ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

UDC: 616.379-008.64:612.015.31

REGULATION OF TISSUE INSULIN SENSITIVITY AS A MECHANISM OF FUNCTIONAL PRIORITY: IMPLICATIONS FOR ADAPTATION, SURVIVAL, AND REHABILITATION

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Background. Insulin Resistance (IR) is traditionally regarded as one of the key mechanisms underlying metabolic syndrome, type 2 diabetes mellitus, and associated cardiovascular complications. However, alterations in insulin sensitivity also occur during fasting, physical exercise, pregnancy, acute stress, trauma, and inflammation, suggesting their potential adaptive role in the regulation of energy metabolism.

Aim. To summarize current evidence on the role of tissue insulin sensitivity in systemic immunometabolic adaptation and to substantiate the concept of its regulation as a mechanism of functional priority.

Materials and Methods. A literature search for the narrative review was conducted in PubMed, Scopus, Web of Science, and Google Scholar. Data synthesis was performed using conceptual and integrative approaches. The study was carried out as a private initiative of the authors, without grant support and state registration of the topic.

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

Results. Available evidence indicates that alterations in insulin sensitivity are tissue-specific and may serve adaptive functions. During acute inflammation, activation of the cytokine network, the hypothalamic-pituitary-adrenal axis, the sympathoadrenal system, and other counter-regulatory mechanisms is accompanied by stress hyperglycemia, mobilization of energy substrates, and selective reduction of insulin sensitivity in skeletal muscle and adipose tissue. These changes increase the availability of energy resources for innate immune cells, the central nervous system, and other vital structures. Regulation of tissue insulin sensitivity is proposed as a mechanism of functional priority that ensures redistribution of resources according to the organism's adaptive needs. The concept of immunometabolic allostasis is substantiated, according to which insulin resistance may represent not only a manifestation of metabolic pathology but also a component of a coordinated adaptive response. Acute post-traumatic and low-grade sterile inflammation associated with metabolic syndrome appear to share common mechanisms of neuroendocrine regulation.

Conclusions. Tissue insulin sensitivity may be regarded as an important component of systemic immunometabolic adaptation. The proposed concept of functional priority provides a basis for considering the regulation of insulin sensitivity as one of the mechanisms involved in the redistribution of energy resources among functional systems according to their importance for adaptation, survival, and recovery.

Keywords: *endocrinology, insulin resistance, immunometabolism, hyperglycemia, allostasis, stress.*

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ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

Цитуйте українською: Білецька ОМ, Гарячий ЄВ, Шевченко ОС. Регуляція тканинної чутливості до інсуліну як механізм функціонального пріоритету: значення для адаптації, виживання та реабілітації. Експериментальна і клінічна медицина. 2026;95(1):16с. In press. https://doi.org/10.35339/ekm.2026.95.1.bgs

Cite in English: Biletska OM, Garyachiy YeV, Shevchenko AS. Regulation of tissue insulin sensitivity as a mechanism of functional priority: Implications for adaptation, survival, and rehabilitation. Experimental and Clinical Medicine. 2026;95(1):16p. In press. https://doi.org/10.35339/ekm.2026.95.1.bgs [in Ukrainian].

Abbreviations

CNS – Central Nervous System.
CRP – C-Reactive Protein.
CVS – CardioVascular System.
GH – Growth Hormone.
GLUT – GLUcose Transporter.
HOMA-IR – Homeostatic Model Assessment of Insulin Resistance.
HPA – Hypothalamic-Pituitary-Adrenal.
HPT – Hypothalamic-Pituitary-Thyroid.
IGF-1 – Insulin-like Growth Factor-1.
IL-1β – Interleukin-1β.
IL-6 – Interleukin-6.
IR – Insulin Resistance.
IS – Insulin Sensitivity.
LT3S – Low T3 Syndrome.
MetS – Metabolic Syndrome.
rT3 – reverse T3.
T2DM – Type 2 Diabetes Mellitus.
T3 – Triiodothyronine.
TGF-β1 – Transforming Growth Factor Beta 1.
TH – Thyroid Hormones.
TNF-α – Tumor Necrosis Factor-α.

Introduction

Insulin plays a central role in the regulation of energy metabolism by coordinating nutrient utilization and storage across different tissues of the body [1, 2]. Traditionally, reduced IS has been considered one of the principal mechanisms underlying obesity, MetS, and T2DM [3–5]. Within this framework, IR is regarded as a pathological condition associated with impaired glucose utilization, hyperinsulinemia, and an increased risk of cardiovascular complications [1; 2; 6].

However, numerous clinical and experimental observations indicate that alterations in IS occur not only in metabolic diseases but also during fasting, physical exercise, pregnancy, acute stress, trauma, and inflammation [7–11]. Under these conditions, such changes may have adaptive significance and contribute to meeting the energy demands of organs and systems involved in priority survival or recovery programs.

Particular interest has recently been focused on the tissue-specific nature of IS. It has been demonstrated that different organs and cell types may respond differently to insulin within the same physiological or pathological state [1; 6; 12]. These findings challenge the concept of IR as a uniform generalized phenomenon and support the existence of a complex system of tissue-specific regulation of energy metabolism.

The importance of tissue-specific regulation of IS is especially evident during acute inflammation, which is accompanied by profound neuroendocrine and immunometabolic reprogramming [11; 13–15]. Increasing evidence suggests that acute post-traumatic inflammation and the low-grade sterile inflammation associated with MetS may share common mechanisms regulating IS while leading to different outcomes in adaptation, recovery, and the development of metabolic disorders. Nevertheless, the role of tissue-specific regulation of IS in the systemic adaptation of the organism to inflammatory injury remains insufficiently understood.

In this review, we introduce the concept of functional priority, which we define as a regulatory mechanism that governs tissue-specific insulin sensitivity to ensure the preferential allocation of energy resources to organs and systems according to their current adaptive significance. The priority of a functional system is determined by the intensity of its energy demand, its role in maintaining vital functions, and the duration of the adaptive response required.

The **aim** of this study was to analyze current concepts of insulin resistance regulation as a mechanism of systemic immunometabolic

ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

adaptation and to evaluate its significance in acute inflammation, maladaptation, and post-traumatic recovery.

Materials and Methods

A narrative review of experimental, clinical, and review studies published between 2000 and 2025 was conducted. The literature search included publications indexed in PubMed, Scopus, Web of Science, and Google Scholar. The following keywords were used: insulin resistance, immunometabolism, hyperglycemia, allostasis, hormonal regulation, and stress.

