TOXICOKINETICS AND MUSCLE-RELATED TOXICITY OF ATORVASTATIN *IN VITRO*

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Background: Atorvastatin (Ator) is one of the most commonly used statins to fight hypercholesterolemia, a major predisposing factor for the development of cardiovascular diseases. Myotoxicity of statins in certain individuals is often a severe side effect leading to withdrawal or poor compliance. Differences in individual susceptibility to Ator-associated myotoxicity exist in clinics. Intuitively, factors influencing intracellular myocyte accumulation might modulate the susceptibility to muscle side effects. From that hypothesis, we assumed that this intracellular accumulation might be controlled by the balanced activities of influx and efflux proteins expressed in the muscle tissue; *i.e.* OATP2B1 (*SLCO2B1*) and MRP1 (*ABCC1*) and that their activity depends on genetic variations. **Method:** Stable recombinant HEK293 human cells overexpressing either OATP2B1 or MRP1 were developed through full length c.DNA plasmid transfection. Next, nonsynonymous single nucleotide polymorphisms (SNPs) rs12422149 (Arg 312 Gln) in *SLCO2B1* and rs45511401 (Gly 671 Val) in *ABCC1* were introduced within the c.DNA sequences through site-directed mutagenesis and stable variant recombinant models were next generated. Models were validated through expression analysis with fluorescence detection techniques (flow cytometry and microscopy). Accumulation experiments were performed by incubating recombinant cells with increasing Ator concentrations in order to evaluate (i) the effect of protein over-expression and, (ii) the impact of SNPs on the Ator intracellular accumulation. **Results:** The accumulation experiments in the validated wild-type recombinant models demonstrated that Ator is a substrate for OATP2B1 and MRP1 as OATP2B1 over-expression is associated with a drastic increase of Ator accumulation (figure 1a) while MRP1 seems to decrease intracellular concentrations (figure 1b) when compared to control cells. Furthermore, we showed that the rs45511401 (Gly 671 Val) SNP in *ABCC1* affects negatively the activity of MRP1 towards Ator. **Conclusions:** OATP2B1 and MRP1 both control the Ator cellular trafficking and are expressed in myocytes. Moreover, the *ABCC1* SNP rs45511401 seems to affect the protective role of MRP1 against an excessive Ator intracellular accumulation. Those results need further investigations but these observations could have important clinical consequences for Ator therapy management.

Keywords: atorvastatin, myotoxicity, influx transporter, efflux transporters, genetic variations, polymedication.

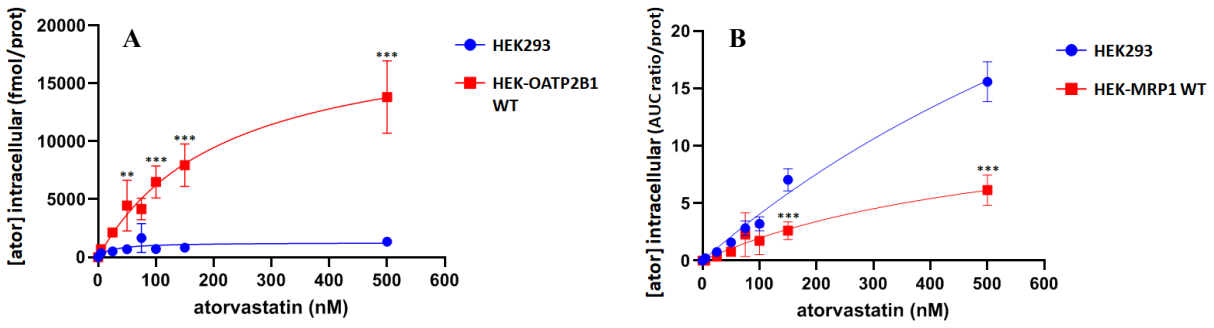

Figure 1. Intracellular Ator amount normalized on total protein content. **(A)** Control cells, HEK293 (blue), compared to recombinant HEK293 cells transfected with pCMV-OATP2B1-C-OFPSpark plasmid (red). **(B)** Control cells, HEK293 (blue), compared to recombinant HEK293 cells transfected with pCDNA3.1- MRP1-C-GFP plasmid (red). (*p<0.05, **p<0.01, ***p<0.001)