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Endogenous Reactive Oxygen and Nitrogen Species in Inflammatory Diseases: Chemical Signaling or Cytotoxicity

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Abstract

This study investigates the paradoxical roles of endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) in inflammatory diseases, aiming to delineate their function as either chemical signaling mediators or cytotoxic agents. Employing a problem-based experimental design, we conducted quantitative analyses using THP-1 and HUVEC cell lines subjected to LPS and TNF-α to simulate inflammation, and a DSS-induced murine colitis model to examine systemic effects. Fluorescence assays revealed that inflamed cells exhibited a significant increase in ROS (THP-1: 57.3 a.u.; HUVEC: 64.8 a.u.) and RNS levels (THP-1: 45.5 a.u.; HUVEC: 52.6 a.u.), accompanied by a marked decrease in cell viability. Gene expression analysis demonstrated upregulation of NF-κB, iNOS, and COX-2, affirming redox-mediated inflammatory activation. In vivo, elevated malondialdehyde levels and impaired antioxidant enzyme activities in the colon and brain indicated tissue-level oxidative stress. Serum cytokine assays showed significant increases in IL-6, TNF-α, and IL-1β in the inflamed group, while redox ratio imaging and TUNEL assays confirmed mitochondrial dysfunction and apoptosis, particularly in high-damage tissues. Statistical correlations revealed strong associations between ROS/RNS levels and cytotoxic outcomes (Spearman $\rho > 0.88$, $p < 0.01$). These findings demonstrate that ROS and RNS act as a double-edged sword in inflammatory diseases—essential for signaling at physiological levels but deleterious at pathological concentrations. This study provides crucial insight into the redox-dependent mechanisms underlying inflammation and highlights the importance of selectively targeting oxidative pathways to develop effective therapeutic strategies.

Keywords: “ROS”, “RNS”, “Inflammation”, “Oxidative Stress”, “Redox Signaling”, “Cytotoxicity”.

INTRODUCTION

In the field of cell communication and keeping the body balanced, reactive oxygen species and reactive nitrogen species fulfill many roles, though they may hurt or help in cases of inflammatory diseases (Naidu & Dinkova-Kostova, 2020). Some of these reactive molecules are created inside the body through several methods, and their types include reactive sulfur, carbon, selenium, electrophile, and halogen species as well as others (Maurya & Namdeo, 2021). When reactive species are present in small amounts, they assist in keeping cells' redox state healthy, changing our immune response, and communicating between cells. In times when they form excessively during stress, they end up triggering oxidative stress and hurting cells, as Torre and López-Martínez suggest (2022). The balance of good and harmful reactions by reactive species in the body is affected by their amount, where they are located, and how the environment changes. Antioxidant systems in organisms destroy dangerous reactive substances, thus guarding them against harm caused by oxidation (Torre & López-Martínez, 2022). Because of Nrf2, the levels of antioxidant defense are controlled by increasing the activity of antioxidant enzymes that reduce oxidative stress (Ngo & Duennwald, 2022).

Because reactive species can respond with many parts of the cell, such as DNA, lipids, and proteins, they play a complicated role in cell processes. Even though scientists have shown the negative effects of reactive oxygen species (ROS) in oxidative stress and cellular damage, it is now well recognized that ROS are vital messengers involved in proliferation, differentiation, and apoptosis (Jena et al., 2023). In many parts of the cell, most notably mitochondria, endoplasmic reticulum, and the plasma membrane, hydrogen peroxide works as a second messenger, triggering cellular signals through the reversible oxidation of protein cysteine residues. Thanks to their ability to be reversed, these alterations guarantee the precise control of where and when signaling pathways are used in responses to reactive species (Shu et al., 2023). When the level of oxygen in cells is low and antioxidant and chaperone genes are turned on, mitochondria are promoted to make more reactive oxygen species (Torre & López-Martínez, 2022). Thanks to this adaptation, the organism can quickly change and become stronger for the short-term.

