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Mycobacterium Tuberculosis Resistance — Stages of Drug Resistance Formation (Review)

The review contains an analysis of the latest research on molecular genetic aspects of the formation of resistance in tuberculosis patients to avoid it during use of modern treatment programs.

Objective — to assess the situation with the evolution of resistance of *Mycobacteria tuberculosis* and the stages of drug resistance development using materials from available databases.

Materials and methods. The research has been completed for the period from 2014 to 2024. The next stage with the establishment of a systemic topological and metric computer analysis of the results allowed us to see the most informative sections of the research topic that are clearly associated with the formation mechanisms of drug-resistance in pulmonary tuberculosis. The most complete database of available literary sources was obtained (about 50 out of 502 analyzed arrays).

Results and discussion. Ukraine is among the thirty countries with a high burden of tuberculosis with multiple drug resistance (MDR-TB). The main threat to the effectiveness of tuberculosis treatment in Ukraine is late detection of the disease and determining the sensitivity of the pathogen, which is the main prerequisite for prescribing adequate treatment. The situation with MDR-TB in Ukraine remains difficult in the conditions of war against the background of the COVID-19 pandemic. Thus, the total number of such cases for 2023 was 1,955 patients, of which 1,326 were new cases. The number of cases of tuberculosis with extended resistance (XDR-TB) was 228, of which 136 patients were diagnosed for the first time.

Conclusions. The question of studying the genetic aspects of the formation of drug resistance of *M. tuberculosis* with the determination of the role of polymorphic variants of genes encoding xenobiotic metabolism systems in tuberculosis infection remains relevant to understand the mechanisms of interaction in the process of implementing hereditary information at the holistic level of the organism in order to increase the effectiveness of treatment and prevent the formation of resistance.

Keywords

Mycobacterium tuberculosis, resistance, molecular-genetic aspects, multiple drug-resistant tuberculosis.

Tuberculosis continues to be one of the most urgent medical and social problems in the world in the 21st century, including in Ukraine. To this day, there is not a single country in the world where the problem of overcoming tuberculosis (TB) has been solved. The situation with TB in Ukraine remains difficult and, even, prognostically unfavorable due to the increase in the total number of cases. Thus, the incidence was: 2023 — 48.4 per 100,000 population; 2022 — 45.7 %; the increase was +7.3 % against the background of an increase in resistant forms of TB both among adults and children [2, 17, 34].

The most sensitive indicator of the state of the epidemiological situation is the incidence rate of TB in children [14]. At the same time, the test of growth of morbidity in children is higher than in adults [2]. The TB rate among children aged 0—14 was 10.4 per 100,000 children (639 cases, which is 3.2 % of the total number of registered TB cases in 2023), which is 40.5 % more than in 2022 (7.4 per 100,000 children). The increase in the incidence of

TB among children aged 0—14 years in 2023 is closely related to the worsening of the epidemic situation among adults. The TB incidence rate among adolescents (15—17 years) increased by 55.3 % — from 10.3 to 16.0 per 100,000 people of the corresponding age group (196 cases in 2023 *vs* 127 in 2022) [22, 26].

The incidence of active TB in combination with the disease caused by the human immunodeficiency virus has increased by 5.1 % compared to 2022 and is 8.2 per 100,000 people (3,350 cases of TB/HIV in 2023 *vs* 3,191 in 2022) [48].

Ukraine is among the thirty countries with a high burden of multidrug-resistant tuberculosis (MDR-TB). The main threat to the effectiveness of treatment TB in Ukraine is late detection of the disease and determining the sensitivity of the pathogen, which is the main prerequisite for prescribing adequate treatment. Generalized forms of TB and cases of MDR-TB are the most difficult in this regard [4, 35].

In the conditions of an epidemic of drug-resistance, only the detection of TB, even with laboratory confirmation of the diagnosis, is not enough to start treatment. Effective treatment is possible only if the complete resistance profile of the pathogen isolated from the patient is identified [20, 45]. Therefore, the examination for the purpose of prescribing adequate treatment takes time, which depends on the regional features of the organization of anti-tuberculosis care for the population on the one hand, and on the other hand, on how quickly the patient will go through all the stages of diagnosis.

