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Original Article

Metabolomic Adaptation And Redox State: Effects Under Stress In Human Disease And On Immune Response

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Abstract: *The ability of organisms to constantly adjust to variably changing environmental and physiological conditions is required for cellular survival. Metabolic rewiring and redox regulation are among the crucial adaptive mechanisms, operating as interactive networks that maintain cellular homeostasis under stress. Cellular stress may be directly the result of a number of factors, including hypoxia, nutrient deprivation, inflammation, infection, mitochondrial dysfunctions and oxidative imbalance deregulation (aging), endoplasmic reticulum stress or toxic environmental exposures. Under these challenging conditions, cells have to implement broad and far-reaching metabolic and biochemical reprogramming to sustain ATP generation, redox homeostasis recovery, and immune signal pathway regulation. Although these adaptive responses are vital for survival, chronic, and/or deregulated metabolic and redox modifications play critical roles in the progression of many diseases such as cancer, neurodegenerative disorders, cardiovascular disease (CVD), diabetes mellitus (DM), autoimmune disorders (AID) and long-term inflammatory syndrome. The recent interface between immunometabolism and redox biology has clarified that cellular metabolism is not just an energy supply but rather a fundamental orchestrator of immune responses, gene expression, signalling pathways, and cellular fate. (Nature) Metabolic rewiring is a dynamic process that results from organisms rearranging with respect to metabolic pathways according to cellular stress or as external environmental pressures change. Under stressful conditions, cells change their battery of glucose, amino acids, fatty acids and mitochondrial substrates for optimal ATP output and biosynthetic processes. Amongst its most recognized hallmarks is the preferential rewiring of metabolic processes toward aerobic glycolysis as opposed to oxidative phosphorylation, known as the Warburg effect. While originally thought to be restricted to the catabolic state of tumour cells, this has since been recognized in other settings such as activated immune cells [5], hypoxic tissues [6] and inflamed microenvironments [7]. Increased glycolysis leads to rapid ATP production and supply of metabolic intermediates necessary for nucleotide synthesis, lipid biosynthesis and cytokine production. At the same time, mitochondrial metabolism is reprogrammed*

Keywords: *Metabolism, redox balance, oxidative stress, immunity, inflammation, adaptation, signalling, disease, mitochondria, antioxidants.*

I. INTRODUCTION

Cells are constantly exposed to internal and external insults that threaten their structural integrity, metabolic fitness and functional ability. In order to survive the dynamic nature of the local environment, cells turn on adaptive mechanisms that sense environmental changes and reposition intracellular biochemical pathways. Many of the most critical adaptive processes such as metabolic rewiring and redox regulation also work together to coordinate energy metabolism, oxidative balance, cellular signalling, and immune function. These mechanisms are critical for cellular homeostasis, serving as adaptive responses to stress conditions including hypoxia, infection, inflammation, and nutrient deprivation (increase of transcription), mitochondrial dysfunction (ROS production), toxic exposure (ubiquitin-proteasome degradation) or errors in protein-folding (unfolded protein response). Although acute metabolic and redox responses are protective and essential for survival, chronic deregulation mediates pathological processes involved in the pathogenesis of many common diseases including cancer, diabetes, cardiovascular disease, neurodegenerative disorders autoimmunity and chronic inflammatory diseases [1]. (Nature)

The term metabolism has ceased to be considered merely as a subsystem generating ATP and performing biosynthetic tasks. Contemporary studies have defined metabolism as an extremely dynamic signalling network that modulates gene expression, immune activation and epigenetic control thereby affecting cell fate. At physiological conditions, cells will have an exquisitely controlled metabolic flexibility and integrate the relative amount of glycolysis, oxidative phosphorylation (OXPHOS), fatty acid oxidation (FAO), amino acids usage and anabolic pathways to tune metabolism according to their energy requirements and environmental conditions. Nevertheless, during cellular stress metabolic pathways are remodel zed promptly for the purposes of survival and adaption. This process, often described as metabolic rewiring redirects substrates

and energetic resources to pathways that enhance stress resistance, inflammatory signalling, tissue repair or proliferation. Metabolic adaptation thus constitutes a major aspect determining the vitality and fate of cells. (Nature)

Perhaps the best-studied metabolic rewiring example is the transition from oxidative phosphorylation in mitochondria to glycolysis under stress conditions. This metabolic change allows for the rapid generation of ATP, even in conditions where oxygen availability is scarce or mitochondrial function is compromised. Even though the ATP yield from glycolysis is lower than can be obtained through oxidative phosphorylation, glycolysis produces intermediate metabolites needed for simple nucleotide synthesis, amino acid biosynthesis and lipid creation. Example 1: Various types of activated immune cells such as macrophages and effector T lymphocytes preferentially adopt a glycolytic metabolism in order to promote rapid proliferation and inflammatory responses. In contrast, metabolic regulation of longer-lived regulatory immune cells and memory T cells more highly relies on oxidative phosphorylation and fatty acid oxidation. These observations suggest that metabolic pathways are closely tied with immune cell phenotype and function. (Nature)

Cellular homeostasis is maintained through redox regulation, which parallels metabolic adaptation. Reactions involving the transfer of electrons between molecules to regulate enzyme activity, signal transduction, mitochondrial respiration, transcription factor activation and immune respond (1) are referred under redox biology(of oxidation–reduction). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced intrinsically in constituents of mitochondrial respiration, activation of inflammatory hotspots, and enzymatic reactions. In appropriate concentrations, they act as signalling mediators involved in the regulation of proliferation, differentiation, host defence and adaptation to stress. However, in excess amounts the generation of ROS leads to oxidative stress and subsequent lipid peroxidation, DNA damage, protein oxidation and mitochondrial dysfunction. Consequently, cells have developed advanced antioxidant systems such as glutathione, catalase, superoxide dismutase, thioredoxin and peroxiredoxins to maintain redox homeostasis. (Sage Journals)

There is a tight connection between metabolism and redox regulation. Importantly, necrotic cell death is associated with a failure to restore cellular reducing equivalents for essential antioxidant defence and biosynthetic reactions as generated by cellular metabolism via NADH and NADPH. For example, the pentose phosphate pathway generates NADPH that is important to recycle glutathione and helps detoxify ROS. At the same time, mitochondrial oxidative phosphorylation generates ROS as by-products of electron transport chain function. Thus, deregulation of metabolic pathways directly impacts redox balance while oxidative stress alters the activity of metabolic enzymes and mitochondrial performance. This reciprocal interaction creates a highly regulated network that establishes how cells respond to stress and environmental changes. Studies performed recently have found that both oxidative stress and reductive stress deregulate cellular physiology, highlighting the importance of maintaining redox homodynamic rather than simply an excess of antioxidants [3]. (Sage Journals)

Metabolic rewiring and redox regulation are indispensable for the coordination of innate and adaptive immunity. Immune cells have a high need for rapid metabolic flexibility to respond to pathogen detection, migrate to inflamed tissues, proliferate and produce cytokines, and eliminate infected or damaged cells. Macrophages respond to inflammatory signals by enhancing glycolysis and ROS generation for antimicrobial activity and cytokine production. Respiratory burst reactions in neutrophils are powered by the glycolytic metabolism and production of reactive oxygen species (ROS) mediated by NADPH oxidase, which help to kill invading pathogens. Similarly, activated T cells experience dramatic metabolic alterations that fuel clonal expansion and effector function. In contrast, anti-inflammatory immune cells depend more on mitochondrial respiration and fatty acid oxidation to preserve tissue repair and tolerance rather than on glycolysis. Metabolic information is integrated with inflammatory responses through the involvement of redox-sensitive signalling pathways, such as NF-κB, HIF-1α, motor, AMPK and MAPK to modulate differentiation and function of immune cells. (Nature)

