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Review

Inflammatory and Oxidative Pathways Driving Multisystem Disease Progression

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Abstract:
Modern epidemic of non-communicable chronic diseases requires changes in paradigm of the classical pattern of single-organ pathology to the model of systemic network dysfunction. The key to this change lies in the fact that chronic inflammation and oxidative stress are not secondary events but the primary and linked cause of systemic disease. They create a vicious cycle where inflammatory signaling triggers enzymes such as NADPH oxidase and mitochondrial disruption which releases reactive oxygen species (ROS); which in turn activate major inflammatory pathways such as NF-kB and NLRP3 inflammasome and oxidative damage produces molecules that sustain immune activation. It is a molecular nexus that is a universal pathological mechanism, which destroys the functioning of organ systems. It pushes endothelial dysfunction in atherosclerosis, stimulates insulin resistance in diabetes, promotes neuroinflammation in neurodegenerative diseases, and propagates dysfunction across, such as the gut-liver-brain axis. The systemic production of inflammatory cytokines and oxidized metabolites perpetuates the cycle and the processes like cellular senescence institutionalize it. Thus, chronic diseases can be interpreted as symptoms of some common underlying condition- the existence of dysregulated circuitry in the system. This redefinition requires an abandonment of an organ-focused approach to the treatment of inflammatory-oxidative loop as the root cause of disease and instead governs treatment with the goal of restoring homeostasis to the entire body circuitry.

Keywords: Chronic inflammation, Oxidative stress, Systemic network dysfunction, Reactive oxygen species (ROS), Vicious cycle

1. Introduction

The model of single-organ pathologies has been the fundamental principle of medical diagnosis and treatment over centuries. This system which has been so successful in attacking acute diseases is a conceptualization of the body as a system of relatively independent systems each of which has its own diseases cardiologists of the heart, neurologists of the brain, gastroenterologists of the gut. A disease is discovered because it is possible to find its main focal point of dysfunction and treat it. But ongoing, global epidemic of chronic, non-communicable diseases, including metabolic syndrome and atherosclerosis, neurodegenerative conditions and autoimmune diseases, has revealed the dire inadequacy of this silo perspective [1]. The conditions are intractable to be limited to a single organ; they have a complicated comorbidity, with a patient with type 2 diabetes having a high risk of cardiovascular disease, kidney failure, and depression. This epidemiological fact has required a new paradigm shift, which is a shift towards a reductionist vision of the body, to a holistic perception of the body as a dynamic network of systemic circuitry. This novel model assumes that chronic illnesses are not single failures but arise as a result of failed communication and feedback processes within and between organ systems, which are driven by shared underlying biological abnormalities. Two molecular processes that cannot be separated from each other are at the core of this network of interconnected circuitry; chronic inflammation and oxidative stress. They collectively constitute the core nexus, the drivers of dysfunction on a systemic level, the propagators of the development of various chronic pathologies. Chronic inflammation is a low grade, smoldering, and systemic condition unlike acute inflammation which is a life saving and self-limiting immune response to injury or infection. It is marked by the chronic stimulation of immune cells (such as macrophages) and the chronic and frequent, but minor, release of pro-inflammatory signaling molecules (cytokines such as TNF-a, IL-1b, and IL-6). This leads to an unfriendly physiological condition leading to abnormal cell functioning. Its regular molecular companion is oxidative stress which is the result of an imbalance between the generation of the reactive oxygen species (ROS) and the antioxidant defenses of the body. ROS occurs as a result of normal metabolism and are increased by inflammatory cues, are extremely aggressive molecules that destroy the essential cellular components- lipids in cell membrane, proteins and DNA [2].

