Crystallographic studies of the xenobiotics receptor PXR bound to pharmaceutical and environmental compounds

Coralie CARIVENC (Centre de Biologie Structurale, CNRS UMR5048, Inserm U1054, UM, Montpellier)
Quentin DEROSA (Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Montpellier)
Savannah SIROUNIAN (Centre de Biologie Structurale, CNRS UMR5048, Inserm U1054, UM, Montpellier)
Marina GRIMALDI (Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Montpellier)
Abdelhay BOULAHTOUF (Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Montpellier)
Vanessa DELFOSSE (Centre de Biologie Structurale, CNRS UMR5048, Inserm U1054, UM, Montpellier)
Patrick BALAGUER (Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Montpellier)
William BOURGUET (Centre de Biologie Structurale, CNRS UMR5048, Inserm U1054, UM, Montpellier)

Abstract

The xenobiotics receptor PXR is a major chemosensory protein that helps the organism adapt to its chemical environment. Indeed, humans are chronically exposed to hundreds of external chemicals of natural origin or produced by human activities. Referred to as xenobiotics, they include environmental pollutants, food components, cosmetics or drugs. A vast body of literature links exposure to xenobiotics with increased incidences of reproductive, developmental, metabolic, or neurological disorders, and even cancers. PXR has the unique property to sense a large variety of xenobiotics and to regulate the expression of phase I (e.g. CYP3A4), II (e.g. UGT1A1) and III (e.g. MDR1) detoxifying enzymes and transporters, leading to the excretion of chemicals out of the organism. However, activation of this pathway can also lead to side effects, such as cross-inhibition or the generation of toxic intermediates, in particular when organisms are repeatedly exposed. Prolonged activation of PXR has been shown to provoke endocrine disruption, drug interactions, resistance to cancer therapy, cell proliferation or increased risk of metabolic diseases. It is therefore important to characterize the interaction of PXR with xenobiotics to better understand, predict and combat the impact of chemicals on human health through their binding to this receptor. Here, we present the structural and functional characterization of the interaction between PXR and two approved drugs (nimodipine and linaraftate), one natural flavor widely used in cosmetics and food industry (sclareol), and one environmentally relevant halogenated derivative of the emblematic endocrine disruptor bisphenol-A (2,2'-dichloro bisphenol-A). The crystal structures reveal different mechanisms of interaction with PXR that help a better understanding of the diverse PXR binding and activation properties of the compounds.