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Review Article

The Exposome Surveillance Hypothesis an Integrative Systems Biology Framework for Environmental Information Processing, Adaptive Regulation, and Chronic Disease

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ABSTRACT

The Exposome Surveillance Hypothesis proposes that health depends on the continuous detection, interpretation, and biological processing of environmental information. Environmental exposures are conceptualised not only as potential sources of injury but also as signals that must be integrated by distributed molecular sensors, barrier tissues, neuroimmune pathways, endocrine networks, autonomic regulation, and mitochondrial signalling. We introduce the Environmental Surveillance System (ESS) as a functional systems biology framework for this distributed information-processing architecture and position the Neuroendocrine-Immune System as its principal adaptive effector network. Transient receptor potential vanilloid 1 is presented as a prototype sentinel receptor illustrating how heterogeneous physical, chemical, inflammatory, and metabolic signals can be translated into calcium-dependent neuroimmune and mitochondrial responses. Within this framework, Adaptive Capacity denotes the organism's integrated ability to respond and recover, whereas Adaptive Debt describes the cumulative unresolved biological burden that develops when recovery remains incomplete. Progressive Adaptive Debt may reduce regulatory flexibility, promote self-perpetuating maladaptation, and contribute to convergent patterns of chronic inflammation, autonomic dysfunction, mitochondrial impairment, pain, fatigue, and multisystem disease. Finally, Guided Restoration of Adaptive Biological Self-Regulation is introduced as a translational framework aimed at identifying and reducing biological constraints before gradually restoring adaptive capacity. The hypothesis generates testable predictions concerning preclinical network dysfunction, multidimensional biomarkers, disease convergence, and reversibility of maladaptive regulation.

Keywords

Exposome, Environmental Surveillance System, Environmental Information, Adaptive Regulation, Adaptive Capacity, Adaptive Debt, Neuroendocrine-Immune System, TRPV1, Systems Biology, Chronic Inflammation, Neuroimmunology, Precision Medicine, Hormesis, Mitochondria.

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Introduction

Living organisms exist in continuous interaction with a constantly changing environment. Throughout evolution, survival has depended not only on the ability to withstand environmental challenges but, more fundamentally, on the capacity to detect, interpret, and appropriately respond to biologically meaningful

environmental information. Health therefore emerges not from physiological constancy alone but from the continuous maintenance of adaptive biological regulation.

Despite remarkable advances in molecular biology, immunology, genetics, and precision medicine, chronic inflammatory and neuroimmune disorders are increasingly recognised as major clinical and research challenges. Conditions including autoimmune diseases, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Long COVID, persistent post-infectious syndromes, mast cell activation disorders, chronic pain syndromes, and environmentally associated illnesses frequently share biological and clinical characteristics despite diverse initiating triggers. Chronic fatigue, cognitive dysfunction, autonomic instability, persistent inflammation, mitochondrial impairment, disturbed calcium homeostasis, and multisystem involvement are observed across disorders that are traditionally regarded as unrelated. These observations suggest the existence of common systems-level mechanisms that extend beyond disease-specific molecular pathways [1-8].

The increasing recognition that health represents an emergent property of highly interconnected biological networks has stimulated a shift from reductionist disease models towards systems biology. Within this perspective, physiological regulation is understood as the coordinated interaction of neural, immune, endocrine, metabolic, and mitochondrial networks that continuously adapt to changing environmental conditions. Disease consequently reflects not only structural pathology or isolated molecular dysfunction but may also arise from progressive impairment of adaptive regulatory processes [1,9-15].

Parallel to these developments, the concept of the exposome has transformed environmental health research. Since its introduction by Wild, the exposome has expanded from a description of cumulative environmental exposures to a comprehensive framework encompassing the lifelong interaction between physical, chemical, biological, nutritional, behavioural, psychosocial, and metabolic influences and the organism's dynamic biological response [16-19].

A central proposition of the present Review is that environmental exposures should not be viewed solely as potential sources of biological injury. Rather, they constitute biologically meaningful environmental information that must be continuously detected, integrated, prioritised, and translated into coordinated adaptive responses. This conceptual distinction shifts the focus of environmental medicine from exposure alone towards the biological processes responsible for environmental information processing.

To explain these processes, we introduce the Environmental Surveillance System (ESS) as a conceptual systems biology framework comprising distributed molecular sensors, cellular signalling pathways, barrier tissues, neuroimmune communication networks, endocrine regulation, autonomic control, and mitochondrial signalling that collectively maintain adaptive regulation. The ESS is not proposed as a discrete anatomical entity but as an emergent functional network responsible for continuous environmental surveillance.

Within this framework, the Neuroendocrine–Immune System (NEIS) functions as the principal adaptive effector network through which environmental information is translated into coordinated physiological responses. Among the molecular components of the ESS, transient receptor potential vanilloid 1 (TRPV1) serves as an illustrative sentinel receptor linking environmental information to calcium-dependent neuroimmune signalling and mitochondrial adaptation. Importantly, TRPV1 represents one element of a much broader surveillance architecture rather than its defining component.

Building upon these concepts, we propose that chronic disease develops through the progressive accumulation of adaptive debt, reflecting a gradual decline in adaptive capacity following persistent cumulative exposome burden. From this perspective, chronic inflammation, mitochondrial dysfunction, autonomic dysregulation, impaired energy metabolism, disturbed calcium signalling, and neuroimmune activation are interpreted primarily as downstream manifestations of impaired adaptive regulation rather than independent initiating mechanisms.

Finally, we introduce Guided Restoration of Adaptive Biological Self-Regulation (GRABSR) as a translational therapeutic framework aimed at restoring adaptive capacity by identifying and reducing the principal biological constraints limiting recovery before facilitating the reactivation of endogenous adaptive mechanisms.

The Exposome Surveillance Hypothesis therefore provides an integrative systems biology framework linking environmental information processing, adaptive regulation, resilience, maladaptation, and chronic disease. By integrating concepts from exposome science, neuroimmunology, systems biology, mitochondrial medicine, and precision medicine, it generates experimentally testable predictions and establishes a coherent foundation for future mechanistic and translational research.

The Human Exposome: From Environmental Exposure to Environmental Information

The concept of the exposome has fundamentally transformed our understanding of the relationship between the environment and human health. Since its introduction by Wild in 2005, it has complemented genomic research by recognising that health and disease are determined not only by inherited genetic variation but also by the cumulative influence of environmental exposures encountered throughout life. Consequently, disease susceptibility arises from the continuous interaction between genetic predisposition and a dynamic environmental landscape rather than from either component alone [16-19].

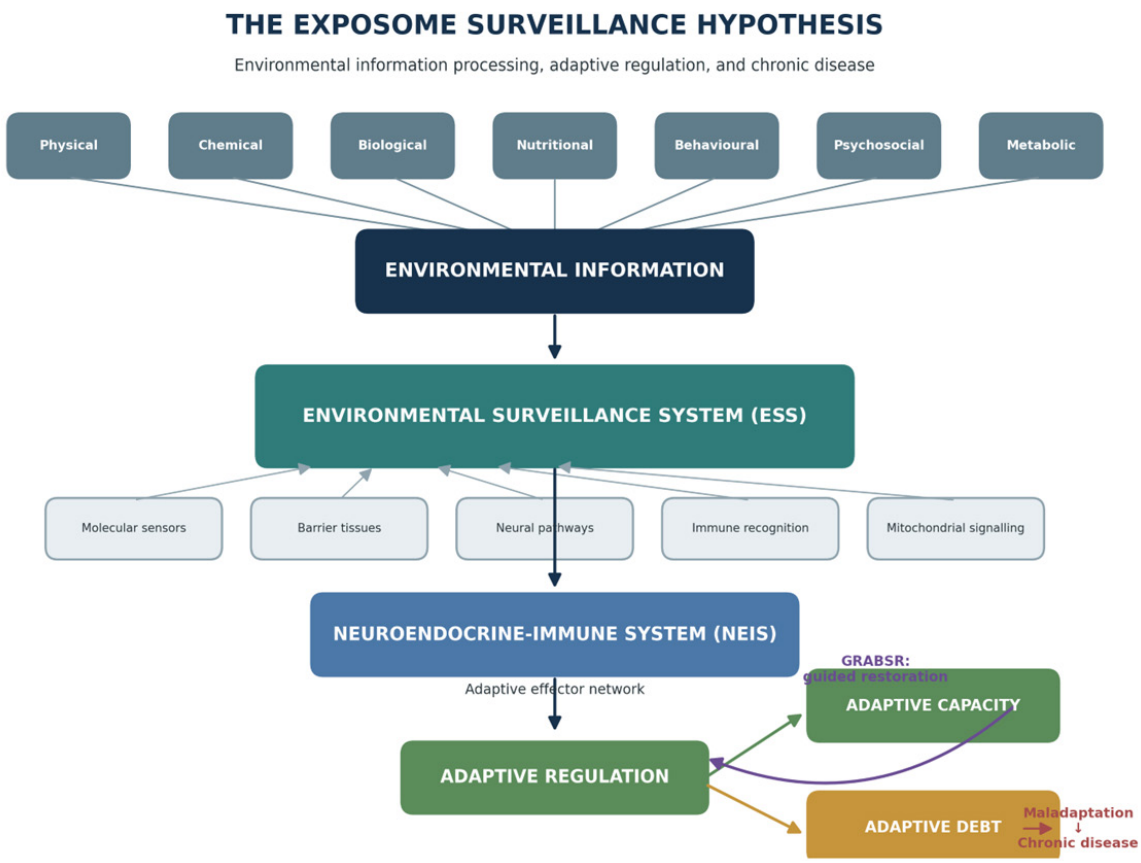

Figure 1: The Exposome Surveillance Hypothesis. Environmental exposures generate biologically meaningful environmental information that is detected and integrated by the Environmental Surveillance System (ESS). The Neuroendocrine-Immune System (NEIS) translates this information into adaptive regulation. Health depends on the preservation of Adaptive Capacity; incomplete recovery promotes Adaptive Debt, maladaptation, and chronic disease. GRABSR represents the translational framework for restoring adaptive biological self-regulation.

