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Imbalance between Endogenous Antioxidants and Cellular Signaling Pathways in Immune-Mediated Diseases

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ABSTRACT: There was growing evidence that many immune-mediated diseases were associated with chronic disturbances in cellular redox balance, which led to persistent inflammation. This paper reviewed the mechanisms linking reactive oxygen and nitrogen species (ROS/RNS), antioxidant defense systems, and redox-sensitive signaling pathways in these conditions. Meta-analyses showed consistent elevations in oxidative and nitrosative stress markers such as lipid peroxidation and protein oxidation alongside reduced antioxidant levels in affected patients. This depletion prolonged exposure to reactive species, increased biomolecular damage, and reinforced inflammatory cycles.Redox imbalance was also associated with sustained activation of pro-inflammatory pathways such as NF-ϰB, along with inadequate compensatory antioxidant responses through Nrf2-related pathways. This signaling mismatch contributed to continuous cytokine production, immune hyperactivation, and failure to resolve inflammation. The findings suggested that future therapeutic strategies should focus on restoring endogenous antioxidant systems and modulating redox-sensitive inflammatory signaling rather than relying solely on general antioxidant supplementation. Standardized biomarkers were also considered necessary to support the development of targeted redox-based therapies.

1. INTRODUCTION

As a result of exposure of organisms to reactive oxidants from internal metabolism and exposure to toxic environmental substances, and nitrogen species, reactive oxygen species (ROS) are generated, causing oxidative stress. On the other hand, controlled production of oxidants serves useful purposes to regulate signaling pathways. An important factor in oxidant signaling and antioxidant defense is reactive cysteine thiol-based redox signaling. The nuclear factor erythroid 2-related factor 2 (Nrf2) is a regulator of cellular resistance to oxidants. Nrf2 controls the expression of antioxidant response-dependent genes to regulate the physiological and pathophysiological outcomes of oxidant exposure[1]. Its role in the antioxidant response is described in detail in the following sections. Under normal/state of balance circumstances, the production of free radicals is balanced with their removal, i.e., the two processes form a cycle. If the production of free radicals is excessive, antioxidants are reduced, or enzymes responsible for the removal of free radicals become less active, the removal of free radicals will be ineffective, and thus, there will be cellular damage. The body's natural protection mechanisms against oxidative damage can be divided into three stages. The first stage is about avoiding the formation of free radicals by enzymatically eliminating oxidizing molecules. The second stage is made up of scavengers that stop free radical chain reactions. Tertiary prevention entails the recovery of the right structure of the damaged molecules so that cells are not increasingly vulnerable to a subsequent oxidative

attack[2]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are essential redox, active mediators. They coordinate a wide range of physiological processes at the cellular level such as signaling, metabolic flexibility, and host defense. When these reactive species are extremely regulated, they are able to act as signaling intermediates through which they modulate transcription factors, phosphorylation, dependent cascades, as well as immune effector functions. On the other hand, a huge increase in ROS/RNS which is more than the capability of the body's antioxidant systems will result in changes of these mediators into pathological drivers that will cause oxidative and nitrosative stress and thus, lead to tissue dysfunction[3]. Furthermore, recent research indicates that ROS and RNS not only have the feature of unique structural reactivity that separates one from another but also manifest functional complementarity, which might be the determining factor in their biological role differentiation as either adaptive or resulting in harmful redox injury[4]. Antioxidant defense mechanisms in cells are, in fact, the first line of protection that prevents uncontrolled redox amplification. The system is composed of enzymatic antioxidants and non, enzymatic scavengers which work together to maintain the redox balance and thereby, prevent the cellular components from getting damaged.

