Department of BioSciences and Nutrition

Oxysterol Receptors LXRs and Coregulators in Cholesterol Metabolism and Inflammatory Transrepression Pathways

AKADEMISK AVHANDLING
som för avläggande av filosofie doktorsexamen vid Karolinska Institutet offentligen försvaras i Hörsalen, Plan 4, Novum, Huddinge

Torsdagen den 30 Juni, 2011, kl 09.30

av

Tomas Jakobsson

Huvudhandledare:
Ph.D. Knut R. Steffensen
Karolinska Institutet
Department of Biosciences and Nutrition

Bihandleare:
Professor, M.D. Jan-Åke Gustafsson
Karolinska Institutet
Department of Biology and Biochemistry
University of Houston
Center for Nuclear Receptor and Cell Signaling
Ph.D. Anette Wärnmark
Karolinska Institutet
Department of Biosciences and Nutrition

Fakultetsopponent:
Professor, M.D. Christopher K. Glass
University of California
Department of Cellular & Molecular Medicine
Department of Medicine

Betygsnämnd:
Docent Line Grönning-Wang
University of Oslo
Department of Nutrition

Professor Björn Vennström
Karolinska Institutet
Department of Cell and Molecular Biology
Docent Tomas Burglin
Karolinska Institutet
Department of Biosciences and Nutrition

Stockholm 2011
ABSTRACT

The LXRs are important sensors and regulators of cholesterol homeostasis in several metabolic tissues including liver, intestine and macrophages. They regulate target genes involved in cholesterol-, lipid- and carbohydrate metabolism. Recently, the LXRs have emerged as important regulators of the innate and adaptive immune system and inflammation. In this thesis we have extend the knowledge of the specific coregulator requirement of LXR in cholesterol metabolism and the anti-inflammatory actions of LXR and LRH-1 in the hepatic acute phase response. Moreover, we also suggest that LXRs protects against the development of colitis.

In Article I we show that RAP250 has a critical role in the canonical TGF-b pathway and interacts with the intracellular mediators, Smad2 and Smad3. The interaction between RAP250 and Smad2/3 is dependent upon the second LXXLL motif in RAP250 and the MH2 domain in Smad2/3. Moreover, activation of the TGF-b and LXR signaling pathways synergistically regulates the expression of the LXR target gene ABCG1. Thus, the cross talk between LXR and TGF-b could play an important role in the cholesterol efflux pathway.

In Article II we demonstrate that LXR and the transcriptional co-regulator GPS2 mediates promoter specific induction of ABCG1 expression and subsequently increased cholesterol efflux from macrophages. GPS2 is selectively required for LXR induced transcription of ABCG1 and depletion of GPS2 diminishes ABCG1-mediated cholesterol efflux in macrophages. GPS2 and LXR authorise histone 3 lysine 9 demethylation-coupled activation of ABCG1. Activation and recruitment of LXR to regulatory LXR binding sites (LXRE) in the ABCG1 gene induce a communication between the promoter and the enhancer LXRE in the ABCG1 gene. Additionally, LXR and GPS2 interactions appear to be AF-2 independent, thus separated from the classical LXXLL interaction domain of common LXR transcriptional co-regulators.

In Article III we show that LXRs and LRH-1 dampened the hepatic acute phase response. This was due to ligand dependent SUMOylation of LXR and LRH-1, which further prevented the dissociation of the NCoR corepressor complex where GPS2 mediates the interaction between SUMOylated NRs and the NCoR corepressor complex. GPS2 binds to SUMO-1 and SUMO-2 via a domain located in the N-terminal part of GPS2, suggesting that SUMOylated LXR and LRH-1 bind to the corepressor complex via docking to GPS2 and this interaction depends on both the SUMO molecule and the receptor. Moreover, transrepression by LXR appears to exclude the heterodimeric partner RXR and in vivo data suggest that LXRb selectively inhibits hepatic APR.

In Article IV we report that the LXRs protect against DSS-induced colitis in mice. Clinical markers of colitis including weight reduction, colon length and diarrhea were significantly more severe in LXRb−/− and LXRαβ−/− mice compared to the wild type (WT) control mice. Further, LXRαβ−/− mice recovered more slowly from the colitis symptoms compared to WT mice. Activation of LXR in human colon cells under inflammatory conditions repressed the expression of several pro-inflammatory factors and LXR is recruited to the promoter of inflammatory genes. The above-mentioned data could be the reason for the increased infiltration of macrophages seen in LXR KO mice and the more severe immune response to DSS treatment in LXR KO compared to WT mice.

In summary, our studies have identified novel molecular mechanisms of LXR signaling in metabolism and inflammation. Modulation of LXR activity affects the expression profiles of both metabolic pathways and inflammatory signaling pathways. Our observations support the notion that LXRs are attractive drug targets for therapeutic intervention of metabolic disorders and inflammatory diseases.