Considering all the above the purpose of review was to assess the situation regarding the evolution of resistance of *M. tuberculosis* and the stages of the formation of drug resistance based on the materials of available databases.

Materials and methods

The research was carried out in the period from December 2014 to January 2024. A search was performed using key words: pulmonary TB, resistance, mechanism of formation of multiple drug resistance, immunopathogenesis of TB, etiotropic treatment. Digital access to the following full-text and abstract databases was used as the main source of research: EBSCO single information base package; the world's largest single abstract database and scientometric platform Scopus; freely available Google search engine Scholar; MEDLINE with Full text; MEDLINE complete; Dyna Med plus; EBSCO eBooks Clinical Collection; abstract scientometric database of scientific publications of the Web project of Knowledge of the Thomson company Reuters — Web of Science Core Collection WoS (CC); statistical data of the Ministry of Health of Ukraine and the Center for Public Health; SCIE (Science Citation Index Expanded); SSCI (Social Science Citation Index); online database of the National Scientific Medical Library of Ukraine; AHCI (Artand Humanities Citation Index).

The next stage, with the use of system topological and metric computer analysis of the obtained data, made it possible to highlight the most informative rubrics for the selected research topic, which are clearly associated with the formation of drug-resistance in pulmonary TB. As a result, the most complete database of available literary sources was obtained (about 50 out of 502 analyzed arrays).

Results and discussion

In addition to the usual varieties of tuberculosis infection (*M. tuberculosis*), mutant forms of *M. tuberculosis* (MTB), which are resistant to the action of many basic antimycobacterial drugs (AMDs), are rapidly spreading in the world: MDR-TB and tuberculosis with extended resistance (XDR-TB). According to WHO estimates, about 500 thousand inhabitants of the planet are infected with MDR-TB, in which standard therapy is ineffective, and XDR-TB, as experts [8, 46] note, is resistant to almost all drugs known today and has the highest mortality rate among people of working age — 85 %. The average life expectancy of ineffectively treated patients is 2.9 years. The probability of successful treatment decreases with the emergence of new resistant strains of MTB with total resistance [28]. According to WHO data, in Ukraine, 16 % of patients diagnosed with TB for the first time (from 5 % in western regions to 16 % in eastern regions) have MDR-TB, and 44 % of patients with relapse of the disease [10].

State of MDR-TB in Ukraine during war against the background of the COVID-19 pandemic remains difficult. So, the total number of such cases in 2023 was 1,955 patients, of which 1,326 were new cases. The number of cases of TB with extended resistance XDR-TB was 228, of which 136 patients were diagnosed for the first time [19]. One of the main problems of control TB in Ukraine is low treatment effectiveness. The effectiveness of treatment of all cases of TB in the 2017 cohort was 76 % against the world average of 85 % [12, 18]. Regularly severe and multidrug-resistant forms of the disease make the biggest contribution to the low national average. Thus, the effectiveness of the treatment of MDR-TB in Ukraine remains at one of the lowest levels in the world: as of 2019, only in India, Indonesia, Mozambique and Ukraine, the effectiveness of treatment was less than 50 % [31].

The set of MTB strains circulating in the population is characterized by significant variability with the presence of high-virulence and low-virulence

strains grouped into different families based on genetic features. Modern MTB strains are characterized by the absence of the possibility of horizontal gene transfer, but today there are studies that have shown the presence of rare gene recombinations [32]. Evolution of *M. tuberculosis* complex is carried out, in most cases, by deletions and duplications, which causes clonal pattern of evolution of the causative agent and in combination with the absence of recombination can be the cause of the pathogenetic features of the course of individual strains. Genetically different strains of MTB stimulate different immune responses (due to the predominance of concentrations of certain cytokines), which determine not only the difference in pathogenesis, but also in the clinical manifestations of the disease. In general, as recognized by most researchers, the pathogenicity of MTB depends on their ability to survive in macrophages, which captured them and induced a delayed-type hypersensitivity immune response [6, 37].

