

FROM ADAPTATION TO RECOVERY: MECHANISMS OF INFLAMMATION RESOLUTION IN IMMUNOMETABOLIC ALLOSTASIS (LITERATURE REVIEW)

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Background. Traditionally, the termination of inflammation has been regarded as a passive decline of the pro-inflammatory response after elimination of the injurious stimulus. However, inflammation resolution is now recognized as an active process involving coordinated immune, neuroendocrine, and metabolic mechanisms required for tissue repair and recovery. This concept provides a basis for new approaches to treatment, metabolic support, and rehabilitation.

Aim. To analyze current concepts of inflammation resolution from an immunometabolic perspective and to substantiate the concept of immunometabolic resolution as a systemic process mediating the transition from adaptation to recovery.

Materials and Methods. A narrative review of studies indexed in PubMed, Scopus, Web of Science, MEDLINE, ScienceDirect, and Google Scholar between 2000 and 2025 was conducted. Studies addressing inflammation resolution, neuroendocrine regulation, tissue insulin sensitivity, thyroid adaptation, mitochondrial function, post-traumatic recovery, and metabolic disorders were analyzed. The study was conducted as a private initiative of the authors, without grant support or state registration of the research topic.

Research Ethics. Only sources that comply with current bioethical standards were selected for the analysis.

Results. Inflammation resolution is associated with a shift in functional priority from survival programs toward tissue repair and recovery. A key event in this transition is the reduction in energy demands of the innate immune system, accompanied by decreased cytokine activation, attenuation of Hypothalamic-Pituitary-Adrenal (HPA) axis activity, and redistribution of energy resources toward tissue repair. Resolution includes restoration of tissue insulin sensitivity, normalization of thyroid status and mitochondrial function, and a shift from predominantly glycolytic to oxidative metabolism. Delayed resolution may contribute to chronic allostatic overload, metabolic syndrome, sarcopenia, and impaired post-traumatic recovery.

Conclusions. The concept of immunometabolic resolution is proposed, according to which termination of inflammation represents an integrated process involving restoration of neuroendocrine regulation, energy metabolism, and functional integrity. Resolution enables the transition from adaptation to recovery and rehabilitation and may provide a target for metabolic support and rehabilitation strategies.

Keywords: *endocrinology, insulin sensitivity, low triiodothyronine syndrome, hypothalamic-pituitary-adrenal axis, tissue repair, sarcopenia.*

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Abbreviations

CNS – Central Nervous System.
CRP – C-Reactive Protein.
CVS – CardioVascular System.
DAMPs – Damage-Associated Molecular Patterns.
GH – Growth Hormone.
HPA – Hypothalamic–Pituitary–Adrenal axis.
HPT – Hypothalamic–Pituitary–Thyroid axis.
IGF-1 – Insulin-like Growth Factor 1.
IL-1 β – InterLeukin 1 β .
IL-6 – InterLeukin 6.
IS – Insulin Sensitivity.
LT3S – Low T3 Syndrome.
MetS – Metabolic Syndrome.
OXPHOS – OXidative PHOSphorylation.
rT3 – reverse Triiodothyronine.
SPMs – Specialized Pro-resolving Mediators.
T3 – Triiodothyronine.
TH – Thyroid Hormones.
TNF- α – Tumor Necrosis Factor α .
Tregs – regulatory T cells.

Introduction

Acute inflammation is a universal adaptive response of the organism to infectious, traumatic, or other forms of injury and plays a key role in ensuring survival and maintaining tissue structural integrity [1–3]. For many years, the termination of the inflammatory response was regarded primarily as a passive process involving the gradual decline of pro-inflammatory mediator production following elimination of the injurious stimulus. However, current evidence indicates that inflammation resolution is an active biological program mediated by specialized pro-resolving mediators, immune cells, neuroendocrine mechanisms, and metabolic signaling pathways [4–7].

Effective resolution not only terminates excessive inflammatory activity but also promotes the clearance of cellular debris, restoration of

tissue homeostasis, regeneration of damaged structures, and return of the organism to normal function [4–8]. Disruption of these processes may be accompanied by incomplete recovery of the body's adaptive reserves, the development of chronic allostatic overload, and the emergence of various forms of metabolic maladaptation, including MetS, sarcopenia, and other chronic disturbances of homeostasis [9–12].

In recent years, increasing attention has been directed toward the role of immunometabolic mechanisms in regulating both the acute inflammatory response and its subsequent resolution [13–16]. Activation of innate immune cells has been shown to be accompanied by profound metabolic reprogramming, including enhanced glycolysis, mobilization of energy substrates, and reorganization of inter-organ metabolic interactions [13–15]. In contrast, successful transition to the resolution and recovery phases requires reactivation of oxidative metabolism, restoration of mitochondrial function, and gradual return to anabolic processes [15; 16].

Neuroendocrine systems play a particularly important role in coordinating these processes. During the acute phase of adaptation, resource mobilization mechanisms predominate, including activation of the HPA-axis, the sympathoadrenal system, and the development of LT3S [19–23; 25]. In contrast, effective recovery requires a gradual decline in catabolic activity, restoration of thyroid function, reactivation of the GH–IGF-1 axis, and recovery of tissue IS [18; 21–27]. Here, immunometabolic resolution is defined as an active systemic transition from the mobilization–catabolic program of acute inflammation toward the neuroendocrine and metabolic support of tissue repair and recovery. This hypothesis-generating whole-

organism framework links established cellular resolution mechanisms to the restoration of endocrine regulation, metabolic flexibility, tissue repair, and functional capacity.

In our previous studies, low T3 states, integration of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes, and tissue-specific regulation of insulin sensitivity were considered within the broader framework of immunometabolic allostasis and functional resource prioritization during acute adaptation [21–26]. However, the mechanisms responsible for terminating this adaptive program and facilitating the transition from resource mobilization to resolution, tissue repair, and functional recovery remain insufficiently understood.

Here, immunometabolic resolution is proposed as a hypothesis-generating whole-organism framework linking established cellular resolution mechanisms to the restoration of endocrine regulation, metabolic flexibility, tissue repair and functional capacity. Unlike established lipid-mediator resolution biology [4–7], and unlike our earlier work on immunometabolic allostasis during acute adaptation [21; 22; 24; 26; 27], this framework addresses the putative transition beyond the acute phase. The integration and timing of these mechanisms have not been validated as a single longitudinal physiological sequence.