II. MOLECULAR MECHANISMS OF METABOLIC REWIRING AND REDOX ADAPTATION TO CELLULAR STRESS

A. Overview of Cellular Response to Stress

Cells are continuously subjected to various stress factors that endanger their structural integrity, metabolic homeostasis, and functional performance. To this end, a wide number of stressors, such as hypoxia, nutrient deficiency, oxidative excess, inflammation, opportunity of pathogens to invade cells or tissues, DNA injury (e.g. through exposure to chemicals and radiation), aberration in mitochondrial function and load with toxins or heavy metals disrupting cellular architecture lead to various aspects of senescence (332). Cells engage adaptive signalling pathways that control a variety of processes, including metabolism, redox homeostasis, protein synthesis, autophagy and apoptosis during such stresses to adapt. Of these adaptive systems, metabolic rewiring and redox regulation represent two of the most tightly coordinated mechanisms by which cells can maintain viability and regain homeostasis during adverse conditions.

Stress-sensing proteins and signalling molecules that detect changes in intracellular energy levels, oxygen concentration, redox state, or nutrient availability initiate cellular stress responses. The key regulators of stress response are

hypoxia-inducible factor-1alpha (HIF-1α), AMP-activated protein kinase (AMPK), mammalian target of kanamycin(motor), nuclear factor kappa B(NF-dB) and nuclear factor elytroid 2-related factor 2(Nrf2)[13,14]. These signalling molecules work as molecular switches by integrating metabolic adaptation with antioxidant defence and inflammatory signal transduction.

In stressed conditions, cells favour pesticide-resistant resources in order to survive; therefore, they switch the utilization of energy and adjust precursors toward ATP synthesis, repair processes and antioxidant defence (Figure 2). Hypoxic conditions, for example, both inhibit mitochondrial oxidative phosphorylation and drive increased glycolytic flux to sustain ATP synthesis even under limited oxygen availability. Likewise, glycolysis and pentose phosphate pathway activity are induced under inflammatory conditions so that immune cells can produce cytokines and reactive oxygen species. These metabolic transitions are not random events, however—they are precisely regulated adaptive programs that optimize cellular function under particular environmental niches.

B. Glycolytic Reprogramming and Mitochondrial Adaptation

Glycolytic reprogramming is one of the most evident characteristics of stress-induced metabolic rewiring. ATP is mainly produced in the mitochondria via mitochondrial oxidative phosphorylation under normal physiological conditions in most cells. On the other hand, under distressful conditions such as hypoxia, inflammation, infection and an accelerated proliferation, cells resort to glycolysis even in oxygen-rich settings. The phenomenon is termed as aerobic glycolysis or more commonly known as Warburg effect which helps a cell to produce ATP in an accelerated manner along with biosynthetic intermediates stringently needed for survival and proliferation.

It has several evolutionary benefits to switch on glycolysis in times of stress. First, it produces ATP faster than oxidative phosphorylation although less efficiently. Second, glycolytic intermediates are channelled into biosynthetic processes that promote nucleotide, amino acid and lipid synthesis. Third, the different degree of reliance on oxygen by glycolysis and its partial inhibition of excessive production of mitochondrial ROS may protect against both oxidative stress during mitochondrial dysfunction. Mitochondria are extensively remodelled during metabolic stress. Mitochondrial fusion, fission and biogenesis, as well as selective mitophagy contribute to the maintenance of mitochondrial quality and bioenergetic efficiency. Mitochondrial fragmentation is frequently elicited under conditions of oxidative damage and inflammatory activation (stress). Mitophagy removes damaged mitochondria to prevent excessive ROS and apoptotic signalling.

C. Redox Signalling and Antioxidant Defences

Redox regulation plays a crucial role in the maintenance of cellular homeostasis in response to stress conditions. The cellular redox status is determined by the balance between oxidant production and antioxidant defence systems. Mitochondrial respiration, inflammatory reactions, enzymatic metabolism, and environmental exposure all continuously produce reactive oxygen species. Some examples of major ROS species are superoxide anion, hydrogen peroxide and hydroxyl radicals. Nitric oxide (NO) and peroxynitrite-containing reactive nitrogen species also participate in cellular redox signalling.

At the physiological level, ROS act as signalling molecules that help to regulate cell proliferation, differentiation and immune activation. ROS can reverse the oxidation of cysteine residues within regulatory proteins, thereby modulating the activity of transcription factors such as NF-dB, HIF-1α, AP-1 and Nrf2. These pathways coordinate antioxidant defence responses, inflammatory processes and metabolic adaptation.

The accumulation of excess ROS eventually leads to oxidative stress and cellular damage. Oxidative damage can target membrane lipids, mitochondrial DNA, nuclear DNA, proteins, and cytoskeletal structures[3]. Chronic oxidative stress is implicated in various processes that become increasingly important with aging, including inflammation, carcinogenesis, cardiovascular disorders and neurodegeneration [6]. Thus, antioxidant defence systems are key to preventing oxidative injury and restoring redox balance.

D. Immunometabolism and Inflammatory Signalling

Metabolic adaptation and the regulation of the cellular redox state are crucial for mounting host defence and inflammatory responses orchestrated by immune cells. Upon activation, immune cells undergo extensive metabolic reprogramming to promote rapid proliferation, cytokine synthesis, migration and antimicrobial activity. This newly formed field of study, immunometabolism, examines the ways in which metabolic pathways control immune cell function and the progression of inflammatory diseases.

Glycolysis, pentose phosphate pathway and ROS production in activated macrophages Glycolytic metabolism promotes ATP generation and inflammatory mediators (interleukin-1β, tumour necrosis factor-alpha, and nitric oxide) production in a rapid manner. NADPH generated via pentose phosphate pathway activation is essential for the respiratory

burst reactions in macrophages and the pathogen-killing properties of ROS. On the other hand, anti-inflammatory macrophages are more dependent on oxidative phosphorylation and fatty acid oxidation. These metabolic pathways allow subsequent tissue repair, production of anti-inflammatory cytokines and induction of immune resolution. In a similar way, while activated effector T cells use glycolysis to sustain proliferation and cytokine secretion, regulatory T cells and memory T cells also rely largely on mitochondrial metabolism.

Table 1: Key Metabolic and Redox Adaptations to Cellular Stress

Cellular Stress Condition	Metabolic Adaptation	Redox Response	Key Signalling Pathways	Disease Association
Hypoxia	Increased glycolysis	Elevated ROS production	HIF-1α, AMPK	Cancer, ischemia
Nutrient deficiency	Fatty acid β-oxidation	Antioxidant activation	AMPK, motor suppression	Diabetes, aging
Inflammation	Glycolytic switch	ROS and RNS production	NF-dB, MAP kinase activation	Autoimmune diseases
Mitochondrial dysfunction	Decreased oxidative phosphorylation	Oxidative stress	Nrf2, mitophagy pathways	Neurodegeneration
Infection	Activation of pentose phosphate pathway	Respiratory burst	NADPH oxidase, NF-dB	Sepsis, chronic infection
Oxidative stress	Increased NADPH production	Activation of glutathione defence	Nrf2, Keap1	Cardiovascular disease
Tumour microenvironment	Aerobic glycolysis	Increased antioxidant defence	HIF-1α, motor	Cancer progression
ER stress	Modification of amino acid metabolism	Control of protein oxidation	Unfolded Protein Response (UPR) pathways	UPR-mediated diseases
Chronic inflammation	Mitochondrial remodelling	Persistent ROS signalling	NF-dB, STAT3	Fibrosis, arthritis

III. REDOX DYNAMIC AND DISEASE PROGRESSION, IMMUNE REGULATION AND METABOLIC REWIRING IN THIS CONTEXT

Cellular response to stress is one of the most basic biological processes necessary for survival and homeostasis (balance). Healthy tissues coordinate metabolic pathways and redox systems to support energy production, biosynthesis, signalling coordination and immune surveillance. Under pathological circumstances including chronic inflammation, hypoxia, infection, nutrients availability imbalance and mitochondrial dysfunction however, cells cause dramatic metabolic rewiring and changes in redox state properties that regulate cell fate decisions or play a key role for the disease progression as well as immune responses. These adaptive processes are networks of interlinked regulatory pathways that mediate cellular fate, endogenous restoration of tissue integrity and systemic homeostasis rather than isolated biochemical events.

