Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*: Intrinsic and acquired resistance

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Introduction

Tuberculosis is a disease caused by the mycobacteria *Mycobacterium tuberculosis*.(1) Currently it can be cured thanks to the antibiotics.
The problem is that the ability of this bacteria can mutate and acquire drug resistance and become MDR-TB or XDR-TB. Figure 1 presents the cases of TB and MDR-TB in Europe from 2005 until 2012

Objectives:

- Define the mechanisms of intrinsic and acquired drug resistance in *M. tuberculosis*
- Describe the drug resistance mutations and their molecular changes.

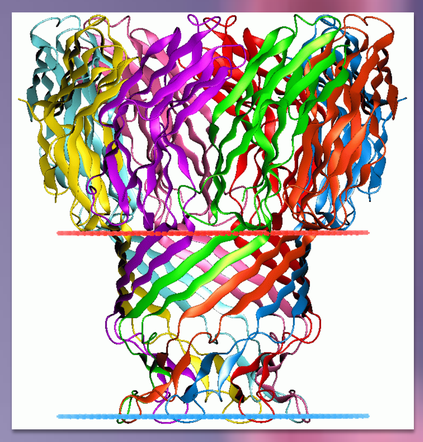

Fig 3: Molecular structure of MspA porin. Source: http://upload.wikimedia.org/wikipedia/commons/0/0f/1uun_opm.gif

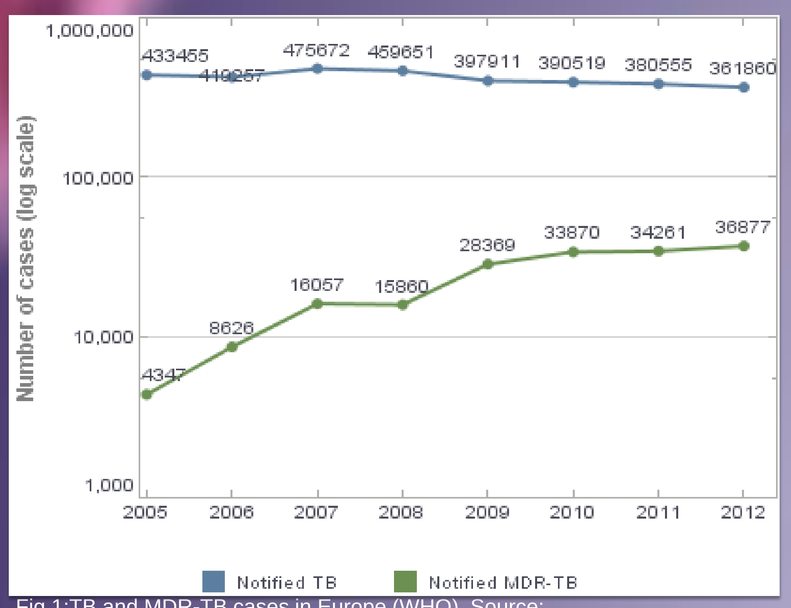

Fig 1:TB and MDR-TB cases in Europe (WHO). Source: https://extranet.who.int/sree/Reports?op=vs&path=/WHO_HQ_Reports/G2/PROD/EXT/MDRTB_Indicators_charts

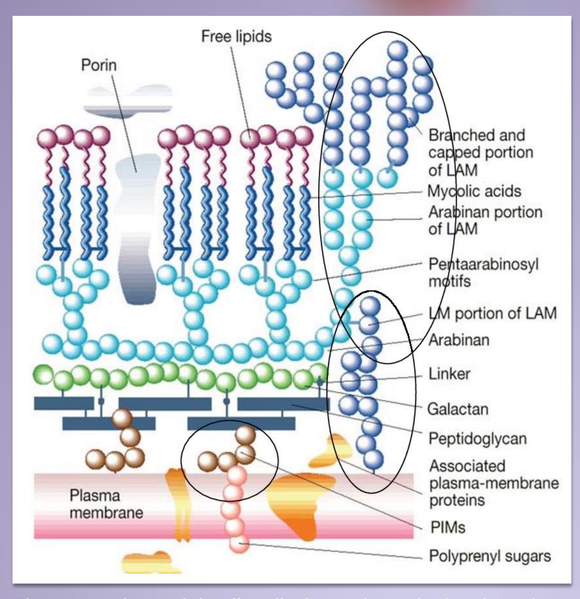

Fig 2: Mycobacterial cell wall of *M. tuberculosis*. Altered source: img.docstoccdn.com/thumb/orig/27038162

Intrinsic antibiotic resistance mechanism

- Mycobacterial cell wall: The Figure 2 shows the structure of the cell wall. The peptidoglycan and the arabinogalactan layer, are covalently linked to a layer of mycolic acids that prevent the drug diffusion between the inside and the outside of the bacteria.(4)
- **Porins:** Research demonstrate that MspA porin in *M. smegmati* makes the bacteria be more sensitive towards the antibiotics. Figure 3 shows the molecular structure of the MspA porin. There is the possibility that the absence/presence of *M. tuberculosis* MctB and OmpA porins may be linked at drug resistance.(5)
- **Efflux pumps**: The main function is to expel waste and toxic substances through the cell wall. There are 18 pumps codified in its genome giving it a low-level drug resistance. The main problem would be a mutation that causes an overexpression of this efflux pumps.(6)

Spontaneous mutations are the only mechanism that can make *M. tuberculosis* a drug resistance bacteria. In chart 1 we can observe the discovered mutations that *M. tuberculosis* can have to protect itself against antibiotics.

