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Review

Therapeutic strategies for rheumatic diseases and disorders: targeting redox imbalance and oxidative stress

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ABSTRACT

Rheumatic diseases and disorders (RDDs) are a group of chronic autoimmune diseases that are collectively called "multicausal diseases". They have resulted from predisposing genetic profiles and exposure to a range of environmental, occupational and lifestyle risk factors. Other causative factors include bacterial and viral attacks, sexual habits, trauma, etc. In addition, numerous studies reported that redox imbalance is one of the most serious consequences of RDDs. For example, rheumatoid arthritis (RA) as a classic example of chronic RDDs is linked to oxidative stress. This paper summarizes the contributions of redox imbalance to RDDs. The findings suggest that establishing direct or indirect therapeutic strategies for RDDs requires a more in-depth understanding of the redox dysregulation in these diseases. For example, the recent awareness of the roles of peroxiredoxins (Prdxs, e.g. Prdx2, Prdx3) in RDDs provided one potential route of therapeutic intervention of these pathologies. Changes in stressful lifestyles and dietary habits may also provide additional benefits in the management of RDDs. Future studies should be directed to explore molecular interactions in redox regulations associated with RDDS and potential therapeutic interventions.

1. Introduction

1.1. RDDs: a brief overview

The global prevalence of rheumatic diseases and disorders (RDDs) in the year 2020 was estimated to be more than 1.1% [48]. Among the RDDs, rheumatoid arthritis (RA) is the most common with an annual incident rate of approximately 40 in 100,000 people in the United States and northern European countries [4]. The risk of developing RA over a lifetime is more than double in women (3.6%) than in men (1.7%) [62, 88]. Organ-specific disorders like Hashimoto's thyroiditis and systemic disorders with multiple organ involvement are both categorized under autoimmune diseases [51]. RA, primary Sjogren's syndrome, systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, systemic sclerosis (scleroderma) (SS), and the systemic vasculitis are among the autoimmune rheumatic diseases, which are disorders that primarily but not exclusively affect joints and muscles [101]. These heterogeneous multisystem autoimmune rheumatic illnesses are accompanied by significant morbidity and mortality. Although these illnesses can exhibit a classic presentation, which facilitates diagnosis, they also share a

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number of characteristics, such as constitutional disturbance, arthralgia and arthritis, myalgia, symptoms of sicca, as well as pulmonary, renal, and neurological involvement, which can make disease differentiation challenging [51]. Rheumatology deals with a wide range of conditions, the majority of which are dys/autoimmune illnesses [39]. By demonstrating how cases of a particular disease cluster among families, family studies aim to imply the existence of a genetic component in its development. An inherited component is assumed to exist if there is a higher prevalence of the disease among first-degree relatives (parents, siblings, and children) of those who are afflicted than in the general population. Recurrence risk, also known as relative risk λ_R (R for relatives), is a helpful metric that compares the disease rate in a patient's first-degree relatives to the rate in the general population [39]. Multiple groups of relatives can have their recurrence risk assessed, typically within sibships (λ_S, where "S" stands for "sibling"). The recurrence risk reflects how hereditary and environmental variables interact [39]. Instead of 0.2–1% in the general population, the prevalence of RA among first-degree relatives of patients ranges from 2% to 12% [37]. RA estimates that S ranges from 3 to 15 [5]. Monozygotic twin concordance rates range from 12% to 30%, while same-sex dizygotic twin concordance rates range from 5% to 10% [98]. λ_S values between 20 and 29 and a concordance rate of 24–57% among monozygotic twins as opposed to 2–5% among dizygotic twins provide evidence that genetic variables play a significant role in SLE susceptibility [3]. The prevalence of SS increased significantly as compared to the general population (2.6% vs. 0.026%, respectively) in a study of family clustering of SS in three North American cohorts, with a λ_R value among first-degree relatives of roughly 13 [6].

The majority of research on environmental RDDs risk factors concentrated on nutrition and/or diet, smoking, and hormones [91]. There were not many environmental factors found. Smoking is the biggest environmental influence [56]. Despite the fact that smoking was linked to RA and the formation of anti-citrullinated peptide antibodies (ACPA), a study has shown that this link is specific to RA [95]. On the other hand, due to the fact that females experience the disease at a much higher rate than males, the majority of studies on environmental risk factors for SLE concentrated on the function of hormones [39]. Breastfeeding was discovered to be protective against SLE in population-based case-control research, with the risk of SLE being associated with both the number of breastfed infants and the total amount of time spent breastfeeding [89]. Moreover, Particular areas have been observed to have a high prevalence of SS, supporting the idea that environmental variables may be involved. Chemicals that are breathed, most notably silica, account for the majority of environmental factors discovered to date [55]. RA sufferers report poor sleep, frequent awakening, early waking, daytime sleepiness, and/or weariness in between 54% and 80% of cases [52]. The sleep architecture is generally normal according to polysomnographic investigations, although there are frequently more nocturnal awakenings, longer waking hours, and a partial lower sleep efficiency [9], particularly during periods of elevated disease activity [17]. As a result, there is a definite positive association between disease activity and reported sleep issues [123]. The Mediterranean diet, omega-3 fatty acids, fish oil, olive oil, meat and protein, and other dietary components have all been related to an increased risk of RDDs. By serving as a dietary supply of arachidonic acid, a fatty acid implicated in the creation of pro-inflammatory eicosanoids, red meat may have pro-inflammatory effects [23]. On the other hand, Less red meat and more fish make up the Mediterranean-style diet, which also emphasizes the use of olive oil as the main source of fat, an abundance of plant-based foods (such as fruits, vegetables, whole-grain cereals, nuts, and legumes), low to moderate consumption of poultry, and moderate wine consumption [34].

RA comprises four distinct immunologic phases: (i) triggering phase: one or multiple factors acting as individual predisposing triggers for the disease; (ii) maturation phase: synovitis not developed yet but anticitrullinated protein antibodies present; (iii) targeting phase: presence of anticitrullinated protein antibodies and arthralgia; (iv) fulminant phase: established RA [88]. To date, over 100 different types of arthritis, mainly affecting the joints, tendons, ligaments, bones, and muscles, and more than 200 distinct rheumatic diseases, such as osteoarthritis, RA, lupus erythematosus, spondyloarthropathies - including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), juvenile idiopathic arthritis, Sjogren's syndrome, scleroderma, polymyalgia rheumatica, gout, and infectious arthritis, have been identified. In addition, a less common type of rheumatic disease, palindromic rheumatism (PR) has also been detected in some patients worldwide. This case presents episodes of arthritis and/or para-arthritis leaving no persistent alterations or radiographic signs [62]. The common denominators of all these diseases, often also called musculoskeletal diseases, are the most frequent symptoms - pain, loss of motion, and inflammation markers (such as swelling, redness, and warmth) in a joint/joints or affected area/areas. The RDDs have significant co-morbidities, with evidence of increased risk of developing cardiovascular (e.g. atherosclerosis, vasculitis, etc.) infectious, respiratory, gastrointestinal, and renal complications [83]. Among the RRDs, RA is considered one of the most disabling (3–10 years of life expectancy lost), due to the comorbidities but also to the significant risk induced by the long-term medication [83].

