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CELL DEATH IN HUMAN PATHOLOGY
КЛІТИННА СМЕРТЬ В ПАТОЛОГІЇ ЛЮДИНИ

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Abstract. *An analytical review of the present article is devoted to the aspects of cell death with emphasis on biochemical, morphological, molecular and cellular mechanisms its development, modulation and progression. The triggers of apoptosis, necrosis, necroptosis, pyroptosis, and autophagy are described. The pathogenetic pathway of the relationship between the inflammatory stimuli, programmed cell death, and immune response are considered. Ferroptosis as a novel type of regulated cell death is presented. The contribution of inflammasomes that promote inflammation by activating the caspase-1 in pyroptosis is shown. The article is focused on the role of the autophagy in age-related and neurodegenerative diseases, its impact on the resistance during anticancer therapy. A promising approach aimed at solving specific problems of numerous diseases with cell death involvement and translation appropriated knowledge in clinical practice is emphasized.*

Keywords: *apoptosis, autophagy, necrosis, necroptosis, pyroptosis, ferroptosis.*

Introduction.

The health and homeostasis of multicellular organisms depend on the tight balance between normal cells proliferation and dysfunctional unregulated cells initiated by external factors such as viral and bacterial infections, toxins, mechanical, thermal, or chemical trauma. The abnormal survival and accumulation of damaged or superfluous cells drives human pathologies. To maintain normal physiology and tissue function, cells that are damaged, or no longer live should constantly cleared via specifically cell death and replaced by new, healthy cells. Hence cell death is an important biological process for tissue development of organisms. Programmed cell death plays a vital role in forming and maintaining the human homeostatic ability, an immune cell defense directed to supporting the cellular response and recovery from acute injury limiting the propagation of the inflammatory stimuli to prevent tissue loss of function. However, remain an unclear issue related to the specific molecular mechanisms and crossregulatory relationship between different forms of cell death and its participation in pathological states. It is important to have more comprehensive understanding the modulation effects of the extrinsic and intrinsic factors on cell death pathway.

Purpose.

The article is summarized the research progress on the insights of the possible triggers, mechanisms and outcomes of different types of cell death.

Methods. Authors carried out the bibliometric analysis of the scientific publications in the available database Scopus, Web of Science, PubMed using appropriate keywords in English.

Results. According to the scientific publications there are some programmed forms of cell death - apoptosis, necroptosis, pyroptosis, and ferroptosis. Necrosis represents the expanding network of non-apoptotic cell death pathways. Recently was created the concept of autophagic cell death.

Necrosis classically takes part in mechanical, thermal or chemical damage of the cell. Necrosis also is considered as cell death, frequently associated with disorders in infectious diseases due to the pathogens, ischemia-reperfusion injury, neurodegeneration [1]. Necrotic cells exhibit cell and organelle swelling and loss of defined cellular architecture and accompanied with a rapid breakdown of the cell membrane and its violations. Membrane destabilization is characterized by mitochondrial calcium overload, bioenergetics effects as well as activation of reactive oxygen species which produce mitochondrial dysfunction, ion balance deregulation [2]. Additionally, necrosis is induced the passive and active release of intracellular mediators into the extracellular space with accumulation of inflammatory/immune cells and the activation of the immune system and causing the acute and chronic inflammatory response [3].

Apoptosis is a highly regulated process aimed to the continuing health of the organism as a whole, especially during embryogenesis, growth, and tissue maintenance. Apoptosis can be initiated by a wide variety of stimuli including radiation, infection, pH, oxygen concentration, DNA damage, nutrient deficiency, endoplasmic reticulum stress, growth factor withdrawal, heat shock, developmental cues [4]. Apoptotic cells have three morphological features: shrinkage; fragmentation into membrane-enclosed structures containing mixtures of cell parts (apoptotic bodies); and phagocytosis of apoptotic bodies by macrophages or neighboring cells [5].

Apoptosis involves a complex signaling cascade whereby extracellular or intracellular signals result in the orderly termination of cells. There are two distinguished pathways in the apoptotic process: the intrinsic pathway and the extrinsic pathway. The intrinsic apoptotic pathway or mitochondrial pathway is a type of regulated cell death through direct activation of mitochondrial effector [6].

The intrinsic pathway initiated by perturbations of the extracellular or intracellular microenvironment including DNA damage, endoplasmic reticulum or oxidative stress, growth factor withdrawal. The extrinsic pathway is activated by external stimuli that connect with various cell transmembrane receptors regards to the tumor necrosis factor superfamily that can activate the extrinsic apoptosis pathway via a conserved cytoplasmic signaling platform called the death domain. The extrinsic pathway is considered as death receptor pathway [7]. Two classes of death receptors have been recognized. Mostly members of the tumor necrosis superfamily activate cell death following ligand binding. In contrast, so-called “dependency receptors,” which are molecularly heterogeneous, transmit death signals only when unliganded. Upon activation of the receptors, multiple intracellular proteins interact with one another in order to form a death-inducing signaling complex that involves cysteine protease of the caspase family such as caspase 8 which drives apoptosis by the elimination of

unnecessary or damaged cells [8].

