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FEATURES OF THE STUDY OF GENETIC MUTATIONS IN M. TUBERCULOSIS FOR THE EMERGENCE OF ANTIBIOTIC RESISTANCE: A LITERATURE REVIEW

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✓ ***Resume***

Scientific studies of combinations of M. tuberculosis nucleic acid triplets have revealed that genetic mutations most often affect the locus of the gene responsible for the expression of the KatG enzyme. This also applies to other structural genes, such as inhA, kasA, ahpC, ndh, nat, and mshA. Recent molecular genetic discoveries of tuberculosis infection with MDR have revealed the relationship between antibiotic resistance of mycobacteria and mutations in the KatG genes, as well as inhA, ahpC and rpoB. MDR TB is rightfully considered the most dangerous form of TB, as strains of M. tuberculosis become resistant to the most highly effective anti-TB drugs, rifampicin and isoniazid. The KatG enzyme is responsible for the resistance of pathogenic mycobacteria to the drug isoniazid. The drug isoniazid is a destructor of mycolic acids of the shell of mycobacteria, the KatG enzyme produced by mycobacteria during the mutation of the KatG gene, due to its catalase and peroxidase activity, activates the prodrug isoniazid, which further has its destructive effect on the cell wall of M. tuberculosis. In connection with the above facts, it seems important to study the mutational variability of various strains of mycobacteria in order to create new generation drugs that will be effective in the treatment of tuberculosis infection.

Keywords. M. tuberculosis mutation triplets, isoniazid, XDR-TB, MDR-TB, KatG, Beijing strain.

ОСОБЕННОСТИ ИЗУЧЕНИЯ ГЕНЕТИЧЕСКИХ МУТАЦИЙ *M. TUBERCULOSIS* НА ПРЕДМЕТ ВОЗНИКНОВЕНИЯ АНТИБИОТИКОРЕЗИСТЕНТНОСТИ

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✓ ***Резюме***

Научные исследования комбинаций триплетов нуклеиновых кислот M. tuberculosis выявили, что генетические мутации чаще всего затрагивают локус гена ответственного за экспрессию фермента KatG. Также это касается и других структурных генов, как inhA, kasA, ahpC, ndh, nat и mshA. Последние молекулярно-генетические открытия туберкулезной инфекции с МЛУ выявили взаимосвязь между антибиотикорезистентностью микобактерий и мутациями в генах KatG, а также inhA, ahpC и rpoB. Туберкулез с МЛУ по праву считается наиболее опасной формой туберкулеза, так как штаммы M. tuberculosis становятся устойчивыми к наиболее высокоэффективным противотуберкулезным препаратам, рифампицину и изониазиду. Фермент KatG является причиной устойчивости патогенных микобактерий к лекарству изониазиду. Препарат изониазид является деструктором миколовых кислот оболочки

микробактерий, фермент KatG вырабатываемый микобактериями в ходе мутации гена KatG благодаря своей каталазной и пероксидазной активности активирует пролекарство изониазид, которое в дальнейшем оказывает свое разрушающее действие на клеточную стенку M. tuberculosis. В связи с вышеизложенными фактами, представляется важным изучение мутационной изменчивости различных штаммов микобактерий, для создания препаратов нового поколения, которые будут эффективны в лечение туберкулезной инфекции.

Ключевые слова. Триплеты мутации M. tuberculosis, изониазид, ШЛУ, МЛУ, KatG, штамм Beijing.

ANTIBIOTIKLARGA QARSHILIK PAYDO BO'LISHI UCHUN *M. TUBERCULOSIS*NI GENETIK MUTATSIYALARNI O'RGANISH XUSUSIYATLARI: ADABIYOT SHARHI