This vicious self-amplifying cycle of synergy between these two forces is what is corrupting systemic circuitry. The triggering of enzymes that result in increased ROS by the inflammatory cytokines and the resulting oxidative stress triggering the activation of important inflammatory pathways (NF-kB system) are interrelated. The inflammatory-oxidative loop is a universal solvent that destroys the integrity of several systems. In the vascular system, it causes injury to the endothelial lining, facilitates the oxidation of LDL cholesterol (one of the major processes in the formation of the plaque), and atherosclerosis, which is directly connected to heart attacks and strokes. This nexus produces muscle, liver, and fat cell insulin resistance, as well as defective insulin secretion by pancreatic beta-cells which comprise the basis of type 2 diabetes dysfunction. It is amazing to note that the same circuitry also goes as far as the brain, where peripheral signals of inflammatory responses can pass through a weaker blood-brain barrier, stimulating the microglia (the brain immune cells) and leading to neuroinflammation and oxidative damage at the core of Alzheimer and Parkinson disease pathology. This loop also has been implicated in the non-alcoholic fatty liver disease and sarcopenia of the gut-liver-axis and the musculoskeletal system, respectively. Thus, chronic inflammation and oxidative stress are not passive observers or symptoms but the key players of a discordant system orchestra. The identification of this nexus compels a redefinition of the meaning of disease as such--as a local phenomenon to a systemic condition of dysregulated signaling. It requires treatment plans that go beyond the use of specific organ-related symptom management to address these cause agents, to break their own cycle and stabilize the whole physiological system [3-5].

2. Foundational Mechanisms of Inflammation and Oxidative Stress

The molecular pathways of inflammation and oxidative stress provide the specific, and dangerous, molecular machinery on which systemic dysregulation of chronic disease is based. To comprehend this, it is important to take a break and investigate the basic structure of immune response and biochemistry of redox balance. The process of inflammatory initiation is carefully regulated and is initiated by the innate immune sensing. Pattern recognition receptors (PRRs), a heterogeneous group of proteins (Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) and various other types are employed by the frontline defenders of the body, macrophages, dendritic cells, etc. These serve as molecular sentinels and constantly scan the cellular environment. Their activation occurs when they bind two major classes of molecules; the pathogen-associated molecular patterns (PAMPs) such as bacterial lipopolysaccharide (LPS) or viral RNA and damage-associated molecular patterns

(DAMPs). DAMPs are the endogenous molecules that are emitted by stressed, traumatized, or necrotic cells, including ATP, uric acid crystals and HMGB1. The pathophysiological revelation about chronic disease is that metabolic dysfunction, cellular senescence, and low-grade tissue harm due to elements such as hypertension or hyperglycemia incessantly discharge DAMPs. This results in a condition of sterile chronic alarm, when the immune system is continuously activated by the self-damaged elements of the body and makes it perceive the internal suffering as an external invasion [6].

The interaction of PRRs with PAMPs or DAMPs causes a rapid intracellular cascade of signaling, which converts to a limited number of center pathways that serve as the grand controllers of the inflammatory gene program. The NF-kB (Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells) is the most important of these pathways. NF-kB is in the cytoplasm in its resting state and is inhibited by the inhibitory proteins (IkBs). PRR stimulation triggers a cascade of phospholipid-dependent kinases that ultimately results in the degradation and phosphorylation of IkB, releasing NF-kB to move to the nucleus. There, it interacts with DNA and induces transcription of a tremendous amount of pro-inflammatory genes, such as cytokines (TNF-a, IL-1b, IL-6), chemokines, adhesion molecules, or enzymes, such as cyclooxygenase-2 (COX-2). Simultaneously with NF-kB, the MAPK (Mitogen-Activated Protein Kinase) (such as ERK, JNK and p38) are signaled which then regulate other transcription factors such as AP-1 that regulate genes related to cellular proliferation, stress reactions, and additional cytokine synthesis. In the case of cytokines that bind to cell surface receptors, including the interferons and most interleukins, the JAK- STAT (Janus Kinase-Signal Transducer and Activator of Transcription) pathway is the major signaling pathway. Attaching to cytokines leads to the dimerization and activation of the accompanying JAKs which phosphorylate the STAT proteins. Stat phosphorylation leads to dimerisation followed by migration to the nucleus and induction of transcription of designated sets of genes capable of enhancing and targeting the immune response. These cascades do not exist in isolation; they interact intensively in a crosstalk forming a robust and redundant network, which is aimed to have a powerful, coordinated defense [7].

Production and release of a symphony of pro-inflammatory mediators is the major transcriptional product of such signaling pathways, which in aggregate perform and enhance the inflammatory response. This consists of cytokines (TNF-a, IL-1b, IL-6), chemokines (such as IL-8) that attract leukocytes, lipid mediators (prostaglandins, leukotrienes) and vasoactive agents. This is a highly self-regulated and restricted process in acute settings. Nevertheless, when encountered in the setting of chronic DAMP signaling or resolution mechanism breakdown, these mediators form positive feedback loops that maintain and amplify the inflammatory response. As an example, TNF-a and IL-1b may also stimulate NF-kB in the producing cell (autocrine) and adjacent cells (paracrine) that results in a cascade of production. It may lead to a life-threatening, systemic hyper-inflammatory condition referred to as a cytotoxic storm- a severe sepsis, or COVID-19. The storm in chronic disease is more of the drizzle of cytotokines, but its effects are just as dissolving in the long term. This pro-inflammatory environment is sustained and this damages the tissues directly, changes the cellular metabolism, and, most importantly, becomes a key driver of reactive oxygen species (ROS) production, creating the key connection to oxidative stress [8-10].

The shift of inflammatory signaling to oxidative stress is mechanically profound and direct. The inflammatory apparatus in itself promotes the production of reactive species. One of the main sources is the phagocytic cell membrane NADPH oxidase (NOX) enzyme. During activation of immune cells such as neutrophils and macrophages by cytokines or PAMPs/DAMPs, they experience a respiratory burst to assemble the NOX complexes to produce superoxide anion (O2.-), a primary ROS, in large quantities to kill pathogens. This system is not suitable and continued to be activated inappropriately in tissues in chronic inflammation. Moreover, pro-inflammatory cytokine TNF-a has the ability to induce mitochondrial dysfunction which in turn causes the electron transport chain, in mitochondria to leak electrons, which upon interaction with oxygen produce superoxide. This converts the mitochondria to major sources of ROS. Moreover, many of the metabolic enzymes such as xanthine oxidase and cytochrome P450 complexes have the ability to be secondary ROS generators during inflammatory conditions. In this way, the inflammatory molecular architecture is connected to the direct initiation of oxidative stress [11]

