknown. Intracellular stress, elicited for instance by enhanced ROS generation, ion fluxes, Golgi disassembly and lysosomal disruption, trigger inflammasome activation [203]. ROS serve as a priming signal for inflammasome activation as well as an activation signal for the inflammasome complex assembly. Intracellular ROS can initiate the priming step through the activation of the pro-inflammatory NFκB pathway [204]. Indeed, NFκB suppression and NLRP3 inflammasome activation by ROS scavengers have proven the role of ROS in the priming step [205].

Mitochondria are another ROS sources that participate in inflammasome activation through mitochondrial DNA (mtDNA) and its interaction with the components of the NLRP3 inflammasome. When mitochondrial ROS generation is induced with a complex I or III inhibitor, the NLRP3 inflammasome gets activated and relocates to the endoplasmic reticulum and the mitochondria-rich perinuclear space [206]. Both intracellular and extracellular mtDNA participate in inflammasome activation. While intracellular mtDNA interacts directly with inflammasome components, extracellular mtDNA also participates in the priming phase of inflammasome [207]. It has been reported that mtDNA repair is impaired and mtDNA leaks into the cytoplasm in T cells from RA patients [208]. However, whether this DNA activates inflammasome has not been proven in RA.

The TRX system has been shown to mediate ROS-dependent activation of the NLRP3 inflammasome through the TRX-interacting protein (TXNIP). When cellular ROS levels increase above a threshold, the TXNIP-TRX complex dissociates, and free TXNIP interacts with NLRP3 [209]. In this respect, TXNIP deficiency in macrophages has been reported to reduce caspase 1 activation and mature IL-1β release following stimulation with various NLRP3 agonists [206]. TXNIP level was found increased in FLS, and miR-20a negatively regulated the inflammasome by targeting TXNIP in an adjuvant-induced animal model of RA [210]. However, the lack of complete inhibition of caspase activity in the absence of TXNIP suggests that other pathways might be also involved in inflammasome activation.

5.2. NRF2-inflammasome interference, besides ROS regulation

The crosstalk between the NLRP3 inflammasome and NRF2 is primarily based on ROS (Fig. 3). However, other mechanisms, such as those mediated by NFκB, NRF2 target genes and non-coding RNA, contribute to the regulatory effect of NRF2 on NLRP3 inflammasome activation. NFκB is an upstream signaling pathway required for the priming step of NLRP3 activation. Several studies have found that NRF2-activating compounds, including dimethyl fumarate (DMF), can ameliorate arthritis in mice by inhibiting the NFκB pathway [211]. These studies suggest that NRF2 can suppress the priming step of inflammasome by inhibiting the NFκB pathway. Moreover, it has been shown that the NRF2 target genes *HMOX1* and *NQO1* are involved in the regulation of inflammasome [212,213]. However, it has not been reported if HO-1 can mediate inhibition of inflammasome in RA. NRF2 can also regulate inflammasome by altering non-coding RNA levels, as shown through the action of various NRF2 activators. Thus, it has been reported that SFN and DMF can suppresses the NLRP3 inflammasome by modulating NRF2-mediated expression of microRNAs (miRNAs) in murine microglia [214], but there are no data showing that NRF2 has such an inhibitory effect on inflammasome in RA.

Contrary to the extensive literature evidencing that NRF2 inhibits the inflammasome, it has been suggested that this pathway is necessary for inflammasome activation. Thus, NRF2 signaling can participate in NLRP3 inflammasome activation, and exacerbates atherosclerosis in mice fed with a high-fat and high-cholesterol diet [215]. NRF2 deficiency in mice leads to impaired activation of the NLRP3 and AIM2 inflammasomes, suggesting that NRF2 is indeed required in inflammasome activation in particular conditions [216].

6. NRF2 and cell death in RA

An important pathologic mechanism in RA resides in the increased survival of both immune cells and FLS. The signals delivered by NFκB and HIF1α in response to TNFα inflict death resistance through increased production of inflammatory cytokines that regulate the survival and aberrant pro-inflammatory functions of synovial cells [186]. It is conceivable that pannus formation results not from intensive proliferation of FLS, but from their resistance to apoptosis [217]. The overgrowth of the synovial membrane is induced by various processes such as: a) abnormal function of mutated p53 in RA [189] and functional inhibition of the wild-type protein under the action of elevated TNFα levels which depletes CBP-induced p53 acetylation, and alters consequently the transcriptional program [218], b) increased expression of myelogenous cell leukemia-1 (MCL-1) in response to elevated levels of IL-1β, leading to up-regulated mitochondrial anti-apoptotic factors [219], and c) endoplasmic reticulum stress which exerts a pro-inflammatory and pro-survival action in RA through activation of multiple TLRs and their ligands [220]. In addition, the increase in the pro-inflammatory leukocytes populations in the synovial niche derives not only from an increased recruitment of these cells in the inflamed synovium, but also from their increased survival. For instance, the documented apoptosis resistance of $CD14^{+}$ monocytes in the peripheral blood and synovial