A recent study identified some high-quality randomized controlled trials (RCT) using acupuncture, Ayurveda, homeopathy, electricity, natural products, megavitamin therapies, chiropractic or osteopathic manipulation, and energy healing therapy for patients with rheumatic diseases [96]. There are various acupuncture treatment modalities available, including moxibustion, laser acupuncture [125], dry needling [112], gold bead implantation [68], electroacupuncture [111], and conventional acupuncture without electricity [19]. Patients with knee osteoarthritis (OA) did not experience any appreciable differences in pain, stiffness, or function after receiving gold bead implantation at acupuncture locations [68]. Burning the herb moxa, also known as *Artemisia vulgaris*, at acupuncture points is a non-invasive treatment called moxibustion [24]. Moxibustion therapy appeared to enhance function and pain scores in patients with knee OA [130]. Similar results were seen with laser acupuncture for people with knee OA [125]. In patients with myofascial pain syndrome, dry needling, which includes inserting needles at trigger points, has been shown to reduce pain [112]. On the other hand, only one high-quality RCT looking into homeopathy found that treating patients with fibromyalgia (FM) resulted in significantly greater improvements in the primary outcomes assessed, including tender point count and tender point pain, quality of life, and overall health [10]. The other RCTs came to the conclusion that treating patients with homeopathy did not appear to have any positive effects on RA and knee OA [90]. Complementary and alternative medicine (CAM) has positive impact on rheumatic disorders, according to placebo-controlled research on nonvitamin, nonmineral, natural products: ShengJinRunZaoYangXue for Sjögren's syndrome (Hu et al., 2014), Chinese Herbal medicine for IBS-C [12], Tong Luo Hua Shi capsules for RA [74], Rose-hip for RA [121], Mahame-Mafasel pomade for knee OA [109], Aflapin for knee OA [118], 4Jointz cream for knee OA [69], topical *Tripterygium wilfordii* for RA [26], oral GCSB-5 for hand OA [93], rose-hip for knee and hip OA [122], willow bark extract for knee and hip OA [104], methylsulfonylmethane (MSM) for knee OA [36], L-carnitine for knee OA [82] and topical glucosamine and chondroitin preparation for knee OA [28]. Moreover, the disease activity of juvenile SLE was improved by vitamin D supplementation [72], while the whole-body bone mineral density of young adults with RA was enhanced by calcium supplementation [79].

1.2. Redox imbalance's contribution to RDDs

An imbalance between the antioxidant defense and pro-oxidant mechanisms in our body is termed "redox imbalance". When the normal redox situation is no longer maintained, usually by weaker antioxidant defense or overproduction of prooxidants, pathologic states

including autoimmune diseases and disorders develop. On the other hand, the function of oxidative stress is also heavily mooted due to the identification of increased levels of pro-oxidants, proinflammatory cytokines (TNF-α, IL-6, IL-17, IL-23, IFN-c, and IL-1β), and proinflammatory enzymes (NADPH oxidase, myeloperoxidase, and xanthine oxidase) [99]. It is hypothesized that the resulting inflammatory milieu will mediate direct harm to macromolecules like lipids, proteins, and DNA [97]. The development of neoantigens, which in turn can improve the generation of autoantibodies, can be aided by reactive oxygen and nitrogen species (ROS and RNS). The increased production of ROS and RNS in conjunction with an inflammatory response is a characteristic of the autoimmune diseases [108]. ROS are physiologically active transcription factors for adhesion molecules, cell cycle-related genes, and pro-inflammatory cytokines. As a result, they may have a significant impact on the severity of the disease as well as the etiology of autoimmune disorders and associated complications [11]. Moreover, one of the primary processes that sets off autoimmune reactions is the activation of apoptosis, which is influenced by ROS generation [92]. To note, protein peroxidation confers alterations in protein structure impairing their functional properties. Proteins with a substantial conformational loss are then potential sources of "neo-antigens [63]. Collectively, these factors exacerbate immune reactions and lead to autoimmunity. On the other hand, Antibodies to antioxidant enzymes may disturb redox balance and cause oxidative stress, which then results in pathogenic alterations. According to this, oxidatively changed autoantigens that act as neo-antigens to promote loss of tolerance to oneself may arise [66].

Thus, redox processes regulate essential immune functions and an imbalance of this system could lead to the development of immunological diseases and disorders, including RDDs. The common terminology used to describe this redox imbalance is oxidative stress which is a consequence of overproduction of reactive species' of oxygen, nitrogen, and sulfur-derived species, and/or a the inadequate functions of physiological antioxidant and repair systems. Our bodies also generate and use these reactive substances, such as reactive oxygen species (ROS), for many purposes including the neutralization of pathogens and oxidative metabolism in the respiratory transport chain. The latter may leak electrons during the metabolism process, which leads to the formation of many types of ROS, including superoxide anion ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$). There is increasing evidence to highlight that redox imbalance and mitochondrial dysfunction contribute significantly to a variety of rheumatoid diseases including degeneratives such as OA, non-degeneratives like FM, inflammatory arthritis (e.g. RA and SLE), or other inflammatory diseases like gout [116]. Different studies found that OA chondrocytes and cartilage both significantly reduced the expression and activity of mitochondrial superoxide dismutase 2 (SOD2), an enzyme that protects mitochondria from oxidative stress [102,2]. A study has recently suggested that the age-related decline in mitochondrial SIRT3 levels could be the cause of the decreased SOD2 activity was supported by increased acetylation-induced inhibition. Furthermore, increasing evidence suggests that variations in the mitochondrial genome, such as mtDNA haplogroups, determine in the chondrocyte a different bioenergetic metabolism, oxidative stress response, and ultimately adaptation to environment, which in turn could define the propensity to develop OA and influence in OA-associated phenotypes [15].

FM is a widespread musculoskeletal syndrome characterized by fatigue and persistent pain. The pathophysiology of FM has been linked to oxidative stress, mitochondrial dysfunction, and inflammation, despite the fact that the disease's cause is still unknown [40]. In individuals with FM, various investigations have found elevated oxidative stress and dysregulated antioxidative markers [40,30], events linked to musculoskeletal symptoms such as fatigue and pain [117]. Inflammatory arthritis, such as RA, juvenile idiopathic arthritis (JIA) or psoriatic arthritis (PsA) are autoimmune joint diseases characterized by synovial proliferation associated with leukocyte extravasation and cytokine-mediated inflammation [116]. Healthy synoviocytes with mitochondrial dysfunction produced both cytosolic and mitochondrial reactive oxygen species (ROS), which resulted in inflammatory response (COX-2, PGE2, and IL-8) and sensitized cells to an increase in cytokine-induced inflammation through ROS production and nuclear factor kappa B (NF-κB) activation [76]. Besides, in a mouse model, increased T_H17 differentiation and aggravated arthritis are also caused by mitochondrial ROS (mtROS) [85]. Together with other damaged/dysfunctional mitochondria release damage-associated molecular patterns (DAMPs, also known as alarmins), mtROS activates the inflammasome directly [132]. In this regard, a recent study found that the NLRP3 inflammasome was strongly activated in the synovia of both RA patients and mice, and that this activation primarily took place in the invading monocyte/macrophages but not in fibroblast-like synoviocytes [54].

SLE is a long-term autoimmune condition that causes systemic inflammation as a result of immunocompetent cells that do not function normally and the generation of a broad range of autoantibodies [75]. $CD4^+$ T cells from SLE patients have abnormalities in lipid metabolism, which affects mitochondrial glucose activation, which results in mitochondrial hyperpolarization and the formation of mtROS [129]. On the other hand, SS, also called scleroderma, is a systemic autoimmune disease that often leads to progressive fibrosis and microvasculature damage in multiple organs like heart, lung, skin, muscle or joints [80]. There is increasing evidence that mtROS plays a significant role in myofibroblast differentiation and fibrosis progression in SSc via activating TGF-elicited signaling pathways [47].

2. Physiological source of reactive species

ROS are of two types: (i) oxygenated radicals, such as $O_2^{\bullet -}$, $^{\bullet}OH$, peroxyl radicals ($ROO^{\bullet}$) and lipoperoxide radicals ($LOO^{\bullet}$); (ii) non-radical oxygen derivatives, such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), singlet oxygen ($^1O_2$) and peroxynitrite ($ONOO^-$). While catalyzing $O_2^{\bullet -}$ in mammals, the superoxide dismutase enzymes (SODs: SOD1 (cytosolic or Zn, Cu-SOD), SOD2 (mitochondrial Mn-SOD) and SOD3 (extracellular Zn or Cu-SOD) produce H_2O_2 ($O_2^{\bullet -} + O_2^{\bullet -} + 2\,H^+ \rightarrow H_2O_2 + O_2$) which can diffuse across cell membranes through aquaporin channels.Catalase (CAT) as physiological antioxidant enzyme converts H_2O_2 into molecular oxygen (O_2) and water (H_2O). Glutathione peroxidase (GPx) reduces H_2O_2 to H_2O with the aid of reduced glutathione (GSH), which oxidizes to dimerize as GSSG On the other hand, glutathione reductase (GPr) converts GSSG back to GSH. Therefore, abnormalities or low physiological levels of these antioxidant enzymes may stimulate ROS-mediated pathologies including RDDs.