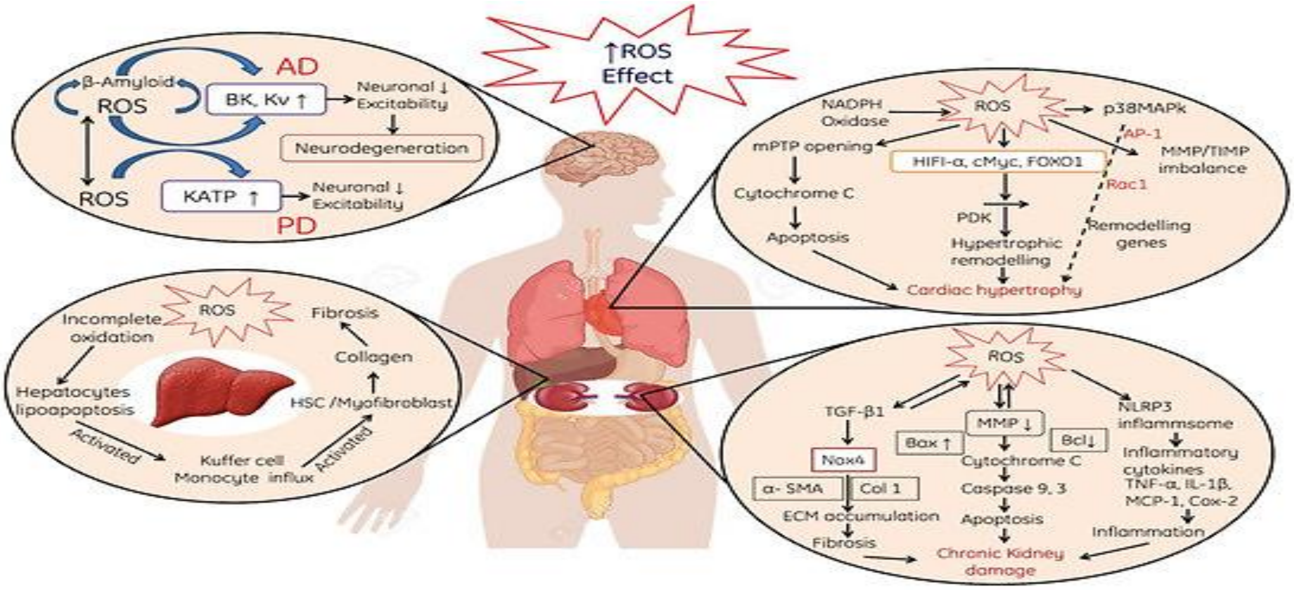

Fig: 1 Effect of reactive oxygen species (ROS). ROS generation induces Alzheimer's disease by accumulation of β-Amyloid proteins, activation of BK and Kv and finally decreases excitability property of neurons and neuro-degeneration of the heart, liver and kidneys, where KATP; ATP-sensitive potassium, NADPH oxidase: Nicotinamide dinucleotide Phosphate reduced, p38MAPK; p38 mitogen-activated protein kinases, MMP; Matrix metalloproteinases/tissue inhibitor of metalloproteinases, HIFA-α; Hypoxia-inducible factor 1-alpha, FOXO1; Forkhead box transcription factors, mPTP: mitochondrial permeability transition pore, PDK: Protein 3-phosphoinositide-dependent protein kinase, NLRP: Nucleotide-binding oligomerization domain, MCP: Monocyte Chemoattractant Protein, TNF-α: Tumor necrosis factor alpha, IL-1β: Interleukin-1 beta. Note: Upward arrows indicate increase and downward arrows indicate decrease.

The effects of such ROS flood are devastating on the biomolecular scale, i.e. oxidative damage to the cell fabric itself. Reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are produced by lipid peroxidation which is oxidative degradation of polyunsaturated fatty acids in cell membranes. These products do not only indicate the presence of damage but are themselves toxic and spread oxidative injury and form adducts with proteins and DNA. The damage of proteins is done by means of carbonylation (irreversible addition of carbonyl groups on amino acid side chains) and nitration (irreversible addition of nitro groups by reactive nitrogen species such as peroxynitrite formed by the reaction of superoxide and nitric oxide). This changes protein structure, impairs enzymatic activity, and distorts essential cellular functions. Worst of all, ROS attack DNA, which results in the strand breakage and the bases alteration (e.g., by the formation of 8-hydroxy-2'-deoxyguanosine, or 8-OHdG). Although DNA repair systems are there, chronic oxidative attack overwhelms them, causing genomic instability, mutations and activation of stress-sensing pathways capable of inducing cellular senescence or apoptosis. This is the cumulative molecular damage, the mechanistic connection between the inflammatory-oxidative nexus and cellular aging, dysfunction and disease-inducing processes such as cancer. To resist this incessant menace, life has developed a complex, multi-layered antioxidant defense mechanism. This system consists of both enzymatic and non-enzymatic components which scavenge ROS, repair damage and keep the cellular redox state. These major enzyme defense mechanisms include superoxide dismutase (SOD), which catalyzes the breakdown of superoxide into hydrogen peroxide (H2O2); catalase, which breaks down H2O2 to water and oxygen; and glutathione (GSH) system. The master redox buffer of cell is a tripeptide thiol, glutathione. Glutathione peroxidase enzyme involves the reduction of H2O2 and lipid peroxides by GSH into water and alcohols and the oxidation of GSH to its dimeric form, GSSG. The GSSG is then recycled by Glutathione reductase to GSH in presence of NADPH. This whole array of antioxidants is orchestrated centrally by the transcription factor Nrf2 (Nuclear factor erythroid 2-related factor 2). Oxidative stress causes Nrf2 to dissociate with its cytoplasmic inhibitor Keap1, relocate to the nucleus and bind to the Antioxidant Response Element (ARE), which leads to expression of more than 200 genes. They are SOD, catalase, glutathione S-transferases, and NADPH-quinone oxidoreductase 1 (NQO1), which amplify the ability of a cell to undertake the detoxification and resilience of a cell [12-14].

