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APOPTOSIS AS A WEAPON, NECROSIS AS A THREAT: A BIOPHYSICAL PERSPECTIVE ON ONCOLOGY

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Cellular death is the founder of the biological process that ensures homeostasis and functioning of all tissues of the body. Under the usual situation, the cells go through the renewal process every time: they die, creating new ones or are deleted if the functionality is violated. There are many types of cell death, and among them the key ones are apoptosis and necrosis, which at their time have biophysical and molecular features. Violation of such processes leads to oncological diseases, where apoptosis contributes to the growth and strengthening of the tumor's immunity, and necrosis forms an inflammatory environment in tumor tissues and cancer progresses. This article examines the biophysical mechanisms of apoptosis and necrosis, the role in oncogenesis, modern research methods and the clinical significance of the diagnosis and treatment of tumors.

Keywords: Apoptosis, necrosis, cell death, biophysical features, oncology, diagnosis, treatment.

Oncology is one of the most severe, but widespread and relevant areas of medicine, as malignant tumors lead to a large number of deaths around the world. Cellular death occupies a fundamental place in understanding how cancers are formed and progress. Apoptosis-programmed cell death at the genetic level necessary to remove dangerous cells or cells with impaired functionality. If this process fails, the cells carrying mutations continue to divide and increase the growth of tumor development. Necrosis - occurs with hypoxia, ischemia, toxic poisoning, that is, with extreme cell damage. Unlike apoptosis, necrosis has two outcomes: in the first it destroys the tumor, and in the second it creates inflammation and angiogenesis that appear as a result of necrotic decay, thereby establishing a favorable environment for cancer progression. Thus, the study of the biophysics of cell death allows us to understand the pathogenesis of cancer and develop new approaches to its treatment. The protective mechanism of our organism, that is, apoptosis, allows you to eliminate defective cells, which are disturbed during the formation of tumors. The main biophysical mechanism of apoptosis is associated with a violation of the membrane

permeability function in mitochondria. In cases where signal cascades are activated or damaged in the membrane, MPTPs (mitochondrial permeability transition time) are formed, thanks to which cytochrome is released into the cytoplasm and further triggers the caspase cascade and leads to cell death. Proteins of the Bcl-2 family block mitochondrial apoptosis in oncology, in most tumors, Bcl-2 hyperexpression leading to the avoidance of death is seen. For example, follicular-type lymphoma contains a diagnostic marker Bcl-2. Ionic ducts also play an important role in which Ca^{2+} activates endonucleases that lead to DNA degradation. For example, it is in calcium ion channels that mutations are often observed, which give advantages to tumor cells. And at the final stage, the cell is divided into apoptotic bodies, the phagocytic of which macrophages without further inflammatory reactions. This gives an advantage to the body as it protects against further damage. At the moment, drugs such as paclitaxel are widespread, doxorubicin acts by inducing mitochondrial apoptosis in tumor cells. Uncontrolled cell death, in other words, necrosis in oncology is typical in fast growing tumor diseases where problems with blood supply are observed. With hypoxia and ischemia, the cell lacks oxygen and nutrient medium, which leads to an energy crisis. As a result, the cell has a disruption of the ion pumps and the loss of osmotic balance, leading to swelling of the organelles and eventually rupture of the membrane. Also, a large number of active forms of oxygen harm lipids and DNA. In tumors, stimulation of mutation, increased malignancy and death of cell parts is caused by increased oxidative stress. For example, in kidney cancer, massive areas of necrosis are associated with low patient survival. Modern science offers a whole set of methods for studying cell death. One of the popular tools is Annexin V (fluorescent marker) which binds to phosphatidylserin exponenting on the surface of apoptotic cells, while propidium iodide penetrates into necrotic cells. Such studies help to distinguish between the processes of apoptosis and necrosis. Confocal microscopy is used for a detailed study of morphological changes, which makes it possible to rebuild the nucleus, cytoskeleton in real time. Another advanced approach is AFM (atomic force microscopy), which evaluates the mechanical properties of tumor cell membranes: in the process of apoptosis, cells become stiffer, while during necrosis, they lose elasticity. Treatment of tumors is often based on stimulation of apoptosis. Various types of chemotherapy drugs, such as cisplatin or etoposide, as well as targeted drugs, including Bcl-2 family inhibitors (e.g. venetoclax), trigger chains of reactions that lead to programmed cell death, which ensures effective destruction of cancer cells. The main problem remains the resistance of tumors to treatment. Often, malignant cells develop resistance to therapy due to mutations in the p53 gene or increased expression of anti-apoptotic proteins. As a result, tumors become less susceptible to standard methods of treatment, which pushes the search for new approaches. Unlike apoptosis, the necrogenic process in the tumor is most often seen as a negative factor predicting an unfavorable outcome of the disease. Thus, in breast cancer and sarcomas, large areas of necrotic tissues reliably correlate