Particular interest arises from the comparative analysis of resolution in acute post-traumatic inflammation and chronic sterile inflammation associated with MetS. Although these conditions share many mechanisms of immunometabolic regulation, they differ fundamentally in the effectiveness of the transition from adaptation to recovery. Whereas uncomplicated acute inflammation typically culminates in resolution and tissue repair, resource-mobilizing mechanisms may persist in metabolic syndrome, contributing to chronic allostatic overload and metabolic maladaptation [10–12; 18].

The **aim** of this review was to analyze current concepts of inflammation resolution as a component of immunometabolic allostasis, to examine the role of neuroendocrine and

metabolic regulation in the transition from adaptation to recovery, and to evaluate the significance of these processes for post-traumatic rehabilitation and chronic metabolic diseases.

Materials and Methods

A narrative review of the literature was conducted focusing on immunometabolic mechanisms of inflammation resolution and their role in shifting the organism's functional priority from survival programs toward tissue repair, recovery, and rehabilitation. Literature searches were performed using the PubMed, Scopus, Web of Science, MEDLINE, ScienceDirect, and Google Scholar databases. Original studies, systematic reviews, meta-analyses, and seminal publications published primarily between 2000 and 2025 were included. Classical studies of fundamental importance for understanding inflammation, resolution biology, immunometabolism, and neuroendocrine regulation were also considered.

Publications were selected using the following keywords: *insulin sensitivity*, *low triiodothyronine syndrome*, *hypothalamic-pituitary-adrenal axis*, *tissue repair*, *sarcopenia*, and *metabolic syndrome*. The literature was analyzed using integrative physiological and immunometabolic approaches, with particular emphasis on the relationships among adaptive mechanisms, inflammation resolution, and organismal recovery.

The review is narrative rather than systematic. The authors should supply the actual database-specific search strings, search dates, applied filters and selection procedure if documented; these details cannot be reconstructed reliably from the published keywords. No PRISMA-compliant selection or quantitative synthesis is claimed.

Results

1. Inflammation resolution as an active process of immunometabolic recovery

1.1. From the classical concept of inflammation termination to the concept of resolution

For many years, the termination of the inflammatory response was regarded as a passive process occurring after elimination of the injurious stimulus as a result of the gradual decline in pro-inflammatory mediator

production and cessation of immune cell activation [3]. However, contemporary studies have demonstrated that resolution represents a distinct genetically and biochemically regulated phase of the inflammatory process rather than merely a consequence of the disappearance of the inflammatory stimulus [4–7].

A major contribution to the development of the modern concept of resolution was made by the studies of Serhan C.N. (2014) [4] and Serhan C.N. & Savill J. (2005) [5], which demonstrated the existence of SPMs, including lipoxins, resolvins, protectins, and maresins [4; 5; 28–31]. These mediators coordinate efferocytosis, leukocyte trafficking, macrophage phenotypic reprogramming, tissue repair, and restoration of homeostasis [4–7; 28–31].

The contemporary concept of resolution considers it an active phase of the inflammatory process involving specific cellular and metabolic regulatory mechanisms. Macrophage phenotypic reprogramming, Tregs, local metabolic adaptations, and activation of tissue repair programs play central roles in this process [6; 7; 32–43]. Thus, resolution represents a distinct biological program aimed at restoring the structural and functional integrity of the organism.

1.2. Resolution as a shift in functional priority

From the perspective of contemporary immunometabolism, acute inflammation may be viewed as an adaptive survival program aimed at localizing tissue injury, eliminating pathogens, and maintaining vital physiological functions [13–16; 19; 20]. Its implementation is accompanied by activation of innate immunity, inflammatory cytokine networks, the HPA-axis, the sympathoadrenal system, and mechanisms responsible for energy resource mobilization [17–20; 24].

Following elimination of the injurious stimulus, the organism's functional priority gradually shifts from resource mobilization and survival toward tissue repair, regeneration, and restoration of organ and tissue function [8; 17; 18; 25]. Within the framework of the proposed concept, this transition may be described as a shift in the dominant program: survival → recovery. This process is accompanied by reorganization of cellular,

neuroendocrine, and metabolic regulatory mechanisms, restoration of HPT-axis activity, increasing importance of anabolic pathways, normalization of tissue IS, and restoration of efficient oxidative metabolism [17; 18; 21–27].

Therefore, resolution should be regarded as an integrated process of immunometabolic recovery that ensures a coordinated transition from mechanisms of acute adaptation to programs of tissue repair, recovery, and rehabilitation. Impairment of this transition may contribute to chronic inflammation, metabolic maladaptation, and impaired tissue regeneration [8–12; 42; 43].

2. Metabolic transition from catabolism to anabolism

2.1. Termination of the resource mobilization program

The acute phase of inflammation is accompanied by activation of mechanisms responsible for energy resource mobilization, which are required to support the immune response and maintain vital physiological functions. Under the influence of pro-inflammatory cytokines, as well as activation of the HPA-axis and the sympathoadrenal system, catabolic processes are enhanced to provide the immune system with energy and metabolic substrates [13–20; 24].

Effective resolution requires timely termination of this program. One of its hallmarks is a reduction in pro-inflammatory cytokine production and gradual attenuation of HPA-axis activity, accompanied by decreased cortisol levels and limitation of catabolism [4–7; 17; 19; 20; 28–31]. Particular importance is attributed to suppression of skeletal muscle proteolysis, which during the acute phase provides amino acids for acute-phase protein synthesis and immune system function but, when prolonged, may impair tissue repair [41–43].

Thus, one of the key features of resolution is the gradual shift of metabolism from substrate mobilization toward substrate utilization for tissue repair and recovery.

2.2. Metabolic switching and restoration of metabolic flexibility

A hallmark of the acute inflammatory response is the metabolic reprogramming of

innate immune cells. Activated macrophages and neutrophils predominantly rely on aerobic glycolysis, which enables rapid ATP production and synthesis of inflammatory effector molecules [13–16; 36]. During the resolution phase, mitochondrial function is progressively restored, the role of OXPHOS increases, fatty acid β -oxidation is activated, and the capacity of cells for complete oxidation of energy substrates is enhanced [14; 15; 45–51]. Persistent activation of catabolic pathways may contribute to skeletal muscle loss and the development of sarcopenia [52; 53].

The transition from a predominantly glycolytic to an oxidative metabolic phenotype is closely associated with macrophage phenotypic reprogramming toward pro-resolving and reparative functions and with the establishment of a metabolic environment favorable for tissue recovery [33–36]. Therefore, meta-

bolic switching from glycolysis to mitochondrial oxidative metabolism represents one of the central mechanisms underlying the transition from acute adaptation to recovery (Fig. 1).