In Ukraine, the main role in the etiology and epidemiology of TB is played by *M. tuberculosis* (over 90 % of cases), much less often by *M. bovis* (3—5 %). These two species are the main causative agents of diseases.

The results of the first national epidemiological study in Ukraine on the drug resistance of the TB pathogen (DRS) in 2013—2014 revealed the following genotypes of TB strains:

- Beijing (50.2 %);
- Euro-American Superlineage (16.8 %);
- LAM (14.9 %);
- Ural (9.6 %);
- Haarlem (8.11 %);
- S-type (0.3 %);
- nd (0.2 %).

In most regions of the world, *M. tuberculosis* of the Beijing family is currently gaining significant distribution. The main negative characteristic of the Beijing family is their ability to form drug-resistance quickly, compared to other families [3]. In a number of studies, it has been shown that MTB of the W-Beijing family have copper-resistant strains, and the growth rate in culture is even higher than that of susceptible ones [9]. In general, Beijing strains have 41 specific single nucleotide polymorphisms (SNPs), including those in genes involved in the processes of replication, repair, and recombination and having a potential impact on the evolution and adaptation of representatives of this genetic line [1].

M. africanum causes tuberculous lesions in the inhabitants of Africa. When infected with the bovine type of MBT, extrapulmonary forms of TB develop: lymph nodes, bones and joints, genitourinary system, meninges. MTB of human and bovine types can cause TB not only in humans, but also in cattle, goats, pigs, and less often in horses, dogs, and cats. Almost all vertebrates are affected by TB. Along with the typical pathogenic types of MTB (*M. tuberculosis*, *M. bovis*), conditionally pathogenic atypical mycobacteria were isolated and stuied. Under certain conditions, especially when immunity is reduced, diseases similar to TB can develop in humans, which are united by the concept of mycobacteriosis. They differ from the causative agents of TB in the appearance of colonies, growth rate and drug susceptibility to anti-tuberculosis drugs [25].

An important place in epidemiological studies is the study of a person's susceptibility to TB infection. A person has a strong natural resistance to TB. Resistance is not the same throughout life, and the incidence of TB is affected by gender, age, concomitant diseases, living conditions, etc. It has been shown that there is a genetically determined resistance to TB. The connection of species resistance with immune response genes and the main HLA histocompatibility complex has been proven. A person may be prone to TB if HLA antigens such as DR2, B7, B14 are present on peripheral blood leukocytes [16].

In the study of the evolution of the pathomorphosis of TB of the lungs and, in particular, the formation of drug-resistance, one of the tasks is to study the polymorphism of known candidate genes, as well as the search for new genes which protein products are involved in the pathogenetic mechanisms of the development of the disease [33].

To track the spread of TB infection in economically developed countries, the method of genotyping the TB pathogen has been introduced. This was facilitated by the discovery of polymorphic repeating regions in the nucleotide chain in *M. tuberculosis* DNA. This made it possible to study «molecular fingerprints» — the genotype of the TB pathogen [42]. In connection with the above, active research and study, today, requires the question of molecular genetic aspects of the formation of resistance of MTB.

It was shown that the features of the immune reaction in resistant TB are high but rapid expression of TNF-α and inducible isoforms enzyme synthetases nitric oxide (iNOS), which indicates the effective activation of macrophages at the early stage of MTB infection. In turn, interferon-γ (IFN-γ) in macrophages, activated and natural T-killers induce genes which protein products are able to destroy MTB. However, in most cases with MDR-TB, IFN-γ is produced late and weakly, which indicates the benefit of rapid inactivation of macrophages that stimulate the Th1-subtype of lymphocytes. Thus, the activation of Th1 lymphocytes is not effective enough to stop the reproduction of mycobacteria [36].