Metabolic rewiring is characterized by the adaptive change of metabolic pathways to environmental and intracellular stress signals. Under a variety of stressful conditions, cells have evolved to reprogram glucose metabolism, lipid oxidation, amino acid utilization, mitochondrial respiration and/or biosynthetic pathways to better survive these conditions. Similarly, redox regulation governs the production and removal of reactive oxygen species and reactive nitrogen species such that intracellular signalling is maintained while cellular oxidative damage is avoided. Collectively, these systems allow cells to respond with a quick time scale when stimuli environments change while performing required physiological functions.

Over the years, the association between metabolism and redox balance has played a more relevant role in elucidating the molecular basis of human diseases. Persistent deregulation of metabolic pathways results in abnormal reactive oxygen species (ROS) generation, mitochondrial injury, inflammatory activation and immune dysfunction. Thus, these disturbances cause cancer initiation and development, diabetes, cardiovascular disease, autoimmune conditions neurodegenerative syndromes or chronic inflammatory diseases. In addition, immune cells during activation, differentiation and inflammatory

response are characterized by significant metabolic and redox reprogramming. Thus, the interaction between immunometabolism and redox biology has become one of the hottest biomedical research topics.

Discoveries in metabolomics, redox proteomics, systems biology and immunology show that metabolic intermediates and ROS can function as signalling molecules affecting gene expression, epigenetic regulation, cytokine production and immune cell differentiation. Together, these findings illustrate how cellular metabolism is increasingly being appreciated as a regulatory hub for controlling inflammatory processes and elucidating mechanisms critical for tissue repair, antimicrobial defence and disease susceptibility. Nrf2, NF-dB, HIF-1α and STAT3 are redox-sensitive transcription factors that coordinate metabolic inputs with stress responses that mediate immune and pathological effectors.

A. Cancer Initiation: Metabolic Reprogramming

Metabolic changes that are essential for tumorigenesis and that differentiate cancer cells from normal tissues. The Warburg effect is one of the most emerged features of tumour metabolism, which relies on aerobic glycolysis even in the presence of oxygen instead of utilizing oxidative phosphorylation like normal cells. This metabolic adaptation facilitates fast ATP production and delivers intermediates for nucleotide synthesis, amino acid biosynthesis, and lipid biosynthesis that are essential for deregulated proliferation.

Tumour cells are surrounded by an invasive tumour microenvironment containing hypoxia, nutrient limitation, oxidative stress and immune pressure. Cancer cells activated signalling pathways like HIF-1α, motor, PI3K/Act and MYC to survive in these conditions which enhanced glucose uptake and expression of glycolytic enzymes. Lactate production increases the acidity of the tumour microenvironment, resulting in invasion, angiogenesis and immune suppression. Lactate accumulation, likewise, impairs cytotoxic T cell function and promotes the establishment of an immunosuppressive phenotype in tumour-associated macrophages.

B. Oxidative Stress and Neurodegenerative Diseases

A disruption in energy metabolism, excess chronic oxidative stress and mitochondrial dysfunction is tightly linked to neurodegenerative diseases. The susceptibility of the brain to oxidative injury is generally associated with its high oxygen consumption, high lipid content and comparatively poor antioxidant capacity. An overproduction of ROS causes damage to neuronal membranes, proteins, mitochondria and DNA causing a series of cellular events that lead to neuronal dysfunction and cell death.

Mitochondrial dysfunction and reactive oxygen species underlie amyloid-beta accumulation and tau protein hyper phosphorylation in Alzheimer's disease. Disruption of Membrane Function and Synaptic Signalling by ROS-mediated Lipid Peroxidation Glucose uptake by neurons is impaired, that worsens ATP production and causes neurodegeneration to happen faster. Neuroinflammation mediated by activated microglia and astrocytes further exacerbate oxidative damage, through the synthesis of cytokines and production of ROS.

C. Redox Imbalance and Cardiovascular Dysfunction

The relationship between metabolic deregulation, oxidative stress, endothelial dysfunction, and chronic inflammation are important foundations of cardiovascular diseases. Due to the continuous contractile activity of the heart, ATP production must be on-going, and thus mitochondrial metabolism is vital for cardiac function. Mitochondrial dysfunction along with the excess production of ROS under these pathological conditions (hypertension; ischemia; obesity, and diabetes) might lead to myocardial injury repair mechanisms and progressive vascular damage.

The signalling of endothelial nitric oxide is impaired by oxidative stress, resulting in the vasoconstriction, inflammation, thrombosis and atherosclerosis [2]. A reaction between superoxide radicals and nitric oxide produces peroxynitrite, which injures vascular tissues and disrupts the regulation of blood flow. Background Endothelial dysfunction is an early feature of many cardiovascular diseases.

D. Metabolic deregulation in diabetes and obesity

Chronic metabolic syndrome including insulin resistance, chronic inflammation, obesity and mitochondrial dysfunction are long-lasting disorder which is commonly seen in diabetes mellitus [1]. The over-intake of nutrients and lipid accumulation perturb normal metabolic homeostasis and activate inflammatory signalling in adipose tissue, liver, skeletal muscle, and the pancreatic cells.

In hyperglycaemia, ROS production is enhanced by mitochondrial overload, with protein gyration and activation of inflammatory pathways [40–42]. Pancreatic beta cells are relatively deficient in endogenous antioxidant capacity [17], and they rapidly undergo oxidative stress. Inconsistencies regarding insulin secretion and resistance eventually accelerate metabolic dysfunction and systemic inflammation.

E. Immunometabolism and Autoimmune Disorders

Immunometabolism in immune cells. Autoimmune diseases are caused by deregulation of immune tolerance so that the survival of self-antigens can change into chronic inflammation. Metabolic rewiring is a major regulator of immune cell activation, differentiation, cytokine production and tissue damage in autoimmune diseases. Glycolysis and Glutaminolysis to support proliferation and effector function of activated T cells. Th17 cells are cell-dependent on glycolytic metabolism whereas regulatory T cells instead rely more on oxidative phosphorylation and fatty acid oxidation (Gonzalez et al., 2018). The turnover of these metabolic programs contributes to autoimmune pathology.

During inflammation activation, both macrophages and dendritic cells are subjected to metabolic reprogramming. Cytokine Production SUPPORTING Inflammation, ROS Generation and Antigen Presentation mediated by glycolysis. Continuous production of ROS enhances tissue damage and stimulates more inflammatory signalling's.

1. These strategies are designed to restore immune homeostasis and minimize damage due to chronic inflammation.

F. Metabolic and Redox Pathways Targeting Therapeutic Strategies

New avenues for therapy across numerous diseases have emerged due to new insights in metabolic biology and redox research. Metabolic rewiring and oxidative stress are key hallmarks many pathologies, therefore targeting these pathways represent a great opportunity for the treatments of various diseases.