This balance however fails in chronic disease. There is the inflammatory-oxidative loop which forms a redox imbalance. The activation of NRF2 may be directly inhibited by pro-inflammatory signaling, especially through the NF-kB, and the cytokine TNF-a, which block the antioxidant response at the time it is most required. At the same time, the unceasing generation of ROS is a drain to the antioxidant reserves; the glutathione levels drop because of the faster production of glutathione than the rate of its production. The resultant oxidative environment consequently triggers NF-kB pathways and MAPK pathways, resulting in a vicious, self-perpetuating cycle of inflammation leading to oxidative stress which leads to further inflammation. It is the synergistic, molecular level dysregulation - the humming of PRR signaling, the continued activation of NF-kB, the drizzle of cytokines, the leak of mitochondrial ROS, the overstrained Nrf2 system - that is the component dysfunction that accumulates to harm tissue functioning, organ communication, and even results in the plethora of chronic systemic diseases. Molecular architecture of inflammation and sources of oxidative stress are not therefore independent systems but complementary parts of an engine which is pathological [15].

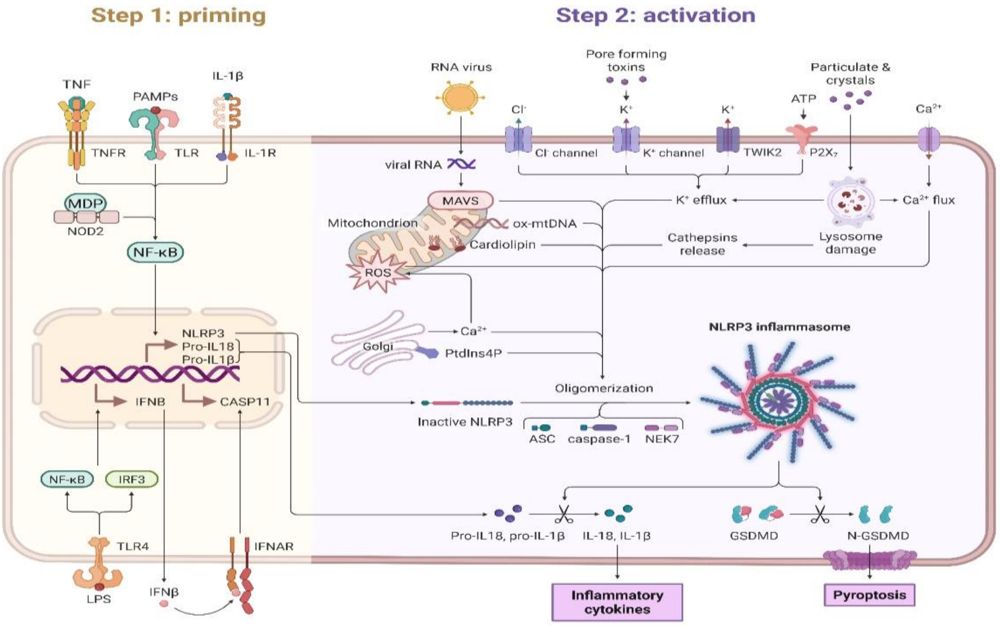

Fig: 2 Inflammasome Activation Pathways in Immune Responses

Pathogenic Crosstalk: A Vicious, Self-Amplifying Cycle

Chronic inflammation and oxidative stress are not directly related, but constitute a feedback loop that is self-destructive and is the key to pathogenesis of systemic disease. This vicious circle is such that once it is started the pathological process becomes self-perpetuating and each element starts to push the rest. The progenitor of oxidative stress is inflammation and its effect on oxidative stress takes place in two main ways. The former is the direct explosive generation of reactive oxygen species (ROS) through the activation of immune cells. When phagocytes such as neutrophils and macrophages come across PAMPs or DAMPs, they assemble and activate the NADPH oxidase (NOX2) complex on their membranes immediately to induce the NADPH oxidase (NOX2) respiratory burst. It is an antimicrobial reaction that deliberately injects large amounts of superoxide anion (O_2^-) into the phagosomal cavity and into the extracellular environment. This is a positive weapon that is controlled and useful in acute infection. In sterile chronic inflammation, the constant, subacute activation of locally resident immune cells however causes a