Drug		Mode of action	Gene	Gene function	Role	Mutation
First-line	Isoniazid	Inhibition of mycolic acid biosynthesis and other metabolic processes	*katG* *inhA* *ndh* *ahpC*	Catalase-peroxidase Enoyl ACP reductasa NADH dehydrogenase II Alkyl hidroperoxidase	Prodrug activation Drug target Activity modulation Resistance marker	Ser-315-Thr -15C->T promotor site Arg-13-Cys and Val-18-Ala --
	Rifampicin	Inhibition of transcription	*rpoB*	B-subunit of RNA polymerase	Drug target	Ser-450-Leu
	Pyrazinamide	Inhibition of trans-translation	*pncA* *rpsA*	Pyrazinamidase S1 ribosomal protein	Prodrug activation Drug target	Asp-12-Ala/Asn, Leu-85-Pro Deletion Ala438
	Ethambutol	Inhibition of arabinogalactan synthesis	*embCAB* *embR*	Arabinosyl transferases *embCAB* transcription regulator	Drug target Drug target expression	*embB*: Met-306-Val/Ile/Leu Unknown
	Streptomycin	Inhibition of translation	*rpsL* *rrs* *gidB*	S12 ribosomal protein 16S rRNA 16S rRNA methyltransferase	Drug target Drug target Target modification	Lis-43-Arg A-1401-G
Second-line	Amikacin/Kanamycin/ Capreomycin/ Vancomycin	Inhibition of translation	*rrs* *tlyA* *Eis*	16S rRNA 16S/23S rRNA methyltransferase enhanced intracellular survival	Drug target Drug target Drug resistance	A-1401-G G-223-T --
	Ethionamide	Inhibition of mycolic acid biosynthesis	*ethA* *inhA* *Ndh*	Flavin monooxygenase Enoyl ACP reductase NADH dehydrogenase II	Prodrug activation Drug target Activity modulation	-- Ile-21-Thr/Val and Arg-13-Cys and Val-18-Ala
	Fluoroquinolones	Inhibition of DNA gyrase	*gyrA* *gyrB*	DNA gyrase subunit A DNA gyrase subunit B	Drug target Drug binding (target)	Ala-90-Val and Asp-94-Gly/Tyr Asn-533-Thr
	P-aminosalicylic acid (PAS)	Unknown	*thyA*	thymidylate synthase A	Drug resistance	Confers susceptibility: Val-261-Gly
	Linezolid	Inhibition protein biosynthesis	*Rrl*	50S ribosomal subunit	Drug target	G-2061-T and G-2576-T
	Macrolides	Increase cell wall permeability	*erm 37*	23S rRNA methyltransferasa	Drug resistance	Intrinsic resistance
	Cicloserine	Inhibition peptidoglycan biosynthesis	--	--	--	--
New-Drugs	SQ109	Inhibition cell wall biosynthesis	*mmpL3*	Mmpl3 transporter	Drug target	Ala-700-Thr and Glut-40-Arg
	TMC207	Inhibition ATP synthase	*atpE*	ATP synthase subunit C	Drug target	Ala-63-Pro and Iso-66-Met
	NAS-21/ NAS-91 analogues	Inhibition fatty acid biosynthesis	*hadB*	FAS-II dehydratase	Drug target	Unknown
	Benzothiazinones	Inhibition arabinan biosynthesis	*dprE1*	decaprenylphosphoryl-beta-D-ribose oxidase	Drug target	Cys-387-Ser
	PA-824 OPC- 67683	NO donor/ Inhibition cell wall biosynthesis Inhibition mycolic acid biosynthesis	*Ddn*	deazaflavin-dependent nitroreductase	Prodrug activation	Unknown

Chart 1. Antibiotics against *M. tuberculosis*, their targets and their main mutation. Source based on: (3)

Conclusions:

As we could see in this review, besides the classic mutations there are other kinds of unknown of molecular changes. That's why we have to keep improving the molecular tools in order to know better its drug resistance mechanism. After that we will be able to make more rational antibiotics or to reform the current treatments. It is also important to use the molecular tools to study how MDR-TB and XDR-TB strains work and to avoid their global expansion. However it's important to keep investigating to discover new possible targets and to develop antibiotics which are effective despite their mutations.

Bibliography

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