fluid of RA patients may be due to the increased expression of miR-155 which inhibits apoptotic factors [221]. Meanwhile, the up-regulation of the Fas-associated death domain-like interleukin 1β-converting enzyme-inhibitory protein protects macrophages by inhibiting Fas-mediated apoptosis [222].

6.1. NRF2 and ferroptosis

Besides the interference of NRF2 with inflammatory pathways that trigger death resistance, NRF2 activation confers by itself a survival advantage to synovial cells, as mainly demonstrated in NRF2-addicted tumors [223]. NRF2 elicits a broad panel of cytoprotective mechanisms that defend cells against various stressors. For instance, it has been shown that NRF2 confers resistance to ferroptosis, a type of programmed cell death characterized by the accumulation of lethal levels of ROS deriving from the reaction between iron and lipid peroxides. Pro-inflammatory cytokines that are intensively produced in the RA (IL-1α, IL-6 and IFNγ) also contribute to the accumulation of iron, leading to dysregulated functions of synovial fibroblasts, macrophages and lymphocytes [224]. Ferroptosis results in oxidative damages, subsequent plasma membrane ruptures and DAMPs release [225] that further propagate inflammation. Ferroptosis is regulated by glutathione in conjunction with peroxidase 4 under the NRF2 control [226]. NRF2 can inhibit ferroptosis in cancer cells by stimulating glutathione biosynthesis through the over-expression of the solute carrier family 7 member 11 (*SLC7A11*) gene that encodes a cystine/glutamate antiporter subunit, and of the *GCLC* and *GCLM* genes involved in the first steps of glutathione biosynthesis [227]. In RA, TNFα can inhibit the onset of ferroptosis by up-regulating the above-mentioned genes [228]. NRF2 is critically involved in iron metabolism, both in heme anabolism and catabolism, through several of its gene targets, such as the genes encoding the ATP binding cassette subfamily B member 6 and ferrochelatase, both involved in heme generation, along with the HO-1 encoding gene (*HMOX1*) [229]. Through its control over the transcription of heavy and light chains of the iron storage ferritin protein, NRF2 regulates the compartmentalization of iron derived from heme catabolism [230]. This is of paramount importance for limiting the formation of the toxic hydroxyl radical through the Fenton reaction. Ferroptosis resistance induced by NRF2 in RA by controlling ROS, iron and heme metabolism [231] results in increased survival of synovial cells that propels inflammation. Additionally, NRF2 greatly helps in the repair of dysregulated bone metabolism in RA, where excessive iron and ROS inhibit the activity of osteoblasts and activate osteoclasts differentiation, finally leading to bone erosion [232].

6.2. NRF2 and autophagy

NRF2 also interferes with autophagy, a homeostatic mechanism for removing damaged organelles and misfolded or aggregated proteins, as well as for recycling intracellular components to sustain the increased demands of activated cells for nutrients [233]. Through the elimination of damaged mitochondria, autophagy participates in the reduction of ROS levels, hence preventing the development of apoptosis in cells challenged by oxidative stress and DNA damage, as seen in RA. In turn, autophagy participates in autoimmunity, considering that oxidized proteins such as citrullinated peptides may become auto-antigens [234], and autophagy promotes their presentation to T $CD4^+$ lymphocytes [235]. There is evidence that autophagy is actively involved in RA, as demonstrated by the detection of autophagosomes in immune cells, that were correlated with inflammatory parameters in RA patients, and were significantly decreased by biological therapy with TNFα or IL-6 receptor inhibitors [236]. NRF2 interferes with autophagy at the level of the p62/SQSTM1 autophagy receptor that binds to ubiquitinated cargo substrates, and targets them for autophagic degradation. The encoding gene (*SQSTM1*) is a target of NRF2 [237]. Through a feed-forward loop, p62 induces non-canonical NRF2 activation by competing for the binding to the KEAP1 repressor of NRF2 [238]. In addition, as p62 is involved in the proteasomal degradation of ubiquitinated proteins, over-abundant p62 levels can delay the delivery of substrates to the proteasome [239]. Defective autophagy leading to the accumulation of p62 can switch cellular responses towards NRF2 activation [240], while the low levels of p62 available in the blood of RA patients [236] might impede on the non-canonical activation of NRF2 through p62. It is worth mentioning that, in physiologic conditions, the p62-dependent activation of NRF2 is responsible for ~50% of basal expression of the classical NRF2 target genes *NQO1*, *GCLC* and *HMOX1* [238].