sustained, inappropriate respiratory burst, saturating the local microenvironment with ROS which injure neighboring healthy cells and the extra-cellular matrix. Secondly, pro-inflammatory cytokines are also strong triggers of intracellular ROS in non-immune cells. The core triumvirate of chronic inflammation i.e. Tumor Necrosis Factor-alpha (TNF-a), Interleukin-1 beta (IL-1b) and Interleukin-6 (IL-6) - express themselves through their respective receptors to interfere with mitochondrial function. They are capable of causing mitochondrial membrane permeability, uncoupling the electron transport chain, and inhibition of antioxidant enzymes, making the mitochondria become dysfunctional and release electrons hence offering a major secondary source of superoxide. Moreover, these cytokines may induce other enzymes that produce ROS, e.g., xanthine oxidase and inducible nitric oxide synthase (iNOS), which exacerbates oxidative stress. In this way, an inflammatory signal is directly converted to an oxidative event [16].

On the other hand, oxidative stress is a strong source of inflammation, which proceeds along both signaling and damage pathways. To begin with, ROS are not simply destructive molecules, at sub-lethal concentrations they serve as important signaling molecules that trigger important pro-inflammatory pathways. Hydrogen peroxide (H2O2), especially, has the ability to oxidize and suppress inhibitory kinases, which results in the activation of the master regulator NF-kB, therefore, directly stimulating the transcription of additional inflammatory genes. More to the point, it is arguably one of the main triggers of the NLRP3 inflammasome, a complex of multi-protein intracellular sensors. Mitochondrial dysfunction, together with oxidative stress, is the required second signal that results in the oligomerization that causes IL-1b and IL-18 to be cleavage and activated by caspase-1. This forms a straight pathway between redox imbalance and maturation of strongly inflammatory cytokines. Secondly, oxidative damage in itself is an abundant source of DAMPs. PRRs recognize the products of lipid peroxidation (such as 4-HNE), oxidized LDL and fragmented extracellular matrix components. Most importantly, oxidative stress on proteins, organelles, and DNA may trigger regulated forms of cell death including necroptosis that lead to the disastrous release of pre-existing DAMPs such as HMGB1 and ATP. By so doing, the damage produced by ROS always replenishes the signals that originally triggered the inflammatory response in an autonomous cyclic mechanism.