2.1. Reactive substance production pathways

In addition to the mitochondrial respiratory pathway, ROS are generated through the following reactions.

NADPH oxidases pathway:

$$O2\bullet- + O2\bullet- + 2H+ \rightarrow H2O2 + O2$$

$$H2O2 + O2\bullet- \xrightarrow{Fe/Cu\ salts} \bullet OH + OH- + O2$$

$$H2O2 + Fe2+ \rightarrow \bullet OH + OH- + Fe3+$$

$$H2O2 + Cl- \xrightarrow{myeloperoxidase} H2O + HOCl$$

Nitric oxide synthases pathway:

$2\,L\text{-arginine} + 3\,NADPH + H^+ + 4\,O_2 \rightleftharpoons 2\,L\text{-citrulline} + 2NO + 4\,H_2O + 3NADP^+$. This reaction is catalysed by several variants of nitric oxide syntheses (NOSs) including the constrictively expressed, and that induced (iNOS) during inflammation.

Nitrite reductase pathway:

$$NO2- + 1e- + 2H+ \xrightarrow{xanthine\ oxidase} NO + H2O$$

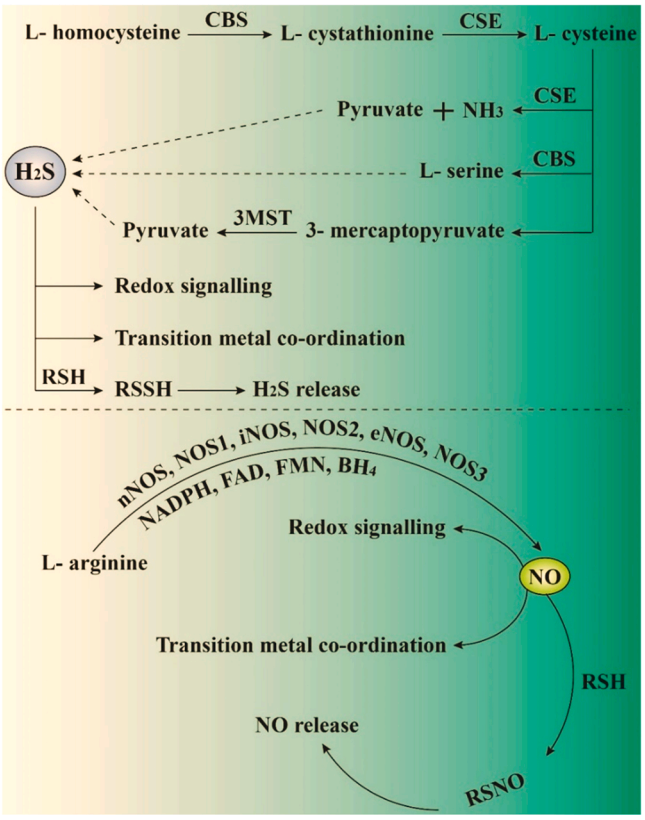

Fig. 1. Schematic presentation of NO and H_2S release mechanisms. The inflammatory insults can lead to the production of certain dangerous reactive substances in RDDs [43,81,124]. Abbreviations: NO: nitric oxide; CSE: cystathionine γ-lyase; CBS: cystathionine β-synthase; 3-MST: 3-mercaptopyruvate sulfide transferase; NOS1: nitric oxide synthase-1; NOS2: nitric oxide synthase-2; iNOS, inducible nitric oxide synthase; NOS3: nitric oxide synthase-3; eNOS: endothelial nitric oxide synthase; NADPH: nicotinamide adenine dinucleotide phosphate; BH4: tetrahydrobiopterin; FAD: flavin adenine dinucleotide; FMN: flavin mononucleotide.

A general outline of NO and H_2S release mechanisms in RDDs is outlined in Fig. 1.

2.2. Reactive substance neutralization pathways

SOD, CAT and GPx mechanism:

$$2H2O2 \xrightarrow{\text{catalase}} 2H2O + O2$$

$$2GSH + H2O2 \xrightarrow{\text{glutathione peroxidase}} GS-SG + 2H2O$$

$$GS-SG + NADPH + H+ \xrightarrow{\text{glutathione reductase}} 2GSH + NADP+$$

The multifunctional molecule nitric oxide ($^{\bullet}NO$) plays an important role in different physiological functions, including immunological processes. It generates $ONOO^-$ and regulates cellular redox balance through its reaction with $O_2^{\bullet-}$. An increased level of $^{\bullet}NO$ is involved in the pathophysiology of a series of chronic multifactorial diseases such as multiple sclerosis, RA, Parkinson's disease (PD), Alzheimer's disease (AD), and inflammatory bowel disease. Hydrogen sulphide (H_2S) synthesized from the amino acids L-cysteine, L-homocysteine or L-cystathionine is oxidized to sulphite and sulphate by activated neutrophils. Recently, H_2S has been recognized as a physiological gasotransmitter that regulates certain oxidative processes [18]. The H_2S also serves as a powerful antioxidant through ROS and reactive nitrogen species (RNS) scavenging. Moreover, it can reduce and/or bind directly to metalloprotein heme centres and cause post-translational alterations of proteins, via adding a thiol (-SH) group onto residues of reactive cysteine (per sulfidation) [18]. The H_2S is produced in mammalian cells and tissues by the action of different enzymes, such as cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercapto pyruvate sulfurtransferase (3-MST). The intestinal microbiota (colonic H_2S-producing bacteria) is also able to produce small amounts of H_2S. Homeostatic levels of H_2S maintenance are necessary for optimum viability and functions of immune cells, i.e., a sub-physiological level of endogenous H_2S due to various diseases or genetic defects may contribute to the occurrence of autoimmune disease or accelerate or worsen the evolution of the immune-mediated diseases, including RA and asthma [14]. Figs. 2 and 3 shows bone conditions over time in RDDs.

3. Origin of reactive species in RDDs

Reactive species (e.g. of oxygen (ROS), nitrogen (RNS), and sulphur (RSS) origin) oxidize cellular biomolecules, including carbohydrates, proteins, lipids, and nucleic acids [86]. Oxidative DNA damage leads to permanent mutations if left unrepaired. Physiological antioxidant enzymes such as SOD, CAT, GPx, GPr, GSH, thioredoxins and peroxiredoxins work against the potentially damaging effects of these reactive species generated by the fact that these antioxidants can scavenge or neutralize free radicals and oxidizing substances. We also have some dietary antioxidants, for example, vitamin A (retinol), vitamin C (ascorbic acid), vitamin E (α-tocopherol), β-carotene and antioxidant minerals, (e.g. copper, ferritin, zinc, manganese, selenium) that contribute to the antioxidant defenses [100]. As mentioned above, a balance between the production and damaging events of the diverse reactive species (ROS, RNS and RSS) produced in mammals as part of physiological functions is required to maintain a normal physiological

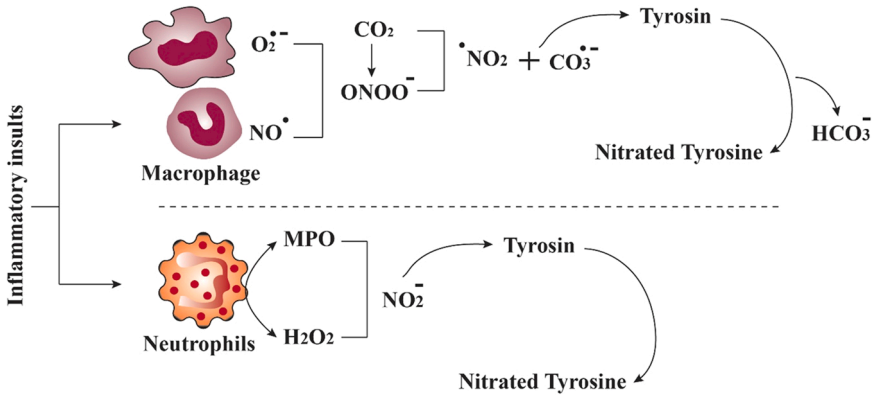

Fig. 2. An inflammatory insult leads to the production of reactive substances. Abbreviation: MPO: myeloperoxidase.

