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MODERN VIEWS ON THE PHENOMENON OF MULTIDRUG RESISTANCE

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SUMMARY
The resistance of tumors to anticancer drugs is called the phenomenon of multidrug resistance. This phenomenon is one of the most difficult problems of modern oncology. Multiple drug resistance regulated with a large number of mechanisms. Multiple drug resistance (MDR) - a very common type of tumor cells resistance to medicines.

KEYWORDS: multiple drug resistance, tumor resistance.

MDR was first discovered in experiments with cultured cells; at present, this is a well-characterized phenomenon, which is characterized by wide cross-resistance (cross-resistance) of cells to various substances that are different in chemical structure and mechanism of action.[1]. The phenomenon of tumor resistance to antitumor drugs, called multidrug resistance, is one of the most difficult problems of modern oncology. Multiple drug resistance can be ascertained upon diagnosis, or acquired after treatment or in remission.[2]

With the development of MDR in cells, there are three groups of major changes

1. Decreased cell accumulation of cytotoxic substances. 2. Changes in the activity or expression of certain cellular proteins, 3. Changes in cellular physiology associated with changes in the structure of the cell membrane, cytosolic pH and the characteristics of intracellular transport of membrane elements

MDR is a serious obstacle to the successful treatment of malignant neoplasms. Recent studies have shown that the molecular mechanisms of MDR are multiple, and the drug resistance of a cell can be determined by the inclusion of various mechanisms characterizing the different stages of the toxic effect of a chemotherapy drug on a cell - from limiting the accumulation of drugs inside the cell to canceling the program of cell death induced by the substance. Often several protective mechanisms are activated in the cell, but most often one mechanism prevails.[3]

A study of the resistance of tumor cells to cytostatic drugs is necessary to understand the mechanisms of cell protection from damage. A study of the resistance of malignant cells to chemotherapy is also important for practical oncology, since it is often associated with failure to treat malignant neoplasms. The ineffectiveness of therapy can be caused not only by changes in tumor cells, but also by a number of other reasons why the drug does not reach the cell in an adequate and active form.[4] The impact on the cell culture of one drug can lead to the emergence of a population that is resistant at the same time to many other substances that the cells have not encountered (cross-resistance). MDR, of course, does not necessarily arise from the effects of drugs on cells. It is often associated with the type of differentiation of tumor cells or with their localization in the body. This is the so-called "natural" MDR (resistance, originally characteristic of these cells).[5]

With natural MDR, all neoplasm cells are resistant to therapy.

Despite advances in modern pharmacology, the effectiveness of tumor chemotherapy remains insufficient. This is due to the most important feature of living systems (including tumor cells) - the ability to adapt to changes in the environment. One manifestation of this plasticity is the development of drug resistance in tumor cells. Multiple drug resistance (MDR) of malignant neoplasms - maintaining cells viability in response to a number of drugs - is one of the main causes of disease progression: the tumor is insensitive to chemotherapy regardless of the combination of drugs used.[6]

The main mechanism of MDR is reduced accumulation of drugs in the cell, due to the active removal of substances into the intercellular environment. Acquired MDR may result from chemotherapy.

As a result of exposure, rare genetic variants of resistant cells can appear in tumor cell populations, which subsequently multiply if they receive a selective advantage.[7]

The multiplicity and variety of mechanisms of MDR significantly complicate both the diagnosis of the causes of patients' resistance to therapy and the development of protocols for overcoming MDR of tumor cells. A discussion of each individual MDR mechanism shows that the sensitivity of tumor cells to therapy depends to a large extent on the combination of the features of regulation of vital cell processes associated with its species, tissue affiliation, as well as with those genetic changes that occurred in the cell during its malignancy and progression of the neoplasm. This phenomenon also complicates the diagnosis of the causes of MDR tumors.

According to the statistics of the American Cancer Society, in newly registered cancer patients in 50% of cases, initial resistance to cytostatics was found, and in 49% resistance to them was manifested during treatment.[7]

Modern chemotherapy usually uses a combination of drugs belonging to different classes and acting on different cellular targets. Obviously, very different drugs damage a variety of targets in the cell. The problems of combined chemotherapy for tumors and the multiplicity of targets for different drugs highlight the multidrug resistance (MDR) of tumor cells.

A decrease in the accumulation of drugs in the cell can be the result of both restricting the entry of drugs into the cell and increasing their elimination from the cell. Since the vast majority of chemotherapeutic drugs penetrate the cell by simple diffusion through the plasma membrane, the entry of a substance into the cell can change if the structure of the cell membrane changes.[8] The discovered modifications could both change the passage of some drugs through the membrane and influence the transmission of signals determining apoptosis.[9]

MDR: detection methods

Obviously, depending on the changes in the cells of this neoplasm of the genes that determine malignancy, and on the nature of the expression of proteins (for example, Pgp) inherent in the normal tissue, the set of genes or proteins studied to diagnose the causes of MDR should be different for different neoplasias.

When planning a set of methods for detecting MDR, one should not forget that, although there are certain mechanisms of drug resistance that are most characteristic of the resistance of cells to this drug, most often the resistance of cells to a particular substance can be determined by several reasons.

For example, resistance to cisplatin may be associated with activation of the glutathione system, increased release of the drug from the cell, changes in the regulation of apoptosis, and an increase in the efficiency of DNA repair.[10]

It is also important to understand that different MDR mechanisms can coexist in the same cell (not to mention a heterogeneous population of tumor cells). Moreover, different MDR mechanisms can be interconnected; these bonds have been little studied, however, examples of such bonds can be given. For example, it was found that if the wild-type p53 protein activity was suppressed in cells (this abolished drug apoptosis), the Pgp protein is activated.[11] Thus, in this case, there was a coexistence and interconnection of two types of MDR - caused by a dysfunction of the normal p53 protein and due to the activity of Pgp.

Thus: MDR is a component of multifactorial defense of cells.

Drug resistance is a complex mechanism, from a primary sensitive tumor to multiple resistance.

The study of molecular events mediating the formation of MDR can contribute to the development of rational approaches to the prevention of this clinically unfavorable phenomenon. It was found that blocking the transmission paths of MDR1-activating signals prevents the development of MDR in cells exposed to chemotherapeutic agents. It seems reasonable to test the combinations of inhibitors of stress signals with antitumor drugs for the long-term preservation of the sensitivity of tumor cells to therapeutic effects. In clinic of Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology over the years, work has been carried out to overcome MDR in various localization of tumors. To do this, we determine the molecular biological markers responsible for drug resistance in malignant tumors (membrane glycoprotein, glutathione-S-transferase and also study the role of genetic markers responsible for drug resistance of the tumor (p53, bcl-2).

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