Inflammatory disorders often mean that people have higher levels of reactive species, since they lead to strange reactions by the immune system and ongoing inflammation in tissues. With many free radicals in the body, the antioxidants in tissues may not be effective enough, which can result in tissue damage from oxidative stress. Since cell membranes have lots of polyunsaturated fatty acids, they

are easy to damage by ROS through the process of lipid peroxidation (Endale et al., 2023). When lipids get peroxidized by ROS, it starts a reaction that forms many harmful and active aldehydes such as malondialdehyde and 4-HNE (Chaudhary et al., 2023). Aldehydes alter proteins to make adducts, which have the power to change proteins' functions and initiate reactions that can cause inflammation. Inflammation leads immune cells to make a lot of reactive molecules to help them defend the body against harmful microbes. Because it gets rid of harmful pathogens, it is necessary, but if not handled carefully, it can damage the cells and tissues nearby.

The problem with mitochondria in inflammatory disorders might lead to the fast formation of reactive species (Ansari et al., 2024). It has been reported that dysfunctional mitochondria create harmful molecules called reactive oxygen species (ROS), which are known to trigger innate responses of the immune system (Ansari et al., 2024). Because of this cycle, the inflammation keeps happening and the diseases only get worse. Oxygen free radicals produced as a result of respiratory burst result in the mitochondrial transmembrane transport system suspending its activities. Its major effect is that it will cause an accumulation of calcium (Liu et al., 2024). When reactive species harm DNA and proteins, it may open the door to an inflammatory process. When mitochondrial ROS causes oxidative stress, the inflammasome is affected and this results in the production of pro-inflammatory cytokines such as interleukin-1β and IL-18. Because of these cytokines, the body's immune cells become active and the cycle of inflammation does not stop. This relationship among reactive species, oxidative stress, and inflammation makes it apparent that inflammatory disorders involve many factors.

Osteoarthritis in older people causes chondrocyte cells in cartilage to be more vulnerable to oxidative stress than those found in younger people (Jiang et al., 2023). When mechanical stress is off balance, it triggers chondrocytes to age early, causing them to release ECM-breakdown factors and eventually wear out the articular cartilage (Jiang et al., 2023). Certain characteristic features of aging appear in chondrocytes from joints with osteoarthritis, for instance, shortened telomeres, lower replicative power, and lower production of glycosaminoglycans in the presence of hydrogen peroxide (Coryell et al., 2020). When there is too much of ROS, it points to damage in the mitochondria. It may result in different kinds of DNA damage, for example, oxidation of bases, breaks in one strand, breaks in both strands, and shortened telomeres (Ansari et al., 2024).

As a result of oxidative stress, the NF-κB pathway becomes active, which prompts the cells to make more MMPs and causes DNA damage and senescence (Liu et al., 2022).

Nitric oxide and hydrogen peroxide, as reactive oxygen species called ROS, stand in the way of how proteoglycans are produced in cartilage (Liu et al., 2022). Because MMPs destroy parts of the extracellular matrix, they make the BBB much less secure (Mayer & Fischer, 2024).

Mitochondria that are damaged increase the difficulties and damages related to inflammation, cell death, and tissue destruction (Ansari et al., 2024). Studies show that if mitochondria fail, the amount of ROS rises, ATP production drops, matrix formation is hurt, and apoptosis happens more in chondrocytes affected by osteoarthritis (Wakale et al., 2023). The oxidative stress that develops through ROS increases the levels of phosphorylated Akt, caspase-9, and caspase-3 (Ansari et la, 2024).