One of the vital vicious cycles in this cycle is the senescence relationship. Cellular senescence is a significant cause of oxidative stress, which is irreversible cell cycle arrest. Senescent cells do not simply adopt an inactive state, but a rotten senescence-associated secretory phenotype (SASP). SASP is also marked by chronic and hyper secretion of a myriad of pro-inflammatory cytokines (IL-6, IL-1b), chemokines, proteases and, of course, additional ROS. This secretory pattern is maintained throughout the cell life and serves as a powerful and localized force of inflammation and tissue destruction. The SASP not only attracts immune cells but also causes senescence to adjacent cells and spreads the damage. Consequently, the senescence caused by oxidative stress creates long-lasting inflammatory hotspots in tissues, which makes the inflammatory condition permanent and the continuous production of inflammatory mediators and other ROS, which seal the vicious circle [17].

Systemic Dissemination and Inter-Organ Communication

The signal and toxin property of circulating mediators, whose presence spreads systemic pathology in response to tissue priming, is not limited to its tissue site of origin but is reflected in a molecular vicious cycle of inflammation and oxidative stress that is disseminated throughout the body. The blood is a pathway toward a pathological conversation, and carries cytokines and chemokines such as TNF-a, IL-6, and MCP-1 between the locations of local inflammation to distant organs, which can recognize their receptors, and cause secondary inflammatory and pro-oxidant conditions. Oxidised metabolites, including oxLDL, malondialdehyde (MDA), and advanced glycation end products (AGES) are equally important. These are not simply biomarkers of harm, but are biologically active compounds capable of directly stimulating immune cells, interacting with PRRs and also continuing to feed upon inflammatory and oxidative processes in remote tissues. This forms a humoral chain of pathology, in which a fire in one organ system emits sparks which trigger other fires. This systemic communication is funnelled and reinforced by a set of certain key inter-organ axes, which serve as conduits of privilege in the spread of disease. One of them is the Gut-Liver-Brain Axis. In the steatotic liver disease (MASLD/MASH) of metabolic dysfunction, a compromised gut barrier (i.e. leaky gut) permits the entry of bacterial endotoxins (e.g., LPS) into the portal circulation. This directly stimulates hepatic Kupffer cells through TLR4 causing local inflammation and oxidative stress, which stimulate steatosis, fibrosis, and systemic cytokine release. These inflammatory mediators, in combination with bile acid changes, may then communicate through the vagus nerve and systemic circulation to the brain, causing neuroinflammation, mood changes and cognitive fog, which is a full chain of malfunction [18-20].

Equally, the Metabolic-Neurodegenerative Axis offers a vivid connection among peripheral illness and central nervous system pathophysiology, as was the case of Type 2 Diabetes (T2D) and Alzheimer disease. The overproduction of ROS and AGEs occurs because of chronic inflammation of the periphery and hyperglycemia. These mechanisms cause insulin resistance in the brain, damage the blood-brain barrier and allow the cytokines to enter the CNS. In this case, they stimulate microglia, resulting in neuroinflammation and oxidative stress that enhances tau hyperphosphorylation and amyloid-beta aggregation and also suppresses neuronal insulin signaling. This pathophysiological interrelation made Alzheimer be referred to as type 3 diabetes in order to highlight the systemic nature of the underlying inflammatory-oxidative perturbation [21].

Lastly, cardiovascular complications have a central pathway, the Vascular-Immune Axis. The dysfunctional, inflamed endothelium, which is the target of the cytokines and oxLDL, is expressed with adhesion molecules attracting monocytes to the arterial intima. This type of monocyte develops into macrophages, which take up oxLDL through the scavenger receptors to form pro-inflammatory foam cells to continue a localized inflammatory-oxidative environment in the atherosclerotic plaque. Moreover, systemic inflammation facilitates a pro-thrombotic condition through the up-regulation of fibrinogen and down-regulation of fibrinolysis. This axis shows that the circulating mediators can change a passive blood vessel to an active participant of immune dysfunction and directly connect the inflammatory-oxidative nexus with clinical outcomes, such as myocardial infarction and stroke. In such a way, via these interrelated axes, a local biochemical imbalance may progress to a full-body syndrome, proving chronic illnesses are systemic circuitry disorders indeed [22-25].