In contemporary physiology, this process is closely linked to the concept of metabolic flexibility, defined as the ability of the organism to adaptively modify substrate utilization according to changing functional demands [2; 13; 14]. Reduced capacity to switch between glucose and fatty acid oxidation is regarded as one of the key mechanisms of metabolic maladaptation [44]. From the perspective of the proposed concept of functional priority, resolution may be viewed as a process of restoring metabolic flexibility following completion of the acute adaptive program. Impaired metabolic flexibility may lead to chronic allostatic overload, metabolic maladaptation, and incomplete recovery processes [8–12; 26; 27; 48–56].

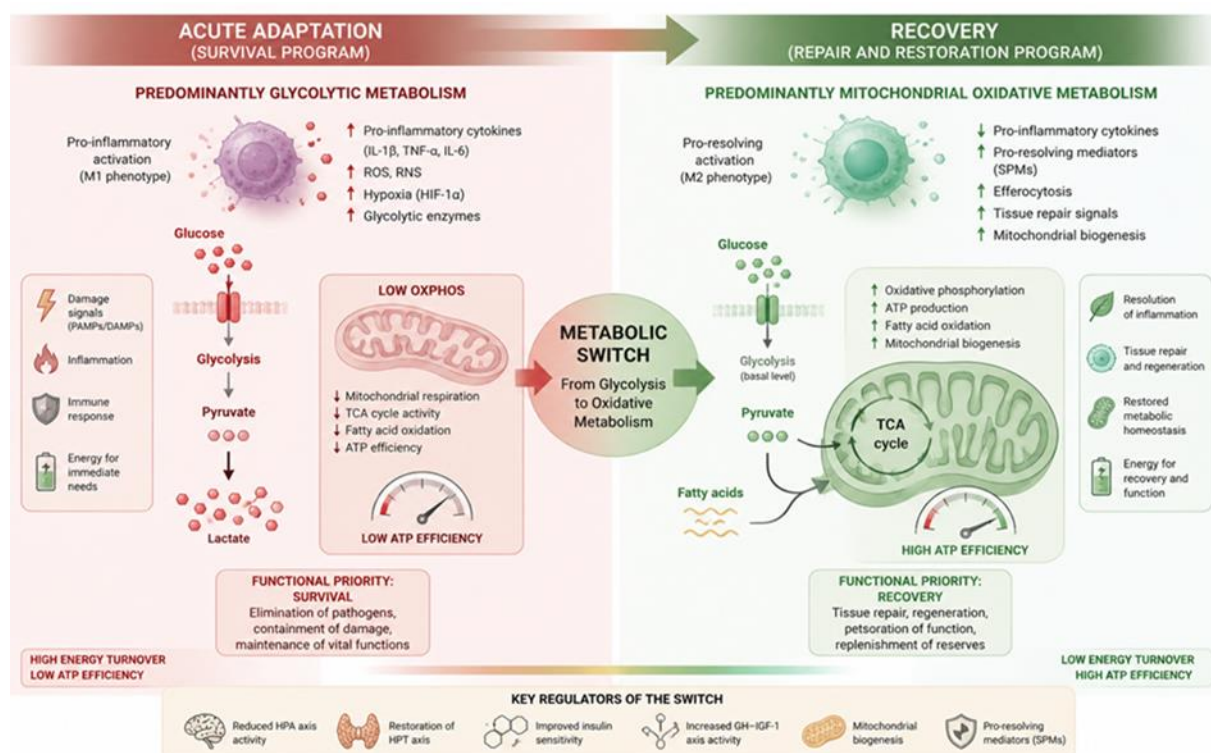


Fig. 1. Metabolic switching from glycolysis to oxidative metabolism as a component of the transition in functional priority from survival to recovery programs.

Notes: DAMPs – damage-associated molecular patterns; M1 – pro-inflammatory macrophage phenotype; M2 – pro-resolving macrophage phenotype; IL-1 β – interleukin-1 beta; TNF- α – tumor necrosis factor alpha; IL-6 – interleukin-6; ROS – reactive oxygen species; RNS – reactive nitrogen species; HIF-1 α – hypoxia-inducible factor 1 alpha; OXPHOS – oxidative phosphorylation; TCA – tricarboxylic acid; ATP – adenosine triphosphate; SPMs – specialized pro-resolving mediators; HPA – hypothalamic-pituitary-adrenal; HPT – hypothalamic-pituitary-thyroid; GH – growth hormone; IGF-1 – insulin-like growth factor 1.

Therefore, restoration of metabolic flexibility may be considered one of the key criteria of successful inflammation resolution, effective tissue repair, and subsequent rehabilitation.

3. Integration of the HPA and HPT-axes in inflammation resolution

3.1. Adaptive role of the HPA-axis during the acute phase

In response to trauma, infection, or other significant injury, the organism activates a complex neuroendocrine adaptation program, the central component of which is the HPA-axis [17–20]. Under the influence of pro-inflammatory cytokines, particularly IL-1 β , IL-6, and TNF- α , the secretion of CRH, ACTH, and cortisol is enhanced [19; 20].

Cortisol stimulates gluconeogenesis and supports lipolysis and proteolysis, thereby ensuring the availability of energy and plastic substrates for organs and systems involved in the acute adaptive response [17; 19; 20]. Simultaneously, it limits excessive cytokine activation and contributes to the prevention of uncontrolled tissue damage. From the perspective of immunometabolic allostasis, these effects can be regarded as interconnected components of a unified adaptive program aimed at maintaining the functional priority of systems critical for preserving homeostasis under conditions of injury [24; 26; 27].

In this context, activation of the HPA-axis may be viewed not only as a mechanism of anti-inflammatory control but, more importantly, as a mechanism for resource mobilization and redistribution according to the demands of the acute adaptive response. Maintaining the availability of energy and plastic substrates creates conditions necessary for the effective functioning of innate immune cells and the implementation of protective responses.

At the same time, the effectiveness of this mechanism depends on its transient nature. Prolonged elevation of HPA-axis activity is associated with persistent catabolic metabolism, suppression of anabolic processes, loss of skeletal muscle mass, impaired metabolic flexibility, and delayed tissue repair [19; 20; 52; 53]. Therefore, successful inflammation resolution is accompanied by a gradual reduction in the need for resource-mobilizing mechanisms and a corresponding decline in

HPA-axis activity, creating the conditions required for the transition from acute adaptation to recovery.