Antioxidant therapy is one of the most studied methods. Compounds such as coenzyme Q10, N-acetyl cysteine, vitamin E and polyphenols are antioxidants types that support mitochondrial health through ROS neutralization. But, an overload of antioxidants may inhibit physiological ROS signalling and immune defence systems. Longer-term therapies specific to mitochondria have the potential to maximize ATP production, blunted ROS generation and restore mitochondrial dynamics. Mitophagy-enhancing agents, those that stabilize activity of the electron transport chain or promote mitochondrial biogenesis have demonstrated efficacy in preclinical models of neurodegenerative and cardiovascular diseases.

IV. ADVANCED CONCEPTS IN CELLULAR STRESS, METABOLIC PLASTICITY AND REDOX HOMEOSTASIS

Cellular systems exhibit extraordinary adaptability to survive in the face of nonsustainable environmental and disease-based challenges. Such adaptive responses communicate and coordinate, through complex networks of metabolic pathways, redox signalling, inflammatory mediators, mitochondrial dynamics and immune regulatory mechanisms. However, the last few years have seen important scientific advances that show such aspects like metabolic rewiring, and redox-regulation are not simply independent biochemical events but rather integrated molecular systems governing cellular communication, gene regulation, tissue remodelling as well as disease progression. Dynamic adaptation of cellular metabolic activity to changes in redox state is an important mechanism for maintaining physiological homeostasis under stress and the failure thereof contributes directly to chronic disease pathogenesis and immune dysfunction.

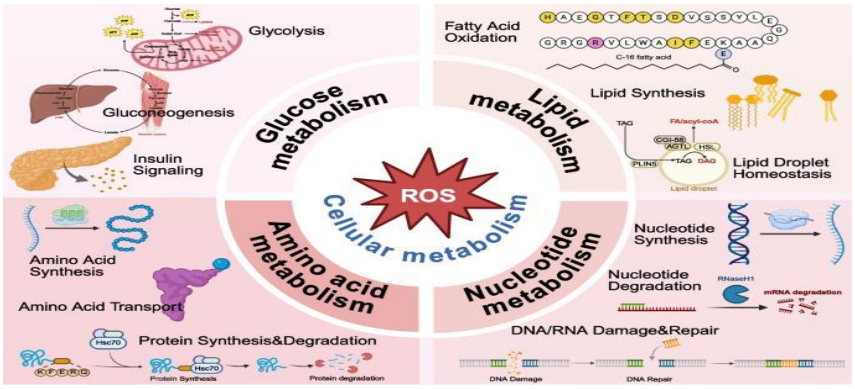

Figure 1: Cellular Metabolism and Redox Homeostasis

The ability of cells to hold metabolic plasticity is how they can adapt and respond according to environmental conditions and energy demands, whether shifting between glycolysis, oxidative phosphorylation or a secondary process such as fatty acid oxidation to produce ATP through electron transport chain, glutaminolysis for ammonium detoxification and anabolic pathways. This flexibility is particularly crucial in the context of hypoxia, nutrient deprivation, inflammation, oxidative injury and infection. In the meantime, redox homeostasis regulates intracellular signalling by balancing production and detoxification of reactive oxygen species (ROS) and reactive nitrogen species (RNS). While moderate ROS levels act as signalling molecules for cell proliferation, differentiation, immune activation and tissue repair, high intracellular ROS concentrations are capable of causing oxidative damage leading to cellular dysfunction.

Mitochondria have a central role in the coupling of metabolic and redox adaptation. In addition to ATP generation, mitochondria also play roles in regulating apoptosis, calcium signalling, immune activation and control of ROS production and metabolic biosynthesis. Thus, mitochondrial dysfunction leads to systemic effects, which link various diseases such as cancer, cardiovascular disorders, metabolic syndrome, autoimmune diseases and neurodegeneration. Similarly, cellular stress can also engage several signalling pathways (AMPK, motor, HIF-1α, NF-dB and Nrf2) that integrate metabolic and redox signals to determine cell fate decision.

A. Mitochondrial Stress Responses and Cellular Adaptation

Mitochondria are the cytoplasmic organelles responsible for energy production, biosynthesis, calcium regulation, apoptosis and intracellular signalling. Mitochondria remodel their structure and function in time of cellular stress to be able to achieve metabolic homeostasis and ensure cellular integrity. These include changes in mitochondrial dynamics, mitophagy, efficiency of oxidative phosphorylation, and ROS signalling. Mitochondrial stress can be triggered as a result of hypoxia, nutrient deprivation, infection/inflammation/toxicity, aging and genetic mutations. In the absence of O 2, mitochondrial electron transport chain dysfunction leads to excessive generation of ROS and decreased ATP synthesis. Mitochondrial ROS above physiological levels causes damages to mitochondria Dan, proteins and membrane lipids resulting in respiration defects and ultimately bioenergetics catastrophe. Major Consequences of Mitochondrial Dysfunction

- Reduced ATP production
- Excessive ROS generation
- Activation of inflammatory pathways
- Impaired calcium homeostasis
- Increased apoptosis and necrosis
- DNA and protein oxidative damage

Mitochondrial dysfunction is an essential contributor to aging and chronic disease. Impaired mitophagy and oxidative stress promote neuronal degeneration in neurodegenerative disorders. In the cardiovascular disease, mitochondrial ROS promotes endothelial dysfunction and fibrosis. Mitochondrial Metabolism Supports Cancer Survival Under Hypoxia and Is Altered in Rhoda-deficient Cells

B. Signalling for inflammation and immune regulation dependent on oxidation/reduction

Inflammation is an innate biological response against pathogens, clearing damaged tissue and restore homeostasis [1]. While acute inflammation is an adaptive response, chronic or deregulated inflammation leads to tissue damage and disease progression. Redox signalling is a unique mechanism of action involved in inflammatory consequences through modulation of cytokines, immune cells activation, transcription factor activity and inflammasome signalling.

Nutrients that boost the response: Reactive oxygen species are produced as by-products of mitochondrial metabolism and generated by NADPH oxidase activity during immune activation. Respiratory burst reactions in neutrophils and macrophages involve the generation of reactive oxygen species (ROS) to kill invading pathogens. Controlled production of ROS thus serves a key antimicrobial role.

- Tissue fibrosis
- DNA mutation accumulation
- Endothelial dysfunction
- Autoimmune activation
- Immune exhaustion
- Cancer progression
- Metabolic syndrome development

C. Interurban Metabolic Communication in Stress Conditions

Stress adaptation is not only intrinsic at the single cellular level but is also inter-influenced through efficient communication systems in a coordinate manner among different tissues and organ systems. During stress condition, the homeostasis of the whole metabolic system relies on important metabolic communication between liver, adipose tissues, skeletal muscle, brain and immune system along with gut micro biota.

Liver is the main metabolic organ which decides glucose production, lipid metabolism, detoxification and driving inflammatory signalling. Under stress conditions, hepatic metabolic flux is redirected to gluconeogenesis, cytogenesis and antioxidant defence. Cytokines and small-molecule metabolite derived from the liver regulate immune response and systemic inflammation.

D. Nova's Technologies Therapeutics e Directors Futures

Background Recent advances in biomedical science has enabled development of new therapeutic strategies to overcome metabolic rewiring and redox deregulation. These novel technologies seek to promote metabolic flexibility, enhance mitochondrial function, mitigate oxidative injury or regulate immune responses implicated in chronic diseases.