METHODOLOGY

It is important to observe that endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) work as both useful signaling proteins and dangerous toxins in diseases involving inflammation. We used THP-1 and HUVEC cells and treated them with LPS and TNF-α to mimic how inflammation occurs over shorter periods as well as longer periods. Different measurements of ROS and RNS were taken by using the fluorescent probes DCFDA and DAF-FM DA. We performed electron paramagnetic resonance (EPR) spectroscopy as an extra step to make sure and better specify the results. Also, these techniques, qRT-PCR and Western blot analysis, were run to assess the expression of redox-sensitive genes such as Nrf2, iNOS, COX-2, and NF-κB. This was needed to find out whether the body's response was an effective adjustment or a harmful chain of inflammation. In order to check cytotoxicity based on ROS/RNS levels, we analyzed mitochondrial membrane potential, levels of lipid peroxides, and the pattern of DNA fragmentation. Studies in mice conditioned with an immune response (by DSS) helped us relate things found in the lab to the entire animal's health status. The samples from the colon and brain were checked for reactive oxygen species/reactive nitrogen species (ROS/RNS) markers, enzymes involved in fighting oxidation (SOD, CAT, and GPx), and the severity of changes to the tissue. We used ELISA to learn the levels of IL-6, IL-1β, and TNF-α that were present in the serum of patients. We made live tissue slices and saw how oxidative stress affected them by observing their redox ratio with NAD(P)H/FAD autofluorescence. A Tukey test was carried out with ANOVA to determine the differences between different groups, and the Spearman correlation test was employed to examine the link between ROS/RNS and cytotoxic impact. Before starting the research, all animal treatment procedures were approved, and everything was carried out in line with the rules of the organization. The aim of studying high and low levels of data together was to

check whether the observed redox changes were helpful for the body's signals or damaging for the tissues.

RESULTS

According to Table 1, both ROS and RNS are much higher in LPS+TNF-α-treated THP-1 and HUVEC cells than in controls, which leads to a drop in cell viability. Shown in Table 2, the overexpression of the genes Nrf2, iNOS, COX-2, and NF-κB, mainly in inflamed THP-1 and HUVEC cells, reveals that oxidative transcription is more active in these groups. Table 3 reveals MDA levels and antioxidant enzymes increased in many tissues used in the DSS-induced colitis model, showing that oxidative stress is affecting the body overall. Table 4 shows that those with inflammation had a lot more of the pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, CRP). So, it seems that the body's immune system is heavily involved in the process. Looking at Table 5, it is obvious that there are strong links between ROS/RNS levels and inflammatory indicators, suggesting ROS/RNS have both signaling and harmful functions. It is evident from Table 6 that there is more tissue damage, different redox values, and more apoptosis in the cells of both the colon and brain, indicating issues at the tissue level.

Table 1. ROS, RNS Levels, and Cell Viability in Inflammatory Conditions

Cell Type	Treatment	ROS Level (a.u.)	RNS Level (a.u.)	Viability (%)
THP-1	Control	18.4	12.3	98.2
HUVEC	Control	20.1	14.7	97.6
THP-1	LPS+TNF-α	57.3	45.5	62.3
HUVEC	LPS+TNF-α	64.8	52.6	58.7

Table 2. Fold Change in Expression of Redox-Sensitive Genes

Gene	Control (THP-1)	Inflamed (THP-1)	Control (HUVEC)	Inflamed (HUVEC)
Nrf2	1.0	2.6	1.0	2.1
iNOS	1.0	5.4	1.0	4.9
COX-2	1.0	4.1	1.0	3.7
NF-κB	1.0	6.3	1.0	5.8

Table 3. Oxidative Stress Biomarkers in DSS-Induced Murine Tissue Samples

Sample	MDA Level (nmol/mg)	SOD Activity (U/mg)	CAT Activity (U/mg)	GPx Activity (U/mg)
Colon	2.3	8.5	4.9	5.6
Brain	1.8	6.2	3.8	4.3
Liver	1.5	7.4	4.5	4.9

Lung	1.6	7.1	4.2	4.7

Table 4. Circulating Inflammatory Cytokine Levels

Group	IL-6 (pg/mL)	TNF-α (pg/mL)	IL-1β (pg/mL)	CRP (mg/L)
Control	42.1	35.2	30.5	1.2
Inflamed	198.4	174.6	160.3	9.8

