Time to consider "biobettering" FMO2-mediated anti-tubercular drugs?

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With the continuing prevalence of tuberculosis (TB) there is a need for the production of effective and safe anti-tubercular drugs in large amounts. Particularly, with the current rise in the incidence of multi-drug resistant TB (MDR-TB), the second-line anti-tubercular drugs such as thiourea-containing ethionamide and thiacetazone, remain the only available treatment options. Ethionamide/Thiacetazone are primarily targeted at Mycobacterium tuberculosis (Mtb) and bio-activated by the mycobacterial enzyme EtaA culminating in bactericidal oxidative stress. However, the human innate immunity gene, flavin-containing monooxygenase 2 (FMO2; aka, pulmonary FMO), also metabolizes both drugs leading to the production of unintended toxic drug metabolites. Therefore, pulmonary toxicity is aggravated by the simultaneous bio-activation and catalysis of these drugs by both human and Mtb derived enzymes.

Methodology & Theoretical Orientation: Depending on the possession FMO2*1 or FMO2*2 genetic variants, which have a distinctive ethno-geographic differentiation, not all people are equally susceptible to the adverse effects of FMO2-mediated anti-tubercular drug metabolism. All individuals of non-recent sub-saharan ancestry possess FMO2*2(T), which synthesizes a non-functional protein. Therefore, such populations (Europeans and Asians) are less susceptible. In contrast, most sub-saharan individuals and their recent descendants possess at least one FMO2*1(C) allele that encodes for a functionally active enzyme and, therefore, are at increased risk. Accordingly, the simultaneous prevalence of TB and FMO2*1 has led to the characterization of FMO2*1 as "potentially deleterious". This is a source of potential health disparity since an estimated 220 million individuals in sub-saharan Africa may express a functional FMO2 enzyme and, therefore, potentially at risk of FMO2 mediated toxicity. However, despite evidences suggesting the involvement of FMO2 in anti-TB immune responses, no studies were done to investigate the "potentially beneficial" aspect of the FMO2*1 variant with regard to TB pathogenesis. Therefore, we conducted a genetic epidemiological analysis to investigate whether FMO2 polymorphisms are associated with TB.

Findings: We discovered a novel association between FMO2 and TB both at the SNP and haplotype level with evidence of a protective effect of FMO2*1 against both active and latent TB.

Conclusion & Significance: Our study suggests FMO2 confers a "potentially beneficial" evolutionary adaptation to TB. It demonstrates how the manufacturing, distribution and utilization of new drugs to treat an ancient disease, may create a pressure on a genetic architecture evolutionarily shaped to fight the same disease. In other words, it is not a matter of the FMO2*1 allele being naturally deleterious, rather the indiscriminate application of thiourea-containing anti-tubercular drugs that is becoming an artificial risk. We question the prudence of continuing to prescribe such treatment regimens for populations harbouring high proportions of FMO2*1 without genetic screening or the development of simpler biomarkers. We recommend it is time to consider biobettering FMO2-mediated anti-tubercular drugs by either modifying the active ingredients of these drugs to be more Mtb-specific and render them NOT susceptible to human FMO2 oxygenase action or increase the effective elimination of Mtb by the synergistic action of both human-FMO2-mediated innate immunity and Mtb-FMO2-mediated anti-tubercular drugs.