Apoptosis is a highly conserved physiological process of programmed cell death which is critical for proper regulation of cell removal and contributes to normal organism development, tissue maintenance, and overall organism homeostasis. Nevertheless, deregulated apoptosis as both excessive and reduced apoptotic rate provokes inflammatory responses by loss of cell membrane integrity with lytic forms of cell death and uncontrolled releasing extracellular vesicles, cell contents, various chemokines and hence distorted apoptotic signaling is involved in the multiple human disorders and can lead to the onset of a numerous diseases such as oncological, cardiovascular, renal, inflammatory and neurological conditions.

Necroptosis is a newly discovered programmed cell death pathway. Necroptosis is a cellular response to environmental stress that can be caused by chemical and mechanical injury, inflammation, or infection. Necroptosis is triggered by many of the same stimuli as apoptosis, including death receptor ligation, DNA damage. Necroptosis occurs when apoptosis is inhibited but extracellular apoptotic stimulation continues. It is characterized by a rapid membrane breakdown, resulting in the release of intracellular compounds, such as heat shock proteins, DNA, and RNA that further promote an inflammatory response. Necroptotic cell death, despite being highly inflammatory, can reduce overall tissue inflammation by removing damaged or infected cells that might otherwise continue to produce large amounts of inflammatory mediators [9].

In contrast with apoptosis, where regulatory mechanisms have evolved to limit inflammation, necroptosis carried out independent of caspase. The signaling pathway for necroptosis is best characterized by tumor necrosis factor receptor 1. Caspase 8-specific inhibitors might be useful in conditions with excessive extrinsic apoptosis, however, as complete caspase-8 inhibition can trigger necroptosis. Necroptosis promotes inflammation through leakage of cellular contents from damaged plasma membranes and early cell lysis without protective mechanisms to limit immunogenicity. In this case, the death of the cell is more important than the prevention of inflammatory consequences. Necroptosis has been found to be involved in numerous pathologic states. Necroptosis is a major pathogenic component of various diseases including conditions of the neurologic, cardiovascular, pulmonary, and gastrointestinal systems, malignant neoplasms, kidney damage, mediates organ rejection in both cardiac and renal allografts [10].

Pyroptosis is considered as a regulated form of cell death which is triggered by various pathological stimuli, such as stroke, heart attack or cancer and crucial for controlling microbial infections. Pyroptosis is typically initiated downstream of inflammasome contributing to the pathogenesis of inflammatory disorders and host defenses against microbial pathogens [11]. Inflammasomes are innate immune mechanisms that promote inflammation by activating the protease caspase. Caspases are key inducers of extrinsic apoptosis and pyroptosis. Active caspase-1 promotes pyroptosis, a necrotic form of regulated cell death that's way pyroptosis named as caspase 1-dependent cell death facilitating the plasma membrane permeabilization and rupture, the release of intracellular proinflammatory molecules, including IL-1 family cytokines and damage-associated molecular patterns [12]. Pyroptosis is a cell death

that plays a central role in inflammation and immunity regarding to the inflammasome signaling similar to apoptosis [13].

Caspase-1 is a promising target for treating IL-1β-mediated conditions. The comprehensive study of the mechanisms underlying inflammasome-associated cell death may contribute to the creation of novel therapeutic strategies for inflammasome-related diseases.

Ferroptosis has been identified as a novel type of regulated cell death that linking metabolism, redox biology and disease because it is triggered when dysregulation of intracellular homeostasis leads to an accumulation cellular iron and toxic phospholipide, reactive oxygen species that derived from iron metabolism [14]. Iron is an indispensable element in human beings, and physiological iron concentration plays multiple roles in metabolic processes, such as oxygen transport, electron transport, and DNA synthesis. Recently investigations revealed that ferroptosis is regulated by a variety of signals from different organelles such as lysosomes, mitochondria, and the endoplasmic reticulum. Due to its ability to accept and donate electrons, pathological iron accumulation can cause oxidative damage and even death of cells [15]. As a result of the lipid peroxidation the biochemical characteristics of ferroptosis are the lethal damage to lipids, proteins, nucleic acids [16]. Hence ferroptosis might be considered as an iron-dependent form of nonapoptotic cell death [17].

Ferroptosis is a biochemically distinct form of regulated cell death and differs from necroptosis, apoptosis, and autophagy. It was shown that a key regulator of ferroptosis is the anti-oxidative enzyme glutathione peroxidase 4 that reduces and prevents lipid peroxidation [18]. Morphological features of ferroptosis include reduced cell volume, mitochondrial outer membrane rupture and activation of caspases [19]. Obtained data indicate that ferroptosis is involved in the regulation and progression of multiple pathological state of different organs and is widely implicated in clinical situation.