Originally, the exposome was conceived as the totality of environmental exposures experienced from conception onwards. Over the past two decades, this concept has expanded considerably and now encompasses a broad spectrum of physical, chemical, biological, nutritional, behavioural, psychosocial, metabolic, and socio-environmental influences that interact continuously with the genome, epigenome, transcriptome, proteome, metabolome, and microbiome. This broader interpretation has established the exposome as one of the central organising concepts of modern environmental health research and systems biology [16-19].

Despite this conceptual progress, the exposome is still predominantly described in terms of exposure. While this perspective has substantially advanced epidemiological and toxicological research, it provides only limited insight into the biological mechanisms through which environmental factors are detected, interpreted, prioritised, and translated into adaptive physiological responses.

We therefore propose an important conceptual distinction between environmental exposure and environmental information.

Environmental exposures represent the physical, chemical, biological, nutritional, behavioural, and psychosocial factors acting upon an organism. Environmental information, by contrast, represents the biologically meaningful signals generated by these exposures after they have been detected and interpreted by specialised surveillance mechanisms. Biological systems do not respond directly to exposure itself; they respond to the information extracted from that exposure.

This distinction has important biological implications. The same environmental exposure may generate profoundly different biological responses depending on its intensity, duration, temporal pattern, cumulative burden, developmental timing, genetic background, previous environmental experience, and the current adaptive state of the organism. Environmental information therefore represents a dynamic and context-dependent biological process rather than a simple physical property of the exposure itself.

From an evolutionary perspective, this distinction is fundamental. Living organisms have not evolved primarily to resist environmental exposures but to continuously interpret

environmental information in order to optimise survival and reproduction. Every environmental change—including variations in temperature, nutrient availability, microbial composition, physical activity, circadian light exposure, emotional stress, or tissue injury—provides information that must be evaluated before an appropriate adaptive response can be generated. The biological significance of an environmental stimulus is therefore determined less by its absolute magnitude than by the manner in which it is interpreted within the organism's existing regulatory architecture [14,15,20,21].

This perspective also changes the interpretation of environmental medicine. Environmental factors should no longer be regarded solely as potential causes of disease. Many environmental stimuli are indispensable for maintaining health because they provide the physiological signals required for adaptive regulation. Physical exercise, dietary variation, microbial diversity, thermal adaptation, circadian entrainment, and social interaction all represent sources of environmental information that continuously shape biological function. Conversely, persistent, repetitive, or excessive environmental stimulation may progressively impair adaptive regulation when the organism's capacity to process environmental information becomes compromised.

Accordingly, health should not be defined simply by the absence of harmful environmental exposures but by the ability of biological systems to accurately detect, integrate, prioritise, and respond to environmental information across changing physiological conditions. This concept naturally extends beyond classical homeostasis and aligns with contemporary systems biology, which views health as an emergent property of continuously interacting adaptive networks rather than as a static physiological equilibrium [1,9-15].

Environmental information is processed simultaneously at multiple biological levels. Barrier tissues such as the skin, respiratory tract, gastrointestinal mucosa, and vascular endothelium form the primary interfaces with the external environment. At these sites, specialised molecular sensors—including transient receptor potential (TRP) channels, pattern-recognition receptors, purinergic receptors, inflammasome complexes, and numerous additional sensory systems—continuously detect environmental signals and initiate local regulatory responses. The resulting information is subsequently integrated through complex interactions involving the nervous, immune, endocrine, metabolic, and mitochondrial systems, allowing rapid coordination between local tissue responses and systemic physiological adaptation [22-33].

Within this framework, we propose that these distributed sensing and signalling mechanisms collectively constitute an Environmental Surveillance System (ESS). The ESS should not be interpreted as a discrete anatomical structure but as a functional systems biology network responsible for the continuous acquisition, integration, prioritisation, and interpretation of environmental information before adaptive responses are initiated.

This interpretation fundamentally shifts the emphasis of the exposome from a passive catalogue of exposures towards an active biological process of environmental information processing. Chronic disease is therefore understood not primarily as the consequence of environmental exposure itself but as the progressive failure of adaptive regulatory systems to accurately process and respond to cumulative environmental information over time.

This conceptual transition from Environmental Exposure to Environmental Information provides the biological rationale for the Environmental Surveillance System developed in the following chapter.

Environmental Surveillance Systems: An Integrative Framework for Environmental Information Processing

The continuous ability to detect and appropriately respond to environmental change is one of the most fundamental characteristics of life. From unicellular organisms to highly complex mammals, survival has depended not on passive resistance to environmental stress but on the continuous acquisition, interpretation, and integration of biologically meaningful environmental information. Throughout evolution, this requirement has driven the emergence of highly conserved molecular and cellular mechanisms that collectively enable organisms to anticipate, evaluate, and adapt to changing environmental conditions before irreversible damage occurs.

Traditionally, these mechanisms have been investigated within separate biomedical disciplines. Immunology has focused on innate immune recognition of pathogens and danger signals, neuroscience on sensory perception and nociception, endocrinology on hormonal regulation of homeostasis, and mitochondrial biology on metabolic adaptation to cellular stress. Although each discipline has generated substantial mechanistic insight, these systems have generally been studied as independent regulatory pathways despite their extensive functional interdependence. Increasing evidence indicates, however, that environmental sensing is fundamentally a systems-level process in which multiple biological networks operate simultaneously rather than sequentially [1,22-33].

Within the Exposome Surveillance Hypothesis, we therefore introduce the concept of the ESS as a functional systems biology framework that integrates distributed molecular sensors, barrier tissues, intracellular signalling pathways, neuroimmune communication networks, endocrine regulation, autonomic control, and mitochondrial signalling into a unified architecture of environmental information processing.

Importantly, the ESS is not proposed as a new anatomical organ, a discrete physiological system, or a single signalling pathway. Instead, it represents an emergent functional network whose defining property is the continuous detection, integration, prioritisation, and biological interpretation of environmental information before adaptive responses are initiated.

This definition extends the classical concept of immune surveillance. Whereas immune surveillance primarily concerns the recognition of pathogens, malignant cells, and tissue injury, the ESS encompasses the full spectrum of environmental information relevant to biological adaptation. These signals include physical variables such as temperature, mechanical forces, osmotic pressure, electromagnetic radiation, and atmospheric conditions; chemical factors including nutrients, xenobiotics, pollutants, endogenous metabolites, and toxins; biological stimuli derived from microorganisms, viruses, allergens, and tissue damage; and behavioural and psychosocial influences capable of modifying neuroendocrine regulation [3-6,22-27,32,33].

A defining characteristic of the ESS is that environmental information is processed simultaneously across multiple biological scales. At the tissue level, barrier organs—including the skin, respiratory tract, gastrointestinal mucosa, and vascular endothelium—serve as dynamic interfaces between the organism and its environment. At the cellular level, specialised molecular sensors continuously detect alterations in the extracellular and intracellular milieu. At the systems level, the nervous, immune, endocrine, metabolic, and cardiovascular systems integrate this information into coordinated adaptive responses. Consequently, environmental surveillance should be understood as a distributed biological process rather than the function of any single receptor, organ, or signalling pathway.

Among the molecular components contributing to this surveillance architecture are TRP channels, including TRPV1 and transient receptor potential ankyrin 1 (TRPA1), pattern-recognition receptors such as Toll-like receptors (TLRs), nucleotide-binding oligomerisation domain (NOD)-like receptors, inflammasome complexes, purinergic receptors, mechanosensitive ion channels, mitochondrial danger-signalling pathways, and numerous additional sensory mechanisms that collectively monitor the organism's internal and external environments. Each of these systems contributes distinct information, yet none functions independently. Continuous molecular crosstalk enables environmental signals detected by one surveillance pathway to influence the responsiveness of many others, creating a highly integrated adaptive network [22-33].