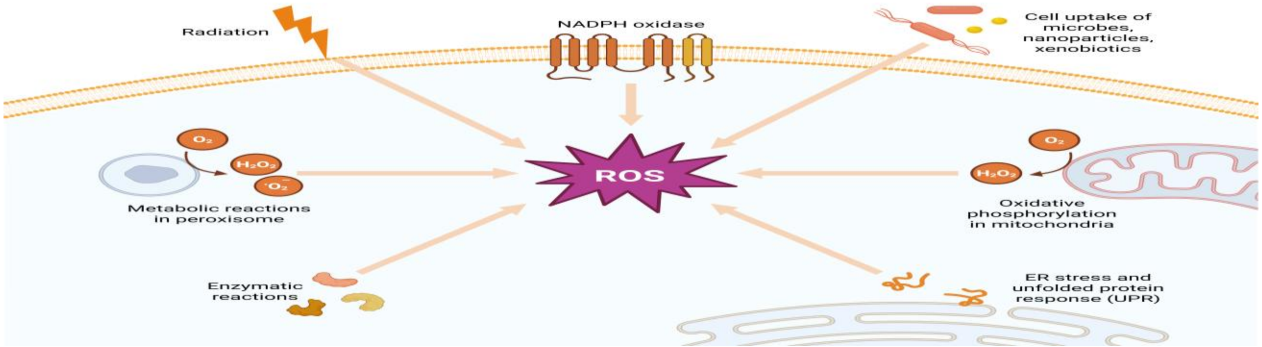

Fig: 3 Sources and Pathways of Reactive Oxygen Species (ROS) Production

Conclusion

The combination of molecular biology, systems physiology, and clinical epidemiology evidence is strongly supporting the need to overhaul the concept of chronic disease. The classical, organ-siloed concept of medicine cannot be used to explain or treat interrelated pathologies that characterize contemporary non-communicable disease epidemics. More likely, a paradigm of systemic dysfunction of the network is developed, and its pathological nexus is made up of chronic inflammations and oxidative stresses. This correlation is characterized not by a chain reaction but the vicious circle developing itself. Persistent immune activation, proved by DAMPs and PRRs, directly causes oxidative stress, produced by such enzymes as NADPH oxidase and dysfunctional mitochondria. ROS and consequent molecular damage, in turn, are strong inflammatory signals that trigger NF-kB, NLRP3 inflammasome, and the production of new DAMPs. This vicious cycle is also reinforced by such processes as cellular senescence and its pro-inflammatory SASP, which leave permanent foci of dysfunction in tissues. Importantly, the localization of this molecular cycle is not permanent. It is propagated throughout the body through circulating cytokines and oxidized metabolites, and spreads dysfunction along pre-existing inter-organ axes including the Gut-Liver-Brain, Metabolic-Neurodegenerative and Vascular-Immune circles. This is why seemingly separate conditions such as atherosclerosis, diabetes, neurodegeneration, and fatty liver disease are often co-morbid because they are different clinical manifestations of the same underlying inflammatory-oxidative dysfunction that is damaging different nodes of the physiological network. Thus, various chronic illnesses may be understood as systemic states that are united by the dysregulated circuitry. Such appreciation necessitates a paradigm change in treatment therapies. Going further than organ-related symptom treatment, the next intervention should seek to interrupt the essential inflammatory-oxidative pathway and regain normalcy in the system. This may include attacking critical nodes such as the NLRP3 inflammasille, augmenting endogenous antioxidant responses through Nrf2 or using lifestyle and pharmacological interventions to address chronic inflammation. By perceiving the body as a system in itself and addressing the shared factors of the maladaptation of the former, medicine will be able to create more efficient, systemic interventions in the struggles with the health issue of our time.

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