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Investigating the Essentiality of Oxazolidinones in Resistance-Proof Drug Combinations in Mycobacterium tuberculosis Selected under in vitro Conditions

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Abstract : Drug resistance in Mycobacterium tuberculosis is primarily attributed to mutations in target genes. These mutations incur a fitness cost and result in bacterial generations that are less fit, which subsequently acquire compensatory mutations to restore fitness. We hypothesize that mutations in specific drug target genes influence bacterial metabolism and cellular function, which affects its ability to develop subsequent resistance to additional agents. We aim to determine whether the sequential acquisition of drug resistance and specific mutations in a well-defined clinical M. tuberculosis strain promotes or limits the development of additional resistance. In vitro mutants resistant to pretomanid, linezolid, moxifloxacin, rifampicin and kanamycin were generated from a pan-susceptible clinical strain from the Beijing lineage. The resistant phenotypes to the anti-TB agents were confirmed by the broth microdilution assay and genetic mutations were identified by targeted gene sequencing. Growth of mono-resistant mutants was done in enriched medium for 14 days to assess in vitro fitness. Double resistant mutants were generated against anti-TB drug combinations at concentrations 5x and 10x the minimum inhibitory concentration. Subsequently, mutation frequencies for these anti-TB drugs in the different mono-resistant backgrounds were determined. The initial level of resistance and the mutation frequencies observed for the mono-resistant mutants were comparable to those previously reported. Targeted gene sequencing revealed the presence of known and clinically relevant mutations in the mutants resistant to linezolid, rifampicin, kanamycin and moxifloxacin. Significant growth defects were observed for mutants grown under in vitro conditions compared to the sensitive progenitor. Mutation frequencies determination in the mono-resistant mutants revealed a significant increase in mutation frequency against rifampicin and kanamycin, but a significant decrease in mutation frequency against linezolid and sutezolid. This suggests that these mono-resistant mutants are more prone to develop resistance to rifampicin and kanamycin, but less prone to develop resistance against linezolid and sutezolid. Even though kanamycin and linezolid both inhibit protein synthesis, these compounds target different subunits of the ribosome, thereby leading to different outcomes in terms of fitness in the mutants with impaired cellular function. These observations showed that oxazolidinone treatment is instrumental in limiting the development of multi-drug resistance in M. tuberculosis in vitro.

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