3.2. Reactivation of the HPT-axis as a component of recovery

One of the characteristic features of acute inflammation is the development of LT3S, which is accompanied by reduced peripheral generation of T3 and accumulation of rT3 [18; 21–25]. For many years, these changes were considered primarily manifestations of endocrine dysfunction or mechanisms for reducing energy expenditure. However, from the perspective of immunometabolic allostasis, the low T3 phenotype may be context-dependent; during acute inflammatory stress, LT3S may be viewed as one component of the adaptive response, ensuring the alignment of energy metabolism with the organism's functional priorities under conditions of injury.

The adaptive significance of LT3S extends beyond the reduction of overall energy expenditure. Given the key role of TH in regulating cellular energy metabolism, LT3S may participate in cellular metabolic reprogramming by promoting a shift from predominantly oxidative metabolism toward rapid energy-generating pathways associated with glycolysis. Simultaneously, mitochondrial biogenesis, OXPHOS, thermogenesis, protein synthesis, growth, and other energy-demanding anabolic processes are attenuated [18; 21–25].

The interpretation of low T3 syndrome as uniformly adaptive is disputed. Early reductions in circulating T3 may be compatible with short-term energy conservation, whereas persistent changes in prolonged critical illness may reflect central suppression, altered deiodination and potentially adverse consequences. Observational associations do not establish that thyroid hormone replacement improves recovery; treatment decisions cannot be inferred from this conceptual model [18; 23; 25; 57–60].

Such changes may reduce tissue requirements for oxygen and energy substrates while creating conditions for the preferential support of the energetic demands of the innate immune system. In this context, LT3S may be regarded as one of the key mechanisms of

immunometabolic allostasis involved in shifting the organism's functional priorities and maintaining an effective adaptive response aimed at restoring homeostasis.

Following elimination of the injurious stimulus, the functional role of the thyroid system changes. Restoration of T3 production creates conditions for the reactivation of mitochondrial biogenesis, OXPHOS, protein synthesis, and other anabolic processes required for effective tissue repair and functional recovery [18; 21–25]. In this context, reactivation of the HPT-axis may be considered an important component of the transition from catabolism to anabolism.

The effectiveness of this process largely depends on the organism's functional thyroid reserve, which determines its capacity to restore T3 production following the acute phase of adaptation [21–25]. Adequate iodine availability may also be important, as iodine deficiency could potentially limit the recovery of thyroid function after severe injury [21; 22; 25].

Thus, inflammation resolution is accompanied by a shift in the functional role of the thyroid system – from predominant participation in acute adaptive mechanisms toward providing the conditions necessary for restoration of oxidative metabolism, anabolic activity, and tissue repair.

3.3. The Concept of HPA→HPT transition

The evidence reviewed suggests that inflammation resolution should be regarded not only as a local immunological process but also as a systemic reorganization of neuroendocrine and metabolic regulation [18–24].

During the acute phase of injury, regulatory mechanisms aimed at supporting the adaptive response and maintaining homeostasis under conditions of increased functional demand predominate. Activation of the HPA axis, development of LT3S, and the associated immunometabolic changes ensure resource mobilization, restructuring of energy metabolism, and maintenance of the effective functioning of systems involved in protective responses [18–27].

As the organism transitions from adaptation to recovery, HPA-axis activity gradually declines, thyroid regulation is restored, OXPHOS is reactivated, anabolic processes intensify,

and tissue repair mechanisms become increasingly dominant [21–25]. Within the framework of the proposed concept, this process may be described as the HPA→HPT transition – a sequential shift in regulatory dominance from mechanisms supporting acute adaptation toward mechanisms promoting metabolic and functional recovery.

The proposed HPA→HPT transition is a conceptual shorthand for changes that may overlap and vary across tissues and clinical conditions. The five components are considered interdependent, potentially partly simultaneous processes rather than five experimentally established sequential stages. Neither a fixed temporal order nor quantitative coupling has been demonstrated in a longitudinal cohort; these predictions require prospective testing.

This approach allows inflammation resolution to be viewed as a specific manifestation of the broader process of immunometabolic adaptation and restoration of homeostasis. In this context, the interaction between the HPA and HPT- axes can be viewed as a component of the modern concept of adaptation, complementing the classical understanding of the general adaptation syndrome through mechanisms of immunometabolic regulation and cellular metabolic reprogramming.

Impairment or incomplete completion of the HPA→HPT transition may contribute to the development of chronic allostatic overload, sarcopenia, metabolic syndrome, impaired regeneration, and delayed post-traumatic recovery. Therefore, assessment of HPA–HPT-axis interactions may represent a promising direction for future studies of inflammation resolution and provide a basis for the development of novel strategies of metabolic support and rehabilitation following severe inflammatory and traumatic injuries.

4. Tissue insulin sensitivity in inflammation resolution

4.1. Insulin sensitivity during the acute adaptive phase

During acute inflammation, the regulation of tissue IS represents an important component of the systemic adaptive response and has been conceptualized as a mechanism of functional priority that redistributes substrates among tissues according

to acute adaptive demands [26]. Under the influence of pro-inflammatory cytokines, cortisol, catecholamines, glucagon, and other counter-regulatory factors, tissue-specific remodeling of insulin signaling develops, ensuring the mobilization of energy resources and their redistribution according to the organism's functional needs [26; 27; 67–70].

The most pronounced reduction in IS occurs in skeletal muscle and adipose tissue, accompanied by decreased glucose utilization, activation of proteolysis and lipolysis, and maintenance of elevated concentrations of energy substrates in the circulation [26; 27; 67–69]. At the same time, innate immune cells, the CNS, and other vital structures retain access to energy substrates through predominantly insulin-independent mechanisms of glucose transport [13; 26; 27].

Within the framework of the functional priority concept, these changes may be regarded as a coordinated mechanism of immunometabolic allostasis aimed at supporting systems and processes critical for maintaining homeostasis under conditions of injury. Temporary reduction of IS limits glucose utilization by major peripheral consumers and promotes the concentration of resources within systems involved in the acute adaptive response [26; 27].

4.2. Restoration of tissue insulin sensitivity following resolution of inflammation

As inflammatory activity declines and counter-regulatory mechanisms subside, restoration of IS becomes an important component of the transition from catabolic to anabolic metabolism [11; 26; 27; 67].

Particular importance is attributed to the recovery of skeletal muscle IS, as skeletal muscle accounts for the majority of insulin-dependent glucose utilization and represents the largest protein reservoir in the body [1; 2]. Normalization of insulin signaling creates conditions for protein synthesis, replenishment of glycogen stores, and regeneration of damaged structures [1; 2; 26; 67–76].

