ABSTRACT

Gram-positive bacteria of *Mycobacterium tuberculosis* complex (MTBC) are causative agents of tuberculosis disease. According to the report of the World Health Organization, tuberculosis is one of the leading causes of mortality worldwide. Moreover, epidemiological data shows that due to the COVID-19 pandemic tuberculosis mortality has risen in comparison with previous years. Drug resistance is another threatening issue when the resistance to antitubercular (anti-TB) drugs makes therapy less effective. Furthermore, drug resistance is often burdened with compensatory mechanisms that overcome fitness defects related to drug-resistant mutations. This review discusses the drug resistance and compensatory mutations in *Mycobacterium tuberculosis* and the current situation with anti-TB drug resistance in the Republic of Kazakhstan.

**Keywords:** *Mycobacterium tuberculosis*, drug-resistance, rifampicin, isoniazid.

INTRODUCTION

Tuberculosis (TB) caused by the *Mycobacterium tuberculosis* complex (MTBC) is a public health concern globally. The most clinically relevant species of MTBC is *Mycobacterium tuberculosis* (*Mtb*). According to the recent WHO report, approximately 6.4 million newly diagnosed cases of TB and 1.6 million deaths were registered in 2021 versus 5.8 million cases of TB and 1.5 million deaths in 2020 [1]. The TB incidence in 2021 rose by 4.5% in comparison with 2020, from 10.1 million to 10.6 million, to be precise. These numbers increase annually [2], [3]. As a consequence of the COVID-19 pandemic, the number of cases could continue to raise in 2023 [1]. Moreover, about 1.5-2 billion individuals are latently infected (LTBI) globally. Depending on the latest data, 5-10% of LTBI cases could turn into the active form of tuberculosis. Therefore, LTBI is a limiting point in managing and controlling the spread of Mtb. Given the risks involved, the epidemiology of tuberculosis plays a significant role in the prediction of TB transmission.

The development of resistance against anti-tuberculosis drugs is another major issue. The burden of drug-resistant TB (DR-TB) is also estimated to have increased between 2020 and 2021, with 450,000 new cases of rifampicin-resistant TB (RR-TB) in 2021 [4]. The anti-TB regimen includes first-line antibiotics such as isoniazid (INH), rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA), and streptomycin (SM). Antibiotic-resistant Mtb strains are classified as multidrug-resistant and extensively drug-resistant strains [5]. The improper treatment strategy followed by the overuse of first-line antibiotic therapy leads to the development of Mtb drug resistance. The first-line antibiotics mainly rely on two drugs, namely, rifampicin and isoniazid. The development of resistance to both of these drugs refers to the multidrug-resistant Mtb strains. While extensively-drug resistance is associated with additional resistance to second-line antibiotics such as kanamycin, capreomycin, amikacin (Table 1), and fluoroquinolones [6].

The Mtb resistance against the drugs could be developed by the interaction of several factors including biological, microbiological, and clinical factors. In summary, the main causes of MDR-TB are related to the health care provider, inadequate supply or quality of the drugs, or inadequate intake...
of drugs [7]. The global distribution of tuberculosis is classified into six major categories severe endemic, highly endemic, endemic, upper-moderate, lower moderate, and low [8]. The classification of countries according to the epidemiological situation as well as the incidence of TB cases based on the recent WHO report is shown on the map (Figure 1). According to the figure, Kazakhstan fits the upper-moderate group with “50-99 new and relapse cases” per 100 thousand population per year.

According to the latest TB report by WHO, Kazakhstan is listed among the 30 high multi-drug resistant (MDR)/Rifampicin-resistant (RR)-TB countries [1]. The total incidence rate of MDR/RR-TB is 22 cases per 100,000. During the last 10 years, the TB incidence and mortality rate in Kazakhstan have decreased, but the MDR-TB incidence rate is still high. Kazakhstan has one of the highest numbers of MDR-TB patients in the world. 26% of newly diagnosed TB patients and 44% of retreatment cases have MDR-TB. On average, more than 30% of all cases refer to drug-resistant strains, predominantly found to be resistant to isoniazid [9]. The main circulating clones were characterized as the L2-Beijing Central Asian/Russian 94-32 sublineage, mainly associated with an MDR genotype.