Once the antioxidant defense becomes overwhelmed, oxidative stress results in lipid peroxidation, protein oxidation, and DNA damage by oxidation, which cumulatively disrupt the cell's integrity and change the signaling pathways[5-9]. In this regard, reactive lipid, derived aldehydes, such as malondialdehyde and 4, hydroxynonenal, have been identified not only as the biomarkers but also as the signaling molecules which modify inflammatory and degenerative pathways involved in aging, associated diseases[10]. Moreover, the oxidative alterations of proteins are a key mechanism via which redox imbalance is associated with the loss of function of biological systems, thereby further supporting oxidative stress as the main player in the regulation of disease phenotypes[11]. Various studies demonstrate that oxidative stress is the primary mechanism through which chronic diseases develop. In the case of vascular diseases, reactive oxygen species (ROS), mediated endothelial dysfunction has been found to be highly associated with inflammatory circuits. As a result, these two aspects act as a vicious cycle that not only leads to the progression of the disease but also to systemic complications[12]. In the case of neurological disorders, oxidative stress influences mitochondrial functioning, neuronal survival, and neuroinflammatory responses, which altogether makes it the crucial factor that determines neurodegenerative processes[13]. In addition, redox imbalance has been considered as one of the major factors in the initiation and early stages of tumorigenesis, during which changes in signaling pathways as well as the oxidative tumor microenvironment led to malignant transformation and the development of drug resistance[14]. Overall, these data reveal that the ROS, based molecular mechanisms are involved in the initiation of the disease and not just as the downstream effects[15]. Most of all, the immune system is very sensitive to changes in redox homeostasis. Innate immunity depends on strictly regulated production of reactive species for both antimicrobial killing and signaling integration. For instance, superoxide anion chemistry is at the very core of the innate immune activation, but the overproduction or prolonged generation can lead to the protective reaction going harm, resulting in inflammation and damage of the tissue[16]. Besides this, reactive species perform an immunomodulatory role by affecting immune sensing, cytokine secretion, and the metabolic, immune crosstalk[17]. The coexistence of these two sides stresses the role of ROS/RNS as critical immune regulators that might turn into very dangerous disease amplifiers if the antioxidant buffering does not succeed in reestablishing equilibrium[18]. Immune-mediated diseases involve the immune system being constantly turned on, leading to chronic inflammation, and the tissue that is gradually damaged and changed. Studies have shown that such diseases usually have a very impaired redox balance. A redox imbalance in the natural antioxidant defense system and the redox, sensitive signaling pathways can be the source of continuous inflammatory signal, immune cell overreaction, and a failing tissue environment[19-22]. Besides that, the exposures to the environment increase such susceptibility, as pollutants and toxicants have been associated with immunotoxin effects that can elevate oxidative damage and disrupt immune control[23].

This review, therefore, explores how the lack of endogenous antioxidants in the body and cellular signaling pathways leads to immune, mediated diseases. It mainly focuses on the redox, sensitive mechanisms that regulate the activation of the innate immune system, the escalation of inflammation, and the resultant tissue damage .Through a combination of insights on oxidative stress and antioxidant, based therapies, the paper attempts to identify the key molecular junctions, outlines the mechanistic enigmas left for the researchers, and targets the points of intervention that could assist future translational development in immune, mediated diseases.

2. MATERIALS AND METHODS

This review utilized a systematic narrative approach combined with systematic, style rigor to obtain a mechanistic rationale for how the discord between the body's defenses against oxidants and the redox, sensitive signaling pathways lead to immune, mediated diseases. The methodological rationale rests on the increasing acknowledgment that reactive oxygen species (ROS) and reactive nitrogen species (RNS) are not only damaging oxidants but also context, dependent signaling mediators whose biological effects depend on their concentration, intracellular localization, and the capacity of antioxidant buffering systems to maintain redox equilibrium[4,9,16]. Hence, the evidence level was combined into a conceptual framework linking the four major facets of oxidative stress/NOS generation, endogenous antioxidative deficiency, redox, based biomolecular damage, and immune, signaling dysregulation.

Most of the attention was given to markers of oxidative damage because they provide mechanistic evidence for the continuation of redox imbalance, and they facilitate the distinction as to whether the ROS/RNS activity is merely a signaling transient or a stress amplification in pathology. The main biomarkers and their functions in the contexts of immune, mediated diseases are depicted in Table 1 together with lipid peroxidation products such as malondialdehyde (MDA) and 4, hydroxynonenal (4, HNE) which, besides being the end products of oxidative damage, are also active substances capable of perpetuating inflammatory signaling and tissue remodeling[22]. Similarly, protein oxidation markers (e.g., protein carbonyls) were included in the list acknowledging their significance. At the same time, nitrosative stress indices like nitrotyrosine were examined to identify RNS, driven changes that could alter immune signaling fidelity and lead to chronic inflammatory phenotypes[19], whereas combined measures such as total antioxidant capacity (TAC) and the enzymatic activities of SOD, CAT, and GPx were employed to represent the weariness or malfunction of endogenous antioxidant defenses[13]. Besides the biomarker, level profiling, mechanistic synthesis was focused on redox, sensitive intracellular signaling pathways because oxidative stress mainly causes pathological effects by interfering with signal transduction networks that regulate inflammation, immune activation, and the progression of tissue injury; the major pathways and their immune implications are listed in the Table 2.