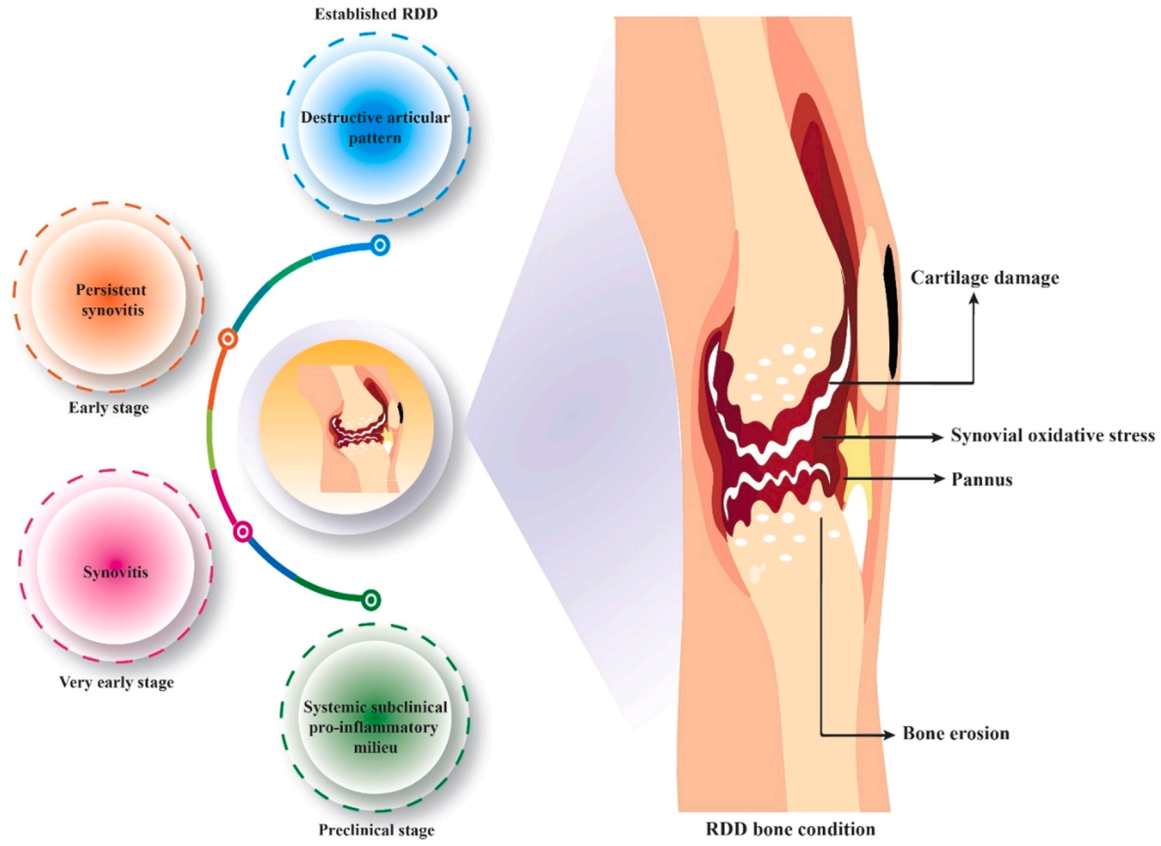

Fig. 3. Normal and destructed joints: the timeline of RDDs.

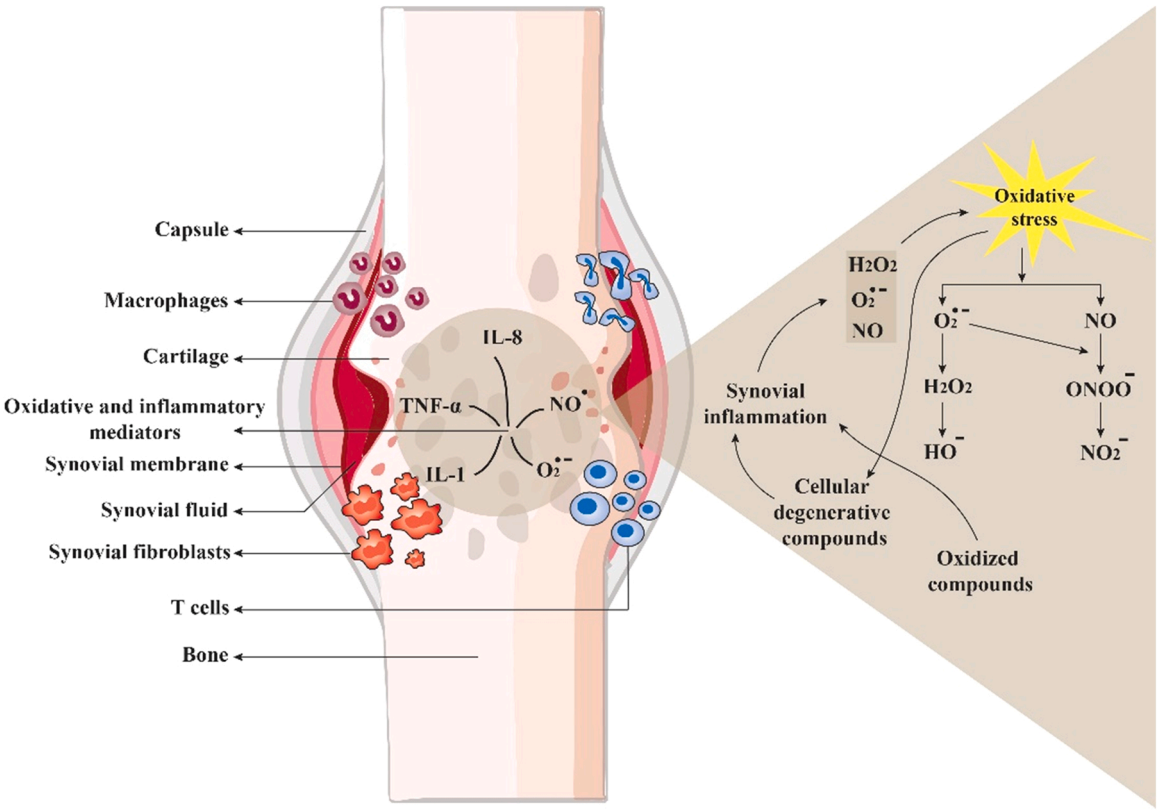

Fig. 4. Interaction of oxidative stress markers and inflammatory mediators in RDDs. Abbreviations: IL-1: Interleukin-1; TNF-α: Tumor necrosis factor-α; IL-8: Interleukin-8.