In adipose tissue, restoration of IS is accompanied by suppression of excessive lipolysis and a shift from continuous mobilization of fatty acids toward more balanced regulation of energy fluxes [11; 16]. Simultaneously, the production of pro-inflammatory

adipokines decreases, weakening the maintenance of systemic inflammation.

Restoration of hepatic insulin sensitivity is equally important. Normalization of hepatic insulin signaling contributes to suppression of excessive gluconeogenesis, stabilization of glycemia, and a shift from predominant production of energy substrates toward their efficient utilization [1; 2; 26; 67].

Thus, inflammation resolution is accompanied not only by attenuation of the inflammatory response but also by restoration of coordinated interactions among the major metabolic organs. Recovery of adequate IS may therefore be regarded as one of the key mechanisms underlying the restoration of metabolic flexibility and systemic metabolic homeostasis.

4.3. Insulin as a hormonal signal of the transition to recovery

Traditionally, insulin has been regarded as the principal anabolic hormone of the body [1; 2]. However, in the context of inflammation resolution, its role extends beyond the regulation of carbohydrate metabolism.

Whereas cortisol and other counter-regulatory hormones ensure resource mobilization during the acute adaptive phase, insulin serves as one of the key hormonal signals of the transition toward recovery. Restoration of IS creates conditions for a shift from catabolism to anabolism, stimulation of protein synthesis, glycogen accumulation, and efficient utilization of energy substrates in tissue repair processes [1; 2; 26; 27].

Importantly, the anabolic effects of insulin are realized through close interaction with thyroid hormones and the GH-IGF-1 axis. Normalization of thyroid status promotes recovery of mitochondrial function and OXPHOS, whereas IGF-1 stimulates cellular growth, proliferation, and regeneration [77–80].

Within the framework of the proposed concept, restoration of IS may be regarded as one of the key markers indicating completion of the resource mobilization phase and transition toward programs of tissue repair and functional recovery. Impairment of this process may contribute to chronic allostatic overload, metabolic maladaptation, and incomplete resolution of inflammation [9–12; 26; 27].

Therefore, insulin participates not only in the regulation of glycemia but also in coordinating the transition from acute adaptation to recovery. For this reason, restoration of tissue insulin sensitivity may be considered one of the central mechanisms underlying successful inflammation resolution and subsequent rehabilitation of the organism.

5. Immunometabolic mechanisms of post-traumatic recovery and rehabilitation

5.1. Characteristics of postoperative and post-traumatic inflammation

Postoperative and post-traumatic inflammation is a physiological component of tissue healing and differs substantially from infectious inflammation in its initiating mechanisms. The principal triggers include tissue injury, the release of DAMPs, activation of innate immune cells, and local production of pro-inflammatory cytokines [3; 8; 33; 34].

During the first hours after trauma or surgery, acute adaptive mechanisms predominate, aiming to limit tissue damage, eliminate necrotic tissue, and maintain vital physiological functions. This period is accompanied by activation of the HPA-axis, the sympathoadrenal system, the development of LT3S, stress-induced hyperglycemia, mobilization of fatty acids and amino acids, and remodeling of tissue IS [17–20; 25–27].

At the same time, the effectiveness of postoperative and post-traumatic recovery depends not so much on the intensity of the acute inflammatory response as on the organism's ability to transition in a timely manner to the processes of resolution and tissue repair. Excessive or prolonged activation of resource-mobilizing mechanisms may delay tissue regeneration, promote muscle wasting, and increase the risk of postoperative complications [41–44; 54–56].

Therefore, post-traumatic recovery should be viewed as a sequential process of shifting functional priorities – from mechanisms of acute adaptation toward mechanisms responsible for tissue repair and restoration of functional reserves.

5.2. Neuroendocrine regulation of tissue repair

As the acute adaptive phase subsides, the pattern of neuroendocrine regulation gradually changes. The importance of mechanisms responsible for resource mobilization and preferential resource allocation declines, whereas systems supporting anabolism, regeneration, and functional recovery assume a leading role [21–24; 65; 66].

One of the key components of this transition is reactivation of the HPT-axis. Restoration of T3 production promotes mitochondrial biogenesis, activation of OXPHOS, and more efficient utilization of energy substrates [18; 21–25; 65; 66]. As a result, conditions are established for the transition from a predominantly catabolic to an anabolic metabolic state.

This transition is accompanied by a gradual decline in HPA-axis activity and a reduced need for emergency resource mobilization. However, restoration of adaptive reserves often occurs more slowly than clinical improvement. Consequently, the early reparative phase may be characterized by a relatively limited capacity to respond adequately to additional physical, metabolic, or psychoemotional stressors.

An equally important role is played by the GH-IGF-1 axis. IGF-1 stimulates protein synthesis, cell proliferation, and tissue regeneration, thereby playing a critical role in skeletal muscle repair and recovery following injury [77–80].

In parallel, tissue IS is restored, allowing more efficient utilization of glucose and other metabolic substrates for protein synthesis, tissue repair, and replenishment of functional reserves [26; 27; 67–75].

Thus, the neuroendocrine regulation of resolution represents a coordinated interaction among the thyroid system, the GH-IGF-1 axis, and insulin signaling pathways, collectively facilitating the transition from catabolism to anabolism and creating conditions necessary for complete recovery.

5.3. Factors determining successful recovery

Current evidence suggests that successful post-traumatic resolution largely depends on the organism's ability to restore efficient utilization of energy and structural resources following completion of the acute adaptive phase [8; 41; 42].

One important factor is normalization of thyroid status. Restoration of T3 levels promotes reactivation of mitochondrial metabolism, increased ATP production, and enhanced functional readiness of tissues for regeneration [21–25; 65; 66].

Equally important are recovery of GH–IGF-1 axis activity and restoration of tissue IS. Normalization of these mechanisms creates favorable conditions for effective anabolism, protein synthesis, skeletal muscle recovery, and regeneration of damaged tissues [26; 27; 67–75; 77–80].

In recent years, particular attention has been devoted to the role of mitochondrial function. Restoration of mitochondrial biogenesis and OXPHOS is essential for meeting the energetic demands of tissue repair, whereas persistent mitochondrial dysfunction may contribute to chronic inflammation, sarcopenia, and incomplete functional recovery [45–51].