Autophagy as the concept was based on observation the accumulation in dying cells the morphological features in a form of the autophagic vesicles [6]. Autophagy correlates with pathological conditions which are accompanied by the mitochondrial dysfunction and oxidative stress. Autophagy represents a homeostatic cellular mechanism directed to remove dysfunctional proteins, damaged organelles, and invading pathogens through a lysosome-dependent degradation pathway by the different mechanisms and mediators. In the process of autophagy, a small cup-shaped membrane precursor namely a phagophore targets cytoplasmic constituents and forms a double-membraned structure known as autophagosome, which is then fused with a lysosome to degrade the engulfed contents [20].

During disorders of redox homeostasis autophagy is aimed for basic catabolic process, serving as an internal engine response to various cellular stresses and facilitates cell survival through the recycling of metabolic precursors, while excessive or uncontrolled autophagy promotes cell death and morbidity [21]. It was suggested that autophagy takes part in regulating the outcome of other programmed cell death forms as apoptosis, necroptosis, and pyroptosis [22].

Autophagy is associated with aging and contributes to the pathogenesis of various age-related diseases such as cardiac fibrosis, heart failure, neurodegenerative diseases,

with a particular emphasis on the pathogenesis of Parkinson's disease, intervertebral disc degeneration, and age-related macular degeneration [23].

Recently new insights into the mechanisms of signal control on autophagy in cancer cells was revealed. Similar to others pathologies cancer is frequently associated with aging and oxidative stress. Different autophagic pathway underlying the relationship between oncogenic effects and the cellular responses have been assessed. The process of autophagosome-associated autophagy is characterized by the direct import of cytosolic proteins into degradative lysosomes. Much less is known about the chaperone-mediated autophagypathway.

The role of autophagy in cancer is complex and especially depends on cancer type and stage of development. The impact of autophagy on cancer cells has dual character and widely discussed. From one side autophagy may play a tumor suppressive role by preserving cellular integrity during tumor development and by possible contribution to cell death. From other side autophagy may also influenced on oncogenic effects by promoting tumor cell survival and preventing cell death. It is important to pay attention on the role of autophagy in cancer, with a particular focus on resistance mechanisms to anticancer drugs application and its possible modulation effect related to autophagy ability to perform detoxification [24]. However, it should be further investigated the biochemical, cellular, molecular conditions when autophagy might potentiate chemoresistance in tumor cells or contributes to cell death

Accumulating evidence suggests that in addition to apoptosis, autophagy, necrosis, necroptosis, pyroptosis, ferroptosis a number of other death programs have emerged including parthanatos, entotic cell death, lysosome-dependent cell death, and immunogenic cell death [25]. The growing and constant interest on this problem underlines the convincing importance of comprehensive understanding the physiological and pathological function of cell death in human health and disease.

Conclusion.

Cell death is a rapidly evolving field of knowledge and might be a prospective tool both in experimental and clinical medicine. Preserving the integrity of the tissue barrier by regulating the rate of cell death is considered crucial for maintaining the human homeostasis. Failure of barrier functions due to an unregulated cell death will contribute to pathogenesis of age-related diseases, neurodegenerative diseases, and cancer. Some cell death take part in classical inflammasome function and its intersection with the inflammatory response are fundamental for outcomes due to the infection pathogens. Nevertheless, there are some unresolved issues regards the interaction between molecular characteristic of different cell death and pathophysiological features of multiply diseases. For future perspectives, a accurate study for the identification of new molecules that drive deregulation of the cell death pathway requires special attention. It should be further investigated whether modulation of cell death could provide novel targets for improving therapeutic approach in treatment some diseases.

Conflict of interests.

The authors declare that there is no conflict of interests regarding the publication of this article.

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Анотація. *Аналітичний огляд присвячено аспектам клітинної смерті з наголосом на біохімічні, морфологічні, молекулярні та клітинні механізми її розвитку, модуляції та прогресування. Описано тригери апоптозу, некрозу, некроптозу, піроптозу та аутофагії. Розглядається патогенетичний зв'язок між запальними стимулами, імунною відповіддю та програмованою клітинною смертю. Подано фероптоз як новітній тип регульованої клітинної смерті. Показано внесок інфламасом, що сприяють запаленню внаслідок активації каспази-1 при піроптозі. Стаття робить акцент на ролі аутофагіїї в залежних від віку і нейродегенеративних хворобах та її впливу на резістентність при проведенні протипухлинної терапії. Підкреслюється перспективний підхід, що має за мету вирішення специфічних проблем при захворюваннях із залученням клітинної смерті та впровадження відповідних знань в клінічну практику.*

Ключові слова: *апоптоз, аутофагія, некроз, некроптоз, піроптоз, фероптоз.*