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МЕХАНИЗМЫ КЛЕТОЧНОЙ АДАПТАЦИИ К ГИПОКСИИ

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MECHANISMS OF CELLULAR ADAPTATION TO HYPOXIA

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Резюме. Когда клетки не получают достаточно кислорода, который необходим для жизни, они пытаются найти другие способы выжить. Эта проблема важна, поскольку она возникает во многих повседневных ситуациях, таких как на большой высоте или при интенсивных физических нагрузках, а также при серьезных заболеваниях, таких как сердечные приступы, инфекции и рак. Клетки, которые не получают достаточно кислорода, склонны прибегать к особым стратегиям выживания, чтобы продолжать функционировать и жить. Самым важным из них является белок, называемый HIF (фактор, индуцируемый гипоксией), который действует как датчик и переключатель. Он помогает включать определенные гены, которые позволяют клетке приспосабливаться. В условиях гипоксии клетки смягчают стресс с помощью транскрипционных и посттранскрипционных механизмов, в первую очередь регулируемых HIF. Эти адаптации позволяют клеткам сохранять кислород, переходя от окислительного метаболизма к гликолизу и снижая потребление энергии для таких процессов, как деление клеток. HIF контролирует гены, отвечающие за поддержание кислородного баланса, включая те, которые связаны с потреблением кислорода, эритропоэзом, ангиогенезом и митохондриальным метаболизмом [1]. Другая ключевая система, задействованная в этом процессе, это активированная протеинкиназа (AMPK) и механистический (млекопитающий) рапамициновый путь (mTOR). Это два белка, которые работают вместе, чтобы управлять энергией клетки. Механизмы сигнализации питательных веществ в основном осуществляются AMPK и mTOR, которые регулируют клеточный гомеостаз, что осуществляется путем обнаружения клеточного АТФ и уровней питательных веществ, в основном глюкозы и аминокислот. В то же время он стимулирует использование накопленных ресурсов для производства энергии, достаточной для выживания. AMPK также блокирует mTOR, который обычно способствует росту и делению клеток, что бесполезно, когда клетка испытывает трудности [2].

Ключевые слова: механизмы, клеточные адаптации, гипоксия.

Resume. When cells do not get enough oxygen, which is a necessity for life, they try and find other ways to survive. This problem is important because it happens in many everyday situations like high altitudes or intense exercise, but also in serious medical conditions such as heart attacks, infections, and cancer. Cells that are not receiving enough oxygen tend to resort to special survival strategies to make sure it continues functioning and living. The most important of these is a protein called HIF (hypoxia-inducible factor), which acts like a sensor and a switch. It helps turn on certain genes that allow the cell to adjust. Under hypoxic conditions, cells mitigate stress through transcriptional and post-transcriptional mechanisms primarily governed by HIF. These adaptations enable cells to conserve oxygen by shifting from oxidative metabolism to glycolysis and reducing energy consumption for processes like cell division. HIF controls genes responsible for maintaining oxygen balance, including those linked to oxygen consumption, erythropoiesis, angiogenesis, and mitochondrial metabolism [1]. Another key system involved is the activated protein kinase (AMPK) and mechanistic (mammalian) rapamycin (mTOR) pathway. These are two proteins that work together to manage the cell’s energy. The mechanisms nutrient signaling are done

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largely by AMPK and the mTOR which regulate cellular homeostasis, which is done by detecting cellular ATP and nutrient levels, mostly glucose and amino acids. At the same time, it encourages the use of stored resources to produce just enough energy for survival. AMPK also blocks mTOR, which normally promotes cell growth and division, something that isn't helpful when the cell is struggling [2].
Keywords: mechanisms, cellular adaptions, hypoxia.

Relevance. Cells are equipped with smart, flexible systems that help them respond to low oxygen levels. By understanding how these systems work, we can learn more about how the body deals with stress and even find new ways to treat diseases where hypoxia plays a role.

Aim: to investigate the mechanisms of cellular adaptation to hypoxia and gain a better understanding of what the human body goes through so we can use this knowledge to better treat diseases that hypoxia plays a role in.

Objective: to study literature data on the mechanisms of cellular adaptions to hypoxia and the different types of mechanisms that take place when the body undergoes hypoxic conditions.

Materials and methods. A collections of research papers were reviewed (HIF factors, AMPK-mTOR pathways) and cross-examined in order to come to a proper conclusion and gain more information.

Results and their discussion. There are many causes of hypoxia or reasons as to why it would be induced. It could be due to physiological conditions, like being in a high-altitude environment, going through extreme exercise, or any other physically straining activity that puts a lot of stress on the body. Hypoxia could also develop due to pathological conditions such as cancer, myocardial infarctions, inflammation, pathogenic microbe infection, acute and chronic diseases and other stress responses [3].

The main regulator responsible for the cellular response to hypoxia is hypoxia-inducible factor (HIF). HIF is a transcription factor which is regulated by many different mechanisms or pathways. Two of these main pathways are metabolic reprogramming and enhanced angiogenesis which are used to counter the effects bought on by hypoxia. Under hypoxic conditions, cells mitigate stress through transcriptional and post-transcriptional mechanisms primarily governed by HIF. These adaptations enable cells to conserve oxygen by shifting from oxidative metabolism to glycolysis and reducing energy consumption for processes like cell division. HIF-1α is hydroxylated by prolyl hydroxylases (PHDs). Hydroxylated HIF-1α is bound by von Hippel-Lindau protein (VHL), leading to proteasomal degradation. Under hypoxia, due to the lack of oxygen, PHDs are inactive, so HIF-1α escapes degradation. HIF-1α is translocated into the nucleus and activates the genes responsible for angiogenesis (VEGF), erythropoiesis (EPO), glucose metabolism (GLUT1 and hexokinase) and cell survival [6].

