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Review

Cellular Signaling Networks Governing Metabolic and Stress Responses

Swesha Chhabra
Research Scientist, AIIMS, New Delhi, 110029

Corresponding Author:
Dr Swesha Chhabra

Email:
sweshachhabra1313@gmail.com

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Abstract:
The combined effect of metabolic and stress-response signaling networks is necessary to maintain cellular homeostasis. The metabolic networks that are based on insulin, AMPK, and mTOR pathways monitor nutrient and energy conditions to mediate anabolic or catabolic programs. There are stress-response mechanisms, such as the NRF2 antioxidant, HIF-1a hypoxic, and UPR proteolytic pathways, which respond to and counteract a particular insult to the cellular integrity. More importantly, such systems are not compartmentalized but extensively crosstalk, constituting a single adaptive network. Signals are incorporated by key hubs such as the AMPK and mTOR, switching the cell between growth and survival state. Examples of this type of integration include metabolic pathways that have a direct effect on the responses to stress, including glutamine metabolism to support antioxidant defense and lipid peroxidation to support ferroptosis. The network is the basis of significant pathologies when maladaptively regulated: the overload of the network by chronic nutrient excess causes the formation of the metabolic syndrome; the cancer cell intrudes into the normal routes of metabolism and stress adaptation, becoming cancerous; a vicious circle of metabolic failure and neurotoxic stress appears in the neurodegenerative diseases. An approach that should be used to decipher this complexity is systems biology, using omics data and computational modeling to track network interactions and predict behaviors. It was described through this network perspective that therapeutic approaches need to shift away at targeting individual molecules to perturbing key nodes and edges in the network to provide a promising platform to address complicated diseases such as diabetes, cancer, and neurodegeneration.

Keywords: Cellular signaling, HIF-1α, NRF2, AMPK, mTORC1.

Introduction

The procurement of resources and the alleviation of threats provide a delicate and dynamic equilibrium of cellular life. Two overriding, highly interlinked systems, metabolic signaling networks and stress response networks, control this balance. Metabolic signaling networks serve as the bureaus of resource control and economic planning of the cell. They are mainly responsible to detect the presence of nutrients and energy-containing substances: to detect the concentration of glucose, amino acids, lipids, and ATP and to implement suitable anabolic (building) or catabolic (breaking down) programs. The insulin signaling pathway, which regulates nutrient storage under plenty, the master energy sensor, AMP-activated protein kinase (AMPK) activated in times of depletion to replenish ATP, and the growth hub of all, the mechanistic target of rapamycin (mTOR) are

among the main regulators. Conversely, stress response networks can be compared to emergency and maintenance crews that are specialized. They are regulated through certain insults: protein misfolding (activation of the Heat Shock Response and Unfolded Protein Response), oxidative damage (activation of the Keap1-NRF2 pathway), oxygen deficiency (stabilization of Hypoxia-Inducible Factor, HIF), or DNA breaks and their aim is to restore the damage, preserve proteostasis, and allow survival. In essence, metabolic networks process the cellular economy whereas the stress networks process the crisis that interferes with the former.

The necessity of crosstalk between these systems is a mere biological fact, namely these processes are metabolism and stress that are closely intertwined. The metabolic reactions feed the cell and produce potentially toxic by-products, including reactive oxygen species (ROS) by the mitochondria. On the other hand, the cost of organizing any powerful response to the stress is energetically costly, and it needs ATP and biosynthetic precursors. Thus, efficiency and survival is a requirement of two-way communication constantly. This crosstalk is not a simple overlap, but a design principle and results in an integrated adaptive system. A good example is central position of AMPK and mTOR as signaling hubs. Low-energy activation of AMPK not only switches on catabolism, but also directly phosphorylates and activates NRF2, the antioxidant response transcription factor, bypassing the connection between energy crisis and defense gene activation. At the same time, mTORC1 is inhibited by AMPK and prevents energy-consuming growth. Practically all key stress signaling pathways, including oxidative, hypoxic, and ER ones, converge to suppress mTORC1. This inhibition has two functions, ATP is preserved to defend against attack and mTOR is relieved to suppress autophagy, which is an essential recycling procedure resulting in the production of internal nutrients and the elimination of damaged parts. Therefore, mTOR is an irreversible switch that makes the cell switch between a growth mode to a survival mode in response to stress.