Publications addressing tissue-specific insulin signaling, systemic adaptation, redistribution of energy resources, and metabolic regulation during acute and chronic inflammation were included in the analysis. Data synthesis was performed using an integrative physiological approach to evaluate the role of tissue IS in immunometabolic adaptation and the implementation of functional priority. Full-text articles published in Ukrainian and English were included in the review.

Results

1. Biological significance of insulin and the regulation of insulin sensitivity

Insulin is one of the central regulators of energy metabolism in the body. Traditionally, it has been regarded as the principal anabolic hormone responsible for maintaining glucose homeostasis, stimulating glycogen, lipid, and protein synthesis, and suppressing catabolic processes. However, current evidence suggests that the physiological role of insulin extends far beyond the regulation of blood glucose concentrations and includes the coordination of energy resource allocation among different organs and functional systems according to their current metabolic demands [1; 2].

Following nutrient intake, insulin promotes the delivery of energy substrates to tissues responsible for their storage or utilization in growth, regeneration, and functional recovery. At the same time, it suppresses glycogenolysis, lipolysis, proteolysis, and gluconeogenesis, thereby shifting the organism from a state of resource mobilization to one of energy storage and efficient utilization [1; 2]. Thus, insulin may be viewed as one of the principal coordinators of energy homeostasis, maintaining the balance between energy mobilization, storage, and consumption.

At the same time, IS differs substantially among tissues. Skeletal muscle and adipose tissue are considered the major insulin-dependent tissues, where glucose uptake is largely determined by insulin-stimulated translocation of the GLUT4 transporter to the cell membrane [1; 6; 8; 13]. Skeletal muscle accounts for the majority of postprandial glucose disposal and plays a pivotal role in maintaining whole-body IS. In addition to serving as an energy reservoir, adipose tissue exerts important endocrine functions and participates in the regulation of appetite, inflammation, and metabolic homeostasis [5; 14; 16].

The liver occupies a unique position within the insulin-regulatory system. Despite relying predominantly on the insulin-independent glucose transporter GLUT2, it remains one of the principal target organs of insulin, which regulates glycogenolysis, gluconeogenesis, and lipogenesis [1; 2]. Consequently, impaired hepatic responsiveness to insulin plays a major role in the development of fasting hyperglycemia and MetS.

In contrast to skeletal muscle and adipose tissue, the brain, erythrocytes, and a substantial proportion of immune cells rely predominantly on insulin-independent glucose transport mediated by GLUT1 and GLUT3 transporters [1; 6; 13]. This organization ensures a continuous supply of energy substrates to vital organs even during fasting or marked fluctuations in circulating insulin levels. This becomes particularly important during acute inflammation, when cells of the innate immune system undergo metabolic reprogramming toward a predominantly glycolytic phenotype and exhibit a markedly increased demand for glucose [13; 17; 18].

For many years, IR was regarded primarily as a pathological condition characterized by impaired insulin action in peripheral tissues and considered a central mechanism underlying MetS, including its associated disturbances of glucose metabolism, particularly T2DM [3–5]. However, accumulating evidence indicates

ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

that alterations in IS are considerably more complex and tissue-specific [6; 12; 19]. Different tissues may exhibit distinct patterns of IS within the same physiological or pathological condition. For example, in MetS, pronounced skeletal muscle IR may coexist with preservation of certain lipogenic effects of insulin in the liver and adipose tissue [2; 19].

Similar patterns are observed during acute inflammation. Activation of the systemic inflammatory response is accompanied by increased secretion of cortisol, catecholamines, glucagon, and GH, resulting in mobilization of energy resources through activation of glycolgenolysis, gluconeogenesis, lipolysis, and proteolysis [10; 20; 21]. Simultaneous reduction of IS in skeletal muscle and adipose tissue limits glucose utilization by these tissues and maintains elevated concentrations of energy substrates in the circulation. Under such conditions, energy resources are redistributed toward innate immune cells and functional systems involved in the inflammatory response, including the liver, the CNS, and the CVS [7; 11; 13; 22].

Additional evidence supporting the tissue-specific nature of IS derives from methods used for its clinical assessment. The widely used HOMA-IR index primarily reflects the relationship between insulin secretion and suppression of hepatic glucose production and therefore predominantly characterizes the hepatic component of IS [23]. The euglycemic hyperinsulinemic clamp, considered the gold standard for assessing IR, primarily reflects insulin-dependent glucose uptake by skeletal muscle [24]. Separate indices have been proposed to assess adipose tissue insulin sensitivity, including the Adipo-IR index, which reflects the ability of insulin to suppress lipolysis [19]. In contrast, clinically applicable methods for assessing IS in immune cells are virtually absent despite their important role in regulating inflammatory responses and immunometabolic adaptation.

2. Regulation of insulin sensitivity as a mechanism of systemic adaptation

Traditional concepts of IR have largely been derived from studies of obesity, MetS, and T2DM, in which it is still considered one of the key components of the pathogenesis of metabolic dysregulation [3–5]. However, numerous clinical and experimental observations indicate that alterations in IS represent a much broader biological phenomenon and occur in a variety of physiological and adaptive conditions [1; 2; 7; 21]. This suggests that the regulation of IS may be viewed as a universal mechanism of systemic adaptation aimed at redistributing energy resources according to the current needs of the organism.

One of the most illustrative examples is fasting and restricted energy intake. Under these conditions, reduced insulin secretion is accompanied by decreased IS in peripheral tissues, particularly skeletal muscle, thereby promoting glucose conservation and preserving its availability for organs with a high dependence on carbohydrate metabolism, most notably the CNS [1; 2; 7]. Simultaneously, lipolysis and the utilization of fatty acids as alternative energy substrates are activated. Thus, alterations in IS contribute not only to the maintenance of glycemia but also to the optimal allocation of limited energy resources among tissues.

Similar mechanisms are observed during physical exercise. Activation of the sympathoadrenal system promotes the mobilization of glycogen and fatty acids, whereas contracting skeletal muscles acquire the ability to increase glucose uptake independently of insulin through contraction-induced activation of GLUT4 transporters [8]. As a result, a complex regulatory mechanism emerges in which individual tissues temporarily modify their IS according to the functional demands of the organism.

Pregnancy provides another example of adaptive insulin signaling reprogramming. During the second half of pregnancy, physiological IR develops in skeletal muscle and adipose tissue, contributing to the maintenance of adequate blood glucose concentrations and ensuring the increasing energy demands of the fetus [9]. This mechanism is believed to have evolved as a means of prioritizing fetal development even under conditions of limited energy availability.