6.3. NRF2 and pyroptosis

It has been shown that NRF2 interferes the NLRP3 inflammasome-induced pyroptotic cell death. Upon NLRP3 inflammasome activation, the aberrant activity of caspase 1 causes the cleavage of Gasdermin D, resulting in pore formation and rupture of cell membrane [241]. NRF2 suppresses pyroptosis by inducing anti-inflammatory and anti-oxidative cytoprotection by eliminating of ROS and/or by modulating the NFκB activity [242].

7. NRF2 and anti-rheumatic therapies

Considering the potential beneficial action of NRF2 up-regulation with respect to anti-oxidation, anti-inflammation and detoxification of xeno- and endobiotics, there are several lines of evidence for pharmacological NRF2 activation in RA: i) inhibition of inflammation- and redox-related pathologic mechanisms in RA; ii) restoration of the defective NRF2 activation capacity in elderly individuals, that underlies a chronic oxidative state in old organisms; iii) alleviation of toxic effects exerted by anti-rheumatic drugs in various organs.

7.1. NRF2 activators

Various natural and synthetic compounds have the ability to activate the KEAP1/NRF2 pathway [243–246]. These compounds can be grouped into two main classes: i) electrophilic compounds that covalently modify critical cysteine residues in the thiol-rich KEAP1 repressor, and alter consequently KEAP1 conformation and its interaction with NRF2 and with the CUL3/RBX1 complex, resulting in stabilization of newly synthetized NRF2 molecules, and ii) protein-protein interaction (PPI) inhibitors (peptides and small molecules) that interfere with the docking of NRF2 to the Kelch propeller of KEAP1, so that newly synthesized NRF2 molecules are no more directed towards KEAP1-mediated proteasomal degradation, but translocate into the nucleus and trigger the transcription of ARE-genes. Albeit the fact that electrophilic compounds are acting through a physiologic mechanism of NRF2 activation, they have important side-effects due to their interaction with other cysteines than those contained in KEAP1, affecting therefore important biologic functions [247]. Meanwhile, PPI inhibitors, exhibiting an increased selectivity for one or both sites of KEAP1 interaction with NRF2, are expected to have less off-target effects, although this assumption has not been proven yet.

Besides antioxidant properties, most of the existing NRF2 activators show also important anti-inflammatory effects that are exerted directly or through the redox control of critical signaling pathways, hence being most suitable for RA therapy. For instance, using a mouse model of experimental autoimmune encephalomyelitis (EAE), it has been shown that DMF exerts anti-inflammatory effects by reducing the frequencies of $CD4^+$ cells producing IFNγ and IL-17, the polarization of monocytes towards the anti-inflammatory M2-phenotype and modulation of MHC class II expression on B lymphocytes [248]. Moreover, DMF ameliorates complete Freund's adjuvant-induced arthritis in rats through the activation of the NRF2/HO-1 signaling pathway that restores the functionality of RA macrophages and FLS [211]. Using NRF2-knockdown mice, it has also been demonstrated that the anti-inflammatory action of DMF

might be exerted also *via* alternative pathways, independent of NRF2. Monomethyl fumarate, the metabolite of DMF, was shown to interact not only with NRF2, but also with the hydroxycarboxylic acid receptor 2 which strongly modulates anti-inflammatory activities by inhibiting NFκB signaling [249,250]. Moreover, NRF2 activation can restore cellular homeostasis by sustaining mitochondria biogenesis both in humans and in mice, which is highly important in RA and other diseases where mitochondrial impairments contribute to pathogenesis [47]. Furthermore, the functional blockade of T cell activation by DMF which binds to particular cysteine residues in protein kinase C [251], as well as the up-regulation of immunosuppressive T regulatory cells [252] argue in favor of applying the DMF treatment in RA. Albeit the fact that the deregulated cytokine network in multiple sclerosis is largely overlapping the RA-specific cytokine profile in terms of IL-17, IL-1β, TNFα and IL-6 dysregulation [253], and that DMF has therapeutic efficacy in the remitting-relapsing form of multiple sclerosis [254], it has not been clinically proven that DMF treatment would have a beneficial effect in RA. This observation is further sustained by the finding that TNFα inhibitors do not affect inflammation in multiple sclerosis, but even hasten disease flares [255].