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✓ ***Rezyume***

M. tuberculosis nuklein kislotasi tripletlari birikmalarining ilmiy tadqiqotlari shuni ko'rsatdiki, genetik mutatsiyalar ko'pincha KatG fermentini ifodalash uchun mas'ul bo'lgan gen lokusiga ta'sir qiladi. Bu inhA, kasA, ahpC, ndh, nat va mshA kabi boshqa strukturaviy genlar uchun ham amal qiladi. Ko‘DQ-TB bilan sil kasalligi infektsiyasining so'nggi molekulyar genetik kashfiyoti mikobakteriyalarning antibiotiklarga chidamliligi va KatG genlaridagi mutatsiyalar, shuningdek, inhA, ahpC va rpoB o'rtasidagi bog'liqlikni aniqladi. Ko‘DQ-TB haqli ravishda silning eng xavfli shakli hisoblanadi, chunki M. tuberculosis shtammlari eng yuqori samarali silga qarshi dorilar - rifampitsin va izoniazidga chidamli bo'lib qoladi. KatG fermenti patogen mikobakteriyalarning izoniazid preparatiga chidamliligi uchun javobgardir. Izoniazid preparati mikrobakteriyalar qobig'ining mikolik kislotalarini destruktori bo'lib, KatG genining mutatsiyasida mikobakteriyalar tomonidan ishlab chiqarilgan KatG fermenti, katalaza va peroksidaza faolligi tufayli izoniazidning oldingi preparatini faollashtiradi, bu esa keyinchalik o'zining halokatli ta'siriga ega M. tuberculosis ning hujayra devori. Yuqoridagi faktlar bilan bog'liq holda, sil infektsiyasini davolashda samarali bo'ladigan yangi avlod dori vositalarini yaratish uchun mikobakteriyalarning turli shtammlarining mutatsion o'zgaruvchanligini o'rganish muhim ko'rinadi.

Kalit so'zlar. M. tuberculosis mutatsion tripletlari, izoniazid, KeDQ-TB (keng dori qarshilik), Ko‘DQ-TB (ko‘p dori qarshilik), KatG, Beijing shtammi.

Relevance

World Health Organization statistics show that tuberculosis is the leading cause of death among human bacterial infections. Tuberculosis and HIV/AIDS remain among the top ten causes of death worldwide. One third of the world's population is infected with *Mycobacterium tuberculosis*, the main etiological agent of tuberculosis, in addition to nine other types of human pathogenic mycobacteria [16].

Pulmonary tuberculosis, the most highly contagious and common form of tuberculosis, is a life-threatening infection. In addition, the situation is exacerbated by the fact that increased susceptibility to tuberculosis among HIV-infected people is another major public health problem worldwide. Over the past decades, the incidence of multidrug-resistant tuberculosis (MDR) has increased in many regions, not only in developing but also in industrialized countries [13].

The global resurgence of tuberculosis, as well as the emergence of new strains with MDR, makes it extremely important to develop new anti-tuberculosis drugs and new protocols for the effective clinical diagnosis of patients with tuberculosis infection.

In the modern world, microorganisms, in particular mycobacteria, are becoming increasingly resistant to drugs. Antimicrobial resistance in mycobacteria is not associated with plasmids. It is spontaneous mutations in the TB genome that can alter proteins that are targeted by drugs, making

bacteria resistant to drugs. Antibiotic-resistant tuberculosis is called MDR, these mycobacteria are resistant to treatment with first-line anti-TB drugs: isoniazid and rifampicin. Single drug resistance is common, which is why treatment is usually with more than one drug. Extensively drug-resistant tuberculosis (XDR TB) is also resistant to second-line drugs. Usually, MDR-TB can be treated with long-term treatment with second-line drugs, but they are more expensive than first-line drugs and have more side effects. The mortality rate for XDR-TB with treatment is about 15%.

For more than 50 years after the advent of rifampicin, the medical pharmaceutical industry did not produce qualitatively new anti-TB drugs, except for rifabutin and rifapentine, in the US and other countries [17]. The study of mycobacteria is expensive, slow and complex, requiring modern laboratories equipped with specialized equipment, the presence of a vivarium with experimental animal models that accurately mimic human tuberculosis disease [21].

The time taken to develop any anti-tuberculosis drug is very long, given that the reproduction rate of mycobacteria is the slowest of all microorganisms. Clinical trials of the drug require a minimum of six months of therapy followed by an observation period of one year or more.

In this regard, many researchers are focusing on increasing knowledge about various mycobacterial virulence genes that will help to concentrate new drug targets for tuberculosis chemotherapy. Based on genomics and proteomics, it will be possible in the foreseeable future to develop drugs that will ensure efficient delivery of drugs to their targets in vivo [29].

Japanese investigators Izumikawa, Ono and Kono [17] reviewed the utility of liposome and polymer based technologies that enable efficient delivery of encapsulated drugs at desired doses over long periods of time with just a single injection. This significantly reduces the side effects of the drug, and also allows a high degree of accuracy to deliver the drug to the desired cells and tissues of the patient. The drug delivery system increased and prolonged the concentration of antibacterial substances in the blood and target organs and increased the duration of sustained release of the drug, respectively.

