

Division of Targeted Research

National Research Programmes

Wildhainweg 20

CH-3001 Berne

Tel. +41(0)31 308 22 22

Fax +41(0)31 305 29 70

E-Mail nfp@snf.ch

NRP Endocrine Disruptors

Intermediate Summary

Environmental disrupter actions in live cells and animals : Elucidating molecular mechanisms of PPAR pathway alterations.
--

Project leader

Prof. Walter Wahli

Team member

Prof. Béatrice Desvergne

Project number

4050-066588

English Summary

Effects of endocrine disruptors on the nuclear receptor PPAR.

Effects of endocrine disruptors on the action of the Peroxisome-Proliferator Activated Receptors in mammalian cells and during early development in *Xenopus laevis*.

Project description:

Research questions

Several pollutants present in the environment have been shown to activate peroxisome proliferator-activated receptors (PPARs), which are key regulators of glucose and lipid homeostasis and have also been shown to play a role in inflammation and wound healing. Hence, endocrine disruptors may affect health and ecosystems not only by impairing reproduction functions but also through the disturbance of other pathways important for development and survival. We want to understand how endocrine disruptors interfere with PPAR-regulated processes at the level of the cell and of the organism, using two different approaches. We are using state-of-the-art fluorescence microscopy techniques to study how endocrine disruptors modulate the capacity of PPARs to regulate gene expression. We are also monitoring and dissecting the impact of endocrine disruptors on the early development of *Xenopus laevis*, an aquatic species where PPARs were shown to be present during embryogenesis.

Results

Our first term in the PNR50 project demonstrated two key points: (i) live cell microscopy is a useful tool to characterize at the molecular level the localization and mobility of nuclear receptors and cofactors, and to analyze in that regard the effects of endocrine disruptors, (ii) PPARs from aquatic species such as *Xenopus* can be activated by endocrine disruptors such as MEHP and the abnormal activation of PPARs at the very beginning of embryogenesis causes permanent developmental defects.

Perspectives

We will pursue in these directions by (i) studying by live cell microscