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