A central principle of the ESS is that surveillance itself is physiologically protective. Acute activation of environmental surveillance pathways is not pathological but represents an essential prerequisite for adaptation, tissue repair, host defence, and maintenance of physiological homeostasis. Chronic disease therefore does not arise because surveillance systems become activated; rather, it develops when the regulation of surveillance becomes persistently dysregulated. Under conditions of sustained cumulative exposome burden, repeated activation may progressively impair the precision, flexibility, and resolution of adaptive signalling. As a consequence, regulatory responses that are initially protective may become self-perpetuating, contributing to chronic neuroimmune activation, disturbed calcium homeostasis, mitochondrial dysfunction, autonomic imbalance, and impaired physiological resilience [3-6,20,21,28-31].

From a systems biology perspective, the ESS therefore functions primarily as an environmental information-processing network. Its principal role is not simply to detect potentially harmful stimuli but to determine their biological significance, integrate multiple sources of environmental information, prioritise competing regulatory demands, and coordinate proportionate adaptive responses. Successful health maintenance depends not on maximal surveillance activity but on the accuracy, flexibility, and timely resolution of this information-processing process.

The Environmental Surveillance System also generates several experimentally testable predictions. First, measurable disturbances in environmental information processing should precede the onset of overt clinical disease. Second, dysfunction of sentinel surveillance receptors and associated signalling networks should correlate more closely with impaired adaptive capacity than with individual disease categories. Third, multidimensional biomarkers reflecting network behaviour should predict disease progression more accurately than isolated molecular markers. Finally, therapeutic interventions that restore physiological environmental information processing should improve adaptive regulation even in disorders with markedly different clinical phenotypes.

Accordingly, the ESS should be regarded as a conceptual framework that organises diverse observations from neuroimmunology, environmental medicine, systems biology, mitochondrial biology, and physiology into a unified model of adaptive regulation. Rather than replacing established biological mechanisms, it provides an integrative perspective explaining how distributed environmental sensing can generate coordinated adaptive responses across the entire organism.

This systems-level interpretation establishes the conceptual basis for the following chapter, which examines the Neuroendocrine–Immune System (NEIS) as the principal adaptive effector network through which environmental information detected by the ESS is translated into coordinated physiological regulation.

The Neuroendocrine–Immune System: The Principal Adaptive Effector Network

The continuous detection of environmental information is only the first step in biological adaptation. Environmental signals must subsequently be interpreted, prioritised, and translated into coordinated physiological responses capable of maintaining functional integrity under continuously changing internal and external conditions. Within the Exposome Surveillance Hypothesis, this integrative function is performed by NEIS, which serves as the principal adaptive effector network linking environmental information processing to systemic biological regulation.

Historically, the nervous, endocrine, and immune systems were regarded as largely independent physiological entities. The

nervous system was considered responsible for rapid information processing, the endocrine system for hormonal regulation, and the immune system for host defence. Over the past several decades, however, extensive experimental evidence has demonstrated that these systems communicate continuously through shared signalling molecules, receptors, neural circuits, cytokines, hormones, neuropeptides, extracellular vesicles, and metabolic mediators. Consequently, they should be regarded not as isolated physiological systems but as highly integrated components of a single adaptive regulatory network [3-6,20,21,28-31].

Within the conceptual framework proposed here, the relationship between ESS and NEIS follows a hierarchical but dynamic organisation. The ESS continuously acquires and interprets environmental information, whereas the NEIS converts this information into coordinated physiological responses. Thus, the ESS primarily answers the question "What is occurring in the environment?", while the NEIS determines "How should the organism respond?"

This distinction provides an important conceptual clarification. The ESS functions primarily as an environmental information-processing network, whereas the NEIS functions as the adaptive regulatory system responsible for implementing appropriate biological responses. Together, they constitute a continuously operating feedback architecture that allows organisms to maintain physiological flexibility rather than static equilibrium.

Environmental Information as the Initiator of Adaptive Regulation

Every environmental stimulus carries biological significance only after it has been detected and interpreted by the ESS. Variations in temperature, nutrient availability, microbial composition, circadian light exposure, psychological stress, physical activity, infection, tissue injury, or chemical exposure are not inherently beneficial or harmful. Their biological consequences depend on how they are integrated within the organism's existing regulatory state.

Following environmental detection, the NEIS coordinates multiple simultaneous adaptive processes. Neural circuits rapidly modify autonomic output and behaviour. Endocrine pathways regulate energy metabolism, circadian timing, tissue repair, and stress adaptation. Immune networks determine the magnitude and duration of inflammatory responses, while mitochondria continuously adjust cellular energy production to match changing physiological demands. These responses occur in parallel rather than sequentially and together determine the efficiency of adaptive regulation.

Bidirectional Neuroimmune Communication

One of the defining characteristics of the NEIS is its continuous bidirectional communication between the nervous and immune systems. Peripheral sensory neurons not only transmit information to the central nervous system but also directly regulate immune-cell function through the release of neuropeptides including substance P and calcitonin gene-related peptide (CGRP). Conversely, cytokines, chemokines, lipid mediators, and danger-associated molecular patterns influence neuronal excitability, autonomic regulation, pain perception, cognition, mood, and behaviour [3-6,26-31].

This reciprocal communication enables rapid physiological adaptation during acute environmental challenges. During infection, tissue injury, or metabolic stress, behavioural responses such as fatigue, reduced physical activity, altered sleep, anorexia, and social withdrawal represent highly conserved adaptive programmes that optimise energy allocation and support immune function. Rather than being pathological per se, these responses are essential components of successful biological adaptation.

However, when neuroimmune signalling persists beyond the original environmental challenge, adaptive programmes may gradually become maladaptive. Protective responses that evolved to facilitate short-term survival become chronically activated, resulting in persistent fatigue, cognitive dysfunction, autonomic instability, chronic pain, and reduced physiological resilience. This transition from adaptive regulation to maladaptation represents one of the central concepts of the Exposome Surveillance Hypothesis.

The Endocrine System as a Temporal Coordinator of Adaptation

The endocrine system provides temporal organisation of adaptive regulation. Hormones integrate environmental information over longer time scales than neural signalling and coordinate metabolism, circadian rhythms, reproduction, tissue regeneration, immune regulation, and stress adaptation.

Among these regulatory systems, the hypothalamic–pituitary–adrenal (HPA) axis illustrates the dual nature of adaptive regulation. Acute activation enhances survival by mobilising energy substrates, maintaining cardiovascular function, and preventing excessive inflammatory responses. In contrast, persistent activation progressively alters glucocorticoid receptor sensitivity, disrupts circadian organisation, impairs mitochondrial metabolism, modifies immune-cell differentiation, and promotes chronic low-grade inflammation. Thus, endocrine responses are determined not only by hormone concentrations but also by their duration, timing, and regulatory context [14,15,20,21].

Mitochondria as Central Regulators of Adaptive Capacity

Recent advances have fundamentally changed our understanding of mitochondrial biology. Rather than functioning solely as ATP-producing organelles, mitochondria are now recognised as dynamic signalling hubs integrating metabolic, inflammatory, endocrine, and neuronal information. Calcium signalling, reactive oxygen species, inflammatory cytokines, glucocorticoids, and autonomic neurotransmitters continuously influence mitochondrial function, while mitochondria reciprocally regulate immune activation, apoptosis, oxidative stress, inflammasome activity, and cellular metabolism [28-31].

Within the Exposome Surveillance Hypothesis, mitochondria represent the energetic core of adaptive regulation. Every adaptive response requires energy, and adaptive capacity therefore depends directly on mitochondrial competence. Progressive mitochondrial dysfunction not only limits ATP production but also amplifies inflammatory signalling, oxidative stress, calcium dysregulation, and neuroimmune activation, thereby reinforcing the cycle of maladaptation.

Adaptive Regulation as Dynamic Network Behaviour

Classical physiology has traditionally described health in terms of homeostasis, implying maintenance of relatively constant internal conditions. While this concept remains fundamental, it incompletely reflects the dynamic behaviour of living systems. Biological health is more accurately characterised by the capacity to continuously adjust physiological processes according to changing environmental demands while maintaining functional coherence across multiple regulatory systems.

Adaptive regulation therefore emphasises flexibility rather than constancy. Healthy organisms are distinguished not by the absence of physiological fluctuation but by the efficiency with which they detect environmental change, coordinate adaptive responses, terminate activation once appropriate, and restore physiological flexibility.

From this perspective, health becomes an emergent property of coordinated network behaviour rather than the sum of independently functioning organs.