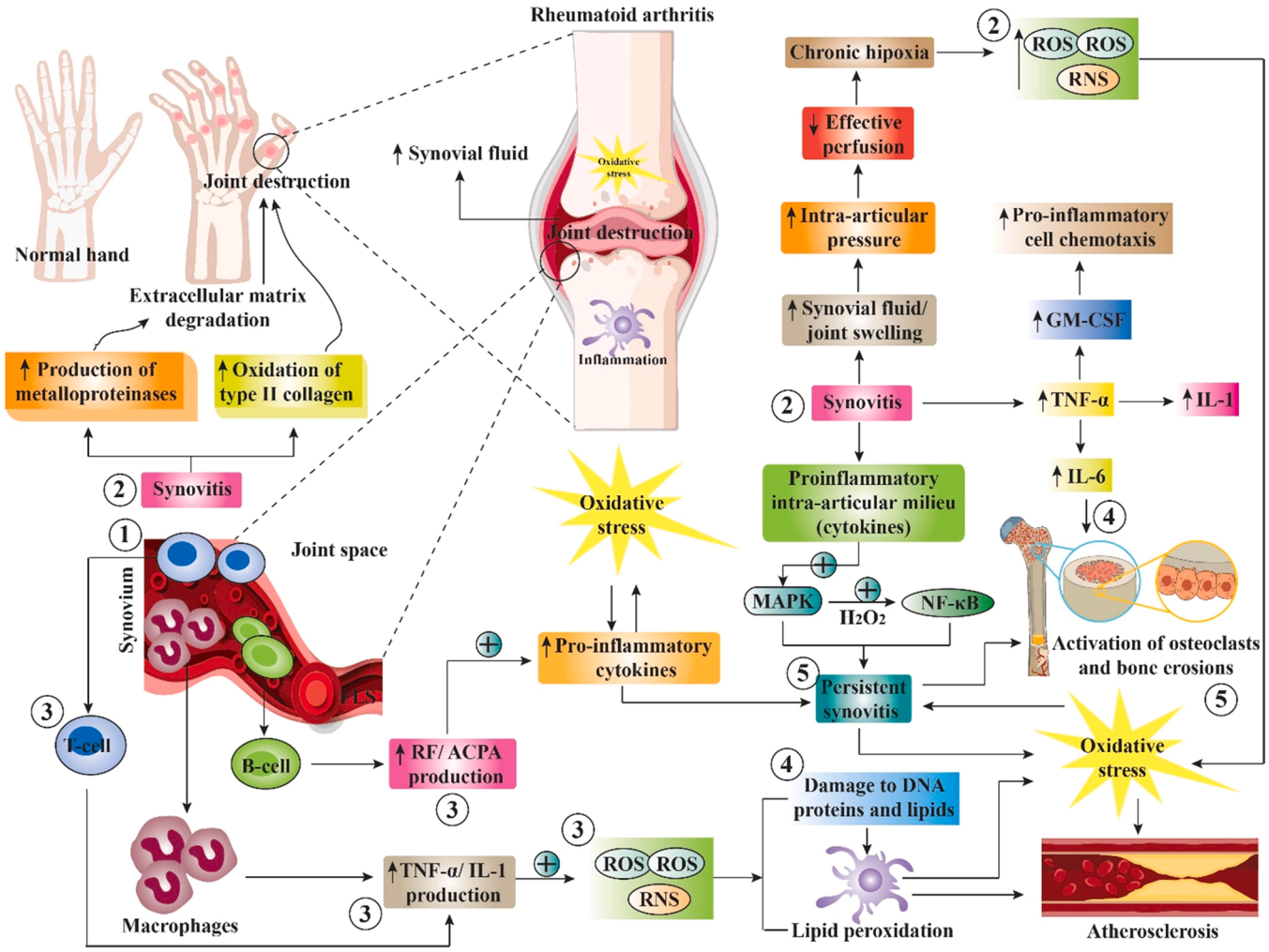

Fig. 5. Possible outlines of molecular interactions of oxidative stress in RDDs. Abbreviations and symbols: ↑increase, ↓decrease, ACPA: anticitrullinated protein antibodies; GM-CSF: granulocyte-macrophage colony-stimulating factor; FLS: fibroblast-like synoviocyte; H_2O_2: hydrogen peroxide; IL-1: interleukin 1; NF-κB: nuclear factor-κB; IL-6: interleukin 6; RF: rheumatoid factor; MAPK: mitogen-activated protein kinase; RNS: reactive nitrogen species; TNF: tumor necrosis factor; ROS: reactive oxygen species.

condition.

Prime sources of oxidative stress and reactive species in RDDs include:

i. chronic inflammation – spontaneous generation by the activated leucocytes
ii. hypoxia-reperfusion cycles – repeated action on RDD joint synovial tissues
iii. augmented metabolic rate of the joint synovial tissues
iv. release of metal ions - free state or ion-containing molecules of transition metals (e.g., haem), which are released during the tissue injury and catalyze free radical reactions.

Hypoxia reperfusion can activate some pro-inflammatory transcription factors, such as HIF-1α (hypoxia-inducible factor-1 alpha) and NF-κB (nuclear factor kappa B), essential for the maintenance of the inflammatory loop. All these mechanisms result in a state called "oxidative stress", which triggers inflammatory signals in mammals. A functional derangement occurs in chondrocytes during the development of osteoarthritis. Oxidative stress leads to cellular aging, which is also responsible for provoking extrinsic senescence by DNA damage events. The consequences of oxidative stress in RDDs include (i) direct and indirect damage to cellular molecules and tissues, (ii) mutations in the genetic materials; (iii) formation of neoepitope; and (iv) redox imbalance [86].

It should be mentioned that direct detection of redox imbalance levels in a physiological system is very difficult. However, excessive levels of oxidatively damaged proteins, lipids, and genetic products can be identified in the RDD joints [42]. Carbonylated proteins, oxidized low-density lipoprotein (ox-LDL) and hyaluronic acid, as well as the level of protein carbonyl groups, can be detected [86]. An increase in oxLDL levels in RDDs can also lead to the development of foam-type cells and atherosclerotic plaques. Mutations in the peripheral blood lymphocytes and tumor suppressor gene p53 have been reported in RDDs [128]. Modified macromolecules can alter the regular structure and normal physiological functions of RDDs. These form an "altered self" that can trigger the host's immune response (also called an autoimmune response) [128]. T cells from RDD patients can produce > 2.5 times more $^{\bullet}NO$ than those from healthy people, and they also exhibit increased cytoplasmic Ca^{2+} concentrations and nitrative/nitrosative modifications [44,114]. Fig. 4 depicts interactions between the inflammatory mediators and oxidative stress biomarkers in RDDs, while Fig. 5 depicts a possible outline of oxidative stress molecular interactions in RDDs.

4. Redox regulation in RDDs

Physiological redox systems regulate key roles in the inflammatory process, immunological activities, and thus in RDDs [53]. For example,

H_2O_2 acts as a paracrine chemotactic signal in injured tissues, which helps to recruit leukocytes to the site of injury [38]. It also positively regulates neutrophilic and phagocytic functions, thereby decreasing inflammatory reactions [45]. Moreover, it acts as a universal second messenger in several cell signaling pathways [53]. The phosphorylation and activation of downstream proteins involved in lymphocyte signal transduction, such as the tyrosine kinases Lck, Fyn, Syk, and ZAP70, results from oxidative inhibition of protein tyrosine phosphatases [53]. Many membrane receptors present on T and B cells also stimulate the intracellular production of reactive species. In B cells, CD40 induced activation of the AKT (protein kinase B), JNK (c-Jun NH2-terminal kinase) and p38 mitogen-activated protein kinase (MAPK) pathways is reactive substance-dependent, while B cell receptor (BCR) signaling may function even in the presence of antioxidants. T cell signaling via T cell receptor (TCR) engagement also proceeds via reactive substance production [20]. One of the major antioxidant enzyme families in humans, peroxiredoxins, are implicated in Toll-like receptor (TLR) signaling. The TLRs are type I integral membrane glycoproteins that play an essential role in innate immune defense [27]. Improper activation of TLR signaling cascades can contribute to RDDs. Bacterial lipopolysaccharide (LPS) acts as the main activator of the TLR4 signaling pathway; therefore, any substance that stimulates the production of LPS can upregulate the LTR4 signaling cascade [27].