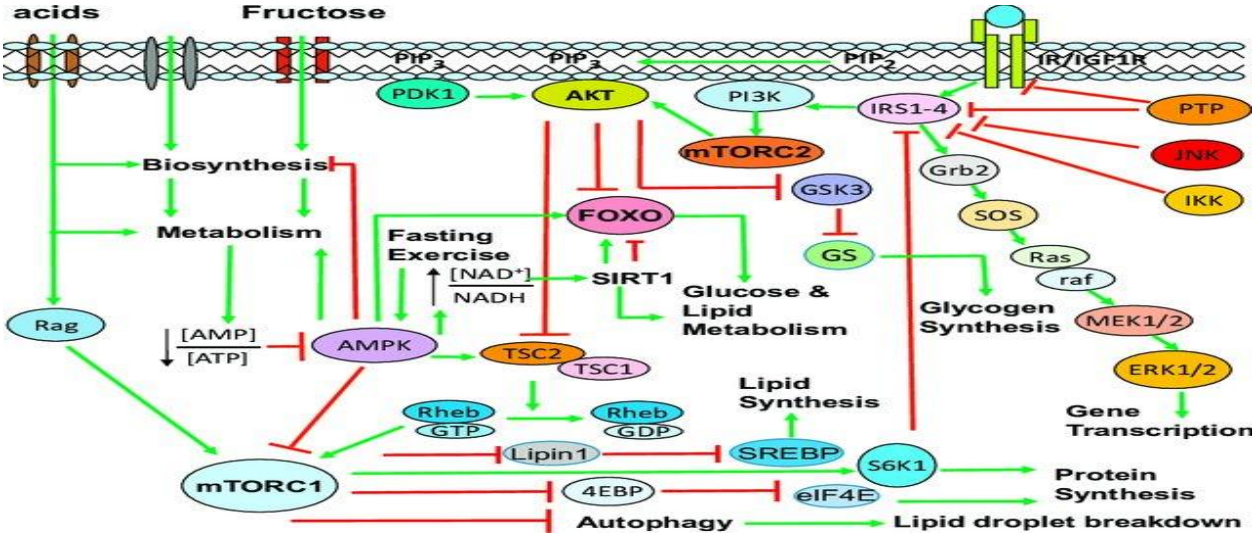

Fig: 1 Insulin signaling and nutrient sensing in hepatocytes. Significant insulin and amino acid signaling pathway signaling cascades are represented by this simplified diagram. Usually, insulin and nutrient signaling is brought together to achieve metabolic homeostasis. Insulin is also important in the metabolism of glucose, lipids, and proteins. The insulin signaling cascade activated on insulin stimulation is the insulin signaling cascade (IR/IRS/PI3K/PDK1/mTORC2/AKT).

Being one of the key kinases in the lineage of the insulin pathway, AKT regulates the hepatic glucose and lipid homeostasis. One of the functions of AKT is the activation of the synthesis of glycogen by inactivation of GSK3 via phosphorylation. In the meantime, AKT suppresses hepatic gluconeogenesis transcriptional activity of FOXO by phosphorylating and excluding FOXO to the nucleus. Lipid and protein synthesis via activation of mTORC1 is also induced by AKT. Besides insulin, amino acids also

stimulate mTORC1 to stimulate protein synthesis and suppress autophagy. mTORC1 activates lipogenesis by activating SREBPs. FOXO also undergoes deacetylation by an NAD th -dependent deacetylase, SIRT1. The metabolic homeostasis is controlled by the energy sensor AMPK, which triggers FOXO and suppresses mTORC1. Abbreviations: IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PDK1, 3-phosphoinositide-dependent protein kinase 1; AKT, RAC-alpha serine/ threonine-protein kinase; mTORC2, mammalian target of rapamylin complex 2; FOXO, forkhead box O; SIRT1, sirtuin 1; AMPK, adenosine.

Such integration forms advanced feedback loops. To provide an example, the hypoxia response through HIF-1a can not only cause glycolysis but also can enhance the ROS generation through altered metabolism which may in turn regulate the stability of HIF and enhance the adaptive response. Likewise, ER stress via the Unfolded Protein Response (UPR) intensively suppresses global translation to abate the protein-folding load which must be precisely coordinated with mTOR and nutrient-sensing signaling. When dysregulation occurs in this complex crosstalk, pathology occurs. The chronic nutrient overload, such as in obesity, causes sustained metabolic cross-signaling which can overwhelm such integrated systems to cause chronic low-grade stress-meta-inflammation, chronic ER stress, and oxidative damage. This, in its turn, interferes with metabolic signaling; such stress-activated kinase as JNK may phosphorylate insulin receptor substrates, which disrupts insulin signaling and builds a vicious cycle of insulin resistance. Such pathogenic interaction is a foundation of diabetes, cancer (with tumor cells using HIF and mTOR to proliferate in hostile microenvironment), and neurodegeneration (with impaired metabolism and proteostatic stress crossing). The complexity of the interconnected networks, in which components are involved in several pathways and interaction processes are not linear, requires a paradigm shift in reductionist biology to the systems perspective. Systems biology gives the computational and conceptual framework in which these networks are modelled as dynamic, interactive wholes and not isolated linear pathways. This method starts with the generation of high-throughput omics data, that is, transcriptomics, proteomics, and metabolomics data, which give global snapshots of cell states in different conditions. This data is then mined by bioinformatics to recreate interaction networks, mapping interactions among proteins, genes and metabolites. Topology analysis of such networks shows that important architectural properties, such as highly connected "hub" nodes (such as p53 or AMPK), whose failure has disproportionately large effects), and repetitive "motifs" such as feedback loops, which provide stability or pulse-like response. The end product is to develop mathematical models of prediction. Kinetic models involve simulation of the time-varying flow of signals with the use of differential equations and need specific biochemical data. In larger, less-quantified networks, logic-based models (Boolean logic or fuzzy logic) reduce components to the states of on/off to have logical rules that effectively summarize the important decision-making logic. In metabolism Constraint-based models Canonical models (e.g., Flux Balance Analysis) rely on stoichiometry of known reactions to make predictions of how metabolic fluxes reroute in response to stress or genetic changes. The strength of these models is that they are able not only to describe a network but also to make predictions and even specific mechanisms: they can predict how a network will behave in response to a given combination of drugs, what node in the network makes the system resistant or delicate, and how an emergent property, such as a bistable switch that it commits a cell to death or survival, is produced. Systems biology informs focused therapeutic approaches by shedding light on the principles of the integrated metabolicstress system, e.g. by combining a hub and its compensatory pathway to overcome resistance in cancer. Therefore, the issue of cellular adaptation needs to be seen through the lens of not only the specialized channels of cellular metabolism and cellular stress, but of an elaborate, emergent logic of the network that emerges when they are integrated.

Core Metabolic Signaling Networks and Nutrient Sensing

The accuracy of the interpretation of nutrient availability is vital to coordinate energy production and biosynthesis to cellular survival. It is a crucial role played by core metabolic signaling networks-

evolutionarily conserved pathways that measure both intracellular and extracellular nutrient concentrations and convert them to growth, division or conservation signals. The most prominent of these is the insulin signaling pathway which is the main orchestra-conductor of anabolic, and the antagonistic duo between AMP-activated protein kinase (AMPK) and the mechanistic target of rapamycin (mTOR) is a central regulatory nexus that coordinates signals about cellular energetics in response to energy status, nutrients and stress. These complex networks are not simply metabolic glitches, but a core cause of disease, as seen in the extreme restructuring of metabolism in diseases such as cancer.