Progressive Loss of Adaptive Capacity

Repeated environmental challenges initially evoke efficient adaptive responses. As cumulative exposome burden increases, however, recovery following activation becomes progressively incomplete. Residual inflammatory activity, autonomic imbalance, mitochondrial dysfunction, endocrine dysregulation, and altered neuroimmune communication accumulate over time. Biological flexibility gradually declines, reducing the organism's capacity to respond appropriately to subsequent environmental challenges.

Within the present framework, this progressive decline in adaptive performance represents the earliest manifestation of impaired adaptive capacity. Chronic disease does not emerge because adaptive regulation is activated but because adaptive regulation progressively loses its efficiency, precision, and capacity for resolution.

This concept provides the mechanistic bridge to the following chapter, in which Adaptive Capacity and Adaptive Debt are introduced as systems-level descriptors of the transition from successful adaptation to chronic maladaptation.

TRPV1: A Prototype Sentinel Receptor within the Environmental Surveillance System

Among the diverse molecular sensors contributing to ESS,TRPV1 channel occupies a particularly important position. Although the ESS comprises numerous receptor families and signalling pathways, TRPV1 is presented here as a prototype sentinel receptor because it exemplifies how highly diverse environmental stimuli are detected, integrated, and translated into coordinated adaptive biological responses.

Originally identified as the receptor for capsaicin, TRPV1 was initially regarded primarily as a nociceptive ion channel involved in pain perception and thermosensation. Over the past two decades, however, its biological significance has expanded considerably. TRPV1 is now recognised as a polymodal environmental sensor expressed not only in sensory neurons but also in immune cells, epithelial tissues, endothelial cells, vascular smooth muscle, keratinocytes, mast cells, and numerous regions of the central nervous system. This broad tissue distribution suggests that TRPV1 participates in systemic environmental surveillance extending far beyond nociception [22-31].

Importantly, TRPV1 does not detect a single environmental stimulus. Rather, it integrates information from multiple physical, chemical, inflammatory, and metabolic signals. Thermal stimuli, tissue acidosis, endogenous lipids, reactive oxygen species, inflammatory mediators, mechanical sensitisation, microbial products, environmental pollutants, dietary components, and xenobiotics are all capable of directly or indirectly modulating TRPV1 activity. Consequently, TRPV1 functions less as a receptor for individual stimuli than as an integrative molecular interface through which diverse environmental information converges into common intracellular signalling pathways.

TRPV1 as an Integrator of Environmental Information

Within the Exposome Surveillance Hypothesis, the principal significance of TRPV1 lies not in its role as a pain receptor but in its ability to transform heterogeneous environmental information into biologically meaningful intracellular signals. This transformation represents a defining characteristic of sentinel receptors within the ESS.

Environmental stimuli rarely occur in isolation. Instead, organisms are continuously exposed to complex combinations of physical, chemical, infectious, metabolic, nutritional, behavioural, and psychosocial influences. TRPV1 integrates these converging inputs, allowing the organism to generate adaptive responses that reflect the cumulative biological context rather than isolated environmental events.

This capacity for signal integration illustrates a broader principle of the ESS: biological adaptation is determined not by single environmental exposures but by the interpretation of multiple simultaneous information streams.

Calcium Signalling: The Universal Translator of Environmental Information

The central intracellular consequence of TRPV1 activation is

calcium influx. Rather than representing merely an ionic movement across the plasma membrane, calcium signalling constitutes one of the most highly conserved biological languages through which environmental information is translated into adaptive cellular behaviour.

Changes in intracellular calcium concentration regulate mitochondrial oxidative phosphorylation, ATP production, gene transcription, vesicular secretion, cytoskeletal organisation, neurotransmitter release, immune-cell activation, endothelial function, epithelial barrier integrity, and apoptosis. Consequently, calcium serves as a universal integrator linking environmental surveillance to virtually every aspect of cellular physiology [28-31].

Within this framework, TRPV1-mediated calcium influx represents one of the earliest intracellular events through which environmental information becomes transformed into adaptive biological regulation.

TRPV1 as a Regulator of Neuroimmune Communication

TRPV1 also occupies a pivotal position at the interface between the nervous and immune systems. Activation of TRPV1-expressing sensory neurons induces the release of neuropeptides including substance P and calcitonin gene-related peptide (CGRP), thereby influencing vascular permeability, local blood flow, mast-cell activation, leukocyte recruitment, cytokine production, and tissue repair. Conversely, inflammatory cytokines, prostaglandins, nerve growth factor, and numerous endogenous mediators sensitise TRPV1, creating reciprocal feedback loops between neuronal and immune signalling [26-31].

These bidirectional interactions illustrate how environmental information detected at peripheral tissues can rapidly influence systemic neuroimmune regulation. Rather than functioning as an isolated sensory receptor, TRPV1 participates in distributed communication networks coordinating adaptive responses across multiple organ systems.

Mitochondrial Integration of TRPV1 Signalling

One of the most important downstream consequences of TRPV1 activation involves mitochondrial regulation. Mitochondria continuously decode calcium signals generated through TRPV1 and other sentinel receptors, adjusting ATP synthesis, reactive oxygen species production, intermediary metabolism, mitophagy, and apoptotic signalling according to changing environmental demands.

Under physiological conditions, transient TRPV1 activation supports mitochondrial adaptation and efficient energy allocation. However, persistent or excessive calcium influx may exceed mitochondrial buffering capacity, resulting in oxidative stress, impaired oxidative phosphorylation, inflammasome activation, and reduced ATP availability. These changes may progressively compromise adaptive regulation throughout the organism.

Accordingly, mitochondrial dysfunction should not be interpreted solely as a primary pathological event but may also represent a downstream consequence of chronically disturbed environmental information processing.

TRPV1 and Adaptive Capacity

A defining feature of biological adaptation is that the same molecular pathway may exert beneficial or detrimental effects depending on its magnitude, duration, and regulatory context. TRPV1 exemplifies this principle particularly well.

Transient physiological activation promotes tissue repair, thermoregulation, host defence, vascular adaptation, nociceptive protection, and metabolic flexibility. In contrast, persistent sensitisation may contribute to chronic neuroinflammation, autonomic dysregulation, mast-cell activation, mitochondrial dysfunction, calcium overload, chronic pain, fatigue, and reduced physiological resilience.

Within the Exposome Surveillance Hypothesis, these observations are interpreted not as contradictory functions but as different manifestations of adaptive regulation across a continuum ranging from physiological adaptation to maladaptation.

TRPV1 within the Environmental Surveillance System

Although TRPV1 is emphasised throughout this Review because of its exceptional capacity to integrate diverse environmental signals, it is not proposed as the sole molecular component of the Environmental Surveillance System. Rather, it serves as a representative prototype illustrating how environmental information is transformed into calcium-dependent neuroimmune regulation within a distributed surveillance architecture.

Other molecular sensors—including TRPA1, Toll-like receptors, NOD-like receptors, purinergic receptors, inflammasome complexes, mechanosensitive ion channels, and additional environmental sensing pathways—operate in parallel and continuously interact with TRPV1 through extensive signalling crosstalk. Together, these distributed sentinel mechanisms enable the organism to maintain adaptive regulation across continuously changing environmental conditions.

Consequently, the importance of TRPV1 lies not in its uniqueness but in the exceptional clarity with which it illustrates the fundamental operating principles of the Environmental Surveillance System.

Transition to the Next Chapter

The extensive biological functions of TRPV1 demonstrate how environmental information can be translated into coordinated cellular and systemic responses. However, the ultimate determinant of health is not the activation of individual sentinel receptors but the organism's ability to sustain effective adaptive regulation over time.

This observation provides the conceptual basis for the following chapter, which introduces Adaptive Capacity as the systems-level property governing resilience, recovery, and long-term physiological stability.

Adaptive Capacity: The Biological Basis of Health and Resilience

A fundamental question in biology and medicine is why individuals exposed to similar environmental challenges frequently exhibit profoundly different clinical outcomes. While some remain healthy despite repeated infections, toxic exposures, psychological stress, or metabolic challenges, others develop persistent inflammatory, neuroimmune, or multisystem disorders after comparatively minor insults. These observations cannot be explained solely by differences in exposure intensity or genetic susceptibility. Rather, they suggest substantial interindividual variation in the ability to maintain adaptive regulation under changing environmental conditions.

Within the Exposome Surveillance Hypothesis, this systems-level property is defined as Adaptive Capacity.

Adaptive Capacity refers to the integrated ability of an organism to detect environmental information, coordinate appropriate biological responses, restore physiological equilibrium after activation, and preserve functional flexibility despite continuous environmental perturbation. Rather than representing the function of any single organ or signalling pathway, Adaptive Capacity emerges from the coordinated behaviour of ESS, NEIS, mitochondrial metabolism, barrier tissues, autonomic regulation, endocrine signalling, and immune communication.

Health therefore depends not on the absence of environmental challenges but on the organism's ability to successfully adapt to them.