Promising preclinical results were obtained also with the NRF2 activator SFN. Thus, in a collagen-induced arthritis model, intraperitoneal administration of SFN reduced the arthritis score and the levels of the pro-inflammatory cytokines IL-6, IL-17 and TNFα as well as of tartrate-resistant acid phosphatase in arthritic joints [256]. Solid arguments in favor of an adjunctive therapy with SFN in RA came from the study of Fragoulis et al. [257] who evidenced the NRF2-mediated cytoprotection in naïve synoviocytes, whilst triggering apoptosis in their inflamed counterparts. Considering that RA FLS have a proliferating, inflammatory and glycolytic phenotype resembling tumor fibroblasts [51], it is of utmost importance that SFN does not shield these cells *via* NRF2 activation, and is even able to induce their death. Moreover, it has been reported that, while restoring the aging-related decrease of Th1 immunity by modulating dendritic cells [258], SFN silences pro-inflammatory Th17/Th1 responses in autoimmune diseases by inhibiting IL-23 and IL-12 production in inflammatory dendritic cells [259].

The list of NRF2 activators and the associated patents is continuously growing [260], but their development has generally remained in the preclinical phase. Few compounds have entered clinical trials for various chronic diseases underlined by low-grade oxidative stress and inflammation [245]. Only DMF was licensed in 2013 under the name of Tecfidera (Biogen, US) as an oral first-line therapy for relapsing-remitting multiple sclerosis. Although a promising phase 3 clinical trial for chronic kidney disease and type 2 diabetes mellitus using the potent NRF2 activator bardoxolone methyl was initially withdrawn due the increased risk for early-onset fluid overload in patients with identifiable risk factors for heart failure, further studies are still underway using a more restrictive selection of patients [261]. The triterpenoid omaveloxolone is now in phase 3 trial for therapy of Friedreich's ataxia, with very promising results (NCT02255435, EudraCT2015-002762-23).

Only two clinical trials on NRF2 activators for the treatment of RA were found in ClinicalTrials.gov in July 2022. The first clinical trial "A Phase 2a, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Efficacy, Safety and Tolerability of BG00012 When Given With Methotrexate to Subjects With Active RA Who Have Had an Inadequate Response to Conventional Disease-Modifying Anti-rheumatic Drug Therapy" (NCT00810836, 2001–2010), initiated by Biogene, investigated DMF in 153 participants, but no results were disclosed. The second clinical trial "Evaluating the Effect of Digoxin and Ursodeoxycholic Acid in Patients With Rheumatoid Arthritis in Egypt" (NCT04834557), initiated in 2021 by Tanta University, Egypt, is evaluating ursodeoxycholic acid [262] in combination with digoxin [263] in 90 participants, but again results were not disclosed.

In this moment, there is an important need to critically analyze by high-throughput and structure-based virtual screening the numerous structures that show NRF2-activating abilities in preclinical models for identifying the most promising candidates in terms of druggability and specificity for the KEAP1/NRF2 pathway as well as potential off-target effects. Selected compounds have to be thoroughly analyzed for absorption, distribution, metabolism, excretion and toxicity profiles for structural optimization, as a mandatory step for fostering their future advancement in the drug development pipeline.

7.2. NRF2 interference with anti-rheumatic therapies

Current therapy for RA patients consists of non-steroidal and steroidal anti-inflammatory drugs for reducing pain and inflammation, and synthetic or biological DMARDs that influence or modify the diseases course. Some of these anti-rheumatic agents have been shown to have antioxidant effects, by directly scavenging ROS or by boosting the endogenous antioxidant system through the NRF2 pathway (Table 1).

