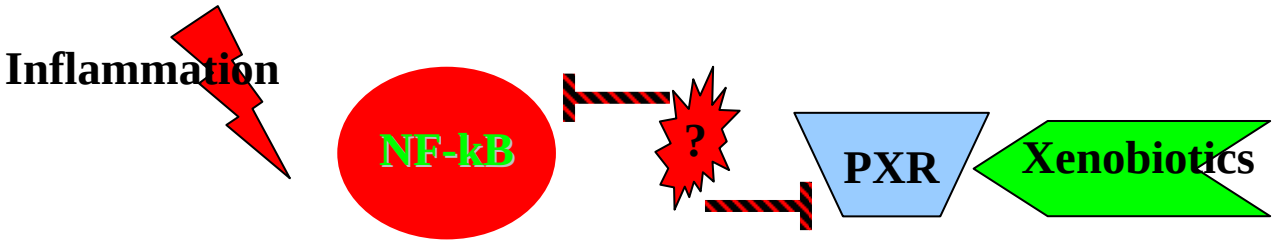
PXR as therapeutic target for inflammatory bowel disease.

Erasmus Medical Centre Rotterdam, the Netherlands
Department of Gastroenterology & Hepatology

Introduction

The Pregnane X Receptor (PXR) is a nuclear receptor for xenobiotics and is manly expressed in hepatocytes and intestinal epithelium. After ligand binding, the nuclear receptors regulate the expression of genes involved in many different cellular processes. Rifampicin (antibiotic) is a specific ligand for PXR and can up-regulates the expression of PXR target gene CYP3A4, which is involved in phase III of the cellular detoxification system.
Patients with inflammatory bowel disease (IBD), comprised of ulcerative colitis (UC) and Crohn's disease (CD), suffer from chronically inflamed intestinal mucosa in with the function of epithelial cells place an important role. Interestingly, the expression of PXR target genes is reduced in the intestinal epithelial cells of patients with IBD suggesting that these cells can have a problem with detoxification.
We and others have recently demonstrated that activated PXR is able to reduce the activity of nuclear factor kappaB (NF-kB), a major inducer of the inflammatory response. Other studies have reported that stimulation of the NF-kB pathway reduces the expression of PXR target genes, as could be the case in the reduced target gene expression in active IBD. Hence, there seems to be mutual inhibitory potential of PXR and NF-kB.



Project

This project will focus on the mechanism behind the mutual regulation between PXR and NF-kB and the potential of PXR as a therapeutic target for IBD patients. Our hypothesis is that activated PXR protein is able to bind NF-kB protein subunits, actively inhibiting its pro-inflammatory transcriptional activity.

Methods and Techniques

Various molecular techniques will be used to study the interaction of PXR with the NF-kB pathway.
Our hypothesis will be tested by using cell lines that have endogenous or over-expression of PXR.
After activation of PXR with rifampicin, immunoprecipitation of the PXR complex followed by western blot or mass spectrometry will show us whether any NF-kB subunits form a complex with activated PXR. The effects of either PXR and/or NF-kB stimulation on the various target genes will be measured using reverse transcriptase and quantitative PCR.

General information

We are looking for a motivated, self-contained student with interests in molecular techniques for a period of at least 6 months. You will join our group and departmental discussions weekly. This project will be closed off with an oral presentation and a written report.
For information please contact:

Jasper Deuring
j.deuring@erasmusmc.nl
tel: 010-7032585
www.gastrolab.nl