Insulin Signaling and the Pathogenesis of Insulin Resistance

The main system through which the body transmits the information of the abundance of nutrients to the individual cells is the insulin signaling pathway. When insulin is bound to its receptor tyrosine kinase, a cascade is triggered such as phosphorylation of insulin receptor substrates (IRS), phosphoinositide 3-kinase (PI3K) activation and the production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3). This lipid second messenger recruits and activates the serine/threonine kinase Akt (PKB), which is involved in the execution of the pleiotropic effects of insulin: glucose uptake through GLUT4 translocation, glycogen and lipid synthesis, and gluconeogenesis and autophagy inhibition.

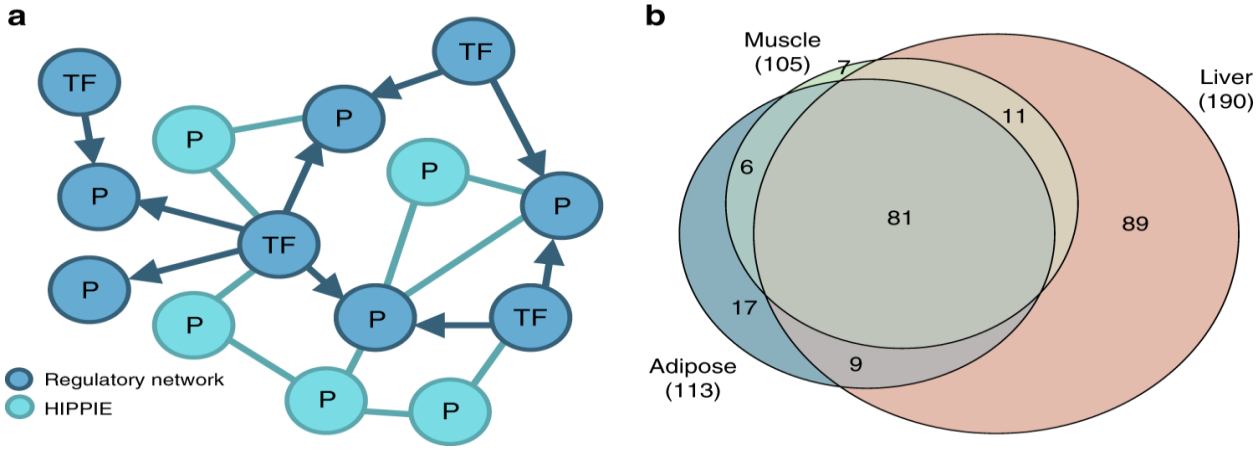

Fig: 2 Determination of MetSyn-related genes. a Venn diagram depicting the intersect of MetSyn genes that were found in GWAS catalog, GWAS summary statistics and text mining. See Supplementary Fig. 2 and Supplementary Data 3. b Pathway enrichment map of the shared gene contents between the pathways enriched in MetSyn genes. All the nodes represent pathways and the edges between pathways represent the existence of common genes. Colors determine the membership to neighborhoods as recognized by random walk clustering algorithm.

This route forms the basis of the postprandial metabolism leading to the storage of the nutrients. Insulin resistance is a condition of reduced cellular sensitivity to insulin that is caused by the chronic disturbance of this finely-tuned system. It is a multifactorial pathogenesis process that revolves around metabolic stress and inflammatory signaling. The permanently increased nutrients especially the free fatty acids and glucose produce intracellular stress. This involves overproduction of reactive oxygen species (ROS) and endoplasmic reticulum (ER) stress by high protein and lipid synthetic loads in the mitochondria and endoplasm, respectively. These stressors stimulate a cascade of stress associated serine/threonine kinases including those of the c-Jun N-terminal kinase (JNK) and the Inhibitor of kB kinase b(IKKb). Importantly, the kinases phosphorylate the IRS proteins at Ser307 (e.g.), preventing their tyrosine phosphorylation and initiating their breakdown as well as interfering with their binding to the insulin receptor. This is a decoupling step in the insulin receptor-downstream effector pathway since the crucial molecular event is this serine phosphorylation of IRS. Moreover, overabundance of nutrients and cytokines such as TNF-z can trigger mTORC1 and protein kinase C

(PKC) isoforms which also worsen this repressive serine phosphorylation. The resultant systemic hyperinsulinemia, hyperglycemia, and lipid spillover caused by the impaired insulin signaling result in a vicious cycle that propagates to cause metabolic syndrome and type 2 diabetes.

Master Regulators of Cellular Energetics: AMPK and mTOR Signaling

Whereas insulin triggers nutrient availability out of the cell AMPK and the mTOR pathways are the yin-yang regulators of cellular metabolism, which monitor and respond to the intracellular energy and nutrient status. AMPK is the major energy sensor of the cell. It is allosterically stimulated by an increase of AMP:ATP ratio, which is a direct indicator of energy depletion. Upon recruitment, AMPK phosphorylates numerous targets to inhibit energy-demanding anabolic signatures (e.g. fatty acid and cholesterol synthesis) and activate energy-yielding catabolic signatures (e.g. fatty acid oxidation and autophagy). It is a crossroads of metabolic stress combination as it is stimulated by the upstream kinase (LKB1) in response to low glucose and by the CaMKKb in response to exercise-induced calcium signaling.