Of note is that indomethacin, a NSAID used in rheumatic diseases for alleviating pain and inflammation [292], has been recently shown to behave like an electrophilic molecule that targets the Cys151 residue of KEAP1, inducing NRF2 activation and increased expression of some canonical NRF2 target genes (Nag-1/GDF15, CAT, GAR, GCLM, HMOX1, NQO1 and TALDO1) in primary human and mouse macrophages, independent of cyclooxygenase inhibition [268]. This study also demonstrated NRF2 target engagement by indomethacin in mice with endotoxemia and gout, but no human study has been so far performed to bring again into focus indomethacin for controlling pain, inflammation and redox disturbances in RA. Therefore, a prospective study to determine if RA patients on indomethacin perform better in the long run than those not taking indomethacin is needed for evaluating the therapeutic efficacy *versus* toxicity in the context of its important side-effects related to gastrointestinal injury. New indomethacin formulations are as well needed for increasing its acceptability in chronic treatment [293].

Form another perspective, as long-term treatment with DMARDs renders part of the RA patients unresponsive to therapy, and therefore new strategies to improve adherence to therapy are highly needed. One such strategy might be the co-therapy with NRF2 activators, which, by down-regulating ROS levels and inflammation, would allow the use of lower doses of DMARDs for controlling disease at multiple levels. Moreover, it has been shown that NRF2 activation with SFN can sustain the antinociceptive action of therapeutic opioids in animals with peripheral inflammation [294]. It is expected that a better disease control using a treat-to-target strategy through synergy of anti-rheumatic drugs and NRF2 activators would reduce the use of strong opioids in RA for controlling rheumatic pain.

In the context of NRF2 involvement, an evaluation of the interference of NRF2-targeted therapy with conventional anti-rheumatic therapies or their side-effects needs to be thoroughly evaluated in RA, as well as the time-window when this adjunctive therapy would bring most benefits, depending on the disease stage and the basic anti-rheumatic therapy administered to the RA patient.

7.3. NRF2 and drug toxicity

MTX remains the gold standard for the treatment of RA, but it is often discontinued, albeit the factual therapeutic benefit. Discontinuation is mainly due to liver, gastrointestinal and renal toxicities that occur even at the low MTX doses used in RA therapy (15–20 mg/week), especially when patients have comorbidities. The study of Buchbinder et al. [295] has shown that, in a cohort of 587 RA patients starting to take MTX, total termination rate at 70 months was 24.4%, with most terminations prompted by drug toxicity which was more frequent at older age, above 65 years. The randomized double-blinded, placebo-controlled trial CIRT-AE is ongoing [296] for a comprehensive assessment of MTX adverse effects at low doses (10–25 mg/week), representing a step forward in shaping a personalized MTX treatment in RA and cardiovascular

Table 1
Antioxidant effects of synthetic and biological agents used in RA therapy. NSAID: non-steroidal anti-inflammatory drug; SAID: steroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drug.

Anti-rheumatic agent	Class	Antioxidant activity	References
Acetylsalicylic acid [264]	NSAID	Induces NRF2-mediated transcriptional activation of HO-1 in human melanocytes exposed to hydrogen peroxide.	[265]
		Suppresses neuronal apoptosis, reduces tissue inflammation and limits astrocyte activation through increased HO-1 signaling in a spinal cord contusion model in Sprague-Dawley rats.	[266]
Indomethacin [267]	NSAID	Indomethacin and ibuprofen induce the expression of canonical NRF2 target genes in mouse bone marrow-derived macrophages through an NRF2-dependent mechanism involving the increased expression of the growth/differentiation factor 15, independent on cyclooxygenase inhibition.	[268]
		Indomethacin and bromfenac inhibit choroidal neovascularization through the NRF2/HO-1 pathway.	[269]
Celecoxib [270]	NSAID	Exerts protective effects in the vascular endothelium *via* COX-2-independent activation of the AMPK-CREB-NRF2 signaling.	[271]
Dexamethasone [272]	SAID	Increases glutathione and NADPH levels in an NRF2-dependent manner in lymphoblastoid cells.	[273]
		Exerts antioxidant effects in autoimmune encephalomyelitis by up-regulating NRF2 and its NQO1 target gene.	[274]
		Inhibits CBP recruitment and NRF2-mediated histone acetylation, hence impairing the antioxidant response in mouse liver.	[275]
Clobetasol propionate [276]	SAID	Inhibits NRF2 in KEAP1-mutant lung cancer cells by promoting β-TrCP-dependent degradation of NRF2 in a glucocorticoid receptor- and GSK3-dependent manner	[277]
Cortisone [278]	SAID	Inhibits the expression of the NRF2 target genes NQO1, HMOX1 and GST2A in transfected cell lines expressing the cortisone reductase 11β-hydroxysteroid dehydrogenase type 1.	[279]
Methotrexate [7]	Synthetic anti-folate DMARD	Directly inhibits in non-cellular system the formation of malondialdehyde - acetaldehyde protein adducts by scavenging ROS (superoxide production).	[280]
		Decreases mitochondrial ROS production by RA neutrophils, slightly increases glutathione and glutathione peroxidase levels.	[281]
		Induces increased malondialdehyde levels and decreased glutathione levels, down-regulates the NRF2-mediated expression of antioxidant genes in Wistar albino rats. These pathologic changes were reversed by the treatment with the NRF2 activator luteolin.	[282]
Leflunomide [283]	Dihydroorotate dehydrogenase inhibiting DMARD	A77 1726, the active leflunomide metabolite, increases HO-1 levels in TCD4+ splenocytes from leflunomide-treated mice.	[284]
Auranofin [285]	Gold-containing DMARD	Increases the expression of HO-1 and γ-glutamylcysteine synthetase in various immune cell lines.	[286]
		Activates NRF2 and Rac1/iNOS in the monocytic cell line THP-1, possibly by increasing ROS levels.	[287]
		Inhibits TXNRD1 and activates the NRF2 pathway, resulting in suppressed IL-1β synthesis in alveolar macrophages.	[288]
		Inhibits TXNRD1 and increase HO-1 in lung epithelia.	[289]
Anti-TNF agents [290]	Biologic DMARDs	TNFα blockade decreases ROS levels in immune and non-immune cells. This affects redox homeostasis, including cytoprotective mechanisms mediated by NRF2.	[291]