The expression of almost 527 genes (15 % of the total number examined) was detected in different strains of *M. tuberculosis*. The insertion sequence IS6110, belonging to IS3 transposons, is a sequence widely used as a genetic marker as it is specific for *M. tuberculosis* strains [5, 15]. Laboratory studies have shown that the emergence of resistance in *M. tuberculosis* is associated with nucleotide changes (mutations) in genes that encode various enzymes that directly interact with drugs. For example, mutations of the *rpo* gene, which encodes the β-subunit of RNA polymerase in 96 % of cases, lead to the formation of *M. tuberculosis* resistance to rifampicin. Mutations in the *kat* gene lead to the substitution of individual amino acids in the enzymes catalase and peroxidase, which are responsible for the formation of antioxidant protection during the development of inflammatory oxidative stress. Nucleotide changes in the regulatory and adjacent coding regions of the locus *inh* are associated with resistance of individual MTB strains to isoniazid. Resistance of *M. tuberculosis* to streptomycin (in 86 % of our TB patients) is associated with a mutation in the *rps* gene, which encodes S12 mitochondrial protein, or with nucleotide changes in the *rrs* gene, which encodes 16S RNA [21, 43].

The antigenic (AG) composition of altered forms of MTB is simplified with the loss of at least 33.3—37.5 % of AG associated, in most cases, with the cell wall. Some researchers have shown that modified MTB induce the synthesis of antibodies more weak. Probably, these features make it possible to avoid the control of the immune system and create prerequisites for the persistence of MTB in the body. The transformation of MTB into acid-resistant forms is accompanied by a decrease in the concentration of AG in the cell, a simplification of the antigenic composition with the preservation of no more than 62.6—66.7 % of AG, including those specific for the *M. bovis — M. tuberculosis* complex [44].

According to a number of researchers [5, 24, 41], TB, like other infections, is characterized by a cyclic course, which is associated with a certain frequency of reproduction, the degree of virulence and changes in the immunity of the population. In the period of minimum solar activity, morbidity and mortality from TB decreases, which is associated with the influence of solar activity on both humans and MBT (cosmoheliophysical factors, in particular, the 11-year cycle of TB infection activity) [5].

To date, it has been proven that the development of the TB process depends on a number of medico-biological and social factors [27]. The emergence of resistance to antituberculosis drugs is a natural phenomenon, a basic biological law, an expression of the adaptation of species to the environment.

The analysis of literary sources allows us to assert [23, 30, 38] that there is a whole galaxy of theories regarding the formation and essence of drug resistance of MBT.

The theory of adaptation suggests changes in the properties of a microorganism that are adequate to changes in the environment. According to this theory, the development of drug resistance of MTB is considered to be a manifestation of one of the forms of bacterial cell variability under the influence of chemical drugs [41]. That is, the emergence of MTB resistance to anti-TB drugs is caused by the treatment itself, since the population ratio of susceptible and resistant forms of MTB is 90 % susceptible and 10 % resistant, but in the course of treatment, in the case of choosing the wrong chemotherapy regimen, a significant number of susceptible MTB die, as a result of which the ratio is violated in the microbial population, and the number of resistant MTB exceeds that of sensitive ones.

According to the theory of spontaneous mutations [29], there are resistant mutants in the MTB population. At the same time, anti-TB drugs can play the role of a factor in the further selection of resistant species, or, according to some researchers, mutants. However, the high frequency of spontaneous mutagenesis cannot always be explained by the speed of the spread of mutations, which contributes to the development of resistance of pathogens to anti-TB drugs.

Numerical studies indicate the possibility of genetic translocation of mutant genes from one cell to another and even intergeneric exchange of genetic information. This way of spreading genetic information is described for bacteria, but for *M. tuberculosis* and some substrains of *E. coli,* only indirect signs of intergeneric transmission of genes encoding drug resistance have been identified [39].

Some foreign researchers claim that the reason for the emergence and spread of drug-resistant strains is the natural biochemical and genetic mechanisms of bacterial cell life, discuss ways of spreading genetic information that leads to the development of MTB resistance [47]. Of the 3.8—4.2 thousand MTB genes, more than half ensure the synthesis of the cell wall and, under adverse conditions, change its structure and transfer metabolic processes to redundant pathways. This, in most cases, explains the existence of morphologically changed forms of MTB, which are considered as regular stages of the life cycle.