In direct antithesis, mTOR, especially in complex 1 (mTORC1) form, is the supreme growth promoter, which triggers anabolism, when the conditions are right: enough growth factors (via PI3K-Akt signaling, inhibiting the TSC1/2 complex) and plenty of intracellular amino acids (detected by the Rag GTPases), and enough cellular energy. Active mTORC1 facilitates mRNA translation by phosphorylating S6K and 4E-BP1, enhances lipid and nucleotide synthesis and, notably, inhibits autophagy. This is an antagonistic relationship: AMPK directly phosphorylates and activates TSC2 and Raptor, which in turn causes a strong inhibition of mTORC1, which in turn makes sure that the growth is held back under energy stress. This self-regulation guarantees that anabolism and autophagy energy-intensive processes, an essential process of recycling and quality-control, are mutually exclusive so that the cell does not eat itself in its attempt to grow in size.

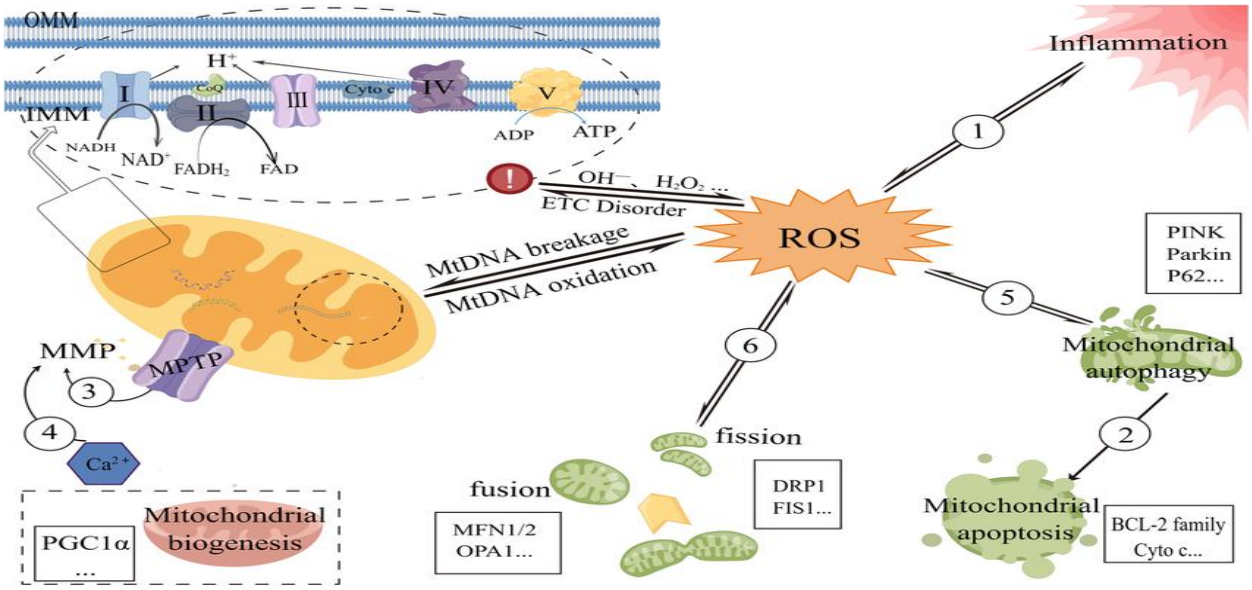

Fig: 3 Figure of certain pathways of mitochondrial dysfunction in metabolic-related kidney disease 1) Oxidized mitochondrial DNA fragments may enter the cytoplasm through MPTP, and bind to NLRP3 and cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS), which may in turn activate the NLRP3 inflammasome. ROS may also cause inflammatory exacerbation. 2) The mitochondrial pathway autophagy breaks the structure of the mitochondrial bilayer, and initiates the apoptosis-related proteins, leading to mitochondrial-pathway apoptosis. 3) Extended MPTP opening leads to release of proteins with negative charge into the mitochondrial matrix which influences concentrations of ions on either side of the inner membrane of the mitochondrion and, eventually, causes a decrease in the MMP. 4) Ca2+ provokes a typical mitochondrial membrane permeability transition (MPT), which leads to atypical MPTP opening, mitochondrial swelling, and reduced membrane potential. 5) Mitochondrial

autophagy preserves the integrity of the mitochondrial function and minimizes the production of ROS and vice versa, excessive ROS may selectively destroy oxidatively damaged mitochondria by using mitochondrial autophagy preferentially reducing its harm to cells. 6) Oxidative stress caused by excessive ROS reduces the fusion and enhances fission of mitochondria. Mitochondrial fission results into alterations of the mitochondrial membrane that causes fragmentation of mitochondria as well as the increase in ROS.

Key Nutrient-Sensing Pathways

Pathway	Primary Stimulus/Sensor	Key Effectors	Primary Cellular Outcome	Integration with Stress Responses
Insulin Signaling	High blood glucose/Insulin receptor	PI3K, Akt, mTORC1	Promotes nutrient storage, growth, and anabolism.	Inhibited by stress kinases (JNK, IKKβ) via IRS serine phosphorylation during metabolic/inflammatory stress.
AMPK Pathway	Low ATP:AMP ratio; Energy stress	AMPK, TSC2, ULK1	Inhibits anabolism (mTOR), stimulates catabolism (autophagy, glycolysis) to restore energy.	Activated by various stresses (hypoxia, ROS). Directly phosphorylates and activates NRF2 for antioxidant defense.
mTOR Pathway	Abundant nutrients (AAs, growth factors), energy	mTORC1, S6K, 4E-BP1	Promotes protein/lipid synthesis, inhibits autophagy; central hub for growth signals.	Directly inhibited by multiple stress pathways (UPR, DNA damage, hypoxia) to halt growth and conserve resources.
Sirtuin Pathway	High NAD+ ratio (low energy status)	SIRT1, PGC-1α, FOXOs	Enhances mitochondrial biogenesis, fatty acid oxidation, stress resistance, and longevity.	Links metabolic state to epigenetic regulation and oxidative stress response; deacetylates and activates PGC-1α, FOXOs.