Mycolic acids are an exclusive component of the cell wall of mycobacteria, the presence of these acids in the *M. tuberculosis* complex makes them resistant to many types of drug treatment. Thus, mycolic acids protect bacteria from enzymatic degradation, dehydration, chemical and thermal effects, and reduce the effectiveness of antibiotics. But the main thing is that mycolic acids are a virulence factor of pathogenic mycobacteria. Thanks to mycolic acids, a cord factor is formed - the main factor in the pathogenicity of tuberculosis pathogens, a toxic glycolipid, which is an ester of trehalose and two residues of mycolic acid [28].

Immunoadjuvant therapy (Freund's complete adjuvant) appears to be promising in improving clinical outcomes for intractable mycobacterial infections. Immunoadjuvant agents potentiate the antimycobacterial activity of macrophages through purinergic P2 receptors [17].

Other researchers have studied the state of immunotherapy in combination with antimycobacterial drugs against the background of mycobacterial infections. The need to develop new classes of immunomodulators, other than the cytokines IL-2, IL-12, IFNγ, GM-CSF, etc., can reduce the severity of side effects of antibiotic therapy and normalize the immune system in tuberculosis pathology. The goal of immunocorrective therapy is the introduction of new drugs and drug therapy regimens for anti-tuberculosis treatment [19].

It should be emphasized that from the beginning of the 1950s, from the very moment when clinical trials of isoniazid began and in the mid-1960s, when rifampicin was invented, many strains of pathogenic mycobacteria developed resistance to them [24]. However, isoniazid, along with rifampicin, is currently a first-line drug. The mechanism of action of rifampicin is associated with the suppression of DNA-dependent RNA polymerase of microorganisms, in contrast to isoniazid, whose action is aimed at inhibiting the synthesis of mycolic acid in the cell wall of mycobacteria [29].

In the light of the above, it is important to study in detail the genetic loci of mycobacteria responsible for the development of antibiotic resistance to first-line drugs, given that these drugs are included in the list of vital and essential drugs. The study of the functional genomics of pathogenic mycobacteria will help solve a number of problems associated with tuberculosis, ranging from preventive measures to create effective vaccines to the treatment of intractable patients with tuberculosis infection.

Scientific publications of the last decades confirm that the isoniazid molecule is activated inside the mycobacterium cell by the action of the KatG enzyme. Isoniazid is a prodrug requiring oxidative activation by the mycobacterial catalase-peroxidase enzyme katG. The most common causes of resistance to isoniazid are point mutations or deletion of the katG gene, which encodes this enzyme [24].

Isonicotinic acid (an isoniazid derivative) undergoes a number of metabolic processes in the body, forming adducts with the NAD+ coenzyme molecule; it acts as an inhibitor of the enzyme involved in the biosynthesis of nucleic acids, as well as mycolic acids, which are components of the cell wall of *Mycobacterium tuberculosis* [29].

There are opinions of various scientific studies about katG, so when studying resistance to isoniazid, it was shown that mutations at the katG level lead to a high level of resistance, and inhA and ahpC to a low level [30]. The isoniazid molecule is activated inside the microbial cell by the action of the enzyme catalase-peroxidase (the katG gene).

Resistance to isoniazid is encoded by several genes: katG controls cellular catalase-peroxidase activity; inhA, control of mycolic acid synthesis; kasA, control of protein interactions. Rifampicin resistance is associated with a single rpoB gene that controls the process of transcription (RNA synthesis). Alterations in the KatG gene encoding the bacterial enzyme catalase peroxidase lead to a lack of activation and a decrease in the effectiveness of isoniazid [4].

Mutations in the katG gene result in a 50% decrease in enzyme activity, being the most common cause of antibiotic resistance in mycobacteria. The conducted genetic studies fully explain the relationship between the catalase activity of mycobacteria and their resistance to isoniazid [9].

Other researchers studying mutations in the katG gene in 46 museum isoniazid-resistant strains of *Mycobacterium tuberculosis* found that the most common mutation was codon 315, which was found in 74% of MDR strains of *Mycobacterium tuberculosis*. The researchers concluded that the presence of mutations in this codon could be a predictor of isoniazid resistance. The authors indicate that among the 16 mutations found at the level of the katG nucleotide sequence, 87.5% led to a change in the amino acids in the KatG polypeptide chain [20].

In addition, most other scientific publications report mutations in codon 315 of the katG gene. About 95% of all katG 315 mutations are cases of amino acid substitution, serine for threonine [26].

Mutations in katG are associated with a wide range of moderate to high levels of isoniazid resistance, above the commonly tested concentrations of 0.2 and 1 mg/L in solid, 0.1 and 0.4 mg/L in liquid medium. In terms of molecular mechanisms, many authors argue that, in addition to katG mutations, isoniazid resistance results from mutations in the inhA promoter region. This phenomenon leads to overexpression of the target of isoniazid (InhA), which requires higher doses of the drug to achieve complete inhibition. The results of most studies show that mutations in the DNA nucleotide sequence are recognized by RNA polymerase, otherwise the inhA promoter tends to lead to a low level of phenotypic resistance, and also confer resistance to the tuberculostatic synthetic drugs ethionamide and prothionamide [13, 29].

Comparative analysis of complete genomic sequences revealed differences between *M. tuberculosis* strains at the level of single nucleotides, the so-called Single-Nucleotide Polymorphism-SNP and longer nucleic acid fragments, Large sequence polymorphisms (LSP). Genetic markers SNP and LSP can be used as an analysis for family-specific typing and the study of mutations leading to the formation of drug resistance in mycobacteria [14].

It has been established that the clinical manifestations of tuberculosis largely depend on the genotype of mycobacteria, a striking example today is the genetic family (genotype) of mycobacteria Beijing. The strains of the Beijing genotype were first detected in patients with tuberculosis infection in the suburbs of Beijing, hence the name of the strain. Unfortunately, today the Beijing strain is a ubiquitous genotype of *M. tuberculosis*, which causes great difficulties in the treatment of infection, since the clinical manifestations of tuberculosis caused by this genotype are extremely unfavorable [25].

The history of the discovery of representatives of the Beijing family, originally known as the W-strain, begins in the 1990s. The Beijing genetic lineage is currently attracting the most attention from researchers around the world. The Beijing strain has a unique genotype, and therefore, in the process of evolution, it has acquired drug resistance. A characteristic feature of the Beijing genetic family is its ubiquitous prevalence, along with high virulence. The highest frequency of occurrence of strains of *M. tuberculosis* variant Beijing was recorded in the countries of Southeast Asia - 43.1% (China, Indonesia, Japan, Vietnam), the lowest - in South America - 0.65% (Brazil, Argentina). Europe is characterized by a low prevalence of the Beijing genotype - 7.1%. According to this indicator, Russia ranks first among European countries [21].

In the structure of the population of tuberculosis pathogens in the Russian Federation, the proportion of Beijing strains, according to various sources, ranges from 50 to 80%. On the territory of St. Petersburg, 81.2% of the studied strains belong to the Beijing genetic family [3]. In addition to the pronounced drug resistance, the strain has properties that have allowed it to spread throughout the world. These properties are: the ability to "escape" BCG vaccination; relatively quickly acquire resistance to anti-tuberculosis drugs [8].

According to the SITVIT WEB database, the world's largest database of *Mycobacterium tuberculosis* genotyping markers, strains of the Beijing genotype are characterized by the SIT 1 (Spoligotype International Type) spoligotype. This spoligotype is determined by the presence of 9 out of 43 spacers in the DR locus, and noncoding DNA regions from 35 to 43 [16, 22].

Representatives of this genotype are divided into atypical and typical strains, while the deletion of RD150 and/or RD142, as well as the presence of a repeating element IS6110 in the NTF region, are considered specific to modern strains [30].

The increased interest in the Beijing genotype is due to the fact that it has the ability to spread rapidly, has a rapidly progressive course, and causes disseminated forms of tuberculosis. Also, the Beijing strain leads to active bacterial excretion in patients along with a difficult cure, as it has the property of high mutation, it is among the strains of the Beijing genotype that extensive drug resistance and MDR are most common.

Russian researchers in their publications report that in South America, Bulgaria and Romania, non-indigenous isolates of the Beijing BL7 (MIT 642) and S (MIT 256) genotype were found. These isolates retained their epidemic significance in the vast territory of North Asia and adjacent regions of the Eurasian continent, and also increased their role in the formation of high levels of MDR prevalence [6].