Mitochondrial was one of the major sectors developing mitochondrial across last 50 years. Mitochondria-targeted antioxidants (e.g. Mite and SkQ1) are intended to concentrate within mitochondria in order to eliminate ROS directly at the site of their origin. These therapies have the potential for application in neurodegenerative diseases, cardiovascular disorders and metabolic syndrome.

Abstract New gene-editing technologies, such as CRISPR-CA's systems, have enabled the development of potential therapies targeting mitochondrial dysfunction and redox imbalance associated with mutations. You have also identified potentialRNA-based therapeutics that may be needed to modulate metabolic enzymes and/or inflammatory signalling pathways.

E. Technologies that are coming into use in treatment and outlooks

There have been significant developments in therapeutic approaches aimed at targeting metabolic rewiring and redox deregulation, harnessing recent advances in biomedical science. The primary goal of these new technologies is to restore metabolic flexibility, improve mitochondrial function, reduce oxidative injury and modulate immune response in chronic disease.

One of the important areas in development is mitochondrial-targeted therapies. Mitochondria-targeted antioxidants, including Mite and SkQ1, which can directly reach the mitochondrion to eliminate ROS. Such therapies are beneficial for neurodegenerative diseases, cardiovascular disorders and metabolic syndrome.

CRISPR-CA's systems as new gene-editing technologies open the doors for precision correction of mitochondrial dysfunction and/or redox imbalance mutations. Data arising from these studies have shown the potential for RNA-based therapeutics to control metabolic enzymes as well as inflammatory signalling pathways.

V. SYSTEMS-LEVEL INTEGRATION OF METABOLISM AND REDOX BIOLOGY WITH CELLULAR INTEGRATED STRESS RESPONSES

The coordinated control of metabolism, redox signalling, mitochondrial function and immune communication is crucial for the maintenance of cellular homeostasis under both physiological and pathological conditions. Throughout our lives, cells are challenged by the stress conditions imposed by environmental change, pathogen attack, nutrient sufficiency and deficiency damage, hypoxia, inflammation, toxic molecules and aging etc.[1]. Cells respond to these challenges by triggering transcriptionally interconnected adaptive processes that include metabolic rewiring and redox regulation. Such responses promote energy production, biosynthetic activity, antioxidant defence and immune competence while minimizing damage to cells. On the other hand, repeated or unmanageable stress breaks these modulatory systems and is implicated in chronic diseases such as cancer, cardiovascular disease, degenerative neurological diseases, metabolic syndrome, autoimmune diseases and inflammation.

Through contemporary research, we have learned that metabolism is more than just energy generation and that it is a central regulatory network governing signalling pathways, epigenetic modifications, inflammatory responses, and cellular differentiation. Likewise, redox biology is much more than oxidative injury and works as an indispensable signalling system that tightly regulates transcription factors, enzyme activity, apoptosis, immune activation and repair (1058). Metabolism and redox regulation act in concert as a frontier biochemical framework that dictates how cells sense and mitigate environmental stressors.

A. Metabolic Plasticity and Cellular Survival Mechanisms

Metabolic plasticity is the ability of cells to adaptively change metabolic pathways to react against environmental and intracellular stressful signals. This flexibility is crucial for adaptively sustaining ATP production, biosynthesis, redox balance and survival with changing physiological conditions. In response to stress, cells transit between glycolysis, oxidative phosphorylation, fatty acid oxidation, amino acid metabolism and ketone processing according to the nutrient availability/oxygen concentration/energy demand.

In normal physiological settings, healthy cells produce ATP using substrates derived from glucose by mitochondrial oxidative phosphorylation, which maintains ordered metabolic activity. But in hypoxia or mitochondrial dysfunction, cells engage glycolytic pathways to allow for continued ATP generation. This allows the cell to undergo a metabolic adaptation mediated largely by hypoxia-inducible factor-1 alpha, which promotes up regulation of glucose transporters and glycolytic enzymes at the same time it represses oxygen consumption within mitochondria.

B. Redox homeostasis and oxidative signalling networks

Redox homeostasis is maintained through a highly regulated balance of oxidant generation and antioxidant defence systems. Introduction to Redox Biology: Delineate the contribution of cellular redox signalling in (1) regulating proliferation, differentiation, apoptosis, immune activation, mitochondrial function and stress adaptation. Piper Cancellatum, Abstract Reactive oxygen species and reactive nitrogen species are constantly produced in a variety of physiology and pathophysiology settings.

Instead of only being harmful by-products of metabolism as previously thought, ROS are actually involved in various cellular functions. At physiological concentrations, they act as signalling molecules that control transcription factor, protein phosphorylation, calcium signalling and immune response Table1. Hydrogen peroxide is an especially crucial one, due to being a semi-reversible signalling agent that can oxidize cysteine residues in proteins and modulating enzyme activity.

C. Immunometabolism and Stress-Induced Remodelling of the Immune System

Metabolic flexibility is critical for the immune system in orchestrating host defence, inflammation, tissue repair and immune tolerance. Depending on their activation state, differentiation status, and micro environmental conditions, immune cells can modulate their metabolic and redox profiles. The research area of immunometabolism is concerned with how certain metabolic pathways can modulate immune activity and progression of inflammatory disease processes.

Innate immune cells activated during inflammatory responses, including macrophages, neutrophils and dendritic cells, rapidly undergo glycolytic activation. ATP for cytokine production, phagocytosis, migration, and antimicrobial activity is driven by glycolysis which produces important biosynthetic intermediates. The activation of the pentose phosphate pathway produces NADPH required by ROS to eliminate pathogens via the respiratory burst [28].

An example of metabolic specialization is the polarisation of macrophages. M1 macrophages, which are pro-inflammatory, predominantly depend on glycolysis and generation of ROS while M2 macrophages mostly rely on oxidative phosphorylation and fatty acid oxidation. Succinate and citrate are in fact metabolic intermediates, but they also have the role of inflammatory signalling molecules.

T lymphocytes differ metabolically based on functional phenotype. Glycolysis and glutaminolysis are highly important in supporting rapid effector T cell proliferation and cytokine synthesis. Regulatory T cells and memory T cells preferentially fuel their long-term persistence and immune modulation with mitochondrial oxidative phosphorylation, lipid oxidation.

Immune activation and the expression of inflammatory genes are strongly influenced by redox signalling. In moderation, ROS generation is beneficial for antimicrobial defence and immune signalling; however, excessive oxidative stress leads to tissue injury and chronic inflammation. Intracellular redox conditions regulate NF-dB, STAT3, HIF-1α, and inflammasome activation [2].

D. Epigenetic regulation of metabolism and redox responses

During cellular stress, epigenetic mechanisms are the focal regulators that link metabolic adaptation and redox signalling. Epigenetics is described in the context of heritable changes in gene expression that arise without any changes to the underlying DNA sequence. Some of the most significant and best-studied epigenetic pathways are DNA (de)methylation, histone modification, and chromatin remodelling, as well non-coding RNA mediated regulation.

Epigenetic enzyme activity directly regulated by metabolic intermediates Histone acetylation is the result of substrates from acetyl-CoA, and α-ketoglutarate regulates both DNA demethylases and histone demethylases. Sit-in activity and chromatin structure are regulated by NAD+ availability Thus, the gene expression and cellular phenotype can be directly affected by metabolic state.

E. Novel Therapeutics and Personalized Medicine Strategies

Recent findings of metabolic rewiring and redox regulation have led to faster discovery of translational therapeutic points or strategies involving cellular responses to stress. More recently, modern therapies have targeted metabolic flexibility, mitochondrial function, oxidative injury or immune activity.

Cancer therapy represents one of the largest scopes of metabolic intervention. These glycolytic inhibitors are designed to inhibit ATP production and biosynthesis in rapidly proliferating tumour cells. Investigation is also on-going into drugs that target glutamine metabolism, fatty acid synthesis and mitochondrial respiration. Metabolic therapies combined with immunotherapy may also improve antitumor immunity while overcoming therapeutic resistance. Therapy based on antioxidant and radical scavengers is still a topic that attracts much attention.

VI. CELLULAR SIGNALING NETWORKS, STRESS ADAPTATION AND NOVEL THERAPEUTIC APPROACHES IN METABOLIC & REDOX BIOLOGY

Living cells depend on their ability to sense environmental changes and rapidly mount adaptive responses for survival and functional stability. Physiological homeostasis is compromised under cellular stress conditions including oxidative imbalance, inflammation, nutritional deficiencies, infectious insults, mitochondrial derangements, toxic exposure and hypoxia which undermine the integrity of the cell. In response, cells enlist finely tuned signalling networks that coalesce rapid metabolic rewiring with redox regulation, mitochondrial adaptations, immune modulation and gene expression control. Such integrated responses allow cells to save energy production, maintain the redox balance, regulate inflammatory pathways and prevent irreversible cellular injury.

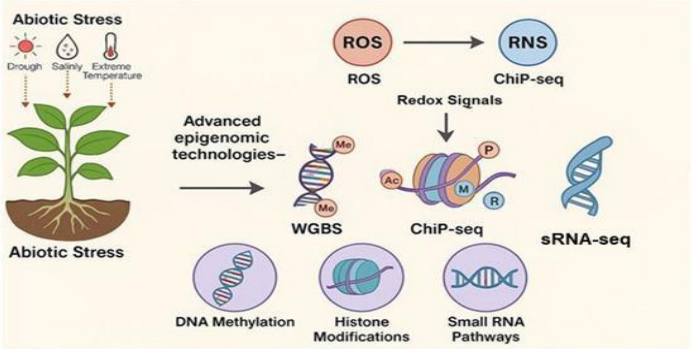

Figure 2: Advanced Omics and Systems Biology Approaches

The recent discovery of metabolism and oxidative signalling ranging from simple biochemical processes to complex, integrative regulatory networks has revolutionized our understanding on how cellular level inputs control immunity, epigenetic programming, and apoptosis, differentiation and disease progression. We now know that metabolic intermediates and reactive oxygen species can function as signalling molecules, altering transcription factor activity and chromatin remodelling and affecting the behaviour of immune cells. In a similar fashion, reversible oxidation-reduction reactions are regulated by redox homeostasis and thereby control mitochondrial respiration, inflammatory activation, and stress-responsive gene expression. Only during pathological conditions is it important that metabolism paralleled redox signalling. Since chronic exposure to stressful events causes widespread persistent mitochondrial dysfunction, inflammatory activation, oxidative injury and metabolic deregulation that are involved in cancer, cardiovascular disease, diabetes mellitus (DM), autoimmune disorder(s) and neurodegenerative syndrome [1], the purposes of this article are: 1. In addition, there are major metabolic and redox reprogramming within immune cells themselves during activation and inflammatory responses. This dedication to research using the nexus of immunometabolism and redox biology has created a new major interdisciplinary area with clinical relevance. AMP-activated protein kinase, the mammalian target of kanamycin, nuclear factor kappa B, hypoxia-inducible factor-1 alpha and nuclear factor elytroid 2-related factor 2 are stress-responsive signalling pathways (8) and play vital roles in metabolic adaptation or antioxidant defence as central regulators. These pathways integrate signals related to the sense of nutrients, mitochondrial function, cytokine production, autophagy, apoptosis and inflammatory response. Their deregulation is directly implicated in the progression of chronic diseases and tissue degenerations.

Capacities to understand cellular stress adaptation has been tremendously advanced through new technologies such as metabolomics, transcriptomics, proteomics, redox imaging and artificial intelligence combined with systems biology. Some of these strategies have uncovered relevant biomarkers and therapeutic targets related to metabolic flexibility, mitochondrial quality control, antioxidant defence and immune regulation. The focus of modern therapeutic strategies is to restore the metabolic balance and redox homeostasis utilizing targeted metabolic inhibitors, mitochondrial therapies, antioxidant modulators (including detoxifying compounds), immunometabolic interventions, and personalized medicine approaches.

Advanced aspects of stress-responsive signalling pathways, autophagy and cellular quality control, metabolic regulation of immune communication and future therapeutic innovation in practical terms for the field of metabolic and redox medicine have been discussed in this chapter. For a different example of how cells sense stress and adapt, see (Box 2), but one mechanism is through the activation or inhibition of various transcription factors such as p53.6.1 Stress-Responsive Signalling Pathways in Cellular Adaptation Cellular adaptation to stress involves the activation of intricate signalling pathways that orchestrate not only metabolic regulation but also antioxidant defences, inflammatory responses, and survival programs. These networks act like molecular sensors that can sense changes and variations in nutrient abundance, oxygen levels, energy status, and oxidative homeostasis.

AMP-activated protein kinase is considered a key energy-sensing molecule for cellular adaptation. During metabolic stress, the rise of AMP and fall of ATP levels in cells activate the AMPK. AMPK, when activated, promotes ATP producing catabolic pathways and inhibits energy consuming anabolic processes. Activation of AMPK stimulates fatty acid oxidation, mitochondrial biogenesis, glucose uptake, and autophagy, which increase cellular stress resistance as well as metabolic efficiency. In contrast to this, mammalian target of kanamycin (motor) signalling sustains anabolic metabolism, protein synthesis and cell growth/proliferation in nutrient-rich conditions. Hyper activated motor due to chronic pathological stimuli pushes cancer progression, obesity, insensitivity, aging and inflammatory disorders (32–36). The decision between survival and growth upon stress is made by a balance between AMPK and motor signalling.

Table 2: Signalling Pathways and Emerging Therapies in Metabolic and Redox Biology

Cellular Stress / Condition	Major Signalling Networks	Metabolic & Redox Adaptation	Therapeutic Approaches	Clinical Relevance
Hypoxia	HIF-1α, AMPK	Enhanced glycolysis, ROS regulation	HIF inhibitors, oxygen therapy	Cancer, ischemic disorders
Oxidative stress	Nrf2–Keap1 pathway	Antioxidant enzyme activation, glutathione synthesis	Antioxidants, Nrf2 activators	Cardiovascular and neurodegenerative diseases
Nutrient deprivation	AMPK, motor suppression	Fatty acid oxidation, autophagy induction	Caloric restriction mimetic, metformin	Diabetes, aging
Endoplasmic reticulum (ER) stress	UPR, PERK, ATF6, IRE1	Protein-folding control, redox balancing	Chemical chaperones, ER stress inhibitors	Metabolic syndrome, neurodegeneration
Mitochondrial dysfunction	Mitophagy pathways, PGC-1α	Reduced oxidative phosphorylation, ROS detoxification	Mitochondrial antioxidants, gene therapy	Parkinson's disease, Alzheimer's disease
Chronic inflammation	NF-dB, STAT3	Persistent ROS/RNS signalling	Anti-inflammatory drugs, cytokine inhibitors	Arthritis, fibrosis
Tumour microenvironment	HIF-1α, PI3K/Act/motor	Aerobic glycolysis, antioxidant defence	Immunotherapy, metabolic inhibitors	Cancer progression
Infection and immune activation	NF-dB, NADPH oxidase	Pentose phosphate pathway activation, respiratory burst	Antimicrobial therapy, immune modulators	Sepsis, chronic infections
Cellular senescence	p53, SIRTuins	Altered mitochondrial metabolism, oxidative imbalance	Senolytics, SIRT activators	Aging-related disorders
Ferro ptosis and lipid peroxidation	GPX4, System Cu–	Lipid ROS accumulation	Ferro ptosis inhibitors, iron cheaters	Cancer therapy, neuroprotection