Metabolic Reprogramming in Disease: The Warburg Effect and Beyond

These fundamental metabolic networks become hijacked and rewired in a disease state in support of pathological development. The best known is the Warburg effect or the aerobic glycolysis in cancer. In this case, the glucose to lactate fermentation is selective in the tumor cells despite the abundant supply of oxygen, which is an inefficient energy production means. This reprogramming is not caused by the dysfunction of the mitochondria but a strategic evolution by oncogenic signaling. Signaling constitutively active PI3K-Akt-mTOR, stabilized HIF-1a in the hypoxic tumor core, and mutations in p53 (which facilitates oxidative phosphorylation) all intersect on the increase in glucose transporters and glycolytic enzymes.

The benefit of such a metabolic transition is twofold. First, it offers quick ATP production to achieve the needs of quick proliferation. Second, and more so, glycolysis and a related diversion of glycolytic intermediates into a branching pathway (the pentose phosphate pathway, serine/glycine synthesis) give the biosynthetic building blocks (nucleotides, amino acids, lipids) required to construct new cells. Third, it aids in the regulation of redox balance by producing NADPH through the pentose phosphate pathway in order to overcome oxidative stress. Accordingly, the Warburg effect is an essential re-evaluation of metabolism as energy-efficient homeostatic production of ATP to an unnecessarily inefficient but biosynthesis-oriented metabolism to unchecked growth.

This metabolic reprogramming concept has a much broader scope than cancer. There is also a comparable glycolytic shift in activated immune cells, e.g. M1 macrophages and effector T cells, when recognizing antigens that is necessary to quickly provide energy to generate cytokines and to drive clonal expansion-the basis of efficient immunology but which can induce inflammatory disease when unregulated. In contrast, in neurodegenerative pathologies such as

Alzheimer, the neurons show an inverse Warburg effect which is reduced glucose metabolism and mitochondrial malfunction causing bioenergetic failure. This is commonly associated with aberrant stress signaling including chronic ER stress and oxidative damage, that also disrupts insulin and AMPK signaling pathways in the brain, which further causes synaptic loss and cell death. The appreciation of these disease-specific rewiring incidences indicates that the metabolic pathways are not inert energy-carrying conduits but dynamic, adaptable entities and their dysregulation is at the root of many pathologies, providing a fertile terrain on which to deploy therapeutic interventions.

Major Cellular Stress Response Systems

Intrinsic and environmental stressors constantly test cellular functioning by posing a threat to the integrity of macromolecules and their homeostasis. In order to survive, cells can use an array of dedicated stress response systems, each of which is optimally adapted to a type of insult. Such pathways sense damage and cause repair programs and, when required, cause programmed cell death so as to preserve the organism. The most important of them is the responses to oxidative, hypoxic, and proteotoxic stresses that are in a combination that ensures the redox balance, oxygen usage, and protein fidelity.

Oxidative Stress and the Keap1-NRF2 Antioxidant Pathway

An imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defence ability of the cell leads to oxidative stress. Although ROS are significant levels of signaling molecules, their accumulation is harmful to lipids, proteins, and DNA. The main defense mechanism is the Keap1-NRF2 pathway. In the basal conditions the transcription factor NRF2 is kept in the cytoplasm by its suppressor Keap1 and is ubiquitinated and degraded in the proteasomes. This forms a sensitive redox sensor ability. The metabolic production of electrophiles or ROS or exposure to xenobiotics alters key cysteine residues on Keap1 and causes a conformational change in the protein, which interferes with its ubiquitinogenic activity on NRF2. Recently produced NRF2 is then no longer degraded, translocates to the nucleus, and heterodiminizes with small Maf proteins. This complex interacts with an Antioxidant Response Elements (AREs) in the promoters of more than 200 genes, which coordinated antioxidant and detoxification program. Genes induced by the mechanism encode glutathione synthesis enzymes (e.g., GCLC, GCLM), ROS-scavenging proteins (e.g., heme oxygenase-1, SOD1), and phase II detoxification enzymes, which restore redox homeostasis. It is an important interface with metabolism because this pathway is regulated by metabolic intermediates and supplies reducing power required by biosynthetic pathways.

Hypoxic Stress/HIF-1a Signaling

Hypoxia (oxygen deprivation) is an extreme menace to aerobic organisms as it paralyzes oxidative phosphorylation. Hypoxia-Inducible Factors (HIFs) that include HIF-1 dominate the cellular response. In normoxia, the subunits of the HIF-1a protein are transcribed at a steady-state level but are instantly hydroxylated on their proline residues by the prolyl hydroxylase domain enzymes (PHDs). This is the oxygen-dependent modification which is the central oxygen-sensing mechanism. The von Hippel-Lindau (pVHL) E3 ubiquitin ligase complex recognizes hydroxylated HIF-1a and triggers its rapid degradation by the proteasome to maintain levels of the protein at low levels. A decrease in oxygen tension inhibits PHD activity, permitting HIF-1a to stabilize, dimerize with its constitutive partner HIF-1b (ARNT) and to bind to Hypoxia Response Elements (HREs). A complete metabolic adaptation is coordinated by HIF-1 transcriptome. It triggers glycolysis with the prompt upregulation of glucose transporters (GLUT1) and all glycolytic enzymes and prevents migration of pyruvate into the mitochondria in favor of lactate, through the activation of pyruvate dehydrogenase kinase (PDK1). At the same time, HIF-1 provokes angiogenesis (through VEGF) and erythropoiesis (through EPO) in order to enhance the supply of oxygen over a long period of time. This reaction is closely connected with oncogenic signaling and most tumors are characterized by constitutive activation of HIF, promoting the Warburg effect and active growth.