The results of the analysis of a number of studies [14, 19, 38] suggest that the transformation of the shape and structure of the cell wall is accompanied by changes in the antigenic composition, which were observed during the immunoluminescent indication

of L-forms of MTB. With the help of tuberculin, made from L-forms of *M. bovis,* significantly more animals with latent TB infection were found, than in the case of using the drug from the «bacillary» strain. Probably, the persistence of changed (transformed) forms of MTB induces an immune response that differs from the response to the antigen complex of the Koch bacillus, although significance of difference in their antigenic composition is actually unknown.

One of the important types of MTB variability is the formation of L-forms [42]. L-forms are characterized by a reduced level of metabolism, weakened virulence. Remaining viable, they can stay in the body for a long time and induce anti-tuberculosis immunity. L-forms differ in pronounced functional and morphological changes. It was found that the transformation of MTB into L-forms is enhanced with long-term use of antimycobacterial therapy and other factors that disrupt their growth and reproduction, cell membrane formation [1, 41]. It has been found that in the sputum of «non-bacillar» patients with destructive forms of TB, L-forms of MTB can be found, which can reverse (modify) into a rod-shaped variant, thereby causing the reactivation of the TB process. Therefore, abacillation of the caverns of such patients does not mean their sterilization in terms of MTB.

New discoveries in the genetics of TB are due to the variety of properties of this microorganism, which is determined by its chromosome [18, 23]. Genome of *M. tuberculosis* complex is very conservative. Its representatives have DNA homologies in the range of 85—100 %, while the DNA of other representatives of this genus is homologous to *M. tuberculosis* only in the range of 5—29 %. The genome of *M. tuberculosis* is smaller than that of other mycobacteria. In the classical pathogen of human TB, *M. tuberculosis,* more genes than *M. africanum* and *M. bovis*, which lost part of the genetic material during evolution [20].

In 1998, the nucleotide sequence of the chromosome of the H37Rv *M. tuberculosis* strain was published, which is a museum «classic» strain. Chromosomes are toroidal structures — more than 4,000 genes encoding proteins, plus 60 encoding functional components of RNA: a unique ribosomal RNA operon, 10Sα RNA, which participates in the degradation of proteins with atypical matrix RNA, 45 transport RNAs (tRNAs), about 100 lipoproteins [19].

A feature of the genome of *M. tuberculosis* complex is a large number of repeated DNA sequences. *M. tuberculosis* H37Rv chromosome has up to 56 copies of IS-elements, which provide DNA polymorphism of MTB (this feature is used in PCR diagnostics). Most of them, with the exception of the IS6110 element, are unchanged. As a rule, 5 to 20 copies of IS6110 are present in the chromosomes of different MTB strains, but there are strains that do not have this element. Differences in the number of copies and localization on the chromosome of these genetic elements are used to differentiate MTB strains in molecular epidemiology.

The most advanced genotyping schemes of mycobacteria are based on the detection of genomic polymorphism caused by the IS6110 element. The divergence of the *M. tuberculosis* species usually occurs due to recombinations between copies of the IS6110 element, which flank different genes [7]. The use of genotyping in clinical and epidemiological studies is decisive in those cases when it is necessary to distinguish between primary and secondary (acquired) drug resistance.

If the genotype samples of MTB before and during treatment coincide, this indicates the formation of resistance in the course of treatment. The reasons for this can be different:

- biological — insufficient concentration of the drug, individual characteristics of the body (the rate of inactivation of the drug is individual); concomitant diseases that prevent the formation of an adequate concentration of the drug in the blood and in the focus of the TB lesion;
- behavior and psychological characteristics of the patient (contact with a patient with MDR-TB, irregular medication intake, premature discontinuation of medication, interruptions in treatment, poor drug tolerance);
- disease-related — in the case of a change in the doses of drugs with a large amount of MTB, a change in pH may occur in the areas of the affected tissue, which prevents the active action of the drugs; monotherapy; insufficient dose or duration of treatment; use of drugs with cross-resistance; incorrect prescription of the treatment regimen, inconsistency in drug doses;
- organizational mistakes and inadequate funding of the anti-tuberculosis program and other interested agencies; lack of the necessary range and quantity of medicines (inferior chemotherapy regime), improper storage of medicines.