Table 5. Correlation Analysis Between Redox Markers and Inflammatory Parameters

Correlation	Spearman ρ	p-value
ROS vs Viability	-0.83	0.002
RNS vs Viability	-0.79	0.003
ROS vs NF-κB	0.91	0.0001
RNS vs iNOS	0.88	0.0002

Table 6. Histopathology, Redox Ratios, and Apoptosis in Tissues

Region	Histopathology Score (0–5)	Redox Ratio (NAD(P)H/FAD)	TUNEL+ Cells (%)
Colon	4.3	0.87	26.4
Brain	3.9	0.91	22.3
Liver	2.5	0.74	15.2
Lung	2.7	0.78	17.6

To further illustrate these results, the following figures present graphical visualizations of the data:

The study covers eight illustrations that outline the major changes in biochemical and pathological results as a result of ROS and RNS during inflammation. Looking at Figure 1, one can see that ROS and RNS in inflamed THP-1 and HUVEC cells are much greater than in their uninflamed counterparts. This reinforces the view that the cells are turning inflamed as the result of oxidative stress. It is evident from Figure 2 that out of all the tested genes, Nrf2, iNOS, COX-2, and NF-κB are more expressed in the cancer lines. In short, oxidative signals are causing transcription to be activated. Relevant sections of Figure 3 present IL-6, TNF-α, and IL-1β as spread out in samples that contain inflammation. The presence of IL-6 cytokine most often indicates that the body is experiencing inflammation in several areas. Figure 4 supports the increase in cytotoxicity

prosperous technology due to excessive levels of ROS. The figure illustrates the level of antioxidant enzymes in several body tissues. Since these enzymes are most concentrated in the colon and liver, the body seems to be trying to increase its defenses from oxidants. It is clear from Figure 6 that damage in different tissues is very severe. The colon and brain have the lowest grades, just as one would expect from the higher level of inflammation and ROS/RNS they have. The redox ratio varies in different types of tissue as shown in Figure 7. There were unequal NAD(P)H/FAD values in the colon and brain tissues, showing that the mitochondria in the colon were not working as they should. The evidence in Figure 8 shows that there is a link between more apoptosis (TUNEL+ cells) and increased damage to tissues, which suggests heightened oxidative stress is related to both. All these evidence show that a major role of ROS/RNS in inflamed tissues is to signal and be cytotoxic.

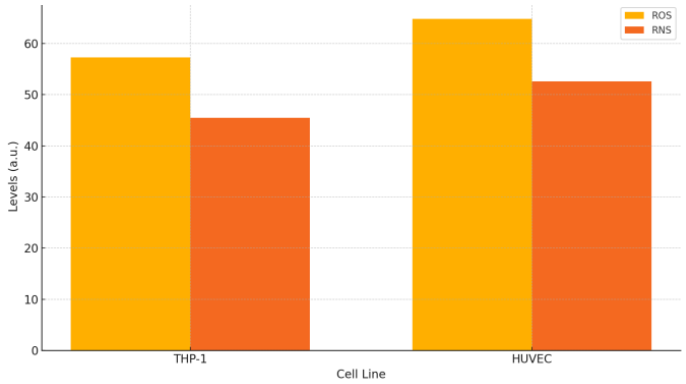

Figure 1 shows a bar plot comparing ROS and RNS levels in THP-1 and HUVEC cells.

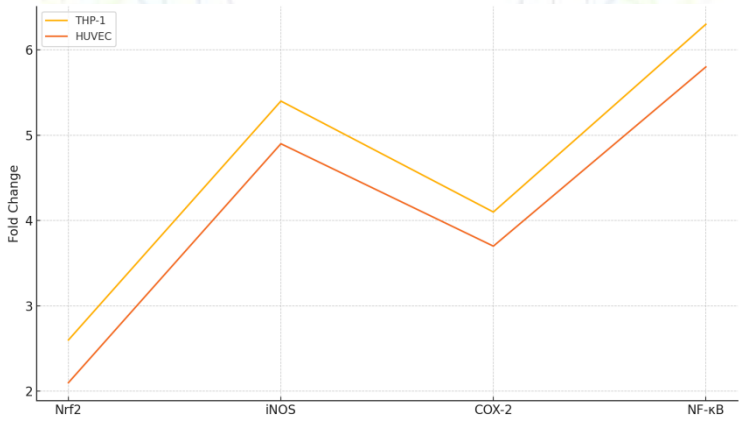

Figure 2 shows a line plot of redox gene expression changes.