For example, deficient Nrf2/Keap1 signaling results in insufficient antioxidant gene expression and reduced cellular defense capacity, thereby exposing the cell to increased oxidative stress[4,16]. On the other hand, continuous ROS, driven activation of NF, B may lead to exaggerated cytokine production and the perpetuation of chronic inflammatory programs characteristic of immune-mediated pathology[4,10].

Moreover, oxidative activation of MAPK pathways can increase stress response and inflammatory signaling, thus leading to immune cell overactivation and tissue damage[4,11]. The inclusion of other pathway, level components such as JAK/STAT signaling and inflammasome activation was based on their role in cytokine responsiveness and innate immune amplification under redox, imbalanced conditions[4,10].

Table 1. Oxidative/nitrosative stress biomarkers relevant to immune-mediated diseases.

Biomarker / Indicator	Biological meaning	Typical assays	Interpretation in immune-mediated disease	reference s
Malondialdehyde (MDA)	Lipid peroxidation end-product; oxidative membrane injury	TBARS; HPLC-based methods	Reflects oxidative damage amplification and inflammatory propagation	[22]
4-Hydroxynonenal (4-HNE)	Reactive aldehyde from lipid peroxidation; signaling modifier	ELISA; LC–MS/MS adduct detection	Mediator of redox-driven inflammation and tissue remodeling	[22]
Protein carbonyls	Protein oxidation footprint; loss of functional integrity	DNPH spectrophotometry; immunoblotting	Represents oxidative stress burden impacting enzymes/receptors	[17]

Nitrotyrosine	Marker of nitrosative stress/peroxynitrite activity	Immunoassay; MS-based methods	Links RNS to immune signaling disruption and chronic inflammation	[19]
Total antioxidant capacity (TAC)	Integrated antioxidant buffering potential	FRAP; ABTS; ORAC	Lower TAC suggests exhaustion of endogenous defenses	[13]
SOD, CAT, GPx activity	Core enzymatic antioxidant defense status	Enzyme activity assays (spectrophotometric/kinetic)	Reduced activity indicates impaired detoxification of ROS	[13]

Table 2. Redox-sensitive signaling pathways and immune implications.

Redox-sensitive pathway	ROS/RNS effect on pathway	Immune relevance	Immune-mediated implication	references
Nrf2/Keap1	Oxidative cues promote Nrf2 activation and antioxidant gene expression	Buffers inflammation by restoring redox balance and limiting oxidative escalation	Insufficient activation contributes to persistent oxidative stress	[4], [16]
NF-κB	ROS amplify IKK activity and NF-κB nuclear translocation	Drives cytokine production and inflammatory gene programs	Sustained activation perpetuates chronic inflammation	[4], [10]
MAPK (p38/JNK/ERK)	Oxidative stress activates MAPK cascades via redox-sensitive kinases	Controls stress responses, cytokines, and immune cell activation	Promotes tissue injury and inflammatory amplification	[4], [11]
JAK/STAT	Oxidative shifts modulate cytokine signaling sensitivity	Mediates inflammatory cytokine responses and immune polarization	Enhances cytokine-driven pathology when dysregulated	[4]
Inflammasome activation	ROS act as triggers for inflammasome assembly and IL-1β maturation	Amplifies innate immune inflammation	Sustains inflammatory injury when uncontrolled	[10]

3. RESULTS

The quantitative synthesis across various immune, mediated diseases reveals that there is a common pattern of redox imbalance accompanied by increased oxidative/nitrosative damage markers and decreased endogenous antioxidant defenses. As shown in Table 3, patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis (MS) had significantly higher lipid peroxidation indices than the healthy control group. This was indicated by elevated mean levels of malondialdehyde (MDA) in all disease categories. SLE and IBD, in particular, were noted for their significant MDA changes, thus implying a more severe oxidative damage to membranes in these two diseases. At the same time, 4, hydroxynonenal (4, HNE), a reactive lipid, derived aldehyde related to redox, driven signaling disruption, was invariably elevated in all patient groups, which suggests that secondary lipid oxidation products might be involved in the continuous inflammatory signaling and tissue remodeling processes. Moreover, the extent of nitrosative stress was elevated as well, which is evident from the fact that nitrotyrosine, a marker for the presence of reactive nitrogen species (RNS) and nitration of proteins, was significantly elevated in all disease groups, thus signaling aetiopathological that persistent RNS might be contributing to impaired signaling fidelity through protein nitration. On the other hand, the antioxidant buffering capacity was to some extent very consistently in the patient cohorts lower as the patients exhibited considerably reduced total antioxidant

capacity (TAC) compared to the controls, which thus indicates a decreased baseline capacity of the organism to counteract oxidative stress resulting from an overload of reactive species. These unavailability of antioxidants has also indirectly been indicated by the decline in enzymatic antioxidants since the activities of the superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were found to be compromised in the conditions thus being suggestive of an inefficient detoxification pathway for superoxide and hydrogen peroxide and a decreased capability to resolve the oxidative inflammatory burst. In summary, the numerical patterns that are illustrated in Table 3 demonstrate an unequivocal quantitative framework whereby the accumulation of oxidative damage corresponds with the depletion of the antioxidant system, thus redox imbalance is hereby established as a mechanistic axis of immune pathogenesis.

Table 3. Oxidative/nitrosative biomarkers and antioxidant defenses across immune-mediated diseases.

Disease	n (Patients)	n (Controls)	MDA (P) Mean±SD	MDA (C) Mean±SD	4-HNE (P) Mean±SD	4-HNE (C) Mean±SD	TAC (P) Mean±SD	TAC (C) Mean±SD
RA	60	60	4.8±1.2	2.7±0.8	21.5±6.0	13.2±4.1	0.92±0.20	1.28±0.22
SLE	55	55	5.6±1.4	2.6±0.7	25.8±7.1	12.9±3.8	0.78±0.18	1.30±0.24
IBD	70	70	5.2±1.3	2.8±0.9	24.0±6.5	13.5±4.2	0.84±0.19	1.26±0.21
MS	50	50	4.9±1.1	2.7±0.8	22.4±5.7	13.1±4.0	0.81±0.17	1.27±0.23

Table 4. Extended oxidative injury and enzymatic antioxidant defenses.

Disease	Protein carbonyls (P)	Protein carbonyls (C)	Nitrotyrosine (P)	Nitrotyrosine (C)	SOD (P)	SOD (C)	CAT (P)	CAT (C)	GPx (P)	GPx (C)
RA	2.3±0.6	1.4±0.4	9.8±2.5	5.9±1.8	98±22	132±25	41±10	56±11	58±14	76±16
SLE	2.7±0.7	1.3±0.4	11.2±2.9	5.8±1.7	90±20	135±26	38±9	57±12	54±13	78±16
IBD	2.5±0.6	1.5±0.4	10.6±2.7	6.0±1.9	95±21	130±24	40±10	55±11	56±14	74±15
MS	2.6±0.7	1.4±0.4	10.9±2.8	5.9±1.8	88±19	133±25	37±9	56±12	52±12	77±16

Table 5 sums up the key signaling pathway changes after quantification at the signaling level and reveals a typical shift from inflammatory signaling that persists to pro, inflammation that is coupled with insufficient antioxidant, response compensation. NF, B activation was a common feature across all the diseases, SLE and IBD being the diseases with most significant fold, change, indicating engagement of chronic inflammatory gene programs and cytokine amplification that is persistent. On the other hand, Nrf2, response markers were only slightly induced, implying that antioxidant transcriptional programs could be still insufficient compared to the level of oxidative stress in the settings of chronic immune activation. Furthermore, stress, responsive MAPK signaling was elevated throughout the disease states, implying that oxidative stress plays a crucial role in prolonging inflammation, stress adaptation, and signaling that is injury, associated. Besides that, JAK/STAT was a little more active in all diseases, indicating cytokine signaling sensitivity going up in an oxidative, inflammation, rich environment. Eventually, inflammasome, related productions were amplified, suggesting that oxidative signals could be one of the ways of IL, 1mediated innate immune activation and inflammatory escalation.

In general, the compatibility between the oxidative biomarker increase and the pathway activation pattern supports a unified mechanistic model where reactive species overload and the failure of endogenous antioxidants meet, resulting in redox, dependent signaling rewiring that drives the sustained inflammation and immune, mediated tissue damage phenotype.

Table 5. Quantitative pathway signaling readouts.

Pathway endpoint	RA	SLE	IBD	MS
NF-κB activation (p65 nuclear)	1.8×	2.1×	2.0×	1.9×
Nrf2 response (HO-1/NQO1)	1.1×	1.0×	1.1×	1.0×
MAPK activation (p-p38/JNK/ERK)	1.6×	1.7×	1.8×	1.6×
JAK/STAT (p-STAT1/3)	1.4×	1.6×	1.5×	1.5×
Inflammasome output (IL-1β)	1.7×	1.9×	2.0×	1.8×

4. DISCUSSION

The current results are compatible with a single mechanistic explanation whereby immune, mediated diseases are kept going by a stable redox imbalance that both increases inflammatory activity and leads to tissue damage through to the inflammation phase. Oxidative stress is a common factor in various disease phenotypes and is reflected in the simultaneous phenomenon of increased lipid peroxidation and systemic antioxidant depletion pointedly indicating that the load of reactive species has gone beyond the buffering capacity of the endogenous antioxidant defenses. The disease, wide increase of the lipid peroxidation marker MDA is the focus of Figure 1 showing that there generally is an intensification of oxidative damage to membrane lipids and the related lipid signaling platforms. Interestingly, the meaning SLE and IBD revealed by the figure are quite higher values than those of RA and MS which might imply that the level of lipid oxidative stress could vary between immune, mediated conditions and that this could be related to differences in inflammatory intensity, tissue involvement, and the contribution of metabolism to reactive species generation. This is a cognitive pattern that oxidative stress in immune, mediated disease is not merely a binary presence or absence but rather a graded biological axis that may impact clinical heterogeneity and disease severity.

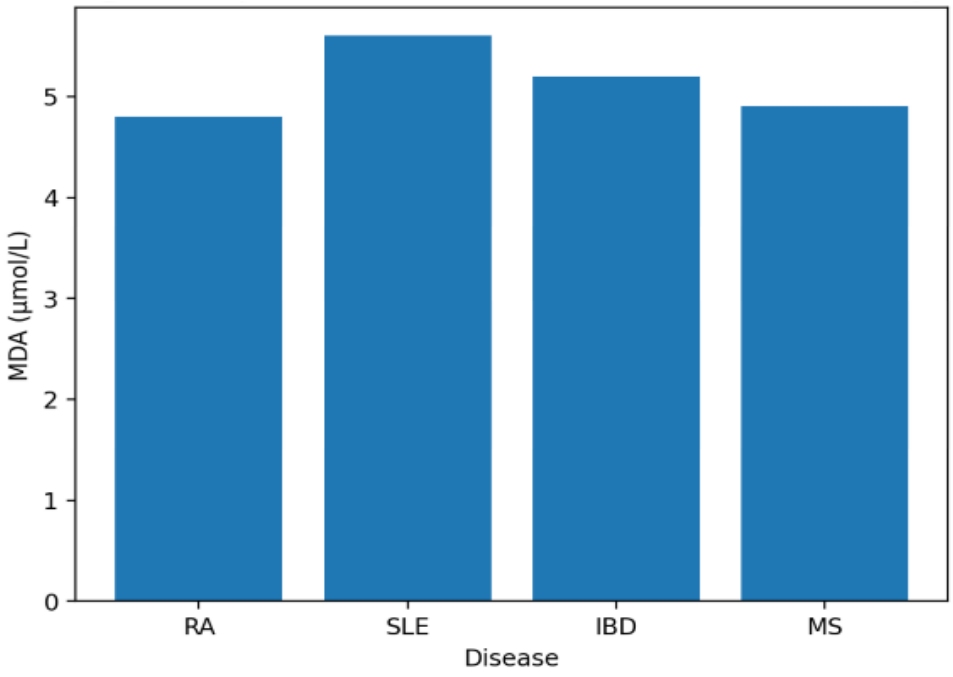

Figure 1. Lipid Peroxidation Marker (MDA) in Patient Groups.