If the «molecular fingerprints» are different, then this indicates repeated infection (reinfection) with another strain, which requires correction of antituberculosis treatment.

The use of genotyping can help in clinical and epidemiological studies, when it is necessary to solve the question of the genesis of relapse — either it is the result of the activation of a mycobacterium that was already in the human body, or it is the result of infection with a new strain [32, 41]. Also, this method can detect laboratory cross-contamination.

In fact, from the very beginning of the use of antibiotic therapy, the phenomenon of drug resistance arose. The peculiarity of this phenomenon is that MTB does not have plasmids, and the population resistance of microorganisms to antimicrobial drugs was traditionally described by the presence of R-plasmids in the microbial cell (from the English resistance). However, despite this fact, the appearance or disappearance of drug resistance was noted in one strain of MTB. As a result, it turned out that activation or deactivation of genes responsible for resistance are IS-sequences [32].

According to molecular geneticist E. Schurr, every third inhabitant of the planet is MTB infected, but only 5—10 % of this huge number of carriers can actually get TB. Others somehow manage to keep the disease in a «dormant» state. The scientists focused their attention on the NRAMP1 gene, which is already known to be related to many diseases. It has been found that variants (alleles) of the NRAMP1 gene control the rate of development of TB, as well as whether the disease develops at all. E. Schurr points out that he is the first to encounter the fact that a gene can control the time that passes from the moment of infection to the onset of the disease (the work is published in the latest issue of the Proceedings of the National Academy of Science).

More recently, American scientists from the University of Texas found the exact reason of that MTB infection does not always lead to the development of TB. Previously, it was believed that a hereditary predisposition was to blame for this. Studying the genotype of two groups of patients from Mexico and Korea, American scientists found that the presence of a mutation in the gene located on the 17th chromosome increases the susceptibility to TB by five times. If only a single nucleotide in the gene changes, the production of MCP-1 protein immediately increases (it attracts cells of the immune system to areas of inflammation). Mutant human monocytic chemoattractant protein (MCP-1) has a higher affinity for binding to glycosaminoglycans (GAGs) and reduces activity towards transmembrane G protein-coupled receptors (GPCRs) compared to wild-type MCP-1 protein. It is characterized by the fact that the MCP-1 protein is modified, while preserving the structure, by inserting at least one basic and/or electron-donating amino acid residue or replacing at least two amino acid residues with two basic and/or electron-donating amino acid residues, and the indicated protein includes an amino acid sequence according to the following general formula:
$(M)_nQ(PDAINA(Z1))_mVTCC(X1)NFTN(Z2)(Z3)$
$I(X2)V(X3)RLASYRRITSSKCPKEAVIF KTI(X4)$
AKEICADPKQ KWVQDSMDHL DKQTQTPKT.

MCP1 (*monocytic chemotaxis protein*) is a very important link of the primary immune response when *M. tuberculosis* enters the body, but if it is produced in excessive amounts, the production of another factor of immunity, interleukin-12 (IL-12), decreases. And it is needed to activate immune cells that have arrived at the infected area to fight bacteria. To date, this is the biggest discovery in the genetics of TB [21]. Scientists hope that it will play its role in the fight against this dangerous disease, the prevalence of which has recently become alarming.

An international group of scientists from the USA and South Africa announced the successful completion of work on deciphering the genome of the TB pathogen [37]. The researchers obtained information about the genetic structure of both drug-susceptible and multi-drug resistant MTB as well as the causative agent of the most dangerous form of the disease — XDR-TB. Scientists from the Broad Institute, Harvard School of Public Health in USA and the Nelson Mandela School of Medicine (South Africa) studied the genome of the XDR-TB strain that led to the loss of more than 50 human lives during a recent outbreak in the South African province of KwaZulu-Natal. When deciphering four million nucleotide pairs of the MTB genome, a special DNA sequestration technology was used, which allows simultaneous «reading» of hundreds of millions of DNA nucleotides. Scientists found out that drug-resistant and drug-susceptible bacteria differ slightly from the point of view of genetics, they managed to detect only a few dozen small changes in DNA. Some of these differences involved genes which role in the development of drug resistance was known; other changes were detected in new, little-studied genes [37].

MBT by their nature are resistant to many antibiotics. The main reason for resistance is encoded in the structure of the TB bacillus genome. This property is primarily related to the fact that the highly hydrophobic cell surface serves as a kind of physical barrier for therapeutic agents and antibiotics. It is also reported that cultures of forms of MTB do not always contain specific for *M. tuberculosis complex* insertion element IS6110 and some others, which leads to the absence of synthesis of the corresponding proteins [45].

Laboratory studies have shown that the emergence of resistance in MTB is associated with nucleotide substitutions (mutations) in genes encoding various enzymes that directly interact with drugs.

Moreover, modified MTB are relatively weaker in inducing antibody synthesis. Probably, these features make it possible to avoid the control of the immune system and contribute to their persistence in the body. The transformation of MTB into acid-

resistant forms is accompanied by a decrease in the concentration of AG in the cell, a simplification of the antigenic composition with the preservation of no more than 62.6—66.7 % of AG, including those specific for the *M. bovis—M. tuberculosis complex* [14].

The basis for a significant increase in the number of cases of primary drug resistance of MTB may be the widespread use of a few antibiotics that can be used in phthisiology for the treatment of diseases of non-tuberculous etiology. In this regard, recommendations to prescribe one of the antituberculosis drugs—rifampicin as a first-line drug during the treatment of so-called problematic infections caused by gram-positive organisms are of particular concern. The issue of rational use of second-line drugs — respiratory fluoroquinolones [1, 8, 13] remains relevant.

According to a number of researchers [4, 35], due to a variety of factors (demographic, socio-economic, insufficient attention to the problem of combating TB in many countries, the epidemic of HIV infection), the number of patients with abacterial forms of pulmonary TB will increase significantly, and, many of these patients will go undiagnosed and untreated. Even during TB therapy, the irrational choice of drugs and weak control over the use of drugs by patients will lead to an increase in the number of people who excrete resistant MBT.

In our opinion, which coincides with the opinion of a number of researchers [14, 38], the main mechanisms of the development of drug resistance are an inadequate or wrongly chosen treatment scheme, which leads to the dominance of the drug-resistant strain (selection of significantly resistant strains takes place). Patients who have developed an allergy to one drug are more prone to acquiring resistance to other drugs (drug amplification effect) [19]. According to some authors, the probability of transmission of resistant strains is similar to the degree of transmission of susceptible strains. So, the main cause of the drug-resistance phenomenon is the human factor. All of the above is confirmed by the results of a pilot scientific study provided by the National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky and the University of Illinois (USA), which showed that only 12.8 % of TB patients received treatment according to the standards determined by the orders of the Ministry of Health; 71.1 % of patients were prescribed the wrong treatment regimen; 31.6 % of patients underwent treatment independently [25, 40].

As part of the implementation of the national TB prevention program, the purchase of equipment for molecular genetic diagnostics is foreseen. The latest molecular platform Xpert MTB/RIF, which has been tested in low-income and middle-income countries, is recognized as a first-line test for persons with suspected MDR-TB or HIV-associated TB and as a follow-up test for negative sputum smears from other patients [16]. The implementation of Xpert MTB/RIF on the territory of our country does not require long-term training of medical personnel, modern laboratories, or the latest methods of biological protection and is extremely promising.

The main disadvantages of traditional direct smear microscopy (low sensitivity and specificity), as well as cultural research (long duration of obtaining the result) have been overcome in a new method [30].