Alterations in IS are particularly important during acute systemic adaptation, including

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trauma and inflammation. Activation of the HPA axis and the sympathoadrenal system is accompanied by elevated cortisol and catecholamine levels, which stimulate glycogenolysis, gluconeogenesis, lipolysis, and proteolysis [10; 20]. At the same time, they reduce IS in selected peripheral tissues, thereby maintaining increased availability of energy substrates for organs and cells involved in the priority adaptive response. In this context, hyperglycemia and IR may be viewed not only as manifestations of metabolic dysregulation but also as components of a coordinated response aimed at ensuring survival [10; 11].

Further evidence supporting the adaptive significance of IS regulation is provided by endocrine disorders characterized by chronic activation of energy mobilization mechanisms. In Cushing's syndrome, excess cortisol leads to persistent hyperglycemia, enhanced gluconeogenesis, and IR [25]. Similar alterations occur in pheochromocytoma, where excessive catecholamine production maintains a state of continuous energy mobilization [10; 20]. Under such conditions, changes in IS may be interpreted as mechanisms that redistribute energy substrates toward functional systems responsible for rapid adaptation to potential threats. Excess catecholamines sustain prolonged activation of the "fight-or-flight" response, resulting in preferential energy supply to the CNS, CVS, and skeletal muscles. In acromegaly, IR may be viewed as a mechanism that limits energy storage and promotes preferential utilization of energy resources for the growth program induced by excess GH [1; 2].

Thyrotoxicosis represents an important exception that illustrates the limitations of equating hyperglycemia with IR. Despite the possible presence of hyperglycemia and impaired glucose tolerance, excess THs are associated with a marked acceleration of metabolic fluxes, increased basal metabolic rate, and enhanced tissue demand for energy substrates. Under these conditions, increased glucose production and circulation may coexist with a high rate of tissue glucose utilization [26–28]. This observation has important clinical implications, as hyperglycemia in thyrotoxicosis should not always be interpreted in the same manner as hyperglycemia associated with MetS or T2DM.

3. Neuroendocrine regulation of tissue insulin sensitivity

Regulation of IS in different tissues is not merely a local cellular process but also an important component of systemic neuroendocrine adaptation. Under physiological conditions, insulin operates in close interaction with other hormonal systems that coordinate the mobilization, redistribution, and utilization of energy resources according to the organism's needs. As discussed in the previous section, alterations in IS contribute to maintaining the availability of energy substrates and their preferential redistribution among functional systems. The implementation of these processes is largely determined by the interaction of the HPA, HPT, and GH axes, as well as the sympathoadrenal system [10; 20; 26–28].

Under the influence of pro-inflammatory cytokines, nociceptive stimuli, and other stress-related factors, the secretion of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol increases [10; 20]. Cortisol promotes the mobilization of energy resources by stimulating gluconeogenesis, lipolysis, and proteolysis while simultaneously limiting insulin-dependent glucose utilization in selected peripheral tissues. As a result, circulating concentrations of glucose, amino acids, and fatty acids increase, creating a reserve of substrates for functional systems involved in priority adaptive responses. Thus, cortisol not only mobilizes energy substrates but also participates in their redistribution through the regulation of IS.

Catecholamines exert similar effects, and their secretion increases markedly following activation of the sympathoadrenal system. Epinephrine and norepinephrine stimulate glycogenolysis, lipolysis, and hepatic glucose production while simultaneously suppressing insulin secretion and attenuating its metabolic effects in certain tissues [10; 20]. This contributes to a rapid adaptive response aimed at maintaining high availability of energy substrates for organs and systems essential for survival under conditions of acute threat.

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Glucagon is another important component of this regulatory network. Together with cortisol, catecholamines, and GH, it is traditionally classified as a counter-regulatory hormone because of its ability to increase blood glucose concentrations. Increased glucagon secretion stimulates hepatic glycogenolysis and gluconeogenesis, thereby maintaining the availability of glucose and other metabolic substrates during fasting, physical exercise, and stress [1; 2; 10]. In combination with cortisol and catecholamines, glucagon contributes to the mobilization of energy resources and their circulation to support adaptive programs.

The IGF-1 axis occupies a special position in the regulation of IS. GH stimulates lipolysis and limits the storage of energy substrates, thereby maintaining their availability for growth-related processes and tissue anabolism. At the same time, through stimulation of IGF-1 synthesis, GH supports cell proliferation, protein synthesis, growth, and tissue repair [1; 2]. Thus, the GH–IGF-1 axis integrates mechanisms of energy mobilization with their subsequent utilization for anabolism and recovery.

THs also play a critical role by determining the overall rate of energy metabolism and the efficiency of substrate utilization. T3 stimulates mitochondrial biogenesis, oxidative phosphorylation, and the synthesis of enzymes involved in energy metabolism, thereby enhancing the capacity of tissues to utilize available energy resources [26, 27]. In addition, T3 exerts an important permissive effect on the GH–IGF-1 axis by supporting GH secretion, IGF-1 synthesis, and tissue responsiveness to anabolic stimuli. During acute stress and inflammation, thyroid hormone metabolism undergoes characteristic reprogramming, resulting in the development of low T3 syndrome (LT3S), which is characterized by reduced peripheral T3 production and increased generation of reverse T3 (rT3) [26–29]. From a contemporary perspective, these changes may be interpreted as an adaptive mechanism that temporarily limits energy expenditure and redistributes resources toward systems involved in priority adaptive responses. Conversely, restoration of thyroid function is an important prerequisite for the return to efficient oxidative metabolism and for the reactivation of the anabolic effects of the GH–IGF-1 axis required for tissue repair and functional recovery [15; 27–29].

A characteristic feature of neuroendocrine regulation is the close interaction among cortisol, catecholamines, glucagon, GH, and THs. Together, these hormonal systems form an integrated network that determines not only the availability of energy resources but also their distribution among organs and functional systems. One of the key mechanisms underlying this coordination is the regulation of IS, which ensures the mobilization, redistribution, and targeted utilization of energy substrates according to the organism's current needs [10; 15; 20; 26; 27].

From the perspective of modern immunometabolism, the interaction among the HPA, HPT, and GH axes can be viewed as a unified allostatic system regulating energy metabolism [15; 30]. During the acute phase of adaptation, mechanisms of resource mobilization predominate and are characterized by increased levels of cortisol, catecholamines, and glucagon, accompanied by reduced circulating T3 concentrations.