Some antioxidant systems such as SOD are poorly regulated in the RDD patients' plasma and synovial fluid, while others are upregulated, for example, thioredoxin (Trx) 1 (Trx1) [78]. The Trx is found on the surface of various cells, including human monocytic cell lines, human lymphocytes, granulocytes, monocytes, macrophages, fibroblasts, endothelial, epithelial, and neuronal cells. Of these, Trx1 is abundant in the cytosol but it can also translocate to the nucleus [78]. In the TNF-α-stimulated cells, Trx1 displays a pro-inflammatory role as it upregulates IL-1 and IL-6 expression. It seems that Trx1 has an important role in RDDs, and it has a reverse correlation with C-reactive protein (CRP) and the number of infiltrating leukocytes [64]. Moreover, there is evidence that TNF-α and H_2O_2 can upregulate Trx1 production at the protein level in synovial fibroblasts [64]. Trx1 can act as a mitogenic cytokine and stimulate IFN-γ production, leading to the induction of a Th1 type response. Moreover, truncated Trx (Trx80) is evidently overexpressed in RDD synoviocytes without any stimulation and causes upregulation and extracellular release of TNF-α and IL-1β. It has cytokine like functions that enhance eosinophil cytotoxicity and stimulates B cell activity. The Trx 80 further activates and helps in the formation of certain monocytes called Trx80-activated monocytes (TAMs), which are characterized by a higher potential of phagocytosis and lysosomal degradation [46]. It also stimulates the proliferation of lymphocytes. The Trx1 regulates CD4 on the Th lymphocytes' surface. In this connection, the D2 domain of CD4 is redox-sensitive. Locking both CD4 and Trx in the reduced state inhibits the entry of HIV-1 to the host cells [46]. Thus, besides Trx1, Trx80 also has a pathophysiological role in RDDs [46]. However, due to cellular stress (e.g., UV radiation, injury), inflammasome-induced activation of the "inflammatory" caspase, caspase-1, causes the secretion of some proteins (e.g. IL-1α and fibroblast growth factor 2 (FGF2)) that are not only involved in tissue repair and cytoprotection but also involved in inflammation [21,46].

Thioredoxin reductase (TR) is secreted through the classical Golgi pathway. Thioredoxin reductase 1 (TR1) and other physiological antioxidants, including peroxiredoxin 2 (Prdx2), CAT, SOD2, glutaredoxin and GPx2 are upregulated at the mRNA level in RDD synovial fibroblasts. It has been demonstrated that TR1 might act as an anti-apoptotic molecule, which can prevent inflammatory synovial cell death by suppressing oxidative molecules [46]. An upregulation of Prdx2 levels is associated with the upregulation of IL-17 and is also seen in osteoarthritis tissue and peripheral blood lymphocytes of RDDS [120]. Moreover, certain antioxidant enzymes, including the nuclear factor erythroid 2 related factor 2 (Nrf2), are overexpressed in RDD synovial cells and subintimal adipocytes. Fig. 6 shows the redox impacts on the lymphocytes of RDD patients and the influence of intracellular and exofacial Prdx2 levels [120].

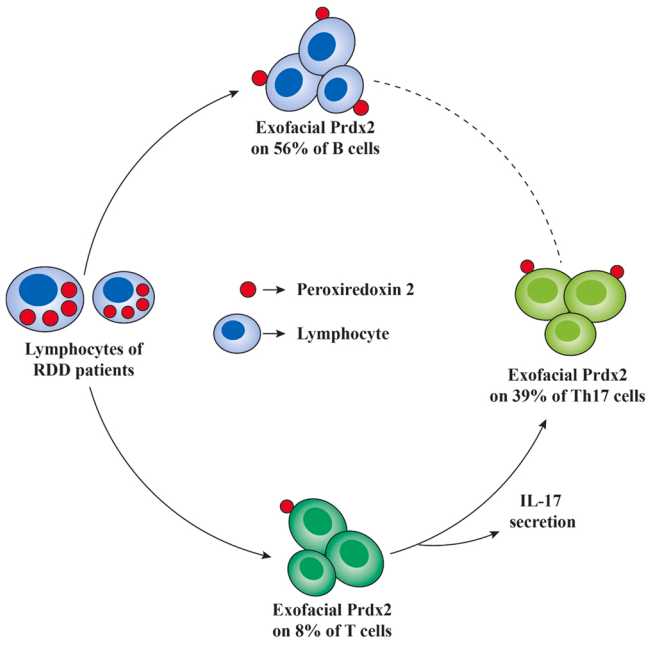

Fig. 6. Redox impacts on lymphocytes of RDD patients and the influence of intracellular and exofacial Prdx2 levels [110]. IL-17: Interleukin-17; Prdx2: Peroxiredoxin-2; Th17: T-helper 17 cells; RDD: Rheumatoid arthritis.

Maintaining an optimum surface thiol level is a prerequisite for increased T cell proliferation. $CD19^{+ve}$ T cells contain more surface thiols than $CD8^{+ve}$ and $CD4^{+ve}$ T cells. Mitogenic activation can increase both surface thiol levels and the proliferation of T lymphocytes [120]. Furthermore, impaired production of reactive species can increase leucocyte surface thiol levels and, therefore, increase the risk of developing RDDs in experimental animals. Certain drugs that are used in RDDs, for example, methotrexate, may generate oxidative stress which can cause the decrease of leucocyte surface thiols, which have important roles in maintaining cellular redox balance, helping in cell signaling and cell proliferation, and modulating surface receptors, such as CD4 and the IL-2 [25].

5. Redox-dependent apoptosis in RDDs

It is crucial to clear the inflammatory immune cells and synovial fibroblasts sufficiently in RDDs [113]. A lack of this activity results in synovial hyperplasia and chronic inflammation. RDD fibroblast-like synovial cells may transform into a tumour-like mass or "stable activation" leading to the development of aggressive tissue. In general, these cell masses can produce cytokines and growth factors (e.g., IL-1, TGF-1β, βFGF and TNF-α) and are resistant to apoptosis due to over-production of $^{\bullet}NO$, sentrin and matrix metalloproteinase-3. The free radical $^{\bullet}NO$ has bifunctional regulatory effects on apoptotic events [113]. This free radical can inhibit respiration at the mitochondrial level, possibly by attaching to the oxygen-binding site of the cytochrome oxidase enzyme. Thus, exposure to $^{\bullet}NO$ may induce a decrease in intracellular ATP levels, which is a leading cause of cell necrosis rather than apoptosis [84]. On the other hand, $ONOO^-$ negatively modulates mitochondrial respiration and permeability transition functions, leading to the release of intracellular structures (e.g., citrullinated proteins) during the necrosis phase, which may play the role of a trigger to autoimmune reactions, contributing to chronic inflammation in RDDs. Peroxiredoxin-based enzyme system also inhibits apoptotic processes; for example, Prdx2 and Prdx3 act as anti-apoptotic factors [84]. Therefore, maintaining an optimal dietary antioxidant supplement along with boosting