Within the functional-priority framework, successful resolution of post-traumatic inflammation may be viewed as the result of coordinated restoration of the major neuroendocrine and metabolic mechanisms that support anabolism, tissue repair, and recovery of functional reserves.

Clinical stabilization and restoration of muscle strength or metabolic function are distinct outcomes, but no validated biomarker currently establishes the end of an integrated immunometabolic recovery phase. Longitudinal assessment could compare CRP and inflammatory mediator trajectories, TSH/free T3, cortisol patterns, measures of insulin sensitivity, muscle strength and physical performance, while controlling for illness severity, nutrition and medication. These are candidate research measures, not established diagnostic criteria or treatment targets [17; 18; 25; 48; 52; 53].

Therefore, post-traumatic resolution should be considered not merely the termination of the inflammatory response but a distinct stage of immunometabolic adaptation, during which the priority of resource allocation gradually shifts from mechanisms of acute adaptation toward processes of tissue repair and recovery. Under certain circumstances, this transition

may be accompanied by a temporary reduction in adaptive capacity and increased sensitivity to additional stressors, potentially affecting the completeness of resolution and contributing to long-term consequences of the inflammatory process.

Accordingly, creating optimal conditions for the completion of resolution and restoration of adaptive reserves may be regarded as one of the key objectives of modern rehabilitation medicine.

6. Concept of immunometabolic resolution

The evidence reviewed in this article indicates that the contemporary understanding of inflammation resolution extends far beyond the traditional view of resolution as a passive cessation of the pro-inflammatory response. According to the modern concept of *resolution physiology*, the termination of inflammation is an active biological process involving coordinated interactions among immune, neuroendocrine, and metabolic mechanisms [4–7].

At the same time, most current studies focus primarily on the cellular and molecular aspects of resolution, including efferocytosis, macrophage phenotype switching, activation of Tregs, and the actions of specialized pro-resolving mediators [4–7; 28–43]. Considerably less attention has been paid to systemic mechanisms responsible for the restoration of energy metabolism and neuroendocrine regulation, despite the fact that successful tissue repair and full functional recovery cannot occur without them.

Based on the analyzed evidence, the concept of immunometabolic resolution is proposed, according to which the termination of inflammation represents an active, integrated process involving coordinated interactions among immune, neuroendocrine, and metabolic mechanisms that shift the organism's functional priority from resource mobilization and survival toward their efficient utilization for tissue repair and anabolic recovery. Key components of this transition include reduced dominance of the HPA axis, reactivation of the HPT axis with restoration of T3 production, normalization of tissue insulin sensitivity, and recovery of mitochondrial

oxidative metabolism, thereby creating the conditions for restoration of adaptive reserves and long-term maintenance of homeostasis.

A key event in this transition is the shift in the organism's functional priority. During the acute adaptive phase, survival mechanisms predominate, ensuring the activity of innate immune cells, the CNS, the CVS, and other structures critical for overcoming injury or infection [13–20; 26; 27]. Following elimination of the damaging factor, physiological priorities gradually shift toward tissue repair, regeneration, and functional recovery [4–8; 33–36]. In this context, resolution may be viewed as a systemic transition from a survival program to a recovery program.

An important mechanism underlying this transition is the reorganization of neuroendocrine regulation. The acute phase is characterized by activation of the HPA-axis, increased cortisol production, and the development of the LT3S [17–25]. From the perspective of immunometabolic allostasis, reduced T3 production may be considered not only a mechanism for limiting energy expenditure but also an important component of metabolic reprogramming. Through its effects on the expression of mitochondrial enzymes and the intensity of oxidative phosphorylation, LT3S contributes to the temporary suppression of energy-demanding processes, including mitochondrial biogenesis, fatty acid β -oxidation, and anabolic activity, thereby matching metabolic activity to the functional requirements of acute adaptation [21–25; 65; 66].

During the resolution phase, several regulatory changes associated with recovery have been described independently, including attenuation of prolonged HPA-axis activation, restoration of thyroid function and T3 availability, and recovery of mitochondrial oxidative metabolism [21–25; 45–51; 65; 66]. Restoration of T3 production is mechanistically consistent with reactivation of mitochondrial biogenesis, oxidative enzyme expression, and OXPHOS, thereby creating metabolic conditions favorable for anabolic recovery [21–25; 65; 66].

In the present review, these individually supported mechanisms are integrated into the conceptual framework of an HPA→HPT transition, which denotes a progressive shift in regulatory dominance from mechanisms supporting acute adaptation toward mechanisms supporting recovery. This sequence should be regarded as a hypothesis-generating synthesis rather than an experimentally established or clinically validated longitudinal pathway. Its temporal order, degree of overlap, and interdependence require prospective investigation.

Another important component associated with resolution is the restoration of tissue IS. While reduced insulin sensitivity during the acute phase may contribute to redistribution of energy resources toward adaptive inflammatory responses [26; 27], restoration of insulin signaling after attenuation of the acute stress response creates favorable conditions for protein synthesis, glycogen replenishment, anabolic processes, and tissue repair [1; 2; 26; 67–71; 75; 76]. Within the proposed framework, this change is considered complementary to, but not necessarily synchronous with, the neuroendocrine changes described above.

An additional key component of resolution is the metabolic shift from predominantly glycolytic energy production to efficient mitochondrial oxidative metabolism. Following the acute phase, OXPHOS, fatty acid β -oxidation, and metabolic flexibility are gradually restored, providing the energetic basis for regeneration, anabolism, and functional recovery [13–16; 45–51]. In the proposed model, these changes are interpreted as part of the broader transition from acute adaptation to recovery; however, their exact temporal relationship to HPA-axis attenuation and HPT-axis reactivation has not been established longitudinally.

A schematic representation of the proposed concept of immunometabolic resolution is shown in *Fig. 2*.