One other major stress-responsive regulator that is activated in response to oxygen deprivation is hypoxia-inducible factor-1 alpha (HIF-1α). In the presence of hypoxia, HIF-1α accumulates and stimulates the transcription of genes involved in glycolysis, angiogenesis, erythropoiesis and mitochondrial adaptation. Low oxygen level induces HIF-1α-mediated glycolytic activation, ATP production is made possible by bypassing mitochondrial O_2 consumption and ROS generation Nuclear factor kappa B acts as a master regulator of inflammation and immune activation. Activation of the NF-dB signalling pathway by ROS, cytokines, microbial products or stress signals induces transcription of inflammatory mediators like TNF-α, IL-1β, and IL-6. The activation of NF-dB is associated with persistent inflammation and tissue damage, chronic inflammatory diseases, autoimmune diseases as well as tumour development.

Nuclear factor elytroid 2-related factor 2 is a key transcriptional regulator of antioxidant protection and detoxification. Nrf2 dissociates from the inhibitory protein Keap1 evading proteasome degradation and trans locating to the nucleus under oxidative stress conditions (17), where Nrf2 activates genes encoding proteins involved in antioxidant

enzymes, glutathione synthesis, and detoxification molecules. Nrf2 signalling has a critical role in protecting cells from mix-related oxidative damage and mitochondrial homeostasis. An important role in the adaptation of cells to stress is also played by the mitogen-activated protein kinase pathways including ERK, JNK and p38 MAPK. These kinases control apoptosis, inflammation, proliferation and differentiation in response to oxidative stress or fluctuations in the environment.

The integration of these signalling pathways involves a highly orchestrated network for the response to stress. Crosstalk between AMPK, motor, NF-dB, HIF-1α and Nrf2 mediates suitable cellular adaptation conversant to the magnitude and timing of stress.

Deregulation of stress-responsive signalling pathways contributes to the pathogenesis of cancer, neurodegeneration, cardiovascular diseases and metabolic syndrome. Hence, they are attractive therapeutic targets for restoring cellular homeostasis and preventing progression of disease.

VII. SYSTEMS LEVEL INTEGRATION OF CELLULAR STRESS, METABOLIC REPROGRAMMING AND REDOX THERAPEUTICS

Cellular stress adaptation is one of the most complex and essential biological processes that are required for survival under changing physiological and pathological environments. Cells are constantly subjected to a number of stressors such as oxidative damage, nutrient deprivation, inflammatory response, foreign pathogen attack, mitochondrial dysfunctions, direct high-energy events such DNA damage caused by radiation exposure and toxic environmental compounds and hypoxia (O_2 tension decrease). To ensure viability and restore homeostasis, cells activate tightly coordinated adaptive systems by rewiring metabolism, regulating redox state, modulating immune responses, remodelling mitochondria, and altering transcription in a site-, time-, and context-dependent manner. These adaptive mechanisms enable the continuation of energy production, antioxidant defence, biosynthetic activity and signalling under adverse environments. Yet, chronic or excessive stress impairs those protective responses and facilitates the progression of chronic diseases.

Metabolic rewiring is becoming a leading feature of how to cope with stress. Instead of being merely highways for ATP production, metabolic networks are now understood to be complex regulatory systems acting at the level of gene expression, epigenetic changes, inflammatory signalling and immune differentiation as well as cell-fate decision-making. In a context-dependent manner, cells transition between different metabolic states—either through glycolysis, oxidative phosphorylation, fatty acid oxidation, amino acid metabolism or cytogenesis depending on environmental conditions and substrate availability. This sharp molecular coordination of such metabolic transitions has its basis in their close coupling to redox signalling pathways that control reactive oxygen species (ROS) formation, antioxidant response and mitochondrial function, as well as stress-responsive transcription factors.

Within cellular systems, reactive oxygen species and reactive nitrogen species have dual functions. ROS play a signalling function at physiological concentrations regulating proliferation, immune activation; differentiation and adaptation to stress. Dose-dependent effects of ROS: On the contrary, too much accumulation of reactive oxygen species (ROS) results in oxidative damage to protein, lipid, mitochondria and nucleic acid which induces inflammation, senescence and apoptosis followed by tissue injury. Consequently, the preservation of redox homeostasis is essential for cellular sustainability and it relies on a network of antioxidant systems including glutathione, thioredoxin, catalase, superoxide dismutase, and regulated signalling mediated by Nrf2.

A. Mitochondrial Bioenergetics and Stress-Induced Metabolic Reprogramming

Mitochondria are dynamic organelles essential for cellular energy production, metabolic integration, apoptosis regulation and oxidative signalling. Under physiological conditions, mitochondria produce ATP with very high efficiency through oxidative phosphorylation via electron transfer along the respiratory chain. Mitochondrial metabolism, however, extensively remodels during cellular stress in order to sustain energy homeostasis and life.

B. Oxidative Stress, Inflammation and damage to Cells Pathways

Oxidative stress, which is defined as an imbalance between the generation of oxidants and antioxidant defence systems. Reactive oxygen species (ROS) are generated in a continuous manner during mitochondrial respiration, enzymatic reactions, immune activation and environmental exposure. However, high levels of ROS produced irreversibly damage cellular components, preventing normal cell function and consequently favouring the course of many pathological processes, while controlled production in appropriate amounts is important for signalling and host defence.

C. Immunometabolic reprogramming and host defence mechanisms

Host defence responses depend critically on metabolic adaptation and redox regulation in the immune system. Even with the diversity in activation signals, many steps of immune cell activation consume large amounts of energy and

biosynthetic resources to enable proliferation, migration, cytokine production, and antimicrobial activity. Thus, there are extensive metabolic changes of immune cells upon inflammatory and infectious challenges.

D. Aging Cellular Senescence and Metabolic Decline

Ageing Part 2203 Aging is associated with progressive deterioration of cellular function, metabolic efficiency, mitochondrial integrity and redox balance. Cellular senescence is thought to be a stable growth-arresting state that can be triggered by oxidative stress, DNA damage, mitochondrial dysfunction and chronic inflammatory signals. Senescence is originally established as a barrier against malignant transformation, but occupancy of senescent cells leads to tissue decline and aging pathology.

E. Early-stage Redox Therapeutics and Precision Medicine Approaches

The broader understanding of metabolic rewiring and redox regulation has made it possible to develop sophisticated therapies aimed at cellular stress pathways. In contrast, contemporary therapeutic approaches are directed towards re-establishing metabolic homeostasis that encompass mitigation of oxidative insult, modulation of inflammation and amelioration of the mitochondrial functionality.

VIII. ABBREVIATIONS ADVANCED CELLULAR STRESS NETWORKS AND THERAPEUTIC OPPORTUNITIES IN METABOLIC AND REDOX BIOLOGY

Cellular adaptation to stress is a coordinated effort whereby metabolism, redox signalling, mitochondrial communication, inflammatory regulation, and immune system coordination are all involved. Each living cell is constantly exposed to extracellular and intracellular stressors that jeopardize its energy homeostasis, protein folding, membrane integrity, and genome stability (1–3). We will focus on various stressors including but not limited to hypoxia, oxidative injury, nutrient deprivation, infection, toxic exposure, mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory cytokines and mechanical damage. Cells adapt to survive under these stressful conditions by inducing gene expression programs that globally remodel metabolic pathways, regulate antioxidant systems, stimulate repair, and coordinate paracrine signalling with neighbouring cells and immune compartment.

