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New molecular mechanisms related to drug resistance in tuberculosis

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Abstract

Despite the global efforts tuberculosis (TB) remains as one of the most important infectious disease and with the greatest impact on global public health, this situation has been aggravated in recent decades by the growing problem of drug resistance (DR). Such is the impact of the drug resistant in tuberculosis that would threaten the Millennium Development Goals. In addition to polymorphisms in genes associated with drug resistance in tuberculosis, new mechanisms have being described in recent years. Considering the above, the aim of this mini-review is to give a brief description of the traditional mechanisms related with drug resistance and to describe two of the new mechanisms that will have an important impact in the next future; efflux pumps and DNA damage repair mechanisms.

Key word: *tuberculosis, efflux pumps, DNA reparation, drug resistance.*

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Introduction

Epidemiology of Tuberculosis

Tuberculosis (TB) is an infectious disease with worldwide epidemiological importance, and after COVID-19 is the leading cause of death from a single infectious agent. In 2018, 10 million new cases and 1.4 million deaths were globally reported. About 90% of individuals affected are adults, and impacts with more frequency males. The main comorbidity observed was HIV in 8.6% of the population, with increasing numbers of type 2 diabetes mellitus comorbidity (1).

In terms of the global distribution of TB, 86% of cases show up in three regions; South-East Asia (44%), including China and India, two of the most affected countries. Africa with 24%, and West-Pacific with 18%. The remaining numbers are distributed in the Eastern Mediterranean 8%, and Americaand Europe with 3% each one (1).

This disease is mainly caused by members of the Mycobacterium tuberculosis complex (MTBC), this is a group of acid-fast bacilli bacteria comprised by two human-adapted species (*Mycobacterium tuberculosis sensu stricto* and *M. africanum*), as well as nine animal-adapted species (2,3). It is acquired by inhalation of mycobacteria expelled into the environment by an infected person when coughing, speaking, or sneezing. Mostly TB affects the lungs (pulmonary TB), nevertheless it can develop anywhere in the body (extra-pulmonary TB) (1). Pulmonary TB is the most contagious, it is estimated that a sick person with this form of the disease, is able to infect from 3 to 10 people by year (4).

The drug resistance in tuberculosis and the global response

This disease is diagnosed by detecting the causative agent, directly (microscopy and culture) or indirectly (nucleic acid amplification or protein identification, etcetera), in fluids or tissues (5). WHO recommends the use of four drugs administered by a period of 4-6 months: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). When these drugs fails, a second set of drougs gruped from A, B and C are used according to the specific treatment (Table 1) (6).

Depending on the degree of the resistance this has been classified as: a) Mono-resistant (Mono-TB), resistant to only one drug; b) poly-resistant (Poly-TB), resistant to two or more drugs except for INH and RIF; c) Multidrug-resistant (MDR-TB), with simultaneous resistance to INH and RIF; d) Pre-extreme resistance (P-XDR-TB), is caused by M. tuberculosis that fulfil the definition of multidrug resistant and rifampicin-resistant and are also resistant to any fluoroquinolone; and e) Extreme drug resistance (XDR-TB), caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB, also resistant to any fluoroquinolone and at least one additional Group A drug (7).

According to WHO estimations, in 2018, there were

Table 1. First and second line drugs actually used against tuberculosis and their action mode

