pharmacogenetic profiling. In addition, we have demonstrated the presence of a non-negligible variant for CYP3A4, CYP3A4*1G, which shows decreased enzymatic activity, and which appears in the Spanish population with a frequency of 13%, which leads us to recommend its inclusion in routine pharmacogenetic analysis.

Role of micro-RNAs 221/222 in statin-induced nitric oxide release in human endothelial cell

Cerda Alvaro, Hirata Thiago D.C., Fajardo Cristina M., Basso Rodrigo G., Hirata Mario H, Hirata Rosario D.C.

Background: Nitric oxide (NO) has been largely associated to cardiovascular protection through improvement of endothelial function. Recently, new evidence about modulation of NO release by micro-RNAs (miRs) has been reported. Whereas miR-1303 has predicted interaction with endothelial nitric oxide synthase (NOS3) mRNA, miR221/222 indirectly regulates NO release by interacting with RIP140, a NFkB cofactor. A number of pleiotropic effects have been described for statin therapy, including anti-inflammatory properties related to vascular endothelium function. Molecular mechanisms of statin-related anti-inflammatory effect and whether or not this depends on intracellular cholesterol reduction remain controversial. Here, we analyzed the effects of cholesterol-lowering drugs including the inhibitors of cholesterol synthesis, atorvastatin and simvastatin, and the inhibitor of cholesterol absorption ezetimibe on NO release, NOS3 mRNA expression and miRs potentially involved in NO bioavailability.
Methods: Human umbilical vein endothelial cells (HUVEC) were exposed to various concentrations of atorvastatin, simvastatin or ezetimibe (0 to 5.0 µM). Firstly, membrane integrity and DNA fragmentation tests were performed using flow cytometry to evaluate the cell viability after treatments. After 12h and 24 treatments, cells were submitted to total RNA extraction using Trizol reagent. Relative quantification by qPCR of NOS3 mRNA and miRs 221, 222 and 1303 were performed using predesigned Taqman gene expression and Taqman Stem-loop assays, respectively (LifeTechnologies, USA). NO release was measured in supernatants by ozone-chemiluminescence.
Results: Cytotoxicity tests showed that all treatments did not affect cell viability up to 5.0 µM. Statins, but not ezetimibe, increased NO levels in supernatants. Although NO levels were increased by both statins, only simvastatin up-regulated significantly the NOS3 mRNA levels. Atorvastatin, simvastatin and ezetimibe down-regulated the expression of miR-221, whereas miR-222 was reduced only after atorvastatin treatment. No influence was observed on miR-1303 expression after treatments.
Conclusion: NO release in endothelial cells is increased by statins but not by the inhibitor of cholesterol absorption, ezetimibe. Our results provide new evidence about participation of regulatory miRs 221/222 on NO release induction mediated by statins. Although ezetimibe did not modulate NO levels, the down-regulation of miR-221 could involve potential effects on endothelial function.

The influence of TNFA genetic polymorphisms in the response to immunomodulatory drugs in patients with rheumatoid arthritis: A systematic review

Clemente Daniela, Santos Marlene.

Introduction: Etanercept, Infliximab and Adalimumab are the best treatment options for improving the life quality of patients suffering from rheumatoid arthritis. However, a substantial proportion of patients (approximately 30-40%) do not respond. Genetic factors are known to influence treatment outcome, and several studies have examined associations between TNF-α genetic variants and immunomodulatory drugs in patients with rheumatoid arthritis. However, inferences from these studies were often hindered by limited statistical power and conflicting results. We aimed to systematically review and summarize the association of TNFA-308A/G single nucleotide polymorphism with immunomodulatory drug response in patients with rheumatoid arthritis.
Methods: Pubmed database was searched for all articles published up to May 2012, which addressed TNFA-308A/G polymorphism and Etanercept, Infliximab and Adalimumab drug response in patients with Rheumatoid Arthritis. After inclusion and exclusion criteria were applied, twelve papers were included in the systematic review. The study quality was evaluated with the DownsBlack scale.
Results: Systematic review showed that patients with the TNFA-308 GG genotype present a better treatment response with Etanercept. Regarding Infliximab, patients with the TNFA-308 GA genotype have a better treatment response. While for Adalimumab, the presence of the variant allele is associated with a good response to therapy.
Conclusion: TNFa-308 genetic polymorphism associations are widely reported in good quality studies and revealed to have an influence in Etanercept and Infliximab treatment response, and more rarely in Adalimumab response.

The iDILIC network: progress in identifying genes relevant to drug-induced liver injury.

Coulthard Sally A, Chamberlain Thomas, Bjornsson Einar, Stevens Camilla, Lucena Maribel, Andrade Raul, Wadelius Mia, Hallberg Par, Maitland-van der Zee Anke-Hilse, Martin Jennifer H, Cascorbi Ingolf, Werk Anneke, Dillon John F, Laitinen Tarja, Larrey Dominique, Molokhia Mariam, Qin Shengying, Menzies Richard, Kullak-Ublick Gerd, Ibanez Luisa, Perez Eulalia, Bessone Fernando, Hernandez Nelia, Arrese Marco, Eliasson Erik, Pirmohamed