For the past decade, work from metabolic biology and redox medicine has established that metabolism is not merely a biochemical process of making ATP. Rather, that metabolic pathways act as dynamic signalling networks that can modulate inflammation, epigenetic regulation, immune activation, stem cell differentiation and apoptosis and tissue regeneration. Similarly, reactive oxygen species are not looked at solely as damaging metabolic by-products. On the other hand, spatially regulated ROS generation is required for signalling within cells, and both antimicrobial immunity and hypoxic adaptation depend on finely-tuned ROS levels to coordinate signalling pathways that modulate transcription factors (TFs) such as NF-dB, HIF-1α and Nrf2 [4]. On the other hand, over-production of oxidants leads to oxidative stress damaging proteins, lipids, nucleic acids and organelles which plays an important role in chronic disease progression and ultimately tissue degeneration.

A. Mitochondrial Dynamics and Oxidative Metabolic Regulation

Mitochondria are dynamic organelles that undergo constant cycles of fusion, fission, biogenesis and mitophagy to preserve functional integrity and metabolic efficiency. They are important processes that modulate cellular adaptation after metabolic stress and oxidative injury. Regulation of mitochondrial dynamics is essential for optimal ATP generation, ROS balance, calcium signalling and apoptosis.

Mitochondrial fusion is responsible for organelle-to-organelle exchange of multiple mitochondrial DNA, proteins and metabolites that may enhance respiratory efficiency and limit localized damage. Mitochondrial fusion is regulated by proteins including mitofusin-1, mitofusin-2, and OPA1 to maintain structural organization of the mitochondrial network.

Mitochondrial fission, on the other hand, separates damaged regions from functional mitochondria. DRP1-mediated fission enables clearance of dysfunctional mitochondria by mitophagy and limits ROS overproduction. This makes controlled fission urgent for mitochondrial quality control and adaptation to stress.

B. Mechanisms of adaptive stress tolerance and cellular resilience

Cells have wonderful survival mechanisms that help them survive changes in environmental and metabolic conditions. Adaptive response to stress includes functional responses such as the coordinated activation of antioxidant defence systems, autophagy, heat shock responses,DNA repair pathways, and metabolic remodelling for protecting cells from injury and recovery homeostasis.

Hermes's is defined as a biological phenomenon whereby mild exposure to stress results in improved resistance to adverse challenges. Low oxidative stress states, calorie restriction, physical exercise and intermittent fasting activate adaptive pathways improving mitochondrial function, antioxidant capacity and cellular survival. These adaptive responses promote long-term stress tolerance and can delay the aging process.

C. Towards Therapeutics: Future Directions and Clinical Translation

Rising knowledge of metabolic rewiring and redox biology have catalysed new therapeutic innovation in chronic disease management. Emerging treatments are more centred around restoring metabolic flexibility, increasing mitochondrial function and immunity, while exhibiting selective actions on oxidative signalling.

Precision medicine strategies combining metabolomics, genomics, transcriptomics and redox profiling discover patient-specific metabolic signature(s). Such profiles can help in devising personalized therapies that may improve the efficacy of treatments without causing undesirable effects. Thus these fields are speeding up this process using the data, which can help analyse these complex metabolic networks and predict a therapeutic response.

IX. CONCLUSION AND FUTURE DIRECTIONS

Biochemical reprogramming and redox control in cellular distress has emerged as the most revolutionary field of research in contemporary biomedicine. In the past several decades, it has been recognized that metabolism and redox biology are not simply separate biochemical systems but they work as highly integrated regulatory networks of cellular adaptation such as those regulating immune function, inflammation, tissue repair, aging and disease progression. Cellular stress responses include dynamic interactions between mitochondrial metabolism, oxidative signalling, inflammatory pathways, epigenetic regulation and interurban communication systems. These orchestrated mechanisms allow cells to sustain life and functionality under ever-changing physiological and pathological settings. In this paper, we have shown that metabolic flexibility is an essential aspect of cellular adaptation. Cells constantly rewire their metabolic pathways based on nutrient conditions, oxygen tension, inflammatory signals, and energetic needs. Not just energy-producing pathways, they are in fact master regulators of signalling and cellular behavior for glycolysis, oxidative phosphorylation, fatty acid oxidation, glutaminolysis and cytogenesis. Metabolic rewiring enables authors to maintain ATP production, produce biosynthetic intermediates and preserve redox balance under the stress conditions of hypoxia, infection (and high parasite burden), oxidative injury and nutrient deprivation.

Mitochondria play a central role in these adaptive systems. Apart from their classical function in ATP production, mitochondria also play a key role in regulating apoptosis, calcium signalling, reactive oxygen species (ROS) generation, immune activation and metabolic crosstalk. Mitochondrial dynamics, such as fusion, fission, biogenesis and mitophagy are critical for maintaining the organelle quality to protect from excessive oxidative damage. Dysfunctional mitochondria are a cause of chronic inflammation, metabolic syndrome, neurodegenerative diseases and cardiovascular pathology as well as aging and cancer. Reactive oxygen species themselves also have been recast to be important signalling molecules instead of just being damaging by-products of metabolism. Physiological levels of ROS specify proliferation, differentiation, immune activation and stress adaptation via redox-sensitive signalling cascades. On the other hand, abnormal levels of ROS accumulation lead to oxidative tissue injury and result in inflammatory response, senescence process, fibrosis and degeneration [5]. The antioxidant systems, including glutathione, thioredoxin, catalase, superoxide dismutase and Nrf2 signalling to maintain redox homeostasis is thus necessary for the integrity of cell function. It recorded the increasing prominence of immunometabolism and its role in disease mechanisms. During activation, differentiation and inflammatory responses, immune cells are subject to profound metabolic and redox reprogramming. Metabolism is most engrafted in macrophage polarization, T-cell differentiation, inflammasome activation and cytokine production. Furthermore, deregulation of immunometabolic pathways is involved in having prominent roles in the development of autoimmune diseases, chronic infections, metabolic syndrome, cancer progression and immune exhaustion.

The role of systemic metabolic communication is also highlighted as a critical component discussed throughout this work. Through hormones, cytokines, metabolites and extracellular vesicles, organs such as the liver, adipose tissue, skeletal muscle, brain and gut micro biota are coordinated into an integrated metabolic response. The compromise of these communication pathways contributes to stunted fucntion, chronic low-degrade inflammation-driven insulin resistance and obesity-associated disease as well as systemic oxidative stress. The association between aging and metabolic-redox disaster has additionally been highlighted. Aging is caused by progressive decline in mitochondrial function, deterioration of antioxidant system, chronic inflammation and decrease of cellular viability. Tissue degeneration and age-related diseases involving cellular senescence and inflammation Comprehension of these processes gives insights into approaches for enhancing health span and disease prevention.

Notably, the advent of new technologies including metabolomics, redox proteomics, transcriptomics, single-cell analysis and artificial intelligence/computational biology has fuelled progress in this area. Together, these technologies have (1) allowed the identification and validation of disease-specific metabolic signatures and (2) provided novel therapeutic targets associated with oxidative stress and mitochondrial dysfunction. The inclusion of metabolic profiling data with genomic and immunological information into precision medicine approaches will probably change disease detection and management in the future.

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