On the territory of the Russian Federation, a clinical and epidemiological analysis of 85 cases of pulmonary tuberculosis with XDR *Mycobacterium tuberculosis* was carried out. Their strains were found to belong to 7 spoligotypes of genetic families: Beijing (81.2%), LAM (14.1%) and Ural (4.7%). Among the examined patients infected with strains of *Mycobacterium tuberculosis* Beijing, men with a tendency to bad habits predominated. The places of infection were not only residential, but also penitentiary foci. This group was characterized by a variety of clinical forms of lung damage with a predominance of fibrous-cavernous tuberculosis and a significant proportion of patients with treatment delays [3].

The distribution of the Beijing genotype in Europe is characterized by a significant diversity in the number of detected strains of this genetic family. For the Russian Federation, Ukraine, Kazakhstan, Uzbekistan, and other countries of Central Asia, the Baltic states, and Transcaucasia, the share of the Beijing genotype was approximately 50%. At the same time, in Poland, Finland, Bulgaria, Turkey, its share did not exceed 10%. The uneven distribution of the Beijing genotype in a number of European countries is a manifestation of factors associated only with certain countries [10].

Among the strains circulating in Belarus, the most frequent mutations were observed in the katG gene, in codon 315. At the same time, in isolates of *Mycobacterium tuberculosis* isolated from patients, mutations leading to MDR were also more often detected in the 315th codon of the katG gene, less often in the 15th and 8th codons of the inhA gene [12].

Conducted molecular genetic studies by VNTR-typing of *Mycobacterium tuberculosis* isolates isolated from 46 patients with pulmonary tuberculosis living in the city of Astana (Kazakhstan) showed a predominance of up to 70% of the isolated isolates of the Beijing genotype. During the study, 23 different genetic profiles were identified, with the identification of mutations in the 315th codon of the KatG gene and in the 531st codon of the rpoB gene with amplification of the fragment containing the 315th codon of the katG gene, and the fragment containing the 531st codon of the rpoB gene. The sample contained both resistant and anti-tuberculosis drug-susceptible isolates of the Beijing family, and no association of this family with drug resistance was shown, which indicates the individual characteristics of these isolates circulating in a particular area [5].

The results of specialists from Kazakhstan showed that among the isolates, the mutation in codon 531 of the Ser→Leu rpoB gene (87.4%) and in codon 315 of the Ser→Thr katG gene (97%) prevailed, causing resistance to rifampicin and isoniazid. More than 80% of *Mycobacterium tuberculosis* strains with MDR were assigned to the most virulent and widespread Beijing genotype in the world [2].

Scientists from Eastern Siberia conducted a bioinformatic search, developed the design of primers and TaqMan probes to detect the DNA of *Mycobacterium tuberculosis* subtypes CC1 and CC2-W148 of the Beijing genotype, as well as the Ural genotype in various isolates by real-time PCR. The results obtained indicated the possibility of using genotyping of *Mycobacterium tuberculosis* and the patient for early

prediction of the development of MDR/XDR and other complications at the stages of the initial examination of newly diagnosed patients [11].

At present, the development of methods of whole genome sequencing and comparative genomics contributes to the intensification of efforts in solving the formulated problems. These methods make it possible to evaluate both microevolutionary changes in the genome, leading, for example, to the development of drug resistance, and to study the macroevolution of *Mycobacterium tuberculosis*, which is very important in connection with the emergence of strains that characterize population success [27].

Among 140 Beijing strains obtained from tuberculosis patients in the Irkutsk region, a higher level of primary drug resistance was noted than among representatives of other genetic families [7].

The prevalence of tuberculosis with XDR *Mycobacterium tuberculosis* in the Omsk region of the Russian Federation was 13.6 per 100,000 population. Among XDR patients, young people aged 25–44 years (63.2%), men (80.9%), persons without official employment (75.6%), with a disease duration of more than 3 years (57.0%)), suffering from pulmonary tuberculosis (69.2%), co-infected with HIV (31.8%). In 10.1% of XDR patients, simultaneous resistance to seven anti-tuberculosis drugs of the main and reserve series was revealed. It is concluded that it is necessary to optimize approaches to the organization of additional measures for the prevention of drug-resistant tuberculosis. The tuberculosis prevalence rate was 269.2 per 100,000 population. For comparison, in the Central African Republic, 540 cases of tuberculosis were detected per 100 thousand people, data for 2018. The population of *Mycobacterium tuberculosis* with MDR is heterogeneous and is represented by strains of different genetic families - Beijing, LAM, S, Haarlem, Uganda [8].