diseases.

It is expected that, through the broad cytoprotective activities of NRF2 related to glutathione S-transferase and the UDP glycosyltransferase family, NRF2 activation would alleviate toxic effects of xenobiotics. For instance, it has been shown that NRF2 has a decisive role in liver regeneration by increasing the expression of antioxidants, including the augmenter of liver regeneration [297]. Therefore, it is expected that treatment with NRF2 activators will be most useful for repairing drug-induced liver damages.

As NRF2 increases the expression of MDR proteins in liver under oxidative conditions, it is expected that NRF2 activators would reduce the liver toxicity of drug conjugates by effluxing them into the bile or blood. It has been shown that livers from hepatocyte-specific glutamate-cysteine ligase catalytic subunit-null mice had increased nuclear NRF2

levels, marked gene and protein induction of the NRF2 target gene *NQO1*, as well as increased basal and/or induced expression of MDR proteins [298], hence protecting livers against drug toxicity.

NRF2 activation is also a promising therapeutic strategy in chronic kidney disease where renal micro-vascular damage, inflammation, increased ROS levels and fibrosis were reported in prolonged DMARDs therapy. Treatment with berberine [299] was shown to attenuate kidney damages in rats treated with MTX by modulating the NRF2/HO-1 and NFκB/p38 signaling pathways, leading to suppressed expression of pro-inflammatory COX2, TNFα and IL-1β. It also inhibited apoptosis and increased the levels of some antioxidant enzymes such as superoxide dismutase, catalase and NQO1 [300]. Moreover, pre-treatment with SFN in arsenic-intoxicated mice was able to prevent nephrotoxicity by attenuating ROS, lipid peroxidation and DNA damage, and by increasing phase II antioxidants *via* PI3K/AKT-mediated NRF2 activation in the renal tissue [301].

Altogether, the extensive preclinical evidence that some toxicity issues related to chronic anti-rheumatic treatments might be significantly alleviated by NRF2 activators, still awaits clinical confirmation.

7.4. NRF2 and drug efflux

RA patients may become in time unresponsive to DMARDs, possibly *via* a multidrug resistance (MDR)-related mechanism. Indeed, it has been shown that many commonly used DMARDs (MTX, sulfasalazine, leflunomide, hydroxychloroquine) are substrates of efflux pumps belonging to the super-family of ATP binding cassette (ABC) proteins that limit the intracellular availability of drugs [302]. It has been found that patients with active RA have an increased function of ABCB1 and ABCG2, disease activity being the main determinant [303]. As such, synovial and blood cells in RA develop a mechanism to resist to some anti-rheumatic therapies with synthetic DMARDs.

NRF2 has been reported to increase the expression of various ABC-transporters. Thus, induction of ABCC2 and ABCG2 by tert-butylhydroquinone in HepG2 cells was shown to be mediated by the NRF2/KEAP1 system, whereas the induction of ABCC1 may involve a KEAP1-dependent but NRF2-independent mechanism [304]. The ABCG2 transporter, which is under the transcriptional control of NRF2 and of the aryl hydrocarbon receptor/transcription factor [305], is expressed in the gastrointestinal tract, liver, kidney and brain endothelium, where it functions as a barrier to drug transport [306]. From this perspective, pharmacological NRF2 activation and the consequent increase of ABC transporters might negatively impact the efficacy of synthetic DMARDs in RA.

In turn, it is known that MDR proteins have an important role in transporting signaling molecules, peptides or small proteins that are involved in inflammatory processes. For instance, MDR proteins could function as efflux transporters for pro-inflammatory cytokines, such as TNFα, that, once released, propagate inflammatory signals in the near-neighborhood. Through a feed-forward loop, pro-inflammatory cytokines like TNFα, IL-1β or IL-6 can up-regulate MDR proteins to increase the release of newly synthesized inflammatory factors [307]. Moreover, it has been reported that ABC transporters have a marked involvement in immunity as they are closely associated with antigen processing that requires the transport of antigenic peptides to the endoplasmic reticulum for association with class I MHC molecules [308]. While this mechanism sustains the immune defense against viruses, it is not clearly described how it may impact sterile inflammation in RA.

8. Future perspectives

There are consistent arguments in favor of an adjunctive therapy in RA addressing the NRF2 pathway (Fig. 4). It is expected that conventional anti-rheumatic therapies would benefit from pharmacologic activation of NRF2, due to its antioxidant and anti-inflammatory effects and to protection of organs affected by chronic treatment with synthetic drugs. In absence of clinical evidence, it is not clear whether the existing NRF2 activators have the ability to suppress inflammation and oxidative stress in the RA synovial niche in the long-run, or which side-effects they have. Noteworthy, in the particular case of RA, NRF2 activators could be administered locally in the inflamed joints, hence reducing their systemic side-effects.

Most of the data on NRF2 activators were obtained in preclinical settings that do not mimic very well the complex pathologic mechanisms of RA, consequently limiting the validity of the proposed biochemical and molecular networks that would be of great help for designing and testing new therapies. Complex diseases, such as RA, have been investigated over time using reductionist approaches that analyze single components of the disorder, leading to fragmented biological knowledge. In contrast, the holistic approach of systems biology aims to dissect the multi-dimensional complexity of human diseases by identifying modules that are temporally and spatially disturbed, by experimental and computational methodologies that integrate information coming from genomic, transcriptomic and proteomic studies. Therefore, a possible solution would be in the short-term to reanalyze gene expression datasets, being expected to improve the design of future secondary studies on large cohorts of RA patients with well-defined endotypes and study endpoints.

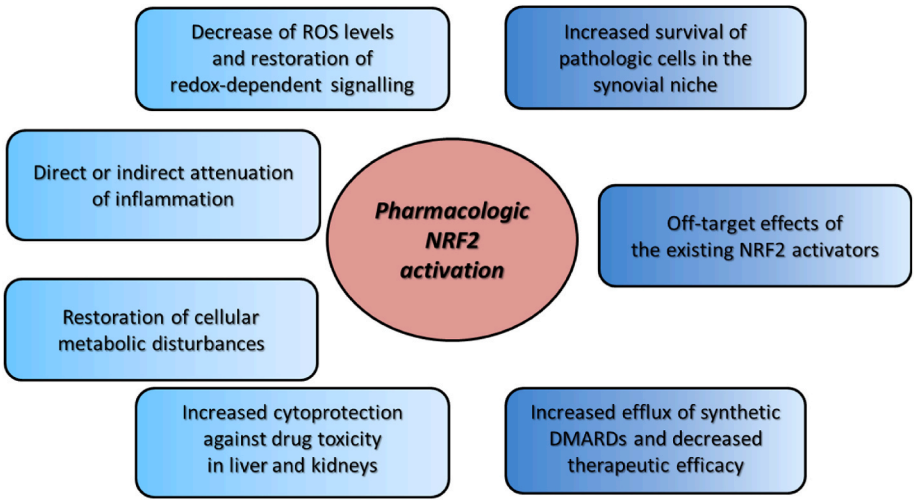

Fig. 4. Arguments in favor (light blue) and against (dark blue) pharmacologic activation of NRF2 in RA. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

For selecting the most promising candidates to be advanced in the drug development pipeline for the treatment of RA, systematic re-evaluation of the existent electrophilic and PPI inhibitor compounds in terms of efficacy and side-effects should be performed using improved *in silico*, cellular and animal models.