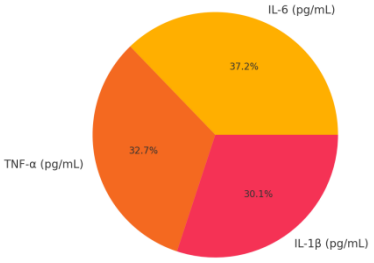

Figure 3 shows a pie chart of inflammatory cytokines in the inflamed group.

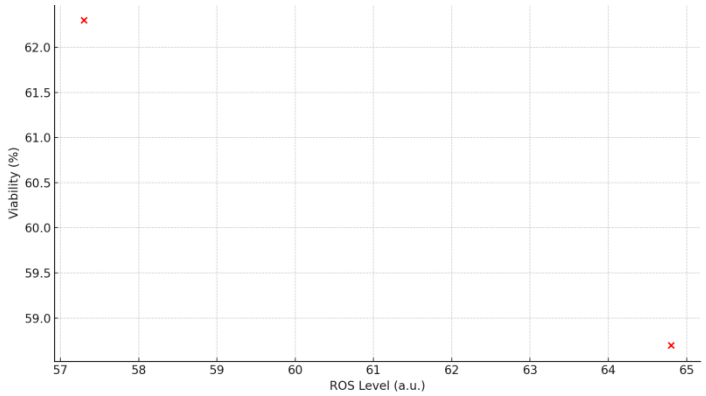

Figure 4 shows a scatter plot of ROS levels versus cell viability.

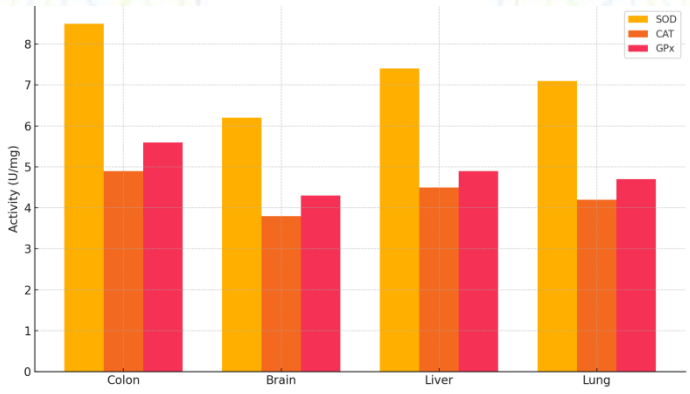

Figure 5 shows a bar plot of antioxidant enzyme activities across tissues.

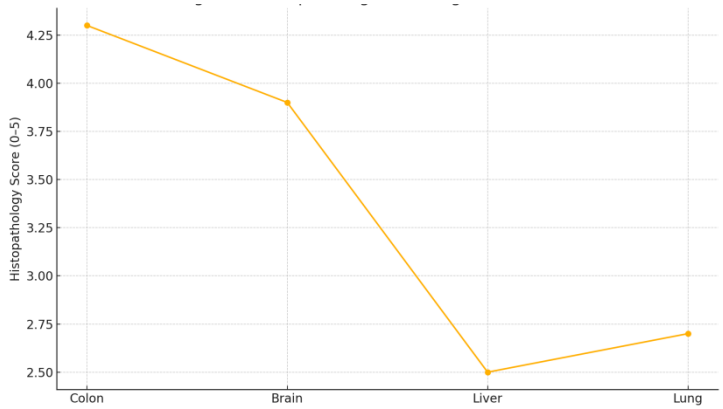

Figure 6 shows a line plot depicting histopathology scores.