Endoplasmic Reticulum Stress and the Unfolded Protein Response (UPR)

Secretory and membrane proteins also undergo their folding in the endoplasmic reticulum, which is very sensitive to energy, calcium, redox, or nutrient deprivation. Misfolded proteins lead to the

accumulation of misfolded proteins causing ER stress, which activates a collective signaling network called the Unfolded Protein Response (UPR). Three sensor proteins that are resident in the endosome (ER) mediate the UPR: IRE1a, PERK, and ATF6. Both of them start different arms of the response. The mRNA of the transcription factor XBP1 is cleaved by IRE1a, an endoribonuclease, to produce a powerful spliced variant (sXBP1) which increases the expression of ER chaperones and ER-associated degradation (ERAD) genes. PERK phosphorylates the translation initiation factor eIF2a, causing the attenuation of protein synthesis to be globally but temporarily decreased to reduce the folding burden, with translation of the transcription factor ATF4, which activates amino acid metabolism and antioxidant response genes of the genome, being selective. ATF6 dissociates to the Golgi where it is cleaved to liberate its active cytosolic segment, which also causes an increase in chaperone genes. This tripartite signaling is integrated to repair proteostasis via enlargement of ER capacity, increased folding and degradation of non-repairable proteins. But intense or chronic ER stresses reverses the UPR signal to a pro-apoptotic signal, mainly via CHOP, and associates chronic metabolic pathology with cell death in conditions such as diabetes and neurodegeneration.

Overview of Major Cellular Stress Responses

Stress Response	Key Initiating Signal/Condition	Central Mediator(s)	Primary Protective Actions	Cross-talk with Metabolism
Oxidative Stress Response	Excess Reactive Oxygen Species (ROS), electrophiles	NRF2 (NF-E2-related factor 2)	Induces antioxidant enzymes (SOD, catalase), glutathione synthesis, and detoxification genes.	Consumes NADPH for reduction; activated by electrophilic metabolites.
Hypoxic Response	Low oxygen tension (Hypoxia)	HIF-1α (Hypoxia-Inducible Factor)	Reprograms metabolism to glycolysis, induces angiogenesis (VEGF), erythropoiesis.	Directly suppresses oxidative phosphorylation; requires functional glycolysis.
Unfolded Protein Response (UPR)	Accumulation of unfolded proteins in ER lumen	IRE1α, PERK, ATF6	Attenuates translation, upregulates ER chaperones, expands ER capacity, enhances ERAD.	Inhibits mTORC1; activated by lipid overload and cholesterol excess.
Heat Shock Response (HSR)	Protein misfolding/denaturation, heat	HSF1 (Heat Shock Factor 1)	Upregulates Heat Shock Proteins (HSPs) as molecular chaperones to refold or degrade damaged proteins.	Requires ATP for chaperone function; inhibited by active mTORC1.
DNA Damage Response (DDR)	DNA strand breaks, replication stress	ATM, ATR, p53	Arrests cell cycle, activates DNA repair machinery, or induces senescence/apoptosis.	Arrests cell cycle to conserve energy; p53 can inhibit glycolysis.

The Heat Shock Response (HSR) and Molecular Chaperones

The major defense mechanism of the cell against proteotoxic stress, which is a consequence of protein misfolding and aggregation, is called Heat Shock Response (HSR), and it is evoked not only by heat but also by toxins, heavy metals, and metabolic inhibitors. The progeny regulator is Heat Shock Factor 1 (HSF1). In non-stressful conditions, the Hsf1 exists in an inactive monomeric form due to inhibitory relations with molecular chaperones such as the Hsp90 and Hsp70. These chaperones are sequestered by the influx of misfolded proteins and HSF1 is released to be used. Released HSF1

trimerizes, becomes activatingly phosphorylated and translocates to the nucleus, where it interacts with Heat Shock Elements (HSEs) of promoters in target genes. This promotes the huge expression of heat shock proteins (HSPs) genes. Hsp70, Hsp90, and small HSPs, which are HSPs, are ATP-dependent molecular chaperones that prevent aggregation, refold denatured proteins, or degrade terminally damaged proteins via the ubiquitin-proteasome system or autophagy. An example of a negative feedback loop that is self-regulating is the HSR: the higher the refolding capacity, the more HSPs re-associate with HSF1 and inhibit it, to reestablish basal activity. This is an essential and vital pathway of proteostasis and its degeneration is linked to aging and protein aggregation neurodegenerative diseases, including Alzheimer and Huntington disease. These large stress response systems never work alone but constitute a dynamic and interactive interconnected network. To provide an example, oxidative stress may trigger ER stress and block PHDs to stabilize HIF-1a, and the UPR and HSR have in common the need to regulate the state of proteostasis in a complementary fashion. The combination with the metabolic networks mentioned above enables the cell to make combined survival decisions, in which the resources are distributed between growth and defense accordingly across a dynamic environment.

Integration and Crosstalk: Metabolic Pathways as Stress Modulators

Integration and Crosstalk: Metabolic Pathways as Stress Modulators

The separation of metabolic and stress signaling processes is mostly artificial; in cellular reality, they are aspects of a single adaptive mechanism. The core metabolic processes do not simply offer passive energy to stress responses but are rewired dynamically to be active contributors in defense, survival and cell fate choices. An example of such integration is provided by the multifaceted functions of glutamine, lipids and iron which are physical coordinated by the mitochondria, converting these basic constituents of metabolism into the much needed stress modulators.