4. Immunometabolic remodeling during acute inflammation

From the perspective of modern immunometabolism, acute inflammation should be regarded not only as a local or systemic immune response but also as one of the most energy-demanding adaptive programs of the organism. The implementation of this program requires activation of innate immune cells, synthesis of inflammatory mediators, leukocyte migration, phagocytosis, intracellular pathogen killing, and subsequent repair of damaged tissues [11; 31; 32]. Consequently, an effective inflammatory response cannot be achieved without coordinated reprogramming of metabolic and neuroendocrine processes aimed at meeting the increased energy demands of the organism [11; 14; 15].

Within this adaptive program, metabolic reprogramming of innate immune cells plays a pivotal role. Following activation, macrophages, neutrophils, and dendritic cells shift

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from predominantly oxidative metabolism to intensive utilization of aerobic glycolysis, resembling the Warburg effect originally described in tumor cells [13; 17; 18]. Despite its lower energetic efficiency, this metabolic pattern provides rapid ATP generation and supplies metabolic intermediates required for the synthesis of cytokines, reactive oxygen species, and other inflammatory effector molecules [13; 17; 18]. As a result, the demand for glucose by activated immune cells increases markedly.

When acute inflammation is viewed as a program of systemic adaptation, pro-inflammatory cytokines, particularly IL-1β, IL-6, and TNF-α, emerge as key coordinators of energy resource redistribution. Their actions extend beyond the regulation of immune cell activity. Cytokines simultaneously influence the function of the liver, adipose tissue, skeletal muscle, the CNS, and the endocrine system, thereby directing the redistribution of energy resources according to the requirements of the inflammatory response [11; 14; 33]. Under their influence, hepatic gluconeogenesis, lipolysis, and proteolysis are enhanced, appetite and feeding behavior are altered, and neuroendocrine adaptive mechanisms are activated [10; 14; 20; 33]. In this context, cytokines may be regarded as key integrators of the immune and metabolic responses.

One of the principal mechanisms mediating this integration is the activation of neuroendocrine systems. Pro-inflammatory cytokines stimulate the HPA axis, resulting in increased cortisol secretion [10; 20]. Cortisol not only limits excessive inflammation but also supports the mobilization of energy resources by stimulating gluconeogenesis, lipolysis, and proteolysis. Simultaneously, the HPT axis undergoes functional reprogramming, characterized by reduced T3 production and the development of LT3S [26–29]. Within the framework of allostatic regulation, these changes can be viewed as interconnected components of a unified adaptive program aimed at redistributing energy resources toward systems responsible for mounting the inflammatory response.

In this context, alterations in IS across different tissues acquire particular importance. These changes develop under the influence of pro-inflammatory cytokines, stress hormones, and other mediators of adaptation and contribute to the redistribution of energy resources among organs and functional systems according to the metabolic demands of inflammation.

Historical clinical evidence supporting the existence of such adaptive mechanisms can be found in descriptions of transient hyperglycemia in severely injured and postoperative patients, known in Eastern European medical literature as Oppel's "surgical diabetes" phenomenon. Although the mechanisms underlying this condition were unknown at the time of its description, from the perspective of modern immunometabolism it may be interpreted as a clinical manifestation of post-traumatic energy mobilization and adaptive reprogramming of IS.

Thus, immunometabolic reprogramming during acute inflammation involves coordinated interactions among innate immune cells, the cytokine network, neuroendocrine systems, and mechanisms regulating IS. In this context, IR may be viewed not only as a consequence of inflammation but also as a component of an adaptive program aimed at ensuring preferential energy supply to systems responsible for host defense and subsequent recovery [13–15; 22]. The specific features of tissue-specific insulin signaling reprogramming are discussed in the following section.

5. Tissue-specific regulation of insulin sensitivity during inflammation

One of the strongest arguments against the simplified view of IR as a generalized condition is the growing body of evidence demonstrating heterogeneous tissue responses to insulin during acute inflammation. Current studies indicate that pro-inflammatory cytokines, stress hormones, and local metabolic factors induce a complex tissue-specific reprogramming of insulin signaling that facilitates the redistribution of energy resources among organs according to their role in the inflammatory response [6; 12; 14; 19].

The most pronounced alterations in IS during acute inflammation are observed in

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skeletal muscle. Under the influence of TNF-α, IL-1β, cortisol, and catecholamines, insulin signaling and GLUT4 translocation to the cell membrane are suppressed, resulting in reduced glucose utilization and activation of proteolysis [1–3; 8]. From an adaptive perspective, these changes contribute to the conservation of glucose for tissues involved in mounting the inflammatory response.

Adipose tissue also undergoes substantial metabolic reprogramming. Pro-inflammatory cytokines and counter-regulatory hormones attenuate the antilipolytic action of insulin, leading to increased lipolysis and elevated circulating concentrations of free fatty acids [5; 14; 16; 19]. At the same time, certain insulin-dependent signaling pathways may retain partial activity even under conditions of systemic IR, highlighting the selective nature of insulin signaling alterations and demonstrating that IR cannot be reduced to a simple suppression of all insulin actions.

The liver occupies a central position in maintaining systemic energy homeostasis during inflammation. Under the influence of cytokines and counter-regulatory hormones, glycolgenolysis and gluconeogenesis are enhanced, thereby maintaining blood glucose concentrations [1; 2; 10]. A characteristic feature is selective hepatic IR, in which insulin-mediated suppression of gluconeogenesis is impaired, whereas some lipogenic effects of insulin remain partially preserved [2; 12; 19].

The CNS is of particular importance for maintaining vital functions. Unlike most peripheral tissues, neurons rely predominantly on insulin-independent glucose transport mediated by GLUT1 and GLUT3 [1; 6]. This arrangement ensures relative stability of cerebral energy supply even in the presence of peripheral IR.

In recent years, increasing attention has been directed toward the role of insulin in immune cells. Despite the predominance of insulin-independent glucose transport mechanisms, insulin can influence intracellular metabolism and the functional activity of immune cells [13; 17; 18]. Evidence suggests that insulin affects immune cell activation, proliferation, and effector functions; however, the mechanisms regulating IS in these cells remain insufficiently understood [13; 14; 17; 18].