with the worst prognosis for patients and a more aggressive course of the disease. One of the promising areas of research is the management of various pathways of cell death. For example, redirecting necrotic processes to apoptosis can help reduce inflammatory activity and improve prognosis. Also, the activation of alternative mechanisms of cell death, such as necroptosis or pyroptosis, can be a promising strategy to overcome drug resistance, especially in situations where traditional apoptotic pathways are blocked. In conclusion, the role of apoptosis and necrosis in oncology is different. Apoptosis can be considered as the "correct" mechanism of cell death. Thus, during the study on colorectal cancer (n=104), a high apoptotic index (AI ≥ 4.1%) was associated with a significantly better five-year survival rate at stage C (68% vs. 33%) (PubMed ID: 9525002). This confirms that the mechanism of apoptosis can be a favorable prognostic marker and increase the effectiveness of treatment. But apoptosis entails not only a positive result and in some aggressive tumors, a high apoptosis rate shows only a high cellular exchange, where proliferation occurs. In addition, many types of cancers develop immunity to apoptosis due to p53 mutation, Bcl-2 or caspase failure. On the other hand, necrosis is more often a negative prognostic marker. According to the I-II stage cancer study, necrosis was observed in 45.1% of patients and showed the worst results of five-year overall survival (PFS = 62.7%). At the same time, this almost doubled the risk of death (HR ≈ 1.9) (PubMed ID: 38727689). Necrotic zones create a microenvironment with hypoxia, inflammation and tumor progression.

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АПОПТОЗ КАК ОРУЖИЕ, НЕКРОЗ КАК УГРОЗА: БИОФИЗИЧЕСКИЙ ВЗГЛЯД НА ОНКОЛОГИЮ

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Клеточная смерть является основным биологическим процессом, обеспечивающим гомеостаз и функционирование всех тканей организма. В нормальных условиях клетки проходят процесс обновления: они погибают, создавая новые, или удаляются при нарушении их функции. Существует множество типов клеточной смерти, среди которых ключевыми являются апоптоз и некроз, обладающие своими биофизическими и молекулярными особенностями. Нарушение этих процессов приводит к развитию онкологических заболеваний: апоптоз способствует росту и укреплению иммунитета опухоли, тогда как некроз формирует воспалительную среду в тканях опухоли и ускоряет прогрессирование рака.
В статье рассматриваются биофизические механизмы апоптоза и некроза, их роль в онкогенезе, современные методы исследования, а также клиническое значение для диагностики и лечения опухолей.

Ключевые слова: апоптоз, некроз, клеточная смерть, биофизические особенности, онкология, диагностика, лечение.

АПОПТОЗ – ҚАРУ, НЕКРОЗ – ҚАУІП: ОНКОЛОГИЯҒА БИОФИЗИКАЛЫҚ КӨЗҚАРАС

Тайбағарова Інжу

Ғылыми жетекші: Абдрасилова В.О.

Жасушалық өлім – организмдегі барлық тіндердің гомеостазын және қызметін қамтамасыз ететін негізгі биологиялық процесс. Қалыпты жағдайда жасушалар жаңару процесінен өтеді: олар өліп, жаңалары түзіледі немесе қызметі бұзылған жағдайда жойылады. Жасуша өлімінің көптеген түрлері бар, олардың ішінде негізгілері – апоптоз бен некроз, әрқайсысының

өзіндік биофизикалық және молекулалық ерекшеліктері бар. Бұл процестердің бұзылуы онкологиялық аурулардың дамуына әкеледі: апоптоз ісіктің өсуіне және оның иммунитетін күшейтуге ықпал етсе, некроз ісік тіндерінде қабыну ортасын қалыптастырып, қатерлі процесті үдетеді. Мақалада апоптоз бен некроздың биофизикалық механизмдері, онкогенездегі рөлі, заманауи зерттеу әдістері және ісіктерді диагностикалау мен емдеудегі клиникалық маңызы қарастырылады.

Кілт сөздері: апоптоз, некроз, жасушалық өлім, биофизикалық ерекшеліктер, онкология, диагностика, емдеу.