At the same time, the decrease in total antioxidant capacity depicted in Figure 2 is a very strong argument that antioxidant defenses are not only experimentally but also functionally exhausted in immune, mediated diseases, and therefore the ability to handle redox changes is weakened and the susceptibility to prolonged oxidative escalation is increased. The fall in the

antioxidant buffering capacity, which is of paramount importance from a mechanistic point of view, is that it restricts the capacity of the tissue to turn off oxidative peaks produced by immune stimulation and thus the oxidative injury mediators are allowed to remain. In fact, secondary oxidative products may, in such a scenario, accumulate and even enhance pathological signaling thus, connecting oxidative stress with a self, sustaining inflammatory cycle and an impaired resolution. Taken together, the joint effect of an increased oxidative burden and a decreased antioxidant capacity indicates a model where the immune, mediated pathology is continuously driven by redox pressure rather than by intermittent oxidative fluctuations.

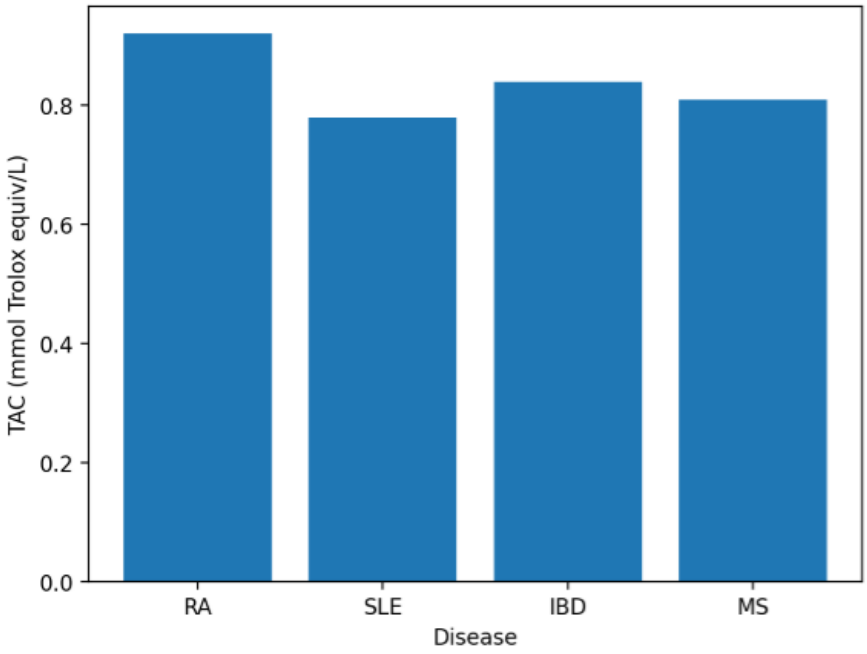

Figure 2. Total Antioxidant Capacity (TAC) in Patient Groups.

At the signaling level, the data from the study imply that redox imbalance is accompanied by a) profound changes in the major intracellular signaling pathways (a characteristic reprogramming of the intracellular signaling pathways), b) the cellular behavior is shifted to a pro, inflammatory phenotype (shift cellular behavior toward pro, inflammatory dominance). Figure 3, which shows the NF, B signaling (a pro, inflammatory transcription factor) is constantly elevated relative to Nrf2, associated antioxidant response (an anti, inflammatory transcription factor) for all conditions analyzed, visually illustrates the above statement. The difference in signaling between the two pathways is highly significant from the mechanistic point of view: on the one hand, chronic NF, B signaling drives the prolonged expression of cytokines and other inflammatory molecules, on the other hand, lack of sufficiently activated antioxidant pathways prevents a return to normal redox homeostasis. The dysregulation of these two antagonistic pathways could explain the long, lasting nature of immune, mediated diseases since the pro, inflammatory transcriptional activity persists even though the antioxidant response is not fully induced. In addition, this discordance may increase the vulnerability of the tissue to damage (tissue susceptibility), by stimulating the production of inflammatory mediators on one side and weakening the capacity to scavenge/reactive to intermediates on the other side. Overall, the synthesis of biomarker changes with signaling directionality provides strong evidence for a reciprocal feedback problem where inflammation first increases the production of reactive species, reactive species in turn keep inflammatory signaling going, and finally, antioxidant depletion acts as a barrier to inflammation resolution. When seen in this light, oxidative stress is not only a sign of disease activity but also plays a key role in immune dysregulation and tissue remodeling. The authors lay out important translational consequences of these findings: therapies that only focus on neutralizing reactive species will probably be inadequate if they do not also lead to the restoration of the native antioxidant system and rebalancing of redox, sensitive signaling pathways. Therefore, interventions that both boost the antioxidant capacity and selectively modulate inflammatory signaling pathways may have the greatest possibilities for breaking the redoximmune positive feedback loops and hence, leading to better disease control in immune-mediated phenotypes.