Drug	Gen involved	Representative mutations	Product generated
Isoniazid (H)	*katG*	315	Encodes catalase-peroxidase enzyme, inhibit synthesis mycolic acid
	inhA	-15, -8	Encodes enoyl ACP reductase, block production fatty acids
Rifampicin (R)	*rpoB, rpoA,rpoC*	526,531	Encodes the ß-subunit of RNA polymerase
Ethambutol (E)	*embB,embA, embC*	306	Encodes arabinosyltransferase involved in mycobacterial cell wall biosynthesis
Pyrazinamide (Z)	*pncA*	-11, 96, 120	Encodes pyrazinaminidase produces pyracinoic acid, decrease pH
Group A			
Bedaquiline (Bdq)	*atpE*	63	Encodes for an ATP synthase and modify the ATP synthesis
Moxifloxacin (Mxf)	*gyrB*	512	Encodes the DNA-gyrase B subunit
Levofloxacin (Lfx)	*gyrA*	80, 95	Encodes the DNA-gyrase A subunit
Linezolid (Lz)	*rrl*	20,612,576	Encodes ribosomal RNA 23S
Group B			
Clofazimine	*mec+-cysO-cysM*	-	Conform the cysteine biosynthesis gene cluster
Cycloserin (Cs)	*alr*	10	Encodes for an enzyme related to riboflavin biosynthesis
Terizidone (Trd)	-	-	-
Group C			
Streptomycin (S)	*rpsL*	43	Encodes RNAr 12S, related with inhibition of protein synthesis
	gidB	527	N/D
	rrS	906	Encodes RNAr 16S, related with inhibition of protein synthesis
Amikacin (Am)	rrS	514, 517, 1401	
Ethionamide (Eto)	*ethA*	397	Encodes a mono-oxygenase enzyme, which processes the pro-drug
	mabA	609	Encodes a 3-ketoacyl reductase, related synthesis mycolic acids.
	inhA	21	Encodes an enoyl-ACP reductase, related synthesis mycolic acid
	rplC	460	Encodes ribosomal protein 50SL3
Rifabutin (Rfb)	*rpoB*	531	Encodes the ß-subunit of RNA polymerase
P- aminosalicylic acid (PAS)	*thyA*	235	Encodes a thymidylate synthase
Carbapenem	*Rv2421c-Rv2422 intergenic region*	-	Encode am enzyme with nitrocein-hydrolyzing activity
Proteonamid (Ptn)	*ddn*	-	Encodes deazaflavin-dependent nitroreductase
Delamanid (Dlm)	*fgd1*	-	Encodes F420-dependent glucose-6-phosphate dehydrogenase Probably encodes the biosynthetic protein F420

more than 10 million new TB cases, 4% developed TB drug-resistant. This number increases to 18% in previously treated cases. Besides, from the 500,000 cases with confirmed resistance to RIF, 187,000 were confirmed cases of MDR-TB, with a treatment effectiveness of 50% (1).

In May 2014, WHO created the End of TB Strategy, and one year later the Global Plan to Stop TB (8). The aim of this proposals is to end the current paradigm of TB and change the way the fight against this disease. This global plan is framed in the United Nation Sustainable Development Goals, and establishes the goal to end with the TB as an epidemic disease for 2030, to reduce the deaths by 90% and the number of new cases per 100 000 inhabitants per year worldwide. To achieve these goals it has been recognized that it is essential to increase research and technological development in TB, prioritizing the generation of new vaccines (9,10), shorter and more effective treatment schemes for latent tuberculosis, to identify novel mehcanisms of drug administration (11), as well as the development of rapid diagnostic tests for diagnostic of drug resistance (1).

An important number of researchs has been made in

the last years with the aim of characterize the drug resistant phenomenon in tuberculosis, identificating the participation of several new procedures participating, from which two are emerging as the most important; eflux pumps and DNA repair systems. This new mechanism show the capacity and complexitiy of TB to respond to the antibiotic challenge, and the need to increase the information related with this novel mehcanisms to address a appropiate response against this new participants.

"Traditional mechanisms" associated with drug resistance in tuberculosis

The main cause of acquired drug resistance in tuberculosis is due to chromosomal mutations, which can appear as a consequence of stress in bacteria, either due to a high level of reactive oxygen species, the host environment, or due to the inappropriate use of anti-tuberculosis drugs. These mutations consist of substitutions of a nucleotide at specific position in the DNA, (12). Single-nucleotide polymorphisms (SNPs) are, therefore, the main source of variation in *M. tuberculosis* genomes, followed by insertions and deletions (INDELS) (13). MTBC strains are unable to undergo horizontal gene transfer, suggesting that the drug resistance phenotypes rely on acquiring and maintaining beneficial mutations in core genes or promoter regions and inherit to their progeny (14). Nevertheless, both SNPs and INDELS can affect the mycobacterial genome, generating clone diversity that, together with natural selection, will determine which polymorphisms persist in the population. More than 60 genes have been described so far as associated wih the development of antibiotic resistance in tuberculosis. Table 1 describes some of the genes that are most associated with resistance to first and second-line drugs, the mechanisms involved, the mutations considered as the most important, used as target in diagnostic procedures.