Drug-resistant strains were initially thought to reduce bacterial fitness. In contrast, some MDR/XDR-TB strains are highly transmitted and cause large outbreaks [10], [11]. This phenomenon was discovered by Comas et al. as a compensatory mechanism in rifampicin-resistant MTBC strains [10]. It has been suggested that compensatory mutations are associated with structural changes in RNA polymerase rpoC, rpoB, and rpoC, which increases the transcriptional activity, following the growth of Mtb. Those mutations are important for the identification of tuberculosis transmission. The classification of drug-resistance and compensatory mutations in Mtb, and the current state of Mtb drug-resistance in Kazakhstan will be discussed in this review article.

MULTI-DRUG RESISTANT TUBERCULOSIS

Multi-drug resistant tuberculosis appears as the result of resistance against the two first-line drugs rifampicin and isoniazid [6]. Isoniazid is the basic drug in anti-TB therapy. The chemical structure of the isoniazid is a pyridine ring with a carboxylic acid group. Isoniazid drug resistance is characterized by mutations in several genes as shown in Table 1. The mechanism of action of isoniazid requires the activation of the drug molecule by the peroxidase enzyme which should be encoded by the katG gene [12]. Predominant mutations occur in the S315T position of the katG gene in multidrug-resistant TB [13]. Activated isoniazid inhibits mycolic acid synthesis. The inhibition of mycolic acid synthesis is carried out through the inhibition of enoyl-ACP reductase which is encoded by inhA [12]. This way, resistance occurs, and activation of the pro-drugs and restriction of mycolic acid synthesis by the mutations in katG and inhA genes [14]. The mutations in the inhA gene cause drug resistance both for isoniazid and for second-line drugs. The researchers reported resistance to ethionamide which is a chemical analog of isoniazid [15]. Harbor et al. reported about half of all isoniazid-resistant strains refer to the mutations found at position 315 in katG. The S315T mutation was found in 46% of all isoniazid-resistant isolates. The second most common mutation at the katG gene is position S315N, which encounters in about 4% out of all isoniazid-resistant strains.

Rifampicin structurally belongs to the ansamycin family of bacterial secondary metabolites. It is another first-line drug recommended by the WHO for tuberculosis treatment. The mechanism of rifampicin is based on the targeting of bacterial RNA polymerase. Due to the interaction, it inhibits its RNA polymerase by blocking the initiation of RNA synthesis. Rifampicin-resistant strains demonstrate the mutation in the rpoB gene. This gene codes β units of the RNA polymerase [16], [17]. Thus, the mutations result in the development of resistance.

Ethambutol is another first-line anti-TB drug. The ethambutol efficiency is based on the inhibition of the polymerization process of arabinogalactan. The embB gene encoded the arabinosyltransferase enzyme. The embB gene is formed in the operon system of MTBC with the others, such as embC and embA [18].

Pyrazinamide is another drug against TB which has efficiency in the low pH range. Mutations in the pncA gene are the predominant cause of drug resistance. The pncA gene coded the transformation of pyrazinamide prodrugs into the active form also known as pyrazinoic acid via the pyrazinamidase [19].

EXTENSIVELY-DRUG RESISTANT TUBERCULOSIS

Extensively drug-resistant tuberculosis (XDR TB) is characterized by resistance to the first-line drugs along with one of the second-line medicines, such as fluoroquinolone and any of the aminoglycoside and cyclic peptide antibiotics (kanamycin, amikacin, capreomycin, etc.). Such resistance leads to treatment difficulties as a consequence of insufficient therapy in the case of acquired resistance.