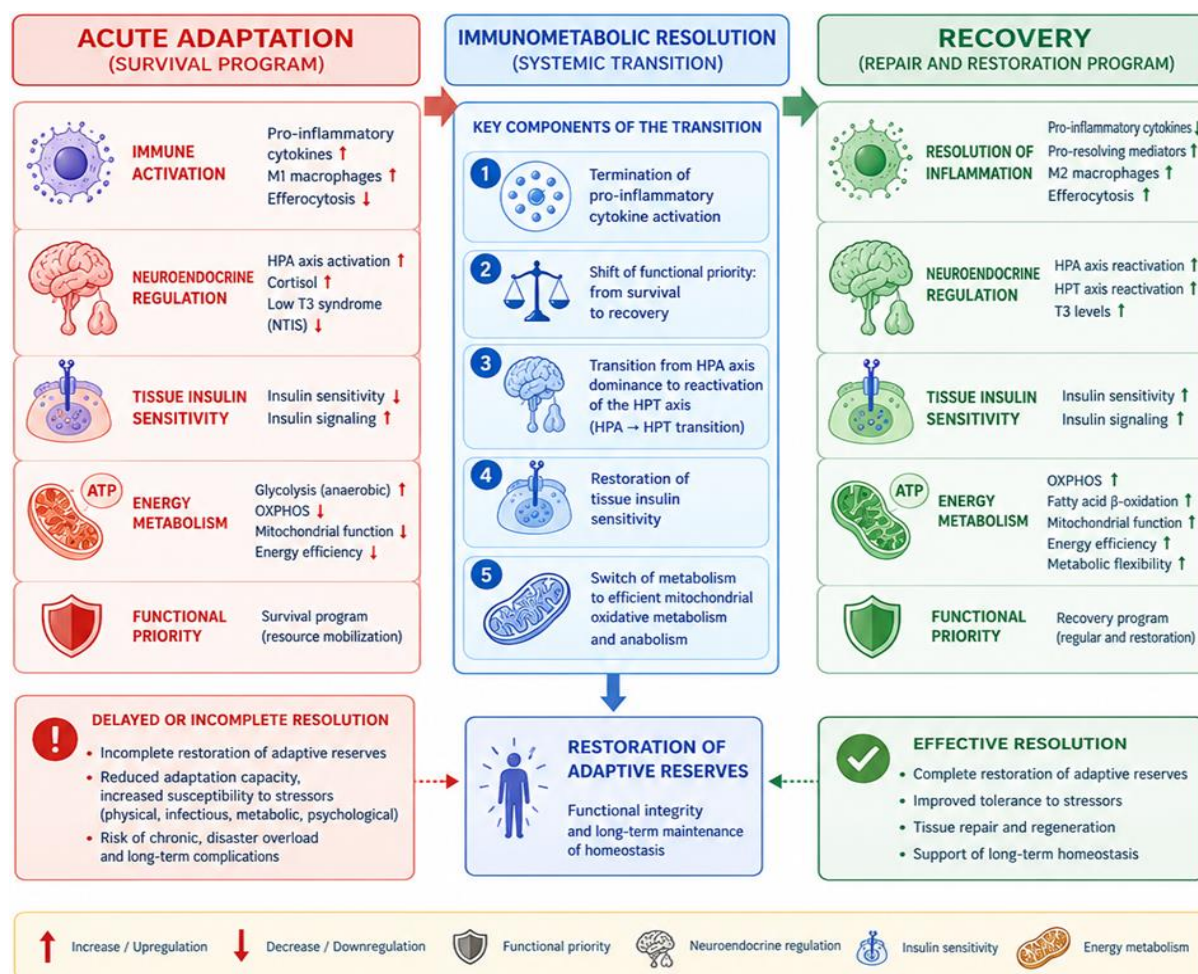


Fig. 2. Immunometabolic resolution: the transition from adaptation to recovery.

Thus, the proposed concept of immunometabolic resolution comprises five interrelated components (Fig. 2):

1. termination of pro-inflammatory cytokine activation;
2. a shift in functional priority from *survival* to *recovery*;
3. transition from HPA-axis dominance to reactivation of the HPT-axis;
4. restoration of tissue IS;
5. metabolic switching toward efficient mitochondrial oxidative metabolism and anabolism.

From this perspective, resolution may conceptually be viewed not merely as the termination of the inflammatory response, but as an integrated process of systemic recovery involving coordinated immune, endocrine, and metabolic regulation and ensuring the gradual restoration of the organism's adaptive reserves.

Discussion

The proposed concept of immunometabolic resolution allows the termination of inflammation to be viewed as a systemic transition from acute adaptation to recovery. Unlike traditional approaches, which primarily emphasize local mechanisms responsible for terminating the inflammatory response, this model integrates immune, neuroendocrine, and metabolic mechanisms within the framework of immunometabolic allostasis. From this perspective, resolution does not complete the entire recovery process but creates the physiological prerequisites for transition to the next functional priority—tissue repair.

From the standpoint of functional systems theory, completion of the acute inflammatory response may be regarded not only as termination of individual pro-inflammatory mechanisms, but also as achievement of an intermediate beneficial adaptive result—limitation

of the tissue threat, elimination of nonviable structures, and formation of a microenvironment compatible with repair. In the proposed interpretation, this result changes the conditions for subsequent afferent synthesis: the dominant unresolved need is no longer clearance of the injured area, but restoration of its structural integrity. This creates the prerequisites for formation of the next phase-coupled functional system—repair. Such an interpretation represents a conceptual development of functional systems theory and requires further experimental and clinical verification.

This approach may help explain clinical situations in which termination of the acute inflammatory response and clinical stabilization are not yet accompanied by complete restoration of the organism's functional and adaptive capacity. After the result of resolution has been achieved, systemic priority may remain directed toward repair, which requires a different neuroendocrine and metabolic organization—reduction of catabolic mobilization, restoration of tissue insulin sensitivity and mitochondrial oxidative metabolism, and enhancement of anabolic resource allocation. Under these conditions, an excessive physical, infectious, metabolic, or psycho-emotional challenge may potentially alter the hierarchy of functional priorities and reactivate resource-mobilizing mechanisms that are necessary for survival but unfavorable for ongoing repair.

A promising area for further investigation is immunometabolic resolution during periods of intensive neuroendocrine reorganization, particularly in childhood and adolescence. It cannot be excluded that impaired or incomplete completion of these processes may contribute to the manifestation of immune-mediated diseases in genetically susceptible individuals. In older age, incomplete resolution may be associated with reduced adaptive reserve, impaired tolerance to stressors, sarcopenia, and slower functional recovery and rehabilitation.

An important modifier of the course of resolution is the baseline functional state of the organism before the onset of acute

inflammation. The effectiveness of this process may potentially depend on comorbidities, nutritional status, age-related characteristics, and availability of micronutrients required to support neuroendocrine regulation. In particular, adequate iodine status is necessary for normal thyroid function and may potentially influence restoration of thyroid regulation after completion of the acute adaptive phase. This issue requires further investigation in the context of resolution and post-traumatic recovery.

Sex-related differences in HPA-axis responses, thyroid regulation, body composition and insulin sensitivity could modify the proposed transition. However, direct sex-stratified longitudinal evidence validating this entire model is lacking; future studies should prespecify sex-stratified analyses rather than assume the direction or magnitude of differences.

Selenium is involved in deiodinase and antioxidant enzyme function, zinc contributes to thyroid and immune signaling, and vitamin D is implicated in immunoregulation. Their biological roles should not be interpreted as evidence that routine supplementation accelerates resolution: baseline deficiency, dose, clinical setting and direct intervention outcomes would need to be assessed. Nutritional status may also confound associations between thyroid biomarkers and recovery.

At the same time, the proposed concept has several limitations. Most available evidence has been generated within separate fields of research, including immunology, endocrinology, metabolism, and rehabilitation medicine. Studies providing an integrated analysis of resolution at the whole-organism level remain limited. In addition, there are currently no generally accepted clinical markers that would allow quantitative assessment of the effectiveness of the transition from adaptation to recovery.

Future studies should focus on the relationships among thyroid regulation, tissue insulin sensitivity, mitochondrial function, and specialized mechanisms of inflammation resolution, as well as on identification of

biomarkers reflecting the effectiveness of the transition from acute adaptation to repair and the subsequent restoration of the organism’s adaptive capacity.

Testable hypotheses include whether trajectories of inflammatory markers, thyroid function and insulin sensitivity predict functional recovery beyond clinical stabilization, and whether multimodal nutritional support and graded rehabilitation influence these trajectories. Such interventions should be evaluated in controlled studies; the present narrative synthesis cannot establish causality or recommend routine thyroid hormone or micronutrient therapy. Search limitations include non-systematic source selection, potential publication and language bias, heterogeneous clinical populations and the absence of pooled effect estimates.

Conclusions

1. Inflammation resolution should be regarded not only as the cessation of pro-inflammatory activity but also as an active process of immunometabolic recovery involving coordinated interactions among immune, neuroendocrine, and metabolic mechanisms.
2. Effective resolution is characterized by a shift in the organism's functional priority from survival programs toward tissue repair, restoration of adaptive reserves, and long-term maintenance of homeostasis.
3. The proposed framework links attenuation of acute stress signaling, changes in thyroid regulation, restoration of insulin sensitivity

and mitochondrial metabolism; their proposed temporal coordination remains unvalidated.

4. Delayed or incomplete resolution may be associated with incomplete restoration of adaptive reserves, reduced adaptive capacity, and increased susceptibility to additional physical, infectious, metabolic, and psycho-emotional stressors.

5. The concept integrates evidence from several fields as a hypothesis-generating framework for prospective studies of inflammation resolution, tissue repair and functional recovery, rather than a clinically validated model.

Declarations

Conflict of interest is absent.

All authors have agreed to the publication of the article under the terms of the Creative Commons BY-NC-SA 4.0 licence and of the public agreement with Kharkiv National Medical University as the founder and publisher of the journal, and to the processing and publication of their personal data.

The authors of the manuscript declare that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative artificial intelligence tools or services to perform any of the tasks listed in the Generative Artificial Intelligence Delegation Taxonomy (GAIDeT, 2025). All stages of the work (from the development of the research concept to the final editing) were performed without the involvement of generative artificial intelligence, exclusively by the authors.

Authors' Contributions

Contributions	A	B	C	D	E	F
Authors						
Biletska O.M.	+	+	+	+	+	+
Garyachiy Ye.V.	+	+	+		+	+
Shevchenko A.S.	+	+		+	+	+

Notes:

A – concept;

B – design;

C – data collection;

D – statistical processing and interpretation of data;

E – writing or critical editing of the article;

F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

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ВІД АДАПТАЦІЇ ДО ВІДНОВЛЕННЯ: МЕХАНІЗМИ РЕЗОЛЮЦІЇ ЗАПАЛЕННЯ В СИСТЕМІ ІМУНОМЕТАБОЛІЧНОГО АЛОСТАЗУ (ОГЛЯД ЛІТЕРАТУРИ)

Актуальність. Традиційно завершення запалення розглядалося як пасивне згасання прозапальної відповіді після усунення ушкоджувального чинника. Проте нині резолюція запалення визнається активним процесом, що включає координовану взаємодію імунних, нейроендокринних і метаболічних механізмів, необхідних для репарації тканин і відновлення організму. Такий підхід створює підґрунтя для розробки нових підходів до лікування, метаболічної підтримки та реабілітації.

Мета роботи. Проаналізувати сучасні уявлення про механізми резолюції запалення з позицій імунометаболізму та обґрунтувати концепцію імунометаболічної резолюції як системного процесу, що забезпечує перехід від адаптації до відновлення.

Матеріали та методи. Проведено наративний огляд досліджень, проіндексованих у базах даних PubMed, Scopus, Web of Science, MEDLINE, ScienceDirect і Google Scholar за період 2000–2025 рр. Проаналізовано роботи, присвячені резолюції запалення, нейроендокринній регуляції, тканинній чутливості до інсуліну, тиреоїдній адаптації, мітохондріальній функції, посттравматичному відновленню та метаболічним порушенням. Дослідження виконано як приватна ініціатива авторів, без грантової підтримки та державної реєстрації теми.

Результати. Показано, що резолюція запалення пов'язана зі зміною функціонального пріоритету організму від програм виживання до програм репарації тканин і відновлення. Ключовою подією цього переходу є зменшення енергетичних потреб системи вродженого імунітету, що супроводжується зниженням цитокінової активації, послабленням активності гіпоталамо-гіпофізарно-наднирничкової (ГГН) осі та перерозподілом енергетичних ресурсів на користь репарації тканин. Резолюція включає відновлення тканинної чутливості до інсуліну, нормалізацію тиреоїдного статусу та мітохондріальної функції, а також перехід від переважно гліколітичного до окисного типу метаболізму. Затримка резолюції може спричиняти розвиток хронічного алостатичного перевантаження, метаболічного синдрому, саркопенії та порушень посттравматичного відновлення.

Висновки. Запропоновано концепцію імунометаболічної резолюції, відповідно до якої завершення запалення є інтегрованим процесом, що включає відновлення нейроендокринної регуляції, енергетичного метаболізму та функціональної цілісності організму. Резолюція забезпечує перехід від адаптації до відновлення і реабілітації та може розглядатися як перспективна мішень для метаболічної підтримки й розробки реабілітаційних стратегій.

Ключові слова: ендокринологія, чутливість до інсуліну, синдром низького трийодтироніну, гіпоталамо-гіпофізарно-надниркова вісь, репарація тканин, саркопенія.

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