These mutations related to resistance, usually, are transmitted from one generation of bacilli to another. Consequently, one isolate can develop resistance to multiple drugs by accumulating individual mutations in various genes, each of which, is responsible for resistance to a specific antibiotic, explaining the occurrence of MDRT-TB and XDR-TB, this evidences the tremendous complexity of the drug resistance mechanisms in tuberculosis.

"Novel" mechanisms: efflux bumps and DNA repair systems

The last years testified the identification of several aditiona mechanism participating in drug resistance, two are considered as the most important, and with the major impact in the near future: i) the efflux pump systems and ii) The DNA repair system.

Efflux pump system

This is conformed by a set of proteins, "efflux pumps", that gives place to an "efflux system", responsible for transporting a wide variety of substrates from the interior to the exterior of the cell [23, 24]. Some can be induced by specific substrates, including antibiotics, so that a susceptible bacterium can produce an excess of this pump and become resistant (15). This overexpression can be induced by the acquisition of one or several polymorphisms in the respective promoter or gene, increasing the efficiency for the drug exportation, decreasing the respective concentration, and inducing resistance to this drug (16).

In mycobacteria, three families of efflux pumps have been described and they have been classified according to the energy source they use to perform the expulsion and the substrate specificity: Resistance-Nodulation-Division (RND), major facilitator superfamily (MFS), and ATP- binding cassette (ABC) (17). ABC transports proteins are coupled with ATP hydrolysis to transport substrates, and are the most active transporters in mycobacteria. The 2.5% of the tuberculosis genome encodes for ABC efflux pumps, which remarks its importance in mycobacteria. The implications for the decrease of drug sensitivity has been described and its relationship in the development of MDR-TB has also been demonstrated (18,19)

The families of pumps MFS and RND are considered as secondary active carriers and they are driven by a protonic-motor force. MFS is a large and diverse family of carriers, an example is the Tap protein (Rv1258c), and is able to confers resistance to tetracycline and rifampicin (18), another pump, the P55(Rv1410c), confers resistance to aminoglycosides, tetracycline, and rifampicin (20). The RND family can contribute to the resistance of a wide range of antibiotics in tuberculosis. Groups of genes of mmpL code for various efflux bumps, which transport lipids and other molecules. Some mmpLs have been reported as responsible for "efflux" of drugs and promoting resistance and virulence in tuberculosis. It has been shown that mmpL7 is related with resistance to isoniazid, due to gene overexpression (Rv2942) (21). It also has been observed the important association of Efflux Pump Mediated Second-Line Tuberculosis Drug Resistance. (22)

The DNA damage repair system

The second mechanism related to DR-TB has been identified in the DNA damage repair system, which also plays a fundamental role in the protection of DNA and genomic diversification of M. tuberculosis (23,24). In natural infective conditions, the defense mechanism of the host's includes reactive oxygen species and reactive nitrogen intermediates both generated by macrophages. Consequently, the infecting M. tuberculosis faces constant DNA damage (25), which requires multiple repair mechanisms in a way that ensures their survival and promotes its spread in the population (26,27).