Reactive oxygen species (ROS) refer to a collection of highly reactive molecules derived from oxygen. In biological systems, ROS generation is balanced by antioxidant defenses, which protect cells from harmful ROS accumulation. Oxidative stress (or "oxidative distress") occurs when this equilibrium is disrupted, leading to excessive ROS levels that damage cellular components. At moderate concentrations, ROS play a critical role in normal cellular functions, a state termed "oxidative eustress." For example, ROS

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modulate key transcription factors, including hypoxia-inducible factor 1α (HIF-1α), influencing gene expression in response to physiological and pathological signals [5].

HIF-1α regulates genes involved in angiogenesis, metabolism, and survival pathways. These adaptations can suppress apoptosis temporarily, allowing cells to cope with low oxygen levels. When hypoxia is severe or prolonged, adaptive mechanisms may fail, leading to the induction of apoptosis. This induction can lead to mitochondrial dysfunction which leads to the release of factors like cytochrome c into the cytosol, which activated caspase enzymes that execute apoptosis. It can lead to the accumulation of reactive oxygen species which damages cellular components and trigger apoptotic pathways. The expression of pro-apoptotic genes such as BNIP3 which disrupts mitochondrial integrity and promotes cell death [1].

Acute hypoxia regulates the activity of specific ion channels in a rapid and reversible manner. Such effects underlie appropriate cellular responses to hypoxia which are designed to initiate cardiorespiratory reflexes and contribute importantly to other tissue responses, all of which are designed to improve tissue oxygen supply. These responses include excitation of chemoreceptors as well as pulmonary vasoconstriction and systemic vasodilatation. However, such responses may also contribute to the adverse responses to hypoxia, such as excitotoxicity in the central nervous system. Whilst numerous ion channel types are known to be modulated by acute hypoxia, the nature of the oxygen sensor in most tissues remains to be identified. Prolonged (chronic) hypoxia regulates functional expression of ion channels, and so remodels excitability of various cell types. Whilst this may contribute to adaptive responses such as high-altitude acclimatization, such altered channel expression may also contribute to the onset of pathological disorders, including Alzheimer's disease. Under hypoxic conditions Na^+/K^+-ATPase activity drops, causing membrane depolarization. Intracellular Ca^{2+} increases, which can trigger apoptosis if prolonged [4].

Calcium- and voltage-activated potassium channels (BK channels) are widely expressed K+ channels that play a vital role in various physiological functions, including the modulation of smooth muscle arterial tone. Their activity is regulated by stimuli such as membrane depolarization and intracellular Ca2+ levels. When BK channels are activated, they induce membrane hyperpolarization, which reduces vasoconstriction and promotes blood vessel relaxation. Alterations in BK channel function can contribute to vascular tone-related disorders, such as hypertension. Hypoxia, characterized by reduced oxygen availability, triggers multiple cellular responses, including changes in gene expression, membrane depolarization, and fluctuations in intracellular Ca2+ levels. It also influences the activity of various ion channels, including BK channels. Several clinical conditions, such as chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea (OSA) are linked to hypoxia and its effects on cellular and vascular function [4].

Hypoxia is the medical terms used when there is inadequate oxygen supply to the cells of the body, since oxygen is supplied through the bloodstream, which nutrients are also transported through, hypoxia is also accompanied by nutrient starvation. Due to this physiological setting, there is a connection between hypoxia signaling and nutrient signaling which are followed by metabolic changes in the organism. In the mechanisms of nutrient signaling, AMP- activated protein kinase (AMPK) and mechanistic (mammalian) rapamycin complex 1 (mTORC1) are largely responsible for balancing cellular homeostasis,

which is done by detecting cellular ATP and nutrient levels, mostly glucose and amino acids. AMPK-mTOR pathway act together with autophagy to adjust metabolic activity in order to adjust to stressful conditions [2].

Conclusion:

1. The hypoxia-inducible factor (HIF) is the primary regulator of cellular responses to low oxygen levels. Under hypoxic conditions, HIF-1α escapes degradation and activates genes critical for survival, such as those involved in angiogenesis (VEGF), erythropoiesis (EPO), and glucose metabolism (GLUT1 and hexokinase). This transcriptional reprogramming allows cells to shift from oxidative metabolism to glycolysis, conserving oxygen and reducing energy consumption. HIF's ability to modulate these pathways highlights its importance in both physiological adaptations (e.g., high-altitude acclimatization) and pathological conditions (e.g., cancer and ischemic diseases).

2. The AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) pathways work synergistically to manage cellular energy during hypoxia. AMPK detects low ATP levels and inhibits mTOR, which normally promotes cell growth and division. This inhibition redirects resources toward essential survival processes, such as autophagy and glycolysis, while suppressing non-critical functions. The AMPK-mTOR axis ensures that cells prioritize energy conservation and utilization of stored nutrients, demonstrating a finely tuned response to metabolic stress caused by hypoxia.

3. While cells employ adaptive mechanisms like HIF activation and metabolic reprogramming to survive hypoxia, prolonged or severe oxygen deprivation can lead to apoptotic pathways. Factors such as mitochondrial dysfunction, reactive oxygen species (ROS) accumulation, and pro-apoptotic gene expression (e.g., BNIP3) can trigger cell death. Additionally, hypoxia-induced changes in ion channel activity (e.g., BK channels) and calcium homeostasis may contribute to both adaptive responses (e.g., vasodilation) and pathological outcomes (e.g., excitotoxicity or hypertension). This duality underscores the complexity of hypoxic responses and their implications for health and disease.

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