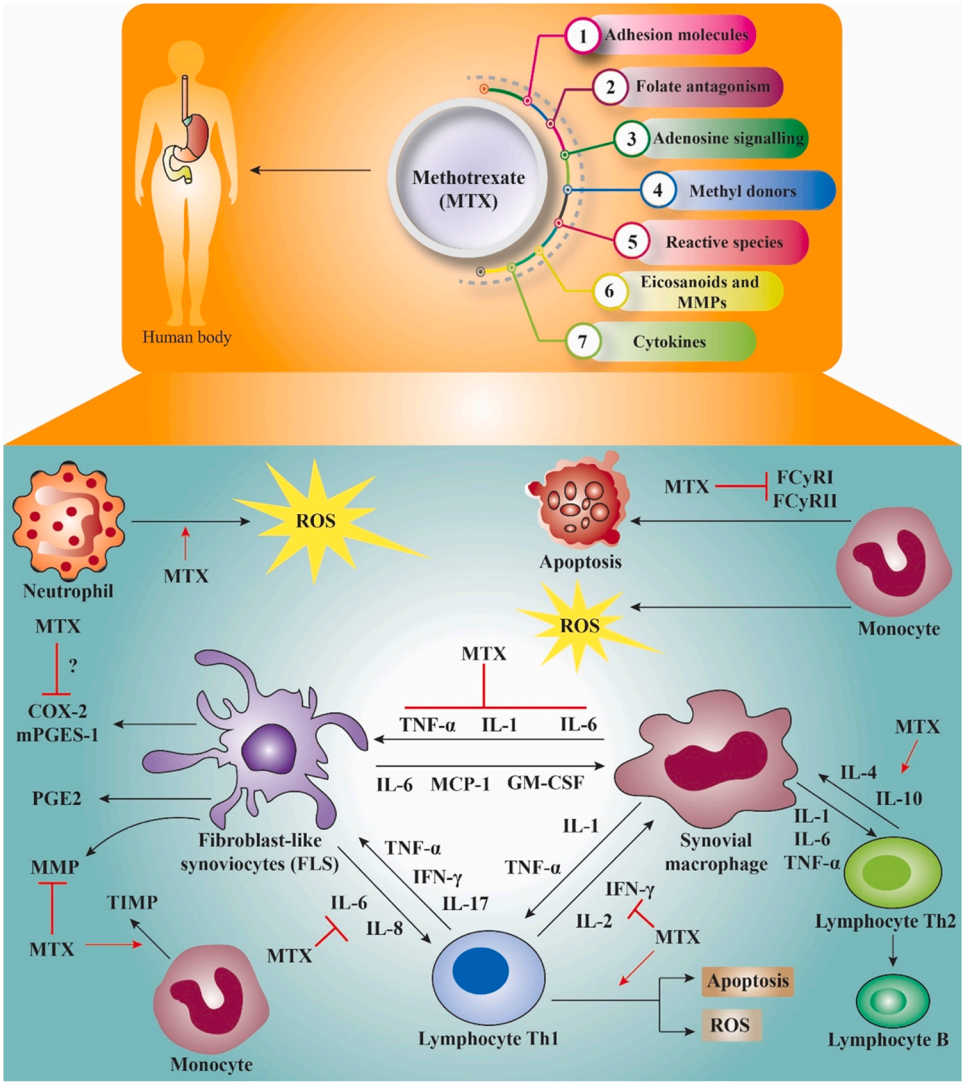

Fig. 7. Proposed molecular interactions of methotrexate in RDDs [32,131]. Abbreviations: MTX: Methotrexate; ROS: Reactive oxygen species; IL-1: Interleukin-1; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; IL-17: Interleukin-17; TNF-α: Tumor necrosis factor-alpha; IFN-γ Interferon-γ; COX-2: Cyclo-oxygenase-2; PGES-1: Prostaglandin E synthase-1; MMP: Matrix metalloproteinases; PGE2: Prostaglandin E2; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; MCP-1: Monocyte chemoattractant protein-1.

physiological antioxidants might be necessary to manage RDDs [46, 107].

6. Redox balancing therapies in RDDs

Reduction of oxidative stress in RDDs is one of the major therapeutic strategies. The anticancer drug methotrexate (MTX), a disease-modifying antirheumatic drug (DMARDs), is still considered a first-line choice in the therapeutic approach of many RDDs, including RA [46]. It inhibits •NO production and induces the secretion of IL-10, an anti-inflammatory cytokine. Besides these, this drug increases reactive species generation in RDD patients [106]. Thus, a decreased production of •NO levels might be necessary to maintain cytokine homeostasis in RDD patients. In contrast, an increased level of reactive species generation causes the apoptosis of inflammatory cells. Besides NO production, MTX inhibits purine and pyrimidine synthesis, governs trans-methylation reactions, translocates NF-κB to the nucleus, gives signals via the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, promotes adenosine release, and enhances the expression of certain long noncoding RNAs [106]. Fig. 7 depicts MTX mediated mechanisms in RDDs.

Cumulative research evidence reports that *N*-acetylcysteine [115], synbiotic supplementation [127], pomegranate (*Punica granatum* L) extract [127], coenzyme Q10 [87], sesamin supplementation [67], rectal insufflation of ozone [105] and laser acupuncture [1] can be used to manage RDDs. A single injection of anakinra (100 or 150 mg, SC) is effective in reducing oxidative stress by decreasing nitrotyrosine, malondialdehyde (MDA), protein carbonyl, IL-6, and endothelin-1 along with the improvement of cardiovascular functions in RA patients [77]. Therapy with simvastatin also attenuated oxidative stress via reductions in oxLDL levels and in the oxLDL/LDL ratio [77]. Oxidative stress causes cartilage degradation in arthritic animals. The Nrf2 regulates phase II antioxidant enzyme expression and acts as a novel upstream regulator of MYC, negatively regulating the receptor that activates the NF-κB ligand (RANKL)-induced osteoclastogenesis through the ERK (extracellular signal–regulated kinase) and p38 MAPK signaling-mediated suppression of MYC transcription [94]. The Nrf2 and its principal negative regulator, E3 ligase adaptor Kelch-like ECH-associated protein 1 (Keap1) play a key role in intracellular redox homeostasis, thereby in inflammation cascades. Moreover, Nrf2 regulates heme oxygenase-1 (HO-1), which is known for its potent antioxidant and anti-inflammatory role [94]. The pro-inflammatory cytokines TNF-α and IL-1β play important roles in synovial inflammation and subsequent bone erosion [103]. An earlier report suggests that Nrf2 activation and/or co-treatment with a suitable anti-TNFα agent might be more beneficial in RDDs [103]. Combination therapy for RDDs could be an intriguing and effective strategy. For example, antioxidant vitamins (e.g., vitamin A, C, and E) when co-treated with conventional DMARDs increased blood concentrations

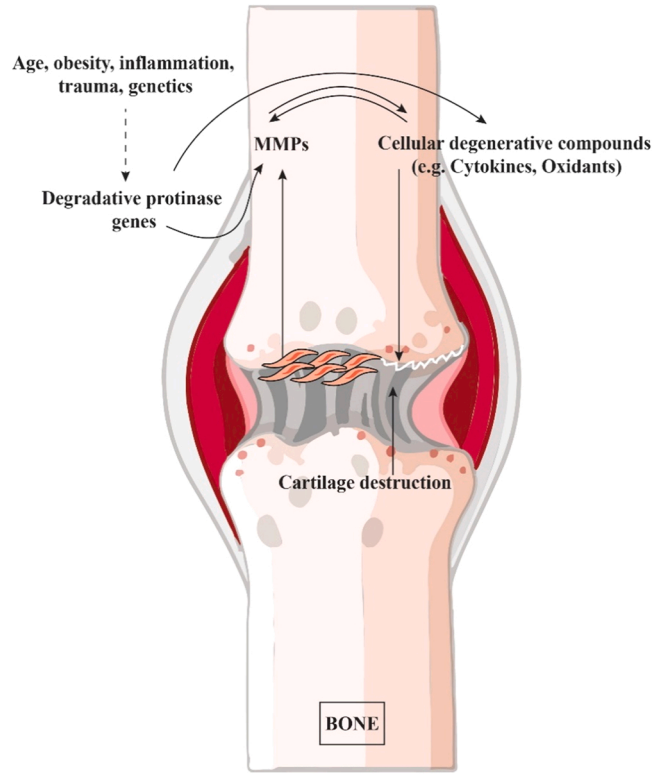

Fig. 8. Synthesis and impacts of MMPs on RDD synovium [59,13]. Abbreviation: MMPs (Matrix metalloproteinases).

of thiols, GSH, and vitamin C, and decreased the levels of MDA in patients with RA [33,44]. A reduced profile of the arthritic index was also reported in this study [44]. Probiotic therapy with *Lactobacillus acidophilus*, *L. casei* and *Bifidobacterium bifidum* was found to be more effective than *L. casei* alone in improving DAS-28 and VAS pain and increasing nitrite, an indirect marker of $^{\bullet}$NO concentrations, and the GSH in plasma [126]. Activation of matrix metalloproteinases (MMPs) results in oxidative stress [71] Global Burden Of 369 Diseases And Injuries In 204 Countries And Territories [49]. MMP-1, 3 and 9 play important roles in both RA synovial and cardiovascular alterations [71]. Fig. 8 shows a general outline for MMPs-mediated effects on RDD synovium. Many therapies and their outcomes are listed in Table 1.