Fluoroquinolones

Fluoroquinolones were discovered in the middle of the 60s, now they have been updated and introduced in new lines of drugs, and have been used in anti-TB therapy. The mechanism of the treatment is based on the targeting of type II DNA-topoisomerase also known as the DNA-gyrase. DNA-gyrase by its chemical compounds is a tetramer that contains two units, each of them encoded via gyrA and gyrB genes, respectively as shown in Table 1. Isolates that have fluoroquinolone resistance have been mutated in the gyrA region [20], [21]. Those mutations present as the changes of Ala and Asp in 90 and 94 positions, accordingly [22]. Besides that, other mutations were studied, and several researchers concluded that changes in codon 95 (S or T) do not play the role in the formation of Mtb resistance [23].

Aminoglycoside and cyclic peptide antibiotics

Aminoglycosides refer to kanamycin and amikacin however the other two antibiotics, viomycin and capreomycin, belong to the cyclic peptide antibiotics. Although they belong to the various categories of antibiotics, their mechanism of action is similar and interferes with the translation of protein. The mutations occur in the gene rrs that are characterized by the mutation at the A140G position [24]. Recent research has studied commonly spread variations in the strains
having resistance against kanamycin and amikacin [25]. Another mutation in the \textit{tlyA} gene leads to the loss of methylation, due to the gene-encoded RNA-methyltransferases [26]. Another mutation has been found in the promoter region of the \textit{eis} gene [27]. These studies described a low level of susceptibility against kanamycin, but not amikacin.

**COMPENSATORY MUTATIONS**

Compensatory mutations mutation arises after the acquisition of resistance mutation and alleviates the fitness cost associated with the acquisition of the resistance-associated mutation. The compensatory mutations were determined as a defect that relates to resistance against isoniazid and aminoglycosides. The mechanism of rifampicin action is based on the binding of RNA-polymerase that is encoded by \textit{rpoB} and that results in inhibition of the transcription process. The rifampicin-resistant clinical isolates of Mtb consist of mutations in an 81bp determinant region of \textit{rpoB} [28].

Casali \textit{et al.} conducted a study where 58 non-synonymous SNPs were identified, including 14 mutations in \textit{rpoA}, while over 30% of the mutations refer to the \textit{rpoC} [11]. In addition, Casali \textit{et al.} studied polymorphic regions of alkyl hydroperoxidase (\textit{ahpC}) that activated as a compensated reaction to lack of peroxidase activity in \textit{katG} of rifampicin-resistant TB strains. The studied isolates had \textit{katG} mutations S315T and S315G [11]. The distribution of these mutations was similar, while another isolate had a wild type.

They identified 11 non-synonymous SNPs in \textit{rpoA} gene including S450L mutation in \textit{rpoB} gene. Otherwise, mutations in T187P/A were acquired at a higher frequency compared with others. Non-synonymous mutations in \textit{rpoC} were often acquired in the samples containing \textit{rpoB} mutations encoded S450L in contrast to wild-type or other nsSNPs as shown in Table 2 [11].

Note: WT – wild-type; nsSNP – non-synonymous single nucleotide polymorphisms; RRDR – rifampicin resistance determining region.

Merker \textit{et al.}, 2018 examined the evolutionary history, resistance, and transmission of \textit{M. tuberculosis} isolates on the territory of Karakalpakstan, Uzbekistan. The cluster named a Central Asian Outbreak (CAO) accounted for about three-quarters of all MDR-TB isolates 2005-2006 [29]. The existence of mutations that should compensate for fitness deficits was related to the transfer of drug-resistant TB. The average number of drug-resistance mutations was higher among the isolates with compensatory mutations (Figure 2A). The isolates with compensatory mutations demonstrated a higher ratio of transmission in comparing the isolates with no com-
pensatory mutations (Figure 2B). The presence of compensatory mutations is related to the size of the cluster and does not depend on the gathering of resistance in Karakalpakstan isolates in the years around the 1980s/1990s (Figure 2C).