Researchers from the Russian Federation determined the incidence of isoniazid-resistant tuberculosis (IR-TB) in the modern population, which characterized the phenotypic sensitivity and genetic determinants of resistance to isoniazid in representatives of this group of *Mycobacterium tuberculosis* on representative material. The frequency of IR-TB was 12% of all detected cases of tuberculosis. Isoniazid-resistant strains of the *Mycobacterium tuberculosis* complex were both mono-resistant to isoniazid (45%) and multi-resistant (resistant to 2-6 anti-TB drugs), and resistance to isoniazid was due to mutations in the katG gene leading to a high level of resistance. Based on the analysis of scientific observations, the importance of developing new simple molecular tests to determine resistance to both rifampicin and isoniazid is emphasized [1].

In studies by West Siberian scientists of the Russian Federation, which included a sample of 82 patients over 18 years old with newly diagnosed pulmonary tuberculosis in the decay phase, the observations showed the following. In the group of patients with an effective course of chemotherapy, carriers of the G allele and T/G genotype at the rs6707530 locus of the FN1 gene were more common. At the same time, the T/T genotype and the T allele dominated among patients with persistent lung tissue destruction after the intensive phase of chemotherapy [9].

In 1998, at the initiative of WHO, the DOTS program was implemented in the Central Asian countries, based on the strategy of treatment of tuberculosis under direct observation. Abbreviation DOTS from English (Directly Observed Treatment Short-course) meant strictly controlled treatment with a short course of chemotherapy. The DOTS strategy covered three regions south of the Aral Sea, was implemented by the humanitarian medical aid organization Médecins Sans Frontières, and was completed in 2003. In the Republic of Karakalpakstan, the Khorezm region of Uzbekistan, and the Dashoguz district in Turkmenistan, more than 8,000 patients were registered and treated in accordance with DOTS by 2002 [23].

Results of drug resistance to 5 first-line drugs showed that in Karakalpakstan, strains of 52% of new patients and 20% of retreatment patients were completely sensitive to all 5 first-line drugs. In Dashoguz, strains from 70% of new patients and 38% of retreatment patients were susceptible to 5 first-line drugs. The most noticeable monoresistance was noted to streptomycin in both regions (in 11% of patients from Karakalpakstan and in 14% of patients from Dashoguz). The highest level of drug resistance was found to streptomycin - 58% of all patients in Karakalpakstan and 37% of patients in Dashoguz. Greater resistance to isoniazid was also observed: 53% of patients in Karakalpakstan and 31% in Dashoguz were infected with resistant strains. Rifampicin resistance has been closely associated with MDR. These studies showed high rates of MDR in the regions of two Central Asian countries [18].

Regional studies in the Republic of Uzbekistan showed that the prevalence of MDR tuberculosis among newly diagnosed patients was 23%, and among relapses 62%. The results of the DOTS strategy have shown the failure of first-line therapy among some patients. In 2002, studies were carried out on the drug

resistance of regional strains. A high level of MDR TB was found in Karakalpakstan, where 13% of patients who had never been treated for TB were infected with the MDR strain [15].

Over the past two decades, Médecins Sans Frontières (MSF) has supported the international TB program, including in Uzbekistan, to improve surveillance, prevention and care of TB patients. The care model focuses on accelerated TB diagnosis and detection of *M. tuberculosis* drug resistance, enabling effective treatment regimens. Long-term investment in laboratory services has enabled the creation of a regional laboratory that performs phenotypic and genotypic diagnostic tests [27].

Conclusion

Thus, we can formulate the following conclusions. Various genetic mutations of strains of mycobacteria with MDR and XDR have been studied. The relationship between antibiotic resistance of mycobacteria and their genetic changes has also been established. In light of this, the problem of the immune status of patients with tuberculosis infection before and after treatment remains poorly understood. Most anti-tuberculosis drugs are unable to have a bactericidal effect on mycobacteria, limiting themselves to bacteriostatic action. At the same time, the high toxicity and especially the hepatotropic effect of anti-tuberculosis drugs undoubtedly affect the functioning of the human immune system. Chemotherapy is the main way to treat tuberculosis patients, and this treatment can be long, at least 6-8 months, while the success of tuberculosis treatment also depends on the state of immunity. A comprehensive study of the mechanisms of genetic mutations in mycobacteria and humoral immunity in tuberculosis with MDR and XDR will undoubtedly increase the level of diagnosis of tuberculosis infection and help in the treatment of this disease. And this is an urgent task today in the light of the fact that no country can ignore the problem of tuberculosis, a socially significant disease, since it threatens the health of the population, the state of the economy and the further development of society.

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