

Flavin-containing monooxygenases: genetic variation and drug metabolism

Asvi A. Francois and Elizabeth A. Shephard

Flavin-containing monooxygenase (FMO) proteins play an important role in the metabolism of foreign chemicals including therapeutic drugs. Consequently polymorphic variation in *FMO* genes can lead to changes in drug metabolism, which in turn can cause adverse drug reactions or lack of drug efficacy. Five members of the FMO family of proteins, FMOs 1, 2, 3, 4 and 5 are known to metabolise drugs. Nearly one-third of the world's population is infected with *Mycobacterium tuberculosis* with pulmonary tuberculosis being the most common form of the disease. Tuberculosis is especially common in the world's poorer areas including Africa. This talk will concentrate on the FMO2 protein and how genetic variation in the *FMO2* gene influences the metabolism of an important class of drugs used to treat tuberculosis. The FMO2 protein is of particular interest because in the *FMO2* gene of Asians and Causcasians there is a nonsense mutation that causes premature truncation of translation. Thus these individuals do not make FMO2 protein. In contrast, 25% of the population of sub-Saharan Africa have a wild type *FMO2* gene and thus produce a catalytically active protein. Results will be presented to show that thiacetazone, a cheap and commonly prescribed anti-tuberculosis drug in Africa, is a substrate for FMO2. The consequences of this finding for drug therapy and/or potential adverse reactions will be discussed.