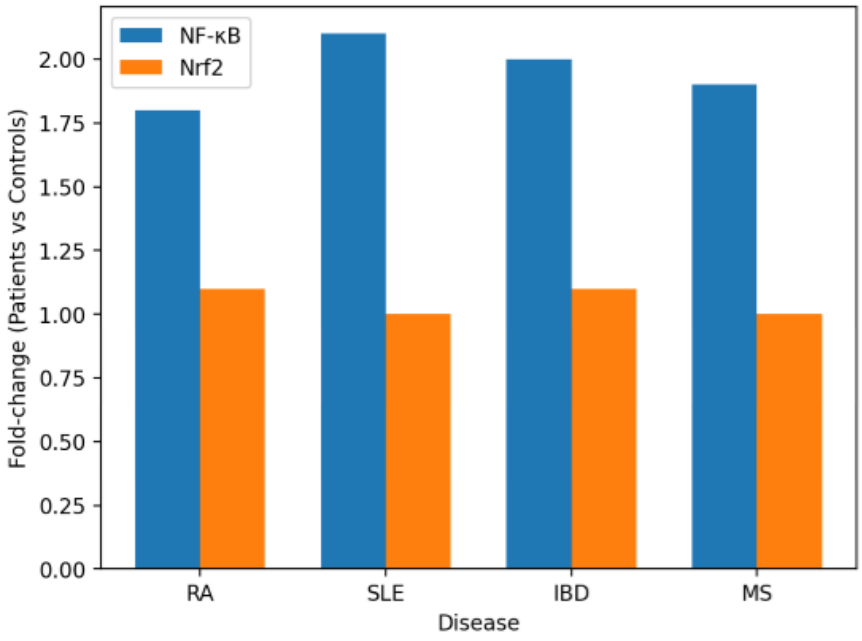

Figure 3. Pro-inflammatory vs Antioxidant Signaling Directionality (NF-ϰB vs Nrf2).

5. CONCLUSION

This review outlines a convergent redoximmune axis that underlies immune, mediated diseases, where overproduction of reactive oxygen and nitrogen species is linked to the depletion or inadequacy of endogenous antioxidant defenses. In different immune, mediated diseases, the data show a clear pattern of a significant increase in oxidative and nitrosative damage markers along with a decrease in antioxidant capacity, thus the idea that redox imbalance is just a secondary effect of inflammation is challenged and it is suggested that redox imbalance actively contributes to the disease refractory nature. The overall results from the integrated study reveal that lipid peroxidation mediators and oxidative protein modifications not only result directly in tissue damage but also lead to the inflammations that worsen the condition. On a cellular, signal level, a constant tilt of balance towards the dominance of pro, inflammatory pathways particularly the prolonged activity of NF, B, together with an insufficient antioxidant, response program, as shown by the limited Nrf2 compensation, explains, at least partly, chronical immune system overactivation and a hindered resolution process. Altogether, these findings imply that to be really effective, the therapeutic strategies should go beyond the mere use of non, specific antioxidant supplements and be more in line with precision medicine that, on one hand, restores redox homeostasis and, on the other hand, controls the redox, sensitive inflammatory signaling networks. The next studies should mainly emphasize using standard biomarker panels, quantifying robustly at the pathway level, and phenotype, specific stratification in order to increase the validity of the model and to discover the targets that are accessible for the redox, informed interventions in the immune, mediated pathology.

REFERENCES

[1] Ma Q. Role of Nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol. 2013;53:401–426.

[2] Andarwulan N, Cahyarani Puspita N, Saraswati, Średnicka-Tober D. Antioxidants Such as Flavonoids and Carotenoids in the Diet of Bogor, Indonesia Residents. *Antioxid (Basel).* 2021;10:587.

[3] Andrés CMC, Pérez de la Lastra JM, Andrés Juan C, Plou FJ, Pérez-Lebeña E. Superoxide anion chemistry-its role at the core of the innate immunity. *Int J Mol Sci.* 2023;24:1841.

[4] Andrés CMC, Pérez de la Lastra JM, Juan CA, Plou FJ, Pérez-Lebeña E. The role of reactive species on innate immunity. *Vaccines (Basel).* 2022;10:1735.

[5] Barrera G, Pizzimenti S, Daga M, Dianzani C, Arcaro A, Cetrangolo GP, et al. Lipid peroxidation-derived aldehydes, 4-hydroxynonenal and malondialdehyde in aging-related disorders. *Antioxid (Basel).* 2018;7:102.

[6] Chaudhary P, Janmeda P, Docea AO, Yeskaliyeva B, Abdull Razis AF, Modu B, et al. Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases. *Front Chem.* 2023;11:1158198.

[7] Collin F. Chemical basis of reactive oxygen species reactivity and involvement in neurodegenerative diseases. *Int J Mol Sci.* 2019;20:2407.
[8] Demirci-Çekiç S, Özkan G, Avan AN, Uzunboy S, Çapanoğlu E, Apak R. Biomarkers of oxidative stress and antioxidant defense. *J Pharm Biomed Anal.* 2022;209:114477.
[9] Desforges J-P, Sonne C, Dietz R, Levin M. Chapter 12 - Immunotoxic effects of environmental pollutants in marine mammals. In: Fossi MC, Panti C, editors. *Marine Mammal Ecotoxicology.* Academic Press; 2018. p. 321-43.
[10] Domínguez R, Pateiro M, Munekata PES, Zhang W, Garcia-Oliveira P, Carpena M, et al. Protein oxidation in muscle foods: a comprehensive review. *Antioxid (Basel).* 2021;11:60.
[11] Gorini F, Tonacci A. Vitamin C in the management of thyroid cancer: a highway to new treatment? *Antioxid [Internet].* 2024;13:1242.
[12] Higashi Y. Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. *Antioxid (Basel).* 2022;11:1958.
[13] Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. *Int J Mol Sci.* 2021;22:4642.
[14] Li L, Liao Y, Fu S, Chen Z, Zhao T, Fang L, et al. Efficient hydroxyl radical generation of an activatable phthalocyanine photosensitizer: oligomer higher than monomer and nanoaggregate. *Chem Sci.* 2024;15:10980–8.
[15] Liu J, Li T, Zhong G, Pan Y, Gao M, Su S, et al. Exploring the therapeutic potential of natural compounds for Alzheimer's disease: Mechanisms of action and pharmacological properties. *Biomed Pharmacother.* 2023;166:115406.
[16] Mandal M, Sarkar M, Khan A, Biswas M, Masi A, Rakwal R, et al. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) in plants– maintenance of structural individuality and functional blend. *Adv Redox Res.* 2022;5:100039.
[17] Martemucci G, Costagliola C, Mariano M, D'andrea L, Napolitano P, D'Alessandro AG. Free radical properties, source and targets, antioxidant consumption and health. *Oxygen [Internet].* 2022;2:48–78.
[18] Pérez-Torres I, Manzano-Pech L, Rubio-Ruíz ME, Soto ME, Guarner-Lans V. Nitrosative stress and its association with cardiometabolic disorders. *Molecules.* 2020;25:2555.
[19] Rahaman MM, Hossain R, Herrera-Bravo J, Islam MT, Atolani O, Adeyemi OS, et al. Natural antioxidants from some fruits, seeds, foods, natural products, and associated health benefits: an update. *Food Sci Nutr.* 2023;11:1657–70.
[20] Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L, Panzarini E, et al. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. *Front Physiol.* 2020;11:694.
[21] Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. *Molecules.* 2019;24:1583.
[22] Tronci L, Serreli G, Piras C, Frau DV, Dettori T, Deiana M, et al. Vitamin C cytotoxicity and its effects in redox homeostasis and energetic metabolism in papillary thyroid carcinoma cell lines. *Antioxid [Internet].* 2021;10:809.
[23] Zhang S, Xiao X, Yi Y, Wang X, Zhu L, Shen Y, et al. Tumor initiation and early tumorigenesis: molecular mechanisms and interventional targets. *Signal Transduct Target Ther.* 2024;9:149.