Thus, acute inflammation involves complex tissue-specific reprogramming of insulin signaling rather than generalized IR. Reduced IS in skeletal muscle and adipose tissue promotes resource mobilization, the liver maintains systemic availability of energy substrates, the CNS preserves stable energy supply, and immune cells acquire favorable conditions for sustaining an energy-intensive inflammatory response. The regulation of these metabolic shifts is mediated by intracellular signaling pathways, including mTOR (mechanistic target of rapamycin) and AMPK (AMP-activated protein kinase), which integrate nutrient and energy signals with immune cell function [38; 39]. Collectively, these changes may be regarded as a coordinated mechanism for systemic redistribution of energy resources in accordance with the organism's functional priorities.

Such tissue-specific organization of the response provides the basis for considering the regulation of IS as one of the mechanisms underlying the implementation of the concept of functional priority during acute inflammation.

6. Regulation of insulin sensitivity as a mechanism of energy resource redistribution

The available evidence suggests that alterations in tissue IS during acute inflammation cannot be fully explained solely by local disturbances of insulin signaling or by the direct effects of pro-inflammatory cytokines. These observations support the existence of systemic mechanisms regulating IS that coordinate the distribution of energy resources among tissues according to the organism's current adaptive needs.

The acute inflammatory response is accompanied by a substantial increase in energy demands and requires the mobilization of available metabolic resources. Under these conditions, hyperglycemia, activation of gluconeogenesis, glycogenolysis, lipolysis, and proteolysis may be viewed as interconnected components of a unified adaptive program aimed at maintaining a high availability of

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energy substrates [10; 14; 20–22]. Simultaneous reductions in IS in skeletal muscle and adipose tissue limit glucose utilization by major peripheral energy consumers and promote its redistribution toward cells and systems involved in the priority adaptive response.

Of particular importance is the fact that innate immune cells, the CNS, and several other vital structures rely predominantly on insulin-independent mechanisms of glucose transport [1; 6; 13]. Under these conditions, the primary target of regulation is likely not IR per se, but rather dynamic tissue-specific IS that changes according to the functional requirements of the organism.

Based on the available evidence, the concept of functional priority within the framework of immunometabolic allostasis may be proposed. According to this concept, pro-inflammatory cytokines, neuroendocrine systems, and mechanisms regulating IS form a unified integrated regulatory network. During the acute phase of adaptation, mechanisms responsible for resource mobilization and redistribution predominate, whereas following the elimination of the injurious stimulus, regulatory priorities shift toward tissue repair, anabolism, and functional recovery [15; 26–29; 31–34].

Thus, the regulation of tissue IS may be regarded as one of the mechanisms integrating immune, neuroendocrine, and metabolic processes during systemic adaptation. In this context, IR emerges not only as a manifestation of metabolic dysregulation but also as a potential adaptive mechanism for energy resource redistribution, the prolonged persistence of which may contribute to the transition from adaptation to maladaptation. The integrated model of immunometabolic adaptation and functional priority proposed in this review is illustrated in *Fig*.

From an evolutionary biology perspective, most mechanisms involved in acute adaptation to injury or infection evolved as survival tools. The mobilization of energy resources, activation of innate immunity, transient suppression of anabolic processes, and tissue-specific reprogramming of insulin signaling enable the organism to respond rapidly to threats while maintaining vital functions [7; 11; 22]. However, the effectiveness of these mechanisms depends on their transient nature. Once the injurious stimulus has been eliminated, they should give way to programs of inflammation resolution, tissue repair, and functional recovery. When this transition fails to occur, adaptive responses may become a source of chronic pathological changes.

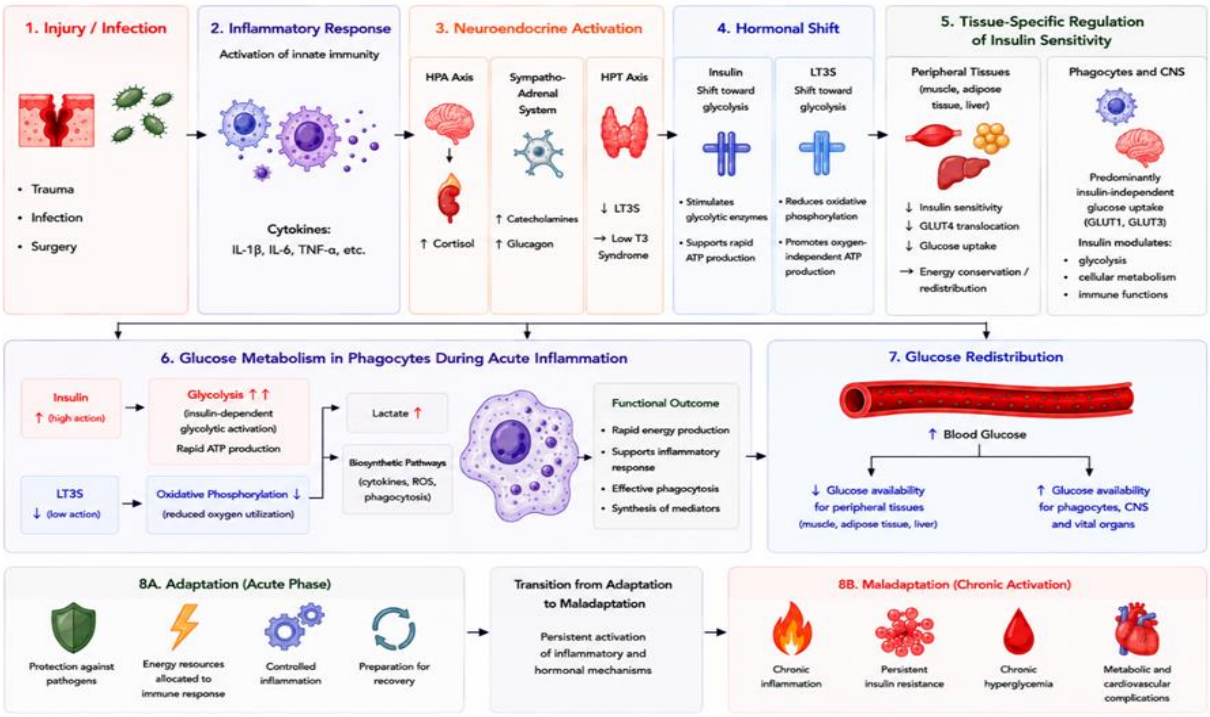

Fig. Proposed concept of functional priority in immunometabolic adaptation

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One of the most characteristic examples of such a transformation is chronic low-grade sterile inflammation, which underlies many contemporary non-communicable diseases [5; 14]. Unlike acute inflammation, it does not culminate in complete resolution and recovery but is characterized by persistent activation of the cytokine network driven by excess adiposity, aging, metabolic disturbances, or chronic tissue injury [14; 16]. Under these conditions, mechanisms of energy mobilization remain active even in the absence of an acute physiological need.