Data availability

No data was used for the research described in the article.

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Abbreviations

ABC	ATP-binding cassette
ACPA	anti-citrullinated protein antibodies
AIF	apoptosis-inducing factor
AIM2	absent in melanoma 2
ALR	AIM2-like receptor
ANCA	antineutrophil cytoplasmic antibodies
AP1	activator protein 1
APE1	apurinic/apyrimidinic endonuclease 1
ARE	antioxidant response element
ASC	apoptosis-associated speck-like protein containing a CARD domain
ATAC-seq	assay for transposase-accessible chromatin using sequencing
ATF1	activating transcription factor-1
BACH1	BTB and CNC homology 1
bZIP	basic leucine zipper
C/EBP	CCAAT/enhancer binding proteins
CARD	caspase activation and recruitment domain
CBP	CREB binding protein
ChIP	chromatin immunoprecipitation
COX2	cyclooxygenase 2
CREB	cyclic-AMP response element binding protein
CRL	cullin-RING ligase
CRP	C-reactive protein
CUL3	cullin 3
CXCL1	C-X-C motif chemokine ligand 1
DAMP	danger-associated molecular patterns
DEG	differentially expressed genes
DEX	dexamethasone
DMARD	disease-modifying anti-rheumatic drugs
DMF	dimethyl fumarate
DMY	dihydromyricetin
EAE	experimental autoimmune encephalomyelitis
FECH	ferrochelatase
FIH	factor inhibiting HIF
FLS	fibroblast-like synoviocytes
FTH	ferritin heavy chain
FTL	ferritin light chain
GCLC	glutamate-cysteine ligase catalytic subunit
GEO	gene expression omnibus
GSK3β	glycogen synthase kinase-3 beta
HAMP	homeostasis-altering molecular processes
HDAC3	histone deacetylase 3
HIF	hypoxia-inducible factor
HMOX1	heme oxygenase 1 gene
HO-1	heme oxygenase 1
IFNγ	interferon gamma
IKK	IκB (inhibitor of κB) kinase
iNOS	inducible nitric oxide synthase
KEAP1	Kelch-like ECH-associated protein 1
LPS	lipopolysaccharide;
MAF	small musculoaponeurotic fibrosarcoma
MAFK	MAF bZIP transcription factor K
MCL1	myeloid cell leukemia-1
MDR	multidrug resistance
MHC	major histocompatibility complex
MPO	myeloperoxidase
MTX	methotrexate
NADPH	nicotinamide adenine dinucleotide phosphate
NEMO	nuclear factor κB essential modulator
NET	neutrophil extracellular trap;
NFκB	nuclear factor kappa B
NLRC4	NLR family CARD domain-containing protein 4
NLRP1/3	NLR family pyrin domain containing 1/3
NOX	NADPH oxidase
NQO1	NAD(P)H:quinone oxidoreductase 1
RF2	nuclear factor erythroid 2-related factor 2
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis
PAMP	pathogen-associated molecular patterns
PHD	prolyl hydroxylase domain enzyme
PI3K	phosphatidylinositol 3-kinase
PPI	protein-protein interaction
PPP	pentose phosphate pathway
PTEN	phosphatase and tensin homolog deleted on chromosome 10
PYD	pyrin domain
RA	rheumatoid arthritis
RAC1	Ras-related C3 botulinum toxin substrate 1
RANKL	receptor activator of nuclear factor κB ligand;
RHD	Rel homology domain
ROS	reactive oxygen species
SAIDs	steroid anti-inflammatory drugs
SCF	Skp, Cullin, F-box containing complex
SLC7A11	solute carrier family 7 member 11
SFN	sulforaphane
SQSTM1	sequestosome 1
TLR	toll-like receptor
TNFα	tumor necrosis factor alpha
TRE	TPA responsive element
TRX/TXN	thioredoxin
TRXR	thioredoxin reductase
TXNIP	thioredoxin interacting protein
VEGF	vascular endothelial growth factor
WAF1/CIP1/CDKN1A	wild-type p53-activated fragment 1/CDK-interacting protein 1/cyclin-dependent kinase inhibitor 1A

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