Adaptive Capacity as an Emergent Systems Property

Adaptive Capacity cannot be measured directly by a single biomarker because it is an emergent property arising from interactions among multiple physiological networks. It reflects the efficiency with which environmental information is detected, integrated, prioritised, and translated into coordinated adaptive responses while maintaining sufficient flexibility for future challenges.

From this perspective, adaptive regulation resembles a dynamic control system rather than a collection of independent physiological processes. Successful adaptation requires continuous communication between environmental sensing, energy metabolism, neuroimmune signalling, endocrine regulation, autonomic control, tissue repair, and behavioural responses.

Accordingly, Adaptive Capacity should be understood as a property of the biological network as a whole rather than of its individual components.

Adaptation Requires Energy

Every adaptive response carries an energetic cost.

Immune activation, neuronal signalling, tissue repair, endocrine responses, mitochondrial remodelling, protein synthesis, detoxification, epithelial barrier maintenance, and autonomic regulation all require substantial ATP availability. Consequently, adaptive regulation depends directly upon mitochondrial performance and metabolic flexibility.

Within this framework, mitochondria serve as the energetic foundation of Adaptive Capacity. Efficient ATP generation enables organisms to respond rapidly to environmental demands while maintaining sufficient energetic reserves for recovery once the adaptive response has been completed.

Conversely, impaired mitochondrial function progressively reduces biological flexibility, slows recovery, amplifies oxidative stress, and increases susceptibility to further environmental perturbation.

Adaptive Capacity Is Dynamic

Adaptive Capacity is not a fixed characteristic but continuously changes throughout life. Early development, nutrition, physical activity, sleep quality, circadian synchronisation, microbial diversity, psychosocial environment, infections, environmental toxicants, ageing, and previous environmental exposures all influence the organism's current adaptive potential.

Importantly, repeated successful adaptation often strengthens future adaptive responses, whereas persistent or unresolved activation gradually diminishes adaptive flexibility.

This concept closely resembles biological conditioning observed during exercise training, thermal adaptation, immune memory, and hormesis, in which appropriately dosed environmental challenges enhance long-term physiological resilience.

Hormesis as an Expression of Adaptive Capacity

Hormesis provides one of the clearest demonstrations that health depends on adaptive regulation rather than avoidance of environmental stimulation.

Moderate physical exercise, intermittent fasting, thermal stress, caloric restriction, cognitive challenge, microbial exposure, and other controlled environmental stimuli initially activate stress-responsive pathways but subsequently improve mitochondrial function, antioxidant defence, immune regulation, vascular adaptation, and metabolic flexibility. These beneficial effects arise because transient activation is followed by complete recovery and functional overcompensation.

Within the present framework, hormesis therefore represents successful environmental information processing resulting in an expansion of Adaptive Capacity.

Conversely, when environmental stimulation exceeds the organism's

adaptive potential or recovery remains incomplete, identical signalling pathways may contribute to progressive maladaptation rather than resilience. Thus, biological outcome depends less on the stimulus itself than on the relationship between environmental demand and Adaptive Capacity.

Loss of Adaptive Capacity

Adaptive Capacity gradually declines when cumulative environmental demands consistently exceed the organism's ability to recover.

Persistent infections, chronic psychosocial stress, environmental toxicants, disturbed sleep, nutritional deficiencies, metabolic dysfunction, recurrent inflammatory activation, chronic pain, autonomic dysregulation, and repeated mitochondrial stress progressively impair biological flexibility.

Initially, compensatory mechanisms maintain apparently normal physiological function despite increasing regulatory burden. Over time, however, compensatory reserve becomes exhausted. Recovery slows, inflammatory activation persists, mitochondrial efficiency declines, calcium homeostasis becomes unstable, autonomic regulation loses precision, and neuroimmune communication becomes progressively dysregulated. Importantly, these changes often precede overt clinical disease by months or even years.

Adaptive Capacity as the Common Denominator of Chronic Disease

Within the Exposome Surveillance Hypothesis, Adaptive Capacity represents the principal determinant of long-term health.

Rather than interpreting chronic inflammatory, neuroimmune, metabolic, or degenerative diseases as unrelated pathological entities, this framework proposes that many apparently distinct disorders share a common systems-level abnormality: a progressive reduction in Adaptive Capacity.

Different clinical phenotypes emerge because adaptive failure occurs within different biological networks, organs, and regulatory circuits. Nevertheless, the underlying systems biology remains fundamentally similar.

This perspective explains why disorders with very different initiating triggers frequently converge towards comparable patterns of chronic inflammation, mitochondrial dysfunction, autonomic imbalance, cognitive impairment, persistent fatigue, and multisystem dysregulation.

Towards Adaptive Debt

Adaptive Capacity does not usually collapse abruptly. Instead, biological systems frequently compensate for prolonged environmental stress by operating under increasing regulatory strain while preserving short-term function. This accumulated physiological burden is not immediately apparent but progressively reduces the efficiency of adaptive regulation and limits future resilience.

Within the Exposome Surveillance Hypothesis, this cumulative biological burden is conceptualised as Adaptive Debt. Adaptive Debt therefore represents the progressive consequence of declining Adaptive Capacity and provides the mechanistic link between successful adaptation and chronic maladaptation.

The following chapter develops this concept and explores its implications for the development of chronic disease.

Adaptive Debt: The Progressive Accumulation of Unresolved Biological Burden

Adaptive responses are rarely without cost. Every successful adaptation requires the coordinated mobilisation of metabolic resources, activation of neuroimmune communication, endocrine regulation, mitochondrial energy production, tissue remodelling, and subsequent restoration of physiological homeostasis. Under normal circumstances, these adaptive processes are transient and followed by complete recovery, allowing biological systems to regain their full adaptive flexibility.

However, recovery is not always complete. Within the Exposome Surveillance Hypothesis, we propose that repeated or persistent environmental challenges may leave residual biological alterations that are not fully resolved before subsequent adaptive demands arise. These unresolved changes gradually accumulate over time, progressively reducing the organism's capacity to maintain efficient adaptive regulation. We define this cumulative biological burden as Adaptive Debt.

Adaptive Debt therefore represents the progressive accumulation of unresolved physiological costs resulting from repeated or incompletely resolved adaptive responses. Rather than reflecting irreversible structural damage, Adaptive Debt primarily describes a systems-level decline in biological flexibility, regulatory precision, and recovery capacity.

Adaptive Debt as a Consequence of Incomplete Recovery

The defining feature of Adaptive Debt is not the intensity of an individual environmental challenge but the failure to achieve complete physiological recovery before the next challenge occurs.

Acute infection, psychological stress, environmental toxicant exposure, sleep deprivation, nutritional imbalance, physical overexertion, chronic inflammation, persistent pain, or metabolic dysfunction each activate adaptive regulatory pathways designed to restore homeostasis. When recovery is complete, no lasting debt remains.

In contrast, repeated activation without adequate resolution progressively leaves residual alterations in inflammatory signalling, autonomic regulation, endocrine feedback, mitochondrial function, calcium homeostasis, epithelial barrier integrity, and immune communication. Individually, these changes may be

clinically insignificant. Collectively, however, they gradually impair the efficiency of adaptive regulation across multiple physiological systems.

Adaptive Debt should therefore be viewed as a cumulative systems-level phenomenon rather than the consequence of any single pathological process.

The Biological Components of Adaptive Debt

Adaptive Debt does not arise from a single molecular mechanism but reflects the integrated accumulation of multiple unresolved regulatory disturbances.

These may include persistent low-grade inflammation, altered cytokine networks, mitochondrial energetic insufficiency, impaired oxidative phosphorylation, disturbed intracellular calcium signalling, oxidative stress, autonomic imbalance, endocrine dysregulation, barrier dysfunction, maladaptive epigenetic programming, immune-cell reprogramming, and impaired resolution of tissue repair.

Importantly, none of these abnormalities alone defines Adaptive Debt. Instead, they represent interacting biological components that collectively reduce adaptive flexibility. Accordingly, Adaptive Debt is best understood as an emergent property of disturbed network behaviour rather than a measurable molecular entity.

Compensation before Decompensation

One of the most clinically relevant characteristics of Adaptive Debt is that biological systems possess remarkable compensatory capacity.

For prolonged periods, individuals may remain apparently healthy despite substantial accumulation of regulatory burden. Compensatory mechanisms involving neuroendocrine adaptation, metabolic flexibility, mitochondrial reserve capacity, autonomic regulation, and behavioural adjustments frequently preserve functional performance even while Adaptive Debt continues to increase. Consequently, conventional laboratory investigations may remain within reference ranges despite progressive deterioration of adaptive regulation.

Clinical disease often becomes apparent only after compensatory reserve is exceeded or an additional environmental challenge surpasses the remaining Adaptive Capacity. This phenomenon may explain why acute infections, surgical procedures, psychological stress, toxic exposures, or seemingly minor physiological insults frequently precipitate chronic multisystem disorders in previously well-functioning individuals.