The Glutamine Metabolism: A Cross-linkage Point of Biosynthesis, Redox Homeostasis and Epigenetic Control

The most common circulating amino acid is glutamine, which is much more than a building block of proteins. Its metabolism or glutaminolysis is a foundation of cell adaptation especially in growing and stressed cells. Glutamine is an anaplerotic source of carbon that replaces the tricarboxylic acid (TCA) cycle initially via glutaminase (GLS) into glutamate and subsequently into a-ketoglutarate (a-KG). This is crucial when the glucose-derived carbons are redirected out of the TCA cycle to be utilized in the biosynthesis, as in the Warburg effect. Other than energy production, glutamine metabolism is central to redox homeostasis. The transformation of glutamate to a-KG produces the reducing power used to keep glutathione in its reduced (GSH) form, the cellular major antioxidant, by the conversion of glutamate to a-KG through malic enzyme or the folate cycle. This is a direct correlation between the glutamine flux and the ability of the Keap1-NRF2 antioxidant system. In addition, glutamine-derived a-KG is a necessary co-substrate to dioxygenase enzymes involved in the epigenetic and hypoxic pathways. It activates JmjC-domain histone demethylases and TET DNA demethylases and thus modulates metabolic state-dependent patterns in gene expression. Importantly, a-KG also prevents HIF-1a stability by increasing PHDs activity, the same oxygen sensors that attacks HIF to be destroyed. Therefore, the hypoxia response can be directly tuned within the environment of glutamine, representing a deep metabolic control of a dominant stress response.

Lipid Metabolism in Stress Adaptation: From Membrane Integrity to Ferroptosis

Lipids are dynamic structural components and signaling molecules the metabolism of which is vastly remodeled during stress. Membrane lipid saturation is rapidly stimulated during cellular stress, e.g. heat shock or oxidative damage. This is prompted by the initiation of stearoyl-CoA desaturase (SCD) inhibition and the augmentation of saturated fatty acid synthesis, which is more compact, augmenting membrane stiffness and making it resistant to permeability. ER stress causes the UPR to induce a significant expansion of the ER membrane and phospholipid synthesis to comply with this increase. However, lipids are also important signaling mediators: such as sphingolipids as ceramide and sphingosine-1-phosphate (S1P) constitute a rheostat

to regulate cell fate choices in response to stress to induce apoptosis or survival, respectively. One of the key crossroads between lipid metabolism and oxidative stress is the newly elucidated ferroptotic pathway of cell death. Ferroptosis is an iron-dependent regulatedodesign of cell death, which is instigated by phospholipid peroxidation namely, those that bear polyunsaturated fatty acids (PUFAs). The balance between peroxidable PUFAs in lipid membranes and various antioxidant systems, primarily glutathione-dependent enzyme glutathione peroxidase 4 (GPX4), that decrease lipid hydroperoxides to non-toxic alcohols determines the susceptibility to ferroptosis. The loss of glutathione or GPX4 inhibition will result in disastrous lipid peroxidation and cell death. This route connects iron toxicity (Section 4.3), antioxidant defense (Section 3.1), lipid metabolism in a single unified cell fate pathway with consequences in cancer, neurodegeneration, and ischemia reperfusion injury.

Iron Homeostasis: Important Cofactor and Coincidental Toxin

Iron is essential because it is a cofactor in a variety of respiration-related (cytochromes) and DNA-related (ribonucleotide reductase) and antioxidative (catalase) enzymes. Nevertheless, the redox-active character of it enables it to catalyze the Fenton reaction, producing highly toxic hydroxyl radicals out of hydrogen peroxide. The cells thus keep the iron homeostasis at an extremely fine-tuned level through the post-transcriptional Iron-Responsive Element/Iron-Regulatory Protein (IRE/IRP) system. Under iron-deficiency conditions, IRPs attach to the IREs of the untranslated parts of mRNAs stabilizing the transferrin receptor mRNA to enhance iron uptake and inhibit the translation of ferritin (the iron storage protein). The opposite is presented in iron sufficiency. This balance is severely upset by stress pathways. IRPs can be inactivated by oxidative stress, which mimics an iron-deficient signal and iron import is increased in iron-deficient cells. Moreover, the UPR is able to stimulate the transferrin receptor directly. This accumulation of iron due to stress produces a vicious cycle by enhancing the generation of more ROS through Fenton chemistry. Iron, on the other hand, has effects on stress responses; it is needed in the work of prolyl hydroxylase of PHDs that break down HIF-1a, and in the work of histone demethylases. This duality of both being a key metabolic cofactor and a powerful catalyst of oxidative damage places iron at the crossroads of metabolic activities, where its regulation can lead to metabolic activities running smoothly or the metabolism degenerating into a destructive oxidative stress.

Mitochondrial Function at the Crossroads of Metabolism and Stress Signaling

The mitochondrion is the structural and functional centre of integration of metabolism and stress signalling. It is the major location of ATP-producing activity through oxidative phosphorylation (OXPHOS), TCA cycle and essential anabolic reactions. It is therefore also a significant contributor to endogenous ROS, and a store of pro-apoptotic factors. The stress-sensing pathways are constantly checking on its function. As an example, energy stress (low ATP/ADP ratio) can be perceived in the mitochondrion, which affects the AMPK activity. One of the most beautiful examples of this would be the mitochondrial UPR (UPR), a specialized form of stress response to the accumulation of misfolded proteins in the mitochondrial matrix. UPR also involves the activation of nuclear-encoded chaperones and proteins of mitochondrial proteostasis. Most importantly, it should be coordinated with other pathways, e.g., it may cause a metabolic shift to glycolysis to decrease the load of the mitochondria. Mitochondria use mitochondrial-derived signals (mitochondrial ROS (mtROS), TCA cycle products (e.g. succinate, fumarate) and released DNA (mtDNA) to report their functional condition. These molecules are able to trigger several stress and inflammatory signals in the cytosol, such as the NLRP3 inflammasome. The choice between survival and apoptosis of cells is finally carried out at the mitochondrial membrane as the regulation of mitochondrial permeability, controlled by the Bcl-2 protein family. An integrated signal of a metabolic insult (e.g., depletion of growth factor signaling, extreme depletion of ATP) accumulates on mitochondria and causes cytochrome c release, thereby triggering apoptosis. In this way, the mitochondrion does not passively respond to stress but is not only a signaling organelle, which deciphers metabolic status, responds to stress, and dictates cellular fate.