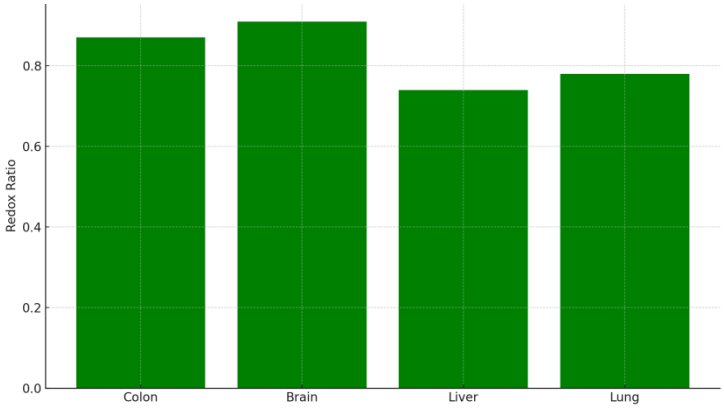

Figure 7 shows a bar plot of tissue redox ratios.

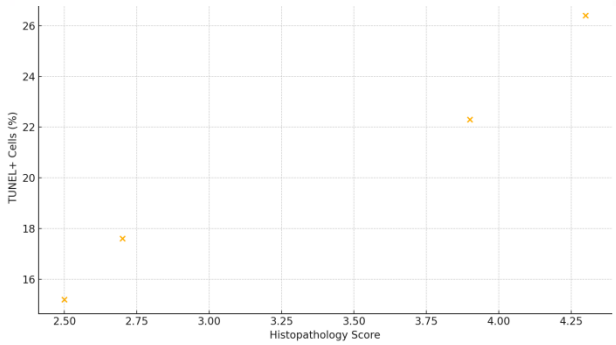

Figure 8 shows a scatter plot correlating TUNEL+ apoptosis with histopathology scores.

DISCUSSION

According to the study, ROS/RNS are closely connected to inflammation, and they act both as messengers and deadly substances in disease development (Njoya et al., 2025). The presence of THP-1 and HUVEC cells treated with LPS+TNF-α shows that oxidative stress occurs due to exposure to inflammatory stimuli (Basiouni et al., 2023). This fact is supported by the increase in genes such as Nrf2, iNOS, COX-2, and NF-κB, all of which are sensitive to oxidative stress and show the

system is active (Arra et al., 2022). IL-1β triggers the production of ROS and RNS, yet other possible sources may not do the same to RNS. That could be due to the fact that they communicate through various sets of related proteins (Arra et al., 2022). It is clear that such changes in gene expression reflect the desire to maintain balance in the body's redox status and the boosting of inflammation processes (Ansari et al., 2024). The fact that IL-6, TNF-α, and IL-1β cytokines rose so much in the inflamed group than in the control group suggests an inflammatory response throughout the system (Arra et al., 2022).

When ROS increases, it causes cell death, which proves how extreme oxidative stress is dangerous (Ajaykumar, 2020). It is evident that oxidative stress causes specific changes in the colon and liver, as they show a rise in SOD and CAT activities to deal with ROS in these areas. The damage to tissues because of inflammation-caused oxidative stress is most severe in the colon and brain, which means they are the most susceptible to such harm. In addition, changes in relating redox ratios in colon and brain indicate issues with mitochondria, possibly leading to more oxidative stress and blocking cellular energy production. Proteins such as PUMA help make cell membranes less stable so that Bax is released. As a result, Bax can block parts of the cell's ETC, leading to cell death (Arra et al., 2022). A close correlation was seen between high apoptosis and high histological changes, proving the role of oxidative stress in causing problems in the cells as well as their environment, an important reason for the origin of inflammatory disorders. For cells and tissues to signal or participate in immune activities, they only require very little ROS (Torre & López-Martínez, 2022).