Adaptive Debt Explains Delayed Disease Onset

A major strength of the Adaptive Debt concept is its ability to explain the temporal disconnect frequently observed between environmental exposure and disease manifestation. Many chronic disorders develop months or even years after the initiating environmental challenge. Traditional disease models often struggle to explain these delayed clinical presentations.

Within the present framework, environmental challenges progressively increase Adaptive Debt while compensatory mechanisms temporarily preserve physiological function. Clinical symptoms emerge only when accumulated Adaptive Debt reduces Adaptive Capacity below the threshold required to maintain effective biological regulation. Disease onset therefore reflects a transition in systems behaviour rather than the occurrence of a single pathological event.

Adaptive Debt and Disease Convergence

One of the most striking observations in clinical medicine is that disorders with very different initiating causes frequently converge towards remarkably similar biological phenotypes. Persistent fatigue, cognitive dysfunction, autonomic instability, chronic pain, neuroinflammation, mitochondrial impairment, endothelial dysfunction, mast-cell activation, disturbed calcium homeostasis, and multisystem involvement occur across infectious, autoimmune, toxicological, metabolic, and environmentally associated diseases.

Within the Exposome Surveillance Hypothesis, this convergence reflects the common accumulation of Adaptive Debt rather than disease-specific molecular pathways. Different environmental triggers therefore generate distinct entry points into the adaptive network but progressively converge upon similar systems-level patterns of impaired adaptive regulation.

Adaptive Debt as a Potential Clinical Construct

Although Adaptive Debt is proposed here as a conceptual systems biology framework, it also generates clinically relevant hypotheses. Rather than searching for a single diagnostic biomarker, future assessment of Adaptive Debt may require multidimensional evaluation integrating inflammatory activity, autonomic function, mitochondrial performance, neuroendocrine regulation, metabolic flexibility, cognitive resilience, sleep architecture, physical recovery, and physiological reserve.

Such composite assessments may prove substantially more informative than isolated laboratory parameters because they better reflect the integrated behaviour of adaptive biological networks. This systems-based perspective may ultimately facilitate earlier identification of individuals at risk before irreversible pathological changes become established.

Relationship between Adaptive Capacity and Adaptive Debt

Adaptive Capacity and Adaptive Debt are complementary rather than opposing concepts. Adaptive Capacity describes the organism's potential to respond effectively to environmental demands, whereas Adaptive Debt reflects the cumulative reduction of that potential resulting from incomplete recovery and unresolved biological burden.

Both concepts evolve dynamically throughout life. Successful recovery decreases Adaptive Debt and restores Adaptive Capacity. Conversely, persistent environmental overload progressively increases Adaptive Debt while simultaneously diminishing Adaptive Capacity. Together, these reciprocal processes determine long-term biological resilience and susceptibility to chronic disease.

Transition to Maladaptation

Adaptive Debt itself should not be regarded as disease. Rather, it represents the intermediate systems state between successful adaptation and chronic maladaptation.

As Adaptive Debt accumulates, adaptive responses gradually lose their precision, flexibility, and capacity for resolution. Protective regulatory programmes become increasingly self-perpetuating, ultimately giving rise to persistent neuroimmune activation, mitochondrial dysfunction, autonomic dysregulation, chronic inflammation, and multisystem disease. This transition from accumulated Adaptive Debt to sustained maladaptation forms the basis of the next chapter.

Maladaptation: When Adaptive Regulation Becomes Self-Perpetuating

Adaptive regulation is fundamentally protective. Throughout evolution, biological systems have developed highly conserved mechanisms that enable organisms to respond rapidly to environmental challenges, preserve physiological integrity, and restore homeostasis following disturbance. Under healthy conditions, activation of these adaptive programmes is transient, proportionate, and followed by timely resolution. Disease does not arise because adaptive regulation exists.

Rather, chronic disease develops when adaptive regulation progressively loses its flexibility, precision, and capacity for resolution. Within the Exposome Surveillance Hypothesis, this transition is defined as maladaptation.

Maladaptation represents the state in which biological responses that originally evolved to protect the organism become persistently activated and increasingly contribute to physiological dysfunction. Importantly, maladaptation does not imply the emergence of entirely new biological mechanisms. Instead, it reflects the inappropriate persistence, amplification, or misdirection of otherwise beneficial adaptive programmes.

The Transition from Adaptation to Maladaptation

The progression from successful adaptation to maladaptation is typically gradual rather than abrupt. Initially, adaptive responses efficiently restore physiological stability following environmental perturbation. As cumulative environmental burden increases and Adaptive Debt accumulates, recovery becomes progressively incomplete. Adaptive Capacity declines, compensatory mechanisms operate under increasing strain, and biological flexibility diminishes.

Eventually, regulatory systems become trapped in persistent activation states. Inflammatory signalling remains chronically elevated despite the absence of acute injury. Autonomic regulation loses dynamic variability. Endocrine feedback mechanisms become progressively dysregulated. Mitochondrial energy production becomes inefficient. Intracellular calcium signalling remains persistently altered. Behavioural programmes originally designed to conserve energy become chronic fatigue, cognitive dysfunction, sleep disturbance, and reduced physical resilience. Thus, maladaptation reflects a qualitative change in network behaviour rather than the failure of an individual molecular pathway.

Persistent Activation of Adaptive Programmes

One of the defining features of maladaptation is the persistence of adaptive responses beyond their original biological purpose. Inflammation illustrates this principle particularly well. Acute inflammatory activation is essential for host defence, tissue repair, and elimination of pathogens. However, when inflammatory signalling fails to resolve appropriately, the same protective mechanisms contribute to tissue damage, altered neuronal function, endothelial dysfunction, mitochondrial stress, and chronic symptom generation.

Similarly, transient activation of the sympathetic nervous system facilitates survival during acute stress by mobilising cardiovascular and metabolic resources. Persistent sympathetic activation, however, promotes autonomic imbalance, impaired vascular regulation, sleep disruption, endocrine dysregulation, and progressive reduction of physiological resilience. These examples demonstrate that chronic disease often results not from excessive activation alone but from the loss of appropriate temporal regulation.

Network Locking: A Systems Biology Perspective

From a systems biology perspective, maladaptation may be interpreted as a phenomenon of network locking. Healthy biological networks continuously alternate between activation and recovery according to changing environmental demands. In maladaptation, regulatory circuits become stabilised in self-reinforcing activation states that persist independently of the initiating environmental trigger.

Bidirectional communication between the nervous, immune, endocrine, metabolic, and mitochondrial systems amplifies these processes. Persistent inflammatory signalling sensitises neuronal pathways. Altered neuronal activity modifies endocrine regulation. Endocrine dysregulation influences mitochondrial metabolism. Impaired mitochondrial function further amplifies inflammatory signalling and oxidative stress. These reciprocal interactions generate positive feedback loops that maintain chronic dysregulation despite removal of the original environmental stimulus.

Consequently, maladaptation should be understood as a property of network dynamics rather than isolated organ pathology.

Clinical Convergence of Chronic Disease

A striking observation across clinical medicine is that diseases with fundamentally different initiating causes frequently develop remarkably similar clinical manifestations. Patients with Long COVID/Post-Vac, ME/CFS, fibromyalgia, mast cell activation disorders, environmentally associated illnesses, autoimmune diseases, persistent post-infectious syndromes, and chronic pain syndromes often present with overlapping patterns of fatigue, cognitive impairment, autonomic dysfunction, exercise intolerance, neuroinflammation, sleep disturbance, sensory hypersensitivity, mitochondrial dysfunction, and multisystem involvement.

Traditional disease models interpret these similarities as coincidental or disease-specific. Within the Exposome Surveillance Hypothesis, these convergent phenotypes reflect common patterns of maladaptive regulation developing within shared biological networks despite diverse initiating environmental challenges. Different triggers therefore produce different entry points into the adaptive system but progressively converge upon similar systems-level states characterised by impaired adaptive regulation.

Maladaptation Is Potentially Reversible

An important implication of the present framework is that maladaptation should not necessarily be regarded as irreversible. Because maladaptation primarily reflects disturbed regulatory behaviour rather than fixed structural pathology, restoration of adaptive regulation may remain possible even after prolonged disease duration.

The degree of reversibility is expected to depend upon multiple factors, including residual Adaptive Capacity, the magnitude of accumulated Adaptive Debt, persistence of environmental drivers, mitochondrial reserve, neuroimmune plasticity, endocrine flexibility, and the integrity of tissue repair mechanisms. This concept provides a biological rationale for therapeutic strategies that seek to restore adaptive regulation rather than merely suppress isolated pathological pathways.

From Maladaptation to Guided Restoration

The recognition that maladaptation represents disturbed adaptive regulation rather than irreversible failure has important therapeutic implications. Conventional medical interventions frequently focus on suppressing individual molecular pathways responsible for specific symptoms or diseases. While such approaches remain essential, they may incompletely address the underlying systems-level disturbance responsible for persistent maladaptive regulation.

Within the Exposome Surveillance Hypothesis, therapeutic interventions should therefore aim to reduce Adaptive Debt, restore Adaptive Capacity, re-establish physiological network flexibility, and facilitate recovery of endogenous adaptive regulation. This systems-oriented therapeutic perspective forms the basis of the next chapter, which introduces GABSR as a translational framework for personalised restoration of adaptive health.

Guided Restoration of Adaptive Biological Self-Regulation (GRABSR): A Translational Framework for Restoring Adaptive Capacity

The Exposome Surveillance Hypothesis proposes that many chronic inflammatory, neuroimmune, metabolic, and environmentally associated disorders arise from progressive impairment of adaptive regulation rather than from isolated dysfunction of individual molecular pathways. If this systems-level perspective is correct, therapeutic strategies should extend beyond suppression of individual pathological mechanisms and instead aim to restore the organism's intrinsic capacity for adaptive biological regulation.

To address this objective, we introduce GRABSR as a translational clinical framework. Thisis not a specific therapeutic intervention, treatment protocol, or disease-specific algorithm. Rather, it represents a systems biology approach that seeks to identify the principal biological constraints limiting adaptive regulation and to guide personalised interventions that facilitate recovery of endogenous self-regulatory capacity. Within this framework, therapy is directed not only towards disease manifestations but towards the restoration of the biological processes that maintain health.

Restoring Adaptive Regulation Rather Than Suppressing Disease

Conventional medical practice has achieved remarkable success by identifying disease-specific molecular targets and developing highly effective interventions directed against individual signalling pathways. Such approaches remain indispensable in modern medicine and have substantially improved outcomes across numerous acute and chronic diseases.

However, patients with chronic multisystem disorders frequently exhibit persistent dysregulation involving multiple interacting physiological networks simultaneously. In these situations, treatment directed against a single pathway may alleviate individual symptoms while leaving the underlying disturbance of adaptive regulation largely unchanged.

Within the Exposome Surveillance Hypothesis, therapeutic success therefore depends not only on reducing pathological activity but also on restoring the flexibility, coordination, and resilience of adaptive biological networks.

Identification of Biological Constraints

The first step of GRABSR is the systematic identification of the principal biological factors limiting adaptive regulation. These constraints differ considerably between individuals despite similar clinical diagnoses and may include persistent environmental exposures, unresolved infections, chronic inflammatory activation, mitochondrial dysfunction, disturbed calcium signalling, oxidative stress, autonomic dysregulation, endocrine imbalance, sleep disruption, nutritional deficiencies, intestinal barrier dysfunction, microbiome alterations, toxicant accumulation, impaired detoxification, psychosocial stress, or reduced physical

conditioning.

Importantly, these factors should not be viewed as isolated disease mechanisms but as interacting contributors that collectively increase Adaptive Debt and reduce Adaptive Capacity. Consequently, personalised assessment becomes an essential prerequisite for effective systems-level intervention.

Reducing Adaptive Debt

Following identification of the dominant biological constraints, therapeutic efforts should first focus on reducing Adaptive Debt. This may involve elimination or reduction of ongoing environmental stressors, treatment of persistent inflammatory or infectious processes, optimisation of sleep and circadian regulation, improvement of nutritional status, restoration of mitochondrial function, reduction of oxidative stress, normalisation of autonomic regulation, improvement of barrier integrity, optimisation of endocrine balance, or other interventions appropriate to the individual's biological profile.

The specific interventions are less important than the systems-level objective: reducing the cumulative biological burden that prevents restoration of adaptive regulation.

Restoring Adaptive Capacity

As Adaptive Debt decreases, the organism's capacity for physiological adaptation may gradually recover. Restoration of Adaptive Capacity requires re-establishment of efficient communication between environmental surveillance, neuroimmune signalling, endocrine regulation, mitochondrial metabolism, autonomic control, tissue repair, and behavioural adaptation.

Importantly, this restoration cannot usually be achieved by passive treatment alone. Controlled physiological stimulation—including appropriately dosed physical activity, nutritional interventions, circadian optimisation, thermal adaptation, respiratory training, cognitive engagement, stress reduction, and other forms of beneficial environmental stimulation—may gradually rebuild adaptive flexibility through mechanisms analogous to hormesis.

Within the GRABSR framework, therapeutic stimulation is therefore carefully matched to the individual's remaining Adaptive Capacity in order to promote recovery without provoking renewed maladaptation.

Precision Medicine through Systems Biology

GRABSR extends contemporary precision medicine by shifting the primary focus from molecular diagnosis alone towards individual adaptive biology.

Two patients with identical clinical diagnoses may differ substantially in Adaptive Capacity, Adaptive Debt, environmental drivers, mitochondrial reserve, neuroimmune regulation, autonomic function, and endocrine flexibility. Consequently, they may require fundamentally different therapeutic priorities despite apparently similar disease phenotypes. The objective is therefore not simply personalised pharmacology but personalised restoration of adaptive regulation.

Dynamic Monitoring of Recovery

Because adaptive regulation changes continuously over time, therapeutic assessment should likewise remain dynamic. Improvement should not be evaluated exclusively through conventional laboratory parameters or symptom severity but also through indicators of restored physiological resilience.

Potential measures may include recovery following physical or cognitive exertion, autonomic adaptability, sleep quality, mitochondrial performance, exercise tolerance, cognitive flexibility, inflammatory regulation, and the organism's ability to tolerate previously challenging environmental conditions.

Future development of multidimensional systems biomarkers may allow direct assessment of Adaptive Capacity and Adaptive Debt during treatment.

GRABSR as a Translational Research Framework

Beyond its clinical implications, GRABSR also provides a platform for future translational research. If Adaptive Capacity and Adaptive Debt represent measurable systems-level properties, future clinical studies could evaluate whether interventions capable of improving adaptive regulation produce comparable benefits across diseases with different clinical diagnoses but shared maladaptive network behaviour.

Such studies would move therapeutic research away from disease-specific categorisation towards biological restoration of adaptive function.

Conceptual Integration

Within the Exposome Surveillance Hypothesis, GRABSR represents the final translational step of a continuous biological sequence:

Environmental Exposure
→ Environmental Information
→ Environmental Surveillance System (ESS)
→ Neuroendocrine–Immune System (NEIS)
→ Adaptive Regulation
→ Adaptive Capacity
→ Adaptive Debt
→ Maladaptation
→ Chronic Disease
→ Guided Restoration of Adaptive Biological Self-Regulation (GRABSR)

Accordingly, GRABSR should be understood not as an alternative to conventional medicine but as an integrative systems biology framework that complements existing therapeutic strategies by addressing the restoration of adaptive biological regulation.

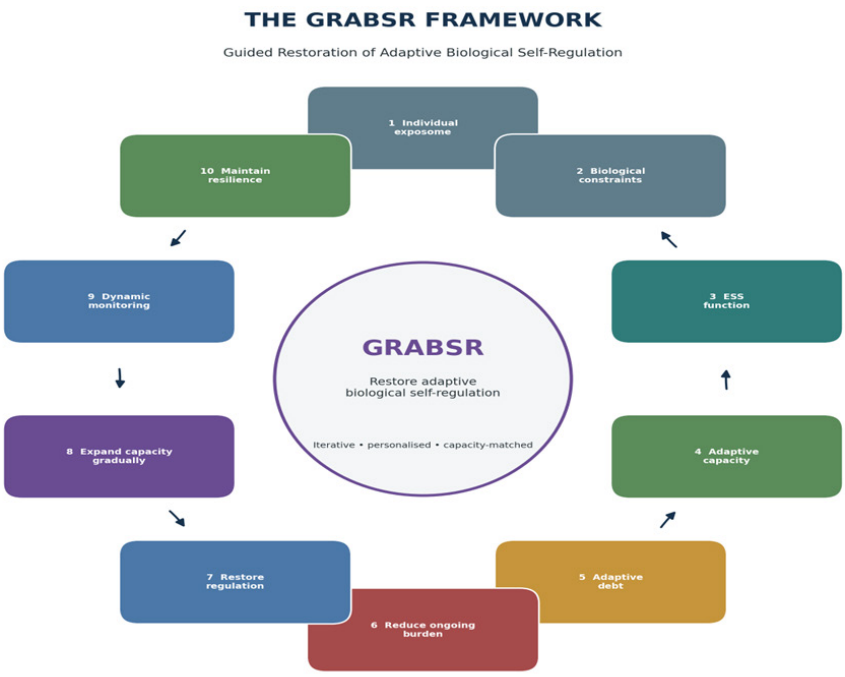

Figure 2: The GRABSR framework. A cyclical model in which individual exposome assessment, identification of biological constraints, evaluation of ESS function, estimation of Adaptive Capacity and Adaptive Debt, reduction of ongoing burden, restoration of regulation, graded expansion of capacity, dynamic monitoring, and maintenance of resilience support renewed environmental information processing.