Disease and Therapeutic Implications Dysregulation

The complexity of crosstalk between metabolic and stress signaling networks is decisive to adaptation but poses a massive deficiency. A single node can have chronic or severe disruption that may spread out to the whole integrated system creating self-reinforcing pathological processes. Such a network-based approach is essential in both comprehending the etiology of complex disease, and in devising intelligent methods of therapeutic intervention which transcends single-target-based approaches to the restoration of systemic homeostasis.

Metabolic Syndrome: A Paradigm of Signaling Network Dysfunction

The classic case of network overload and its resulting system-wide failure is metabolic syndrome (MetS). Hereditary nutrient surplus especially of glucose and free fatty acids is the main insult. This long-term stimulates the anabolic mTORC1 signaling and inhibits catabolic AMPK signaling. The resultant lipid deposition in non-adipose tissues (liver, muscle) and the prolonged high insulin concentration cause metabolic stress. Mitochondria and the endoplasmic reticulum (ER) are overloaded: mitochondria form excessive amounts of reactive oxygen species (ROS), and the ER contains misfolded proteins, which triggers the UPR. These strains activate the JNK and IKKb/NK-kB kinases. Importantly, these stress-related kinases phosphorylate insulin receptor substrate (IRS) proteins on inhibitory serine residues, which uncouples the insulin receptor with its downstream PI3K-Akt pathway-which is the definition of insulin resistance. It is a vicious cycle: hyperglycemia and additional lipid spillover are the consequences of insulin resistance, which leads to the intensification of metabolic stress, causing it in the first place. At the same time, NF-kB activation facilitates a condition of chronic low-grade inflammation (meta-inflammation), which releases cytokines that continues to inhibit the insulin signal in a paracrine and endocrine fashion. Therefore, MetS is not a disease of a single hormone but a failure of the system of interaction between the energy intake, storage, and stress defense.

Cancer: The networks of adaptation are used by cancer cells to survive and multiply. They demonstrate oncogene-reprogrammed metabolisms (e.g. the Warburg effect) to keep up with fast growth. This is supplemented with an intense stress resilience phenotype. Activation of PI3K-Akt-mTOR axis leads to glycolysis and proliferation being constitutive. At the same time, to live in nutrient-poor, hypoxic, and acidic tumor microenvironment, cancer cells overactivate stress-response pathways. Angiogenesis and glycolysis are encouraged by HIF-1a stabilization. NF-2 antioxidant is constitutively active and provides some defense against excessive ROS produced by the rapid metabolism and affords cells an opportunity to escape the death caused by oxidative damage. The UPR and autophagy are not controlled as the last-ditch survival strategies, but are sustained as tools of continual maintenance to handle the proteotoxic and metabolic stress of uncontrolled growth. This results in an impressive fluidity: by blocking a single route of action (e.g. glycolysis) one may provoke the compensatory rewiring (e.g. elevated glutaminolysis or autophagy) of these interconnected networks, which is a major mode of therapeutic resistance. Hijacked network plasticity is, therefore, the strength of the cancer cell.

Neurodegenerative Disorders: Diseases such as Alzheimer disease (AD) and Parkinson disease (PD) are an example of a slow- paced network breakdown in which metabolic and proteostatic stresses are joined. The extreme energy needs of the organism cause such a sensitivity of the brain to metabolic disruption. Older age, deterioration of mitochondrial functions, insulin signaling in the brain (brain insulin resistance), and glucose metabolism put an individual in a condition of chronic bioenergetic deficit. This disrupts the activity of the ATP-dependent chaperones (HSPs) and ubiquitin-proteasome system, which inhibits the capacity of the cell in processing misfolded proteins such as amyloid-b or a-synuclein. Subsequently, the protein aggregates formed further impair mitochondrial activity and cause oxidative/ER stress, which further destruction to metabolic pathways. Furthermore, weakened autophagy, which is clear of mTOR hyperactivity as well as aging, inhibits the elimination of impaired organelles and protein aggregates. This vicious circle between energetic failure and proteotoxicity is the agent force that leads to progressive neuronal loss. The network viewpoint clarifies the finding of common traits of

mitochondrial dysfunction and oxidative stress with diseases having different primary protein aggregates.

Conclusion

It has been discovered that cellular signaling teaches a basic lesson: the metabolic and stress response pathways are closely interconnected in a dynamic, complex network that is vital to the adaptation process and survival. This review has described the role of core metabolic sensors such as AMPK and mTOR as central processors and perceive nutrient and energy status, but are directly inputted by key stress pathways. This crosstalk guarantees that the allocation of resources to the cells is optimally adapted to their cellular requirement by channeling energy away resource allocation to defense in case of need The pathological implications of network failure highlight its physiological significance. Metabolic syndrome develops as a positive feedback loop of nutrient overload, metabolic stress and inflammatory signaling which impairs insulin action as explained. The cancer cells are good examples of network hijacking, which involves re-using metabolic restructuring (the Warburg effect) along with constitutive stress resistance (through NRF2, HIF, UPR) to survive in a hostile environment. An example of a slow network breakdown can be found in neurodegenerative diseases, where bioenergetic and proteostatic losses complement each other. Such cases, together with systems genetics data (e.g. MetSyn gene networks, Fig. 2) and mechanistic analysis of organelle pathophysiology (e.g. mitochondrial roles, Fig. 3) have shown that complex diseases should be viewed not as impairments of single parts, but as a condition of network imbalance. This network view is the future of biomedicine. Network dysregulation-based diseases cannot be treated using the classical paradigm of one drug, one target. Rather, network pharmacology is the future: the careful identification and therapeutic targeting of the key hubs, combinations of nodes, or architecture of dysregulated interactions. This involves further development of systems biology- the combination of multi-omics data and computational models to generate patient-specific network maps. The end-result is a transformation of reactive treatment to proactive network correction to restore the complex metabolic-stress system to resume the healthy, homeostatic dynamics to obtain long-term health.

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