ABC-transporters expressed on endothelial cell membranes efflux anti-HIV drugs

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Researchers at Tulane University Medical Center in New Orleans (USA) have discovered that drug-efflux pumps, belonging to the ATP-binding cassette (ABC) transporter family, are constitutively expressed on vascular endothelial cells. Transcripts for several different ABC-transporters, e.g. MDR-1 (P-gp) and MRPs, were detected in endothelial cells, obtained from brain, aortic artery, pulmonary artery, dermal microvessels and umbilical veins.

The ABC-transporter mediated efflux mechanisms decreased intracellular concentrations of the anti-HIV drugs, saquinavir, an HIV protease inhibitor (HPI) and zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), which are critical components of highly active antiretroviral therapy (HAART) against HIV. Inhibition of ABC-transporters, by using verapamil or MK-571, was shown to increase the intracellular retention of these anti-HIV agents.

The MRP transporters were found to play a more dominant role in drug-efflux from endothelial cells. Pre-incubation of cells with the MRP-inhibitor, MK-571 significantly enhanced the intracellular levels of anti-HIV drugs. This study, entitled 'MRP (ABCC) transporters-mediated efflux of anti-HIV drugs, saquinavir and zidovudine, from human endothelial cells,' will be published in the September 2008 issue of *Experimental Biology and Medicine*.

These investigations led by Dr. Debasis Mondal, an assistant professor of Pharmacology, and co-authored by Mr. Mark Eilers and Dr. Upal Roy,

demonstrated the significance of blocking MRP-transporters on endothelial barriers of blood vessels, in order to increase the pharmacokinetic efficacy of both HPIs and NRTIs. Drug-efflux pumps expressed on the blood-brain-barrier (BBB) were previously known to decrease drug entry into the central nervous system (CNS), however, this is the first evidence that endothelial cells from other organs express functional ABC-transporters, as well. The functional expression of MRPs on vascular endothelial barriers implicates their crucial role in facilitating the persistence of sub-endothelial HIV reservoirs.

"Although we have a significant armament of therapeutic agents against HIV, factors that dictate the pharmacokinetics of anti-HIV drugs need to be accounted for in order to have HAART efficacy in sequestered viral reservoirs. Several P-gp inhibitors are currently under clinical trial, however, very little is being done to target the MRP-transporters. Our studies using the anti-HIV drugs, saquinavir and zidovudine, clearly implicated that inhibition of MRPs, rather than P-gp, would be a more beneficial approach to facilitate the entry of HAART drugs into the sub-endothelial reservoirs of HIV, especially within the brain. Unpublished findings from our laboratory suggest that, similar to MK-571, other leukotriene receptor antagonists, e.g. montelukast (SingulairTM) and zafirlukast (AccolateTM) can suppress MRP-mediated efflux of these anti-HIV drugs, as well. We believe that adjunct therapy with these clinically approved MRP inhibitors may improve HAART efficacy in HIV-positive patients, deter the selection of drug resistance and delay the progression of AIDS." Dr. Steve Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "this study by Dr. Mondal and colleagues has crucial implications in the persistence of sub-endothelial HIV reservoirs and will be important to the development of future therapies".

Source: Society for Experimental Biology and Medicine