The Ten Principles of GRABSR

Identify the Individual Exposome

Characterise the patient's cumulative environmental information landscape, including physical, chemical, biological, nutritional, behavioural, psychosocial, and metabolic influences.

Identify Biological Constraints

Determine the dominant factors limiting adaptive regulation, such as persistent inflammation, chronic infection, mitochondrial dysfunction, disturbed calcium signalling, autonomic imbalance, endocrine dysregulation, environmental toxicants, nutritional deficiencies, impaired barrier function, or psychosocial stress.

Assess Environmental Surveillance Function

Evaluate how effectively the Environmental Surveillance System (ESS) detects, integrates, and interprets environmental information.

Potential domains include:

- Barrier integrity
- Neuroimmune communication
- TRPV1 and other sentinel pathways
- Autonomic responsiveness
- Inflammatory regulation

Estimate Adaptive Capacity

Assess the organism's current ability to mount effective adaptive responses and recover following physiological challenges.

Adaptive Capacity is reflected by biological flexibility rather than isolated laboratory values.

Estimate Adaptive Debt

Determine the cumulative burden of unresolved adaptive responses.

Potential indicators include:

- Persistent low-grade inflammation
- Mitochondrial dysfunction
- Impaired recovery
- Autonomic instability
- Chronic fatigue
- Exercise intolerance
- Cognitive impairment
- Reduced physiological resilience

Reduce Ongoing Biological Burden

Prioritise interventions that remove or reduce the principal biological constraints.

Examples include:

- Treatment of persistent infections
- Reduction of environmental toxicant exposure
- Optimisation of sleep
- Correction of nutritional deficiencies
- Improvement of mitochondrial metabolism
- Reduction of oxidative stress
- Restoration of barrier integrity
- Autonomic stabilisation

Restore Adaptive Regulation

Support re-establishment of coordinated communication between:

- ESS
- NEIS
- Mitochondria
- Endocrine system
- Immune system
- Autonomic nervous system

The therapeutic objective is restoration of regulatory flexibility rather than suppression of isolated pathways.

Gradually Expand Adaptive Capacity

Introduce carefully individualised physiological stimulation according to the patient's remaining adaptive reserve.

Potential interventions may include:

- Graded physical activity (when tolerated)
- Respiratory training
- Circadian optimisation
- Nutritional strategies
- Thermal conditioning
- Cognitive rehabilitation
- Stress modulation
- Hormetic stimulation

The intensity of stimulation should remain below the threshold that induces renewed maladaptation.

Monitor Recovery Dynamically

Evaluate longitudinal improvement using systems-level indicators, including:

- Recovery after exertion
- Autonomic variability
- Mitochondrial performance
- Sleep quality
- Inflammatory regulation
- Cognitive recovery
- Exercise tolerance
- Quality of life

Maintain Adaptive Resilience

The ultimate objective is not simply symptom reduction but sustained restoration of adaptive biological self-regulation, enabling the organism to respond effectively to future environmental challenges while preventing renewed accumulation of Adaptive Debt.

Future Perspectives and Testable Predictions

The Exposome Surveillance Hypothesis proposes that health emerges from the continuous processing of environmental information through distributed surveillance networks that coordinate adaptive biological regulation. If this framework is valid, it should generate experimentally testable predictions that distinguish it from existing disease-centred models.

Rather than representing a purely conceptual construct, the hypothesis provides a systems biology framework capable of guiding future mechanistic, translational, and clinical research across multiple chronic diseases.

Prediction 1

Disturbances in environmental information processing precede overt clinical disease

The hypothesis predicts that dysfunction within ESS will occur before structural pathology becomes clinically apparent. Consequently, early alterations in environmental sensing, neuroimmune communication, autonomic regulation, mitochondrial function, or physiological resilience should be detectable before conventional diagnostic criteria are fulfilled.

Prediction 2

Adaptive Capacity predicts disease susceptibility better than exposure alone

Individuals exposed to similar environmental challenges should exhibit markedly different clinical outcomes according to their remaining Adaptive Capacity rather than the magnitude of exposure itself. Future prospective studies should therefore demonstrate that measures reflecting adaptive regulation outperform isolated exposure metrics in predicting disease development.

Prediction 3

Adaptive Debt accumulates before disease onset

Adaptive Debt should progressively increase during repeated environmental stress long before chronic disease becomes clinically evident. This predicts the existence of a prolonged preclinical phase characterised by incomplete recovery, reduced physiological flexibility, impaired resilience, and subtle systems-level dysregulation.

Prediction 4

Different diseases share common maladaptive network signatures

Despite diverse initiating triggers, disorders such as Long COVID/Post-Vac, ME/CFS, fibromyalgia, autoimmune diseases, mast cell activation disorders, environmentally associated illnesses, and chronic pain syndromes should exhibit overlapping disturbances within adaptive regulatory networks. Consequently, multidimensional systems biomarkers should demonstrate greater similarity across these disorders than disease-specific classifications currently suggest.

Prediction 5

Network biomarkers outperform single biomarkers

No individual laboratory parameter is expected to adequately represent Adaptive Capacity or Adaptive Debt. Instead, composite biomarkers integrating inflammatory regulation, mitochondrial performance, autonomic function, endocrine signalling, metabolic flexibility, and cognitive resilience should provide superior diagnostic and prognostic accuracy.

Prediction 6

TRPV1 represents one prototype of distributed environmental surveillance

Modulation of TRPV1 signalling should influence adaptive regulation across multiple physiological systems. However, similar effects should also be demonstrable through other sentinel receptors participating within the Environmental Surveillance System, supporting the concept of distributed environmental surveillance rather than dependence upon a single molecular pathway.

Prediction 7

Reduction of Adaptive Debt improves multiple diseases simultaneously

Interventions capable of reducing Adaptive Debt should improve adaptive regulation across apparently unrelated chronic diseases. Clinical improvement should therefore correlate more closely with restoration of Adaptive Capacity than with suppression of isolated disease-specific molecular pathways.

Prediction 8

Adaptive regulation is reversible

Because maladaptation primarily reflects disturbed regulatory network behaviour rather than irreversible structural damage, restoration of adaptive regulation should remain possible even after prolonged disease duration, provided sufficient Adaptive Capacity persists. This prediction provides a biological rationale for personalised therapeutic strategies directed towards restoring physiological resilience rather than exclusively suppressing pathology.

Prediction 9

Health should be redefined as adaptive competence

Future systems biology research should increasingly describe health not as the absence of disease but as the capacity of biological systems to continuously detect, interpret, and appropriately respond to environmental information while maintaining adaptive flexibility. Accordingly, Adaptive Capacity may ultimately become a fundamental physiological descriptor comparable to concepts such as homeostasis, resilience, and physiological reserve.

Prediction 10

The Exposome Surveillance Hypothesis provides a unifying systems biology framework

Finally, the hypothesis predicts that many apparently independent concepts—including exposome science, systems biology, neuroimmunology, mitochondrial medicine, environmental medicine, resilience biology, hormesis, and precision medicine—will progressively converge within a common framework centred on environmental information processing and adaptive biological regulation.

If validated, this framework could fundamentally reshape the understanding of chronic disease from a collection of organ-specific pathologies towards a dynamic systems biology model of health, adaptation, and maladaptation.

General Conclusions

The Exposome Surveillance Hypothesis proposes a conceptual shift in the understanding of chronic disease by redefining health as the dynamic capacity to process environmental information and maintain adaptive biological regulation. Rather than viewing environmental exposures solely as pathogenic influences, the hypothesis recognises them as sources of biologically meaningful information that must be continuously detected, interpreted, and translated into coordinated physiological responses.

Within this framework, the Environmental Surveillance System (ESS) functions as a distributed network of environmental information processing, while the Neuroendocrine–Immune System (NEIS) serves as the principal adaptive effector network. Together, these systems determine the organism's Adaptive Capacity, whose gradual decline contributes to the accumulation of Adaptive Debt, the emergence of maladaptation, and ultimately the development of chronic disease.

Importantly, the hypothesis does not replace established molecular mechanisms but integrates them into a broader systems biology perspective. By connecting concepts from exposome science, neuroimmunology, mitochondrial biology, environmental medicine, and precision medicine, it provides a coherent explanatory framework for the shared biological features observed across many chronic inflammatory and neuroimmune disorders.

The proposed model generates experimentally testable predictions and establishes a foundation for future mechanistic, translational, and clinical research. Furthermore, the GRABSR framework extends these concepts into clinical practice by emphasising the restoration of adaptive biological self-regulation rather than the isolated treatment of disease manifestations.

Ultimately, the Exposome Surveillance Hypothesis suggests that chronic disease is best understood not simply as the consequence of pathological insults but as the progressive failure of adaptive biological regulation within an organism that continuously interacts with its environment.

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