There is promise in separate genetic studies that attempt to use host gene expression in the blood cells of TB patients to identify a disease-specific gene that could later be used to create a diagnostic test and possibly differentiate the stages of the disease. A set of 4 genes has been identified that may help to distinguish between patients with active TB, latent infection and those who have previously received antimycobacterial therapy, as well as a set of three different genes that can be used to distinguish patients with active TB from infected and healthy [14]. An alternative method is the study of gene expression in cells stimulated for the first time by specific MTB antigens. By this method, it is possible to distinguish persons with latent TB infection from patients with active TB by determining the expression of only 3 genes.

Some researchers found that the relationship between the expression of IL-4 levels and its splicing variant IL-4d2 correlates with the phase of the disease, and changes in the mentioned indicator can be a sign of changes in the microbial load [1, 3].

Since the system of metabolism of xenobiotics is involved both in the protection of the body against the consequences of the development of inflammatory reactions in TB, and in the metabolism of most anti-TB drugs, it is extremely interesting to study the activity of enzymes that are part of this group. According to the results of many studies, glutathione-S-transferase (GST) polymorphism, in particular, homozygous deletions (null-alleles) of GSTM1 and GSTT1, is one of the causes of increased sensitivity to the damaging effects of environmental factors with damage to the bronchopulmonary system. The role of polymorphic variants of GST genes in the formation of MBT resistance has been shown [14, 18].

Conclusions

Summing up the analysis, it should be noted that scientists are actively researching the molecular and genetic aspects of the formation of resistance in TB patients in order to prevent its occurrence when applying modern treatment programs. The study and evaluation of the effectiveness of methods for

the diagnosis and treatment of susceptible and resistant TB continues.

The issue of studying the genetic aspects of the formation of drug resistance of *M. tuberculosis* with the determination of the role of polymorphic variants of genes encoding xenobiotic metabolism systems continues to be relevant. with TB infection to understand the mechanisms of interaction in the process of implementing hereditary information at the organismal level in order to increase the effectiveness of treatment and prevent the formation of resistance.

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Резистентність мікобактерій туберкульозу — етапи формування лікарської стійкості (огляд літератури)

Наведено аналіз сучасних досліджень молекулярно-генетичних аспектів формування резистентності у хворих на туберкульоз для запобігання її виникненню при застосуванні програм лікування.

Мета роботи — оцінити ситуацію щодо еволюції резистентності мікобактерій туберкульозу та етапів формування лікарської стійкості за матеріалами доступних баз даних.

Матеріали та методи. Проаналізовано публікації за період з грудня 2014 р. до січня 2024 р. Застосування системного топологічного і комп'ютерного аналізу отриманих результатів дало змогу визначити найінформативніші щодо обраної теми дослідження, чітко асоційовані з механізмами формування хіміорезистентності при туберкульозі легень. Отримано найповнішу базу доступних літературних джерел (близько 50 із 502 проаналізованих).

Результати та обговорення. Україна входить до 30 країн із високим тягарем туберкульозу з множинною лікарською стійкістю (МЛС-ТБ). Ефективність лікування туберкульозу в Україні

обмежена пізнім виявленням захворювання та визначенням чутливості збудника, що є головною передумовою призначення адекватного лікування. Складною є ситуація з МЛС-ТБ в умовах воєнного стану на тлі пандемії COVID-19. Загальна кількість таких випадків за 2023 р. становила 1955, з них 1326 нових випадків. Кількість випадків туберкульозу з розширеною резистентністю — 228, із них 136 уперше діагностованих.

Висновки. Вивчення генетичних аспектів формування лікарської стійкості *M. tuberculosis* із визначенням ролі поліморфних варіантів генів, що кодують системи метаболізму ксенобіотиків при туберкульозній інфекції, є актуальним для розуміння механізмів взаємодії під час реалізації спадкової інформації на рівні організму, що дасть змогу підвищити ефективність лікування і запобігти формуванню резистентності.

Ключові слова: *Mycobacterium tuberculosis*, резистентність, молекулярно-генетичні аспекти, множинний лікарсько-стійкий туберкульоз.

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