Several studies show that the major feature of the increasing tuberculosis incidence across the globe is associated with the putative fitness of the *M. tuberculosis* strains. The majority of investigations examined obtaining resistance against antibiotics by bacteria affiliated with a fitness cost [10], [30], [31]. The mutations may lead to structural, and functional changes in bacterial proteins. Resistance may evolve rapidly when mutations occur in genes that control transcription and protein synthesis [32], [33].

Otherwise, exists a hypothesis that claimed the fitness cost of bacterial strains leading to resistance decreased via compensatory mutation progression. Despite the limited studies concerning the mechanism of compensatory mutations for MTBC, interesting results for *E. coli* were published by Reynolds [34]. The mutations in *E. coli* and *Salmonella* spp. affected translation process through the action of adjustment for fitness cost. The general schemes of the drug resistance progression and acquisition of the compensatory mutations under the factors in *M. tuberculosis* were demonstrated by Nguyen *et al.* in Figure 3 [35].

Comas *et al.* investigated the compensatory acquisition of compensatory mutations by various types of strains including strains isolated from patients diagnosed with TB, as well as laboratory-grown strains with mutations acquired after rifampicin treatment. It turned out that the acquisition of mutations in several genes conferring resistance to rifampicin was conducive to strains with a considerable degree of fitness. Subsequently, a summary of results from laboratory and clinical isolates has described more than 50 mutations in various genes and intergenic regions [10]. A similar classification of putative mutations that might occur in Rifampicin resistant *M. tuberculosis* shown in the paper published by Emane *et al.* [36]. They illustrated the structure of RNA-Pol including motifs with subunits coding by *rpoB* and *rpoC* as shown in Figure 4. After the joining of the β-units, there has occurred limitation of RNA elongation. The authors asserted the prevalence of the compensatory mutations in α- and β-units.

<table>
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<tr>
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<th>rpoC</th>
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<tr>
<td>G332S/R/C</td>
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<tr>
<td>N416T/S</td>
<td>2,1</td>
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<tr>
<td>V431M</td>
<td>4,1</td>
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<tr>
<td>G433S/C</td>
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<td>P434R/Q</td>
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<tr>
<td>K445R</td>
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<tr>
<td>L449V</td>
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</tr>
<tr>
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<td>P601L</td>
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<tr>
<td>S1124A</td>
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Figure 2 – The compensatory mutation stages [29]. The ratio of isolates with (orange) and without (blue) compensatory mutations (A). The transmission ratio of isolates relates to acquiring of resistance against anti-TB drugs (B). The influences of resistance and compensatory mutations to the transmission of the Beijing-CAO clade in Karakalpakstan, Uzbekistan (C).

Figure 3 – Origin and evolution of drug resistance in *Mycobacterium tuberculosis* [35]. The figure represents the evolution of bacteria from wild-type to drug-resistant mutants with fitness advantages and illustrates several different mechanisms of fitness increase. (a) Wild types can acquire different drug resistance-associated mutations in the same gene with high or low biological costs. The bacteria with low biological cost mutations will be selected under drug pressure by clonal interference and will propagate. (b) Under drug pressure, positive epistasis may favor the acquisition of compensatory mutations to alleviate the fitness cost exerted by certain drug resistance-associated mutations. (c) Driven by positive epistasis, drug-resistant mutants are likely to be more prone to accumulate drug-resistance-associated mutations at higher frequencies.
coding by rpoA and rpoC, correspondingly. The researchers reported that these genes encode subunits of the RNA polymerase. Consequently, according to the study non-synonymous differences in rpoA and rpoC were detected after rifampicin treatment.

In addition, the paper published by Walker et al. claimed that through the 40 thousand specimens analyzed via whole genome sequencing more than 13 thousand unusual mutations acquired against drugs were identified [37]. Majority of mutations were related to first-line antibiotics. The prevalence of resistance to first-line drugs ranged from 14% (pyrazinamide) to 35% (isoniazid), respectively. For rifampicin, 92% of resistant isolates contained one of the 23 data-derived resistance mutations. Otherwise, the number of isoniazid-resistant samples was about 12 thousand, while almost 11 thousand had one of 5 data-derived mutations [37].