The consequences of such maladaptation are most clearly manifested in MetS and T2DM. Many of their clinical and metabolic features resemble elements of the acute adaptive response, including hyperglycemia, elevated circulating fatty acids, skeletal muscle IR, activation of lipolysis, alterations in neuroendocrine regulation, and increased levels of pro-inflammatory cytokines [1; 3–5]. Unlike acute inflammation, however, these processes are no longer directed toward achieving a specific adaptive outcome and are not followed by a complete recovery phase. As a result, a state of chronic allostatic overload develops, gradually leading to pancreatic β-cell dysfunction, impaired glycemic control, and progressive metabolic dysregulation [1; 2; 30]. Moreover, different tissues may retain varying sensitivity to specific insulin actions, highlighting the complexity and heterogeneity of the IR phenomenon [12; 19].

Another consequence of prolonged predominance of catabolic mechanisms is sarcopenia. During the acute phase of inflammation, activation of proteolysis provides amino acids required for the synthesis of acute-phase proteins, gluconeogenesis, and immune function [31; 32]. In contrast, during chronic inflammation or inadequate restoration of anabolic pathways, the progressive loss of skeletal muscle mass acquires independent pathological significance. Additional contributing factors may include persistent LT3S, reduced activity of the GH–IGF-1 axis, skeletal muscle IR, and physical inactivity [26–28; 35].

Similar mechanisms may also contribute to impaired post-traumatic recovery. Effective tissue repair requires a timely transition from acute adaptive responses to mechanisms of inflammation resolution and anabolic recovery [31; 32; 34; 36]. If cytokine activation, hypercortisolemia, LT3S, or tissue-specific IR persist for an excessive period, regenerative processes may become delayed or incomplete. Conversely, successful recovery depends on the activation of resolution pathways, normalization of thyroid metabolism, and gradual restoration of anabolic processes. One potential manifestation of a disturbed transition from the resource mobilization phase to the recovery phase is excessive lactate accumulation. If activation of glycolytic metabolism persists in the setting of insufficient recovery of oxidative phosphorylation and mitochondrial function, adaptive energy-producing mechanisms may evolve into metabolic maladaptation, potentially resulting in lactate accumulation and the development of severe metabolic acidosis.

Thus, within the framework of the proposed model of immunometabolic allostasis, MetS, T2DM, sarcopenia, certain forms of impaired post-traumatic recovery, and potentially other chronic metabolic disorders may be viewed as different manifestations of a common pathophysiological process-namely, the prolonged persistence or incomplete termination of an adaptive program. The boundary between adaptation and maladaptation is determined not by the mechanism regulating IS itself but by its appropriateness to the organism's current functional requirements. Potential indicators of this transition include persistently elevated cortisol levels, a low T3/rT3 ratio (<0.3), prolonged stress hyperglycemia lasting more than 48 hours after resolution of the acute insult, and sustained elevation of inflammatory markers such as CRP and IL-6. The combination of these biomarkers may serve as an early warning signal for the shift from adaptive to maladaptive metabolic reprogramming. Mechanisms that promote survival and subsequent recovery during acute inflammation may, when persistently activated, contribute to the development of chronic metabolic and inflammatory diseases. Therefore, understanding the mechanisms underlying the transition from adaptation to maladaptation may provide

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an important foundation for the development of modern strategies for prevention, treatment, and rehabilitation of patients with inflammatory, post-traumatic, and metabolic disorders.

Discussion

Regulation of tissue insulin sensitivity as a mechanism of functional priority

The evidence reviewed in this article provides an opportunity to reconsider the role of insulin and IR in systemic adaptation. Traditionally, IR has been viewed primarily as a pathological condition underlying MetS, T2DM, and their associated cardiovascular complications [1–5]. However, contemporary studies indicate that alterations in IS also occur in a variety of physiological and adaptive states, including fasting, physical exercise, pregnancy, acute stress, and inflammation [8–10; 30]. These observations suggest that changes in IS should be regarded not only as consequences of pathological processes but also as one of the mechanisms of adaptation.

In this review, we propose the concept of functional priority, according to which the regulation of IS represents one of the mechanisms responsible for the redistribution of energy resources among functional systems according to their importance for survival, adaptation, and recovery.

In this context, stress-induced hyperglycemia may be interpreted as a mechanism that increases glucose availability for cells relying predominantly on insulin-independent glucose transport, including innate immune cells and the CNS [1; 6; 13; 17; 18]. The combination of hyperglycemia with reduced IS in selected peripheral tissues creates conditions that direct energy resources toward systems engaged in the priority adaptive response.

The proposed concept does not challenge the pathogenic role of IR in MetS and T2DM, but rather provides a framework for understanding the transition from adaptation to maladaptation.

Particular interest arises in the context of acute inflammation in patients with MetS and T2DM. Under physiological conditions, tissue-specific alterations in IS are transient and adaptive, facilitating the redistribution of energy resources. However, in the presence of pre-existing IR, these mechanisms may lose their coordination. As a consequence, excessive hyperglycemia, impaired utilization of energy substrates, and insufficient transition to reparative programs may contribute to unfavorable outcomes of acute inflammation, infectious diseases, and post-traumatic recovery.

At the same time, the unfavorable course of acute inflammation in diabetes mellitus may be related not only to impaired systemic metabolic control. Although glucose transport into innate immune cells is largely mediated by insulin-independent mechanisms, insulin participates in the regulation of intracellular metabolism, particularly glycolytic processes required for the functional activity of phagocytes [37]. This suggests that impaired insulin signaling or insulin deficiency may affect not only systemic energy metabolism but also the efficiency of infection containment, the inflammatory response, and subsequent tissue recovery.

From a clinical perspective, this may partially explain the increased susceptibility of patients with decompensated diabetes mellitus to extensive purulent-necrotic processes, including phlegmons, wet gangrene, and prolonged impairment of tissue repair. Within the framework of the proposed concept, such changes may be interpreted as consequences of impaired coordination between mechanisms responsible for energy resource mobilization and their effective utilization by cells involved in the inflammatory response. As a result, both the implementation of adaptive inflammatory responses and the subsequent transition to the phases of resolution, tissue repair, and functional recovery may be compromised.