7. Conclusions

Redox imbalance in RDD patients induces oxidative stress through numerous pathways. Neutralization of oxidative stress is therefore an important strategy in the management of RDDs. Targeted therapies, using effective inhibitors of reactive species-generating enzymes/cascades offer bright hope to manage autoimmune diseases, including RDDs. Some of the promising treatments for RDDs might be: (i) reduction of oxidative stress in RDD joints; (ii) boosting physiological antioxidant systems (enzymatic and non-enzymatic pathways); (iii) dietary modifications: diets with sufficient antioxidants; (iv) targeted therapies (e.g., Nrf2, MPO dependent pathways); (v) combined therapeutic strategies: targeted therapy with conventional therapies; (vi) miscellaneous: surgery, gene therapy, etc. If that, a separate, as of yet undiscovered mechanism may be used in the formation of RDD in those who did not respond Alternatively, given that individuals with the most severe symptoms respond the least to all medications, this phenomenon could be the result of a natural restriction in sensitivity to therapy. By virtue of biomarkers, we are still unable to anticipate which form of tailored treatment will be most effective for which patient. Even though we are aware that clinical progress early in the course provides for optimal

Table 1
Conventional to successful antioxidant therapies in RDD patients: mechanisms and outcomes.

Therapy	Cellular and molecular mechanisms	Outcomes	References
Vitamin A, E, and C plus conventional drugs for 3 months	↑thiols, ↑GSH, ↑vitamin C ↓MDA	↓RADAI scores	[61]
Simvastatin (40 mg/day) for 4 weeks	↓oxidative stress, ↓oxLDL ↓oxLDL/LDL ratio ↓total cholesterol↓ LDL cholesterol ↓apolipoprotein B ↓aspartate aminotransferase	↑endothelial function	[58]
Infliximab (3 or 5 mg/kg, i.v. at 0, 2, and 6th week) plus MTX (15 mg/week) and NSAIDs or 10 mg/day of prednisone	↓oxidative stress ↓protein carbonyls ↑GSH, ↑GSH-peroxidase ↑CAT, ↑SOD	↓BASDAI ↓DAS-28 scores	[41]
MTX therapy (7.5–15 mg/kg/week) for 6 months plus folate supplementation (1–2 times/week) up to 5 mg	↓·NO ↑ROS	↑IL-10	[73]
Infliximab (3 mg/kg IV for 6 weeks) plus conventional drugs	↑GSH, ↑GPx, ↑CAT, ↑SOD ↑carbonylated proteins ↓MPO, ↓lipid peroxidation	↓ESR ↓CRP	[16]
Anakinra (single injection: 100 mg SC) and MTX 7.5 mg once/week, leflunomide 20 mg, and prednisolone 5 mg	↓serum MDA, ↓nitrotyrosine ↓protein carbonyls, ↓IL-6 ↓endothelin-1	↑cardiovascular functions with RDD conditions	[29]
3 aerobic exercise sessions per week for 3 months	↓3-nitrotyrosine	↓DAS-28	[119]
Coenzyme Q10 supp. capsules (100 mg/day for 2 months) plus MTX, sulfasalazine, hydroxychloroquine and prednisolone	↓serum MDA, ↓TNF-α no alteration of total antioxidant capacity and IL-6 levels	-	[22]
Sesamin supp. (200 mg/once/day for 6 weeks) plus MTX, prednisone, sulfasalazine, and hydroxychloroquine	↓serum MDA ↑total antioxidant capacity	↑anthropometric indices, ↓lipid profile ↓blood pressure	[57]
Laser acupuncture 3 days/week for 4 weeks plus MTX	↓oxidative stress ↓inflammation, ↓plasma MDA, ↓serum nitrate and nitrite, ↓CRP, ↓IL-6, ↓GPx ↑SOD, ↑GR, ↑CAT, ↑GSH	↓ESR and pathological states	[7]
Saline balneotherapy for 2 weeks with a thermal pool with mineral water for 20 min 6-day/week and conventional DMARDs/ corticoids	↑NSSA	significant clinical improvement of tested parameters, ↑HAQ-DI, ↑DAS-28, ↑ESR and pain scores	[65]
Ozone (rectal insufflation) combined with MTX (12.5 mg)	↓anti-CCP levels, ↓CRP ↓oxidative stress ↑GSH level	↑MTX's clinical benefits	[70]

(*continued on next page*)

Table 1 (*continued*)

Therapy	Cellular and molecular mechanisms	Outcomes	References
+ ibuprofen (400 mg) + folic acid (5 mg) for 3 months			
Pomegranate (*Punica granatum* L) extract containing 40% ellagic acid orally, 2 capsules of 250 mg POMx/once a day for 8 weeks and conventional medications	↑GPx level ↓serum oxidative status	↑DAS-28, ↑HAQ scores and morning stiffness	[50]
Symbiotic capsule supplements (*Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum*) orally for 8 weeks	↑nitrite and GSH levels in plasma ↓ serum hs-CRP levels ↓insulin values, ↓HOMA-IR ↓HOMA-B	↑DAS-28, ↑VAS pain scores	[126]
N-acetylcysteine (600 mg/twice a day for 12 weeks, orally) and conventional medications	↓oxidative stress	↑GH, ↑VAS for pain severity, ↑HAQ scores	[8]
Enriched Grape Juice (EGJ) containing 234.5 mM microcrystalline KCl (a total of 6000 mg of K in 2 EGJ split into 2 intakes daily for 28 days)	↓pain intensity	-	[35]
Hyperbaric oxygen therapy (1.5 h, once daily, five times a week for 8 consecutive weeks (40 treatments with 100% oxygen at 2.0 ATA)	↑oxygenation of ischemic areas ↑oxidant-antioxidant system ↑angiogenesis, ↑neurogenesis	↓inflammatory response\ ↑brain neuroplasticity analgesic effect	[31]
MTX and/or doxycycline 200 mg, once a day orally for 3 months	↓DAS28, ↓ESR, ↓CRP, ↓MMP-3, ↓MMP-9 s	-	[60]

Abbreviation and symbols:↑ increase, ↓decrease, GSH: Glutathione; LDL: Low-density lipoprotein; CAT: Catalase; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; ROS: Reactive oxygen species; MDA: Malondialdehyde; IL-6: Interleukin-6; GR: Glucocorticoid receptor; ESR: Erythrocyte sedimentation rate; MMP-3: Matrix metalloproteinase-3; CRP: C-reactive protein; MMP-9: Matrix metalloproteinase-9; MTX: methotrexate; HOMA-IR: Homeostatic model assessment of insulin resistance; HOMA-B: Homeostatic model assessment of beta cell function; TNF-α: Tumor necrosis factor-alpha; RADAI: Rheumatoid Arthritis Disease Activity Index.

clinical results, we are still using a trial-and-error methodology. In order to succeed in the search for curative or preventive therapies, which remains a crucial item on the agenda of basic and clinical investigators, additional study is still required to tie the genetic, epigenetic, environmental, and therapeutic factors together. Hopefully, this will be accomplished within the next decade.

CRediT authorship contribution statement

All authors contributed equally and made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The study is not being considered for publication elsewhere, all authors have seen and approved submission to Biomedicine and Pharmacotherapy, all authors have made a significant contribution to the study and paper and declare no conflicts of interest.

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