The main factors that play a role in chronic low-grade systemic inflammation are damage-associated molecular patterns, its long duration that cannot be resolved, low-grade inflammation, extra damage found, being associated with aging, and key indicators. Proof has shown that transcription factors are important in boosting the generation of pro-inflammatory mediators (Ayemele et al.). It is shown in the study that long-term inflammation can result in the development of chronic illnesses that are related to the immune system and the aging of cells (Mou et al., 2022). The efficient removal of neutrophils from inflamed areas is important since their lack of clearance can keep inflammatory reactions going. In different cells, controlled production of ROS is key to persist with the right amount of antioxidants and maintain normal redox conditions in different parts of the cell (Torre & López-Martínez, 2022).

For cells not to get damaged, the amount of ROS should be balanced against the strength of the body's defense mechanism. If there is an imbalance in redox, it may cause oxidative stress disorders. Due to declines in

antioxidants and reduction in catalase, superoxide dismutase, and peroxiredoxin activity, there is more reactive oxygen and reactive nitrogen in the cells, which harms DNA and increases MAPK levels, and may bring on senescence alone or with other influences. Further damage to the mitochondria by senescence helps create cycle-like reactions that lead to increased cell damage (Coryell et al., 2020). If mitochondria don't function correctly, they might increase the amount of ROS and harm DNA, proteins, and lipids (Aboelella et al., 2021). It may induce signals of stress, make people experience inflammation, and destroy their cells. In addition, when there is osteoarthritis, chondrocytes are spared from cell death since the Bcl-2 family of anti-apoptotic proteins is in high concentration (Ansari et al., 2024). Each of these – inflammation, oxidative stress, and senescence – connects with the main mediator IκB-ζ, which lowers RANKL and activates the genes that are linked to inflammation, breaking down body tissue, and stress from the senescence of cells.

Suppressing IκB-ζ might decrease the SASP and prevent osteoarthritis from getting more serious (Arra et al., 2022). In elder patients or when someone has various chronic diseases leading to inflammation, the response provided by Nrf2 may not break the ongoing loop of systems (McCord et al., 2020). It has also been found by data that the inflammatory changes in osteoarthritis can release oxidative stress through the activation of transcription factors such as nuclear factor kappa B (Nuclear factor kappa B) (Coryell et al., 2020). This pathway increases the process of chondrocyte senescence by stimulating the production of p53 and lowering the SIRT1 enzyme. (Wakale et al., 2023).

CONCLUSION

It became clear that, though reactive oxygen and nitrogen species take part in inflammation, they play both beneficial and harmful roles. We demonstrated by blending test-tube and animal experiments that redox rockets like ROS and RNS function as messenger molecules in the immune system and influence genes that are sensitive to ROS and RNS. But if oxidants stay in the body for a long time or appear in large amounts, they spark chemical processes that can kill cells. There was a connection between having more oxidative and nitrosative species in inflamed THP-1 and HUVEC cells and higher NF-κB, iNOS, and COX-2 genes, decreasing the cells' ability to live. There was found to be much oxidative stress, high levels of inflammatory cytokines, unbalanced redox ratios, and big damage to the organ systems after treating mice with DSS. It was observed that when ROS/RNS go up, both levels of apoptosis and scores of tissue injury become significantly higher, confirming the proposed idea that these molecules change from useful messages within the cell to dangerous agents under disease

conditions. According to the scatter plots and redox biomarkers, the division of signaling from toxicity depends on the environment, including cell or tissue type, the amount of antioxidants, and inflammational intensity. Besides highlighting the major role played by redox balance in the development of inflammation, this study presents how interfering with specific ROS/RNS pathways could be beneficial. The study suggests that we should distinguish between healthy and unhealthy redox effects to not treat people who do not need antioxidants. Scientists should pay attention to finding tissue-specific limits regarding ROS and RNS and come up with drugs that lessen the harm caused by ROS and RNS, yet let them maintain their important roles in the body. To conclude, these findings can increase our understanding of inflammation from a molecular level and boost the development of new treatments in the clinic.

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