Nonetheless, the previous studies showed that M. tuberculosis strains with acquired resistance to rifampicin contain multiple mutations in rpoB. It might be achieved through compensatory mutations as a consequence of specific alterations in the gene to overcome the fitness cost [11], [38].

Nguyen et al. noticed that compensatory mutations for the most part might be found in the dominant clones with drug resistance against several anti-TB drugs in a number of countries with high-level of TB-incidence [35], [39]. The researchers illustrated the interdependence of mutation in the rpoC with S531L mutation in rpoB, thus they observed a correlation between compensatory mutations and mutations related to drug resistance. This mechanism might be responsible for the high-level distribution of S531L mutation in the rpoB amid the rifampicin-resistant clinical strain of M. tuberculosis and characterize it with the low cost of fitness. Mostly observed compensatory mutations related to S531L mutation in rpoB were identified through the L2/Beijing clusters of M. Tuberculosis [35].

MULTI-DRUG RESISTANT TUBERCULOSIS IN KAZAKHSTAN

According to the latest WHO report on TB, Kazakhstan is listed among the 30 high MDR-cases countries [1]. TB incidence was 13.000 cases and the percentage of mortality in 2021 for Kazakhstan was approximately 4.7% [1]. The differences in incidence rates between 2015 and 2020 are 15%. In comparison with the previous report, the incidence rate increased to 1.4% in Kazakhstan.

Kazakhstan has established an efficient surveillance sys-
tem to monitor drug resistance in the past years, with initially 18 tuberculosis dispensaries (14 regional, 2 urban and 2 zonal), recently increased to 27. Phenotypic Drug susceptibility Testing (DST) is currently performed by 22 laboratories and 12 laboratories are reported to be able to run Line Probe Assays (LIPAs, Hain Diagnostics, Germany). Among the 30 high MDR-TB burden countries, 14 had MDR/RR-TB cohorts in 2014 with more than 1000 cases [1]. Among these, Kazakhstan, (together with Myanmar and Viet Nam) reported treatment success of more than 75%. In this context, high-throughput predictive genotyping of drug susceptibility testing could be a faster alternative to phenotypic DST or LIPAs, with high reliability if done in a limited number of certified reference laboratories.

Klotoe et al., 2019 performed an in-depth genetic diversity and population structure characterization of MTBC genetic diversity in Kazakhstan [40]. This was national recruitment study performed in Kazakhstan, and characterized by two high-throughput genotyping methods. A convenience sample of 700 MTBC DNA culture extracts from 630 tuberculosis patients recruited from 12 regions in Kazakhstan, between 2010 and 2015, was independently studied by two high-throughput hybridization-based methods, TB-SPRINT (59-Plex, n = 700), TB-SNPID (50-Plex, n = 543). DNA from 391 clinical isolates was successfully typed by two methods. To resolve the population structure of drug-resistant clades in more detail two complementary assays were run on the L2 isolates: an IS6110-NTF insertion site typing assay and a sigE SNP polymorphism. Strains belonged to L2/Beijing and L4/Euro-American sublineages; L2/Beijing prevalence totaled almost 80%. Approximately 50% of all samples were resistant to RIF and INH. Subtyping showed that all L2/Beijing were “modern” Beijing; most of these belonged to the previously described 94–32 sublineage (Central Asian/Russian); at least two populations of the Central Asian/Russian sublineages are circulating in Kazakhstan, with different evolutionary dynamics.

This study was one of the first to describe exhaustively the genetic diversity and population structure of Mtb genotypes circulating in Kazakhstan with sample size over 500 Mtb isolates. This study was compared to previous local studies, such as Skiba et al., 2015 which genotyped 159 Mtb isolates [41]. The results suggested a region-specific spread of a very limited number of Lineage 2 (L2) clonal complexes in Kazakhstan, many of them being strongly associated with an MDR phenotype. Other minor, yet historically important genotypes, such as the L4.2 “Ural” lineage, were also shown to be present in Kazakhstan.

Akisheva et al. studied the isolates restricted by the Astana region, the number of tuberculosis cases 1090, and the classical method of mycobacteria’s growth has confirmed 389 positive Mtb cultures. More than half out of all specimens refer to the new incidents while 2/5 of them were relapse cases. The total number of registered patients with drug resistance was 137, which is 37.5% of the total number of cases [9]. Mono-drug resistance to the isoniazid or rifampicin was also found along with multi-drug resistance. The ratio between the mono-drug resistance and MDR was 1:3. The patients with new cases of tuberculosis have been found with multi-drug resistance predominantly to the isoniazid, followed by the combination of isoniazid with rifampicin, streptomycin, and ethambutol, and pyrazinamide to a less degree. Whereas, multi-drug resistance was identified in 10% of all relapse cases [9]. Another study described eight Mtb isolates in Nur-Sultan sequenced by next-generation sequencing and phylogenetic analysis. The analysis demonstrated that drug resistance has been developed against first- and second-line antibiotics including ethambutol, amikacin, and kanamycin [42]. The sequencing confirmed that the circulating Mtb strain is a part of modern East Asian lineage also known as L2 [42], [43].

Another study by Mokrousov et al. identified 24 SNPs specific for the Central Asian/Russian Beijing 94-32 cluster. Up to the present time, Beijing is the one the most common family of Mtb in the Central Asian region, including Kazakhstan, Uzbekistan, Russia, and to a lesser extent China. The authors have described SNP that occur in the sigE gene of codon 98, suitable for the PCR analysis [43]. Thereby, such experiments allow rapid detection of the clinically significant cluster of Mtb isolates. Merker et al. analyzed the compensatory mutations amongst the Beijing family in the specimens from Eurasia as the consequences of the rapid distribution of an outbreak-related multi-drug resistant Mtb clonal complexes. As the authors noticed, Central Asian countries with prevalence of L2 lineage of Mtb show high incidence of MDR TB. Acquisition of compensatory mutations in local L2/Beijing isolates were significantly associated with an MDR genotype [40].

CONCLUSION

Tuberculosis is a public health concern globally. The percentage of susceptibility against first-line antibiotics rapidly decreases as stated by the current WHO report on TB. As detailed in this review, drug resistance evolution in M. tuberculosis is driven by various factors with different effects. The mutation frequency and type can be affected by the drug-resistant patterns and genotypes. Different mutations can cause different levels of drug resistance and different fitness cost. In this review, drug resistance, compensatory mutations and the current situation with anti-TB drug resistance in the Republic of Kazakhstan was discussed. L2/Beijing clonal complexes are shown to spread rapidly in Central Asia. It is associated with MDR TB as well as with high level of drug resistance and fitness-compensatory mutations. New approaches and new anti-TB drugs are required to fight drug-resistant tuberculosis. In this sense, the detailed knowledge of evolutionary mechanisms will help develop accurate models for better control of drug resistance.

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LITERATURE


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АННОТАЦИЯ
Возбудителем туберкулеза является грамположительные бактерии комплекса Mycobacterium tuberculosis. Согласно отчету Всемирной организации здравоохранения, туберкулез является одной из превалирующих причин смертности во всем мире. К тому же, эпидемиологические данные и статистика демонстрируют повышение смертности от туберкулеза, связанное с пандемией COVID-19. Другой актуальной проблемой является устойчивость к противотуберкулезным препаратам. Приобретение лекарственной устойчивости к противотуберкулезным препаратам снижает эффективность терапии. Помимо этого, при появлении лекарственной устойчивости МТБ возникают компенсаторные мутации, помогающие восстановлению жизнеспособности бактерий, связанной с появлением лекарственно-устойчивых мутаций. В данной статье рассматривается лекарственная-устойчивость и механизмы компенсаторных мутаций штаммов Mycobacterium tuberculosis, а также текущая ситуация с распространением M. tuberculosis в Казахстане.

Ключевые слова: Mycobacterium tuberculosis, лекарственная устойчивость, рифампицин, изониазид.