The role of the thyroid system also deserves particular attention. Recent evidence suggests that LT3S during the acute phase of inflammation may represent a component of an energy-conservation program aimed at ensuring preferential energy supply to priority adaptive systems [15; 26–29]. In this context, alterations in thyroid status and IS may be regarded as interconnected components of a unified system of immunometabolic allostasis.

ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

Several limitations of the proposed model should be acknowledged. These include the limited number of studies addressing the integrated analysis of systemic energy resource redistribution, as well as the restricted ability to assess insulin signaling in specific immune cell populations. Future research should focus on the mechanisms underlying the transition from adaptive to maladaptive alterations in IS and on the identification of biomarkers reflecting the transition from resource mobilization to the phases of inflammation resolution, tissue repair, and recovery. Equally important is the investigation not only of glucose transport mechanisms in individual cells and tissues but also of the regulation of intracellular glucose metabolic pathways during acute inflammation, adaptation, and maladaptation.

The proposed concept of functional priority expands current understanding of the role of IS and suggests that it may represent one of the mechanisms integrating immune, neuroendocrine, and metabolic processes that support adaptation, survival, inflammation resolution, and subsequent recovery of the organism.

It should be noted that the majority of the fundamental studies on molecular mechanisms of tissue-specific insulin sensitivity and immunometabolic adaptation were published between 2005 and 2017, reflecting the period of most active investigation in this field. Although the literature search covered the period from 2000 to 2025, the temporal distribution of citations is methodologically justified by the availability and relevance of the evidence base required to support the proposed integrative framework. Future research is expected to provide further insights into these mechanisms.

Conclusions

1. Tissue insulin sensitivity should be considered not only as a mechanism regulating carbohydrate metabolism but also as an important component of systemic immunometabolic adaptation that participates in the redistribution of energy resources according to functional demands.

2. During acute inflammation, tissue-specific reprogramming of insulin signaling, in combination with stress-induced hyperglycemia, activation of neuroendocrine systems, and mobilization of energy substrates, contributes to the preferential energy supply of the innate immune system.

3. The regulation of IS is implemented through interactions with the hypothalamic–pituitary–adrenal, hypothalamic–pituitary–thyroid, and growth hormone axes and may be regarded as a component of an integrated neuroendocrine and immunometabolic regulatory system that maintains immunometabolic allostasis.

4. Prolonged activation of mechanisms responsible for the mobilization and redistribution of energy resources, or impairment of the transition to programs of inflammation resolution, tissue repair, and functional recovery, may contribute to the development of chronic metabolic maladaptation, including metabolic syndrome, type 2 diabetes mellitus, sarcopenia, and impaired post-traumatic recovery.

5. The concept of functional priority is proposed, according to which the regulation of tissue insulin sensitivity may be regarded as one of the mechanisms responsible for the directed redistribution of energy resources among functional systems according to their importance for survival, adaptation, and recovery. Further investigation of tissue-specific regulation of IS may contribute to the development of novel approaches to metabolic support, rehabilitation, and prevention of chronic diseases.

Declarations

The authors declare no conflict of interest.

The authors declare that no generative Artificial Intelligence (AI) tools or services were used in conducting the research, preparing, or editing this manuscript for any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of the work – from the development of the research concept to the final editing – were performed by the authors. ChatGPT, v. GPT-5.5 (OpenAI, USA), was used to create the figure.

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Funding and Acknowledgments

This study was conducted without specific financial support and was carried out within the framework of the authors' academic work. The research topic was not officially registered in the national registry of scientific research projects.

Authors' contributions

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

Notes:

A – concept; B – design;

C – data collection;

D – statistical analysis and data interpretation;

E – writing or critical revision of the manuscript;

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

References

1. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018;98(4):2133-223. DOI:10.1152/physrev.00063.2017. PMID: 30067154.

2. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest. 2016;126(1):12-22. DOI: 10.1172/JCI77812. PMID: 26727229.

3. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J* Clin Invest. 2006;116(7):1793-1801. DOI: 10.1172/JCI29069. PMID: 16823477.

4. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177-85. DOI: 10.1038/nature21363. PMID: 28179656.

5. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 2017;127(1):1-4. DOI: 10.1172/JCI92035. PMID: 28045402.

6. Rask-Madsen C, Kahn CR. Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2012;32(9):2052-9. DOI: 10.1161/ATVBAHA.111.241919. PMID: 22895666.

7. Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot JD, et al. Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation. Cell. 2016;166(6):1512-25.e12. DOI: 10.1016/j.cell.2016.07.026. PMID: 27610573.

8. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. Physiol Rev. 2013;93(3):993-1017. DOI: 10.1152/physrev.00038.2012. PMID: 23899560.

9. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30(Suppl_2):S112-9. DOI: 10.2337/dc07-s202. PMID: 17596458.

10. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5(7):374-81. DOI: 10.1038/nrendo.2009.106. PMID: 19488073.

11. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428-35. DOI: 10.1038/nature07201. PMID: 18650913.

12. James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol. 2021;22(11):751-771. DOI: 10.1038/s41580-021-00390-6. PMID: 34285405.

13. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016;16(9):553-65. DOI: 10.1038/nri.2016.70. PMID: 27396447.

ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

14. Hotamisligil GS. Foundations of immunometabolism and implications for metabolic health and disease. Immunity. 2017;47(3):406-20. DOI: 10.1016/j.immuni.2017.08.009. PMID: 28930657.

15. Biletska OM, Garyachiy YeV, Markovska OV, Latohuz SI, Shevchenko AS. Integration of the hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid axes in immunometabolic allostasis of the acute phase of inflammation: A unified cytokine-mediated regulatory complex. Medicine Today and Tomorrow. 2025;94(4):18p. In press. DOI: 10.35339/msz.2025.94.4.bgm. [In Ukrainian].

16. Chawla A, Nguyen KD, Goh YPS. Macrophage-mediated inflammation in metabolic disease. Nat Rev Immunol. 2011;11(11):738-49. DOI: 10.1038/nri3071. PMID: 21984069.

17. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity. 2013;38(4):633-43. DOI: 10.1016/j.immuni.2013.04.005. PMID: 23601682.

18. Ganeshan K, Chawla A. Metabolic regulation of immune responses. Annu Rev Immunol. 2014; 32:609-34. DOI: 10.1146/annurev-immunol-032713-120236. PMID: 24655299.

19. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med. 2017;23(7):804-14. DOI: 10.1038/nm.4350. PMID: 28697184.

20. Chrousos GP, Gold PW. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351-62. DOI: 10.1056/NEJM199505183322008. PMID: 7715646.

21. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000;106(4):473-81. DOI: 10.1172/JCI10842. PMID: 10953022.

22. Medzhitov R. Disease tolerance as a defense strategy. Science. 2012;335(6071):936-941. DOI: 10.1126/science.1214935. PMID: 22363001.

23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-95. DOI: 10.2337/diacare.27.6.1487. PMID: 15161807.

24. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979;237(3): E214-23. DOI: 10.1152/ajpendo.1979.237.3. E214. PMID: 382871.

25. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol. 2016;4(7):611-29. DOI: 10.1016/S2213-8587(16)00086-3. PMID: 27177728.

26. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. J Endocrinol. 2010;205(1):1-13. DOI: 10.1677/JOE-09-0412. PMID: 20016054.

27. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3(10):816-25. DOI: 10.1016/S2213-8587(15)00225-9. PMID: 26071885.

28. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014;24(10):1456-65. DOI: 10.1089/thy.2014.0201. PMID: 24845024.

29. Biletska OM, Golka GG, Danylchenko SI, Arestova TV, Shevchenko AS. Low triiodothyronine in metabolic and inflammatory stress: A context-dependent model of thyroid adaptation. Inter Collegas. 2026;13(1):9p. In press. DOI: 10.35339/ic.2026.13.1.bgd.

30. McEwen BS, Wingfield JC. What is in a name? Integrating homeostasis, allostasis and stress. Horm Behav. 2010;57(2):105-111. DOI: 10.1016/j.yhbeh.2009.09.011. PMID: 19786032.

31. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. Science. 2017;356(6342):1026-30. DOI: 10.1126/science.aam7928. PMID: 28596335.

32. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. Immunity. 2016;44(3):450-62. DOI: 10.1016/j.immuni.2016.02.015. PMID: 26982353.

33. Kelley KW, Bluthé RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, et al. Cytokine-induced sickness behavior. Brain Behav Immun. 2003;17(Suppl_1):S112-8. DOI: 10.1016/S0889-1591(02)00027-6. PMID: 12615196.

ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

34. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510(7503):92-101. DOI: 10.1038/nature13479. PMID: 24899309.

35. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, et al. Inflammation and sarcopenia: a systematic review and meta-analysis. Maturitas. 2017;96:10-5. DOI: 10.1016/j.maturitas.2016.11.006. PMID: 28041587.

36. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008;453(7193):314-21. DOI: 10.1038/nature07039. PMID: 18480812.

37. Cruz-Pineda WD, Parra-Rojas I, Rodríguez-Ruíz HA, Illades-Aguiar B, Matia-García I, Garibay-Cerdenares OL. The regulatory role of insulin in energy metabolism and leukocyte functions. J Leukoc Biol. 2022;111(1):197-208. DOI: 10.1002/JLB.2RU1220-847R. PMID: 33724523.

38. Weichhart T, Hengstschläger M, Linke M. Regulation of innate immune cell function by mTOR. Nat Rev Immunol. 2015;15(10):599-614. DOI: 10.1038/nri3901. PMID: 26403194.

39. O'Neill LA, Hardie DG. Metabolism of inflammation limited by AMPK and pseudo-starvation. Nature. 2013;493(7432):346-55. DOI: 10.1038/nature11862. PMID: 23325217.

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РЕГУЛЯЦІЯ ТКАНИННОЇ ЧУТЛИВОСТІ ДО ІНСУЛІНУ ЯК МЕХАНІЗМ ФУНКЦІОНАЛЬНОГО ПРІОРИТЕТУ: ЗНАЧЕННЯ ДЛЯ АДАПТАЦІЇ, ВИЖИВАННЯ ТА РЕАБІЛІТАЦІЇ

Актуальність. Інсулінорезистентність (ІР) традиційно розглядається як один із ключових механізмів розвитку метаболічного синдрому, цукрового діабету 2 типу та пов'язаних із ними серцево-судинних ускладнень. Водночас зміни чутливості до інсуліну виникають також під час голодування, фізичного навантаження, вагітності, гострого стресу, травми та запалення, що свідчить про їхню можливу адаптивну роль у регуляції енергетичного обміну.

Мета. Узагальнити сучасні дані щодо ролі тканинної чутливості до інсуліну в системній імунометаболічній адаптації та обґрунтувати концепцію її регуляції як механізму функціонального пріоритету.

Матеріали та методи. Пошук наукових джерел для наративного огляду проведений в PubMed, Scopus, Web of Science та Google Scholar. Узагальнення даних здійснювали з використанням концептуального та інтегративного підходів. Дослідження виконано як приватна ініціатива авторів, без грантової підтримки та держаної реєстрації теми.

Етика дослідження. Для аналізу відібрані лише ті джерела, де дотримані сучасні біоетичні норми.

Результати. Наявні дані свідчать, що зміни чутливості до інсуліну мають тканинно-специфічний характер і можуть виконувати адаптивну функцію. При гострому запаленні активація цитокінової мережі, гіпоталамо-гіпофізарно-наднирникової осі, симпатоадреналової системи та інших контрінсулярних механізмів супроводжується стресовою гіперглікемією, мобілізацією енергетичних субстратів і вибірковим зниженням чутливості до інсуліну у скелетних м'язах та жировій тканині. Це сприяє підвищенню доступності енергетичних ресурсів для клітин вродженого імунітету, центральної нервової системи та інших життєво важливих структур. Запропоновано розглядати регуляцію тканинної інсулінової чутливості як механізм функціонального пріоритету, що забезпечує перерозподіл ресурсів відповідно до адаптаційних потреб організму. Обґрунтовано концепцію імунометаболічного алостазу, в межах якої ІР може виступати не лише проявом метаболічної патології, а й елементом координованої адаптаційної відповіді. Показано, що гостре посттравматичне та низькоінтенсивне стерильне запалення при метаболічному синдромі використовують спільні механізми нейроендокринної регуляції.

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Висновки. Тканинна чутливість до інсуліну може розглядатися як важливий компонент системної імунометаболічної адаптації організму. Запропонована концепція функціонального пріоритету дає підстави розглядати регуляцію чутливості до інсуліну як один із механізмів перерозподілу енергетичних ресурсів між функціональними системами залежно від їхнього значення для адаптації, виживання та відновлення організму.

Ключові слова: *ендокринологія, інсулінорезистентність, імунометаболізм, гіперглікемія, алостаз, стрес.*

Received: 16 Dec 2025
Accepted: 29 Mar 2026
Published: 31 Mar 2026

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