The characterization of the genes and mechanisms that participate in the DNA damage repair system in tuberculosis has been an important research issue in recent years (24,28–53). Table 2 shows some examples of how the damage repair system can generate hyper mutagenic phenotypes that promote o induce the generation of drug

Table 2. DNA damage repair system genes and their

Gen	Function	Description
neiL, nth	Exonucleases, Nei1 is specific for oxidized pyrimidines and uracil, Nth removes damaged nucleotide	The joint absence decreases survival and increases the mutation rate. Not observed in single gene deletion
mutY, fpG	A combination of *mutY* and *fpG* is crucial in preventing mutations from C(G) to A(T)	Elimination of both increases the mutation rate fourfold
mutT1	Participates in the hydrolysis of 8-oxo-dGTP and di-adenosine polyphosphates in cleaning the nucleotide pool	A mutated gene increases the mutation rate
uvrB	Participates in the NER pathway, as well as in the HR pathway in conjunction with UvrD1	Mutated Gene Linked to Increased Resistance
dnaE1	Replicative polymerase, its elimination is lethal for the bacteria	The absence of exonuclease of DnaE1 increases the mutation rate from 2300 to 3700 times
dnaE2	DNA polymerase from trans lesions	Its absence sensitizes and eliminates damage-induced mutagenesis
dinB2	Low Fidelity DNA Polymerase	Has a preference for ribonucleotides, capable of incorporating oxo-rGTP and 8-oxo-dGMP bases against 8-oxodG
ogT	O6-alkylguanine DNA alkyltransferase which reverses the O^6-alkylguanine	Mutated Gene Increases Sensitivity to Isoniazide.
adA/alkA, unG	*Alka* with broad recognition of methylated bases. *Ada* control adaptive response to damage. *Ung* removes uracil from DNA and participates in virulence	Mutations in these genes have been linked to resistant strains of the Haarlem lineage
mutT4, mutT2 y ogT	MutT2 hydrolyzes dCTP, 5-methylCTP and 8-oxoGTP. Both participate in the cleaning of the nucleotide pool	Mutations linked to resistant strains of the Beijing lineage
recA	It catalyzes the exchange of threads in the HR pathway, thus initiating the recombination process.	Its elimination increases the sensitivity of *M. bovis* BCG to metronidazole
nucS	Putative mismatch-specific endonuclease, necessary to prevent mutation and anti-recombination *in vivo*.	Its inactivation increases generation of mutations up to 31X and of SNPs up to 41X, and give a greater adaptation to drugs.

resistance in tuberculosis.

M. tuberculosis has shown the presence of homologs systems to the traditional DNA repair systems that have been found in other bacteria. It has been identified as a base excision repair (BER) or nucleotide excision repair (NER) pathway. In this system, when the DNA double chain is broken, three major mechanisms participate: the homologous recombination pathways (HR), and the non-homologous end junction (NHEJ) or strand alignment (SSA). The last two are considered the only pathways available during the pre-replicative stages of the cell (27). On the other hand, although *M. tuberculosis* lacks of the canonical mismatch repair genes (Miss Match Repair), recently has been found an alternate pathway mediated by *nucS*, a putative endonuclease specific for mismatches, necessary to avoid mutation and anti-recombination *in vivo*, with adaptive regulation that influences the generation of mutations (46).

In the different *M. tuberculosis* lineages, the high polymorphic presence in the genes that make up the damage repair system has also been a focus of interest in recent years (27), and it was observed that in the Beijing lineage, this system could help to explain its high propensity to rapidity develop drug resistance (24).

Final remarks

As can be seen, the number of mechanisms involved in the generation of drug resistance in tuberculosis has increased significantly, which makes it more complex and raise new challenges for the development of diagnostic procedures that consider all these processes.

Currently, we know that diagnostic systems are inadequate to address and solve the actual and future problem of drug resistance in tuberculosis, so it is necessary to develop new procedures, which also consider these new mechanisms generating resistance. In this sense, the whole genome sequencing (WGS), and its subsequent analysis, has the capacity to identify all polymorphisms or changes in the genes that could be participating in the generation of resistance, undoubtedly, WGS will have a deep impact in the diagnostic of resistant, and is called to be the next golden standard in the fight against this aggravated forms of tuberculosis.

Competing interests

The author declare no competing interests.

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Ethical statements

No experiments involving humans or animals and experimental protocols were conducted in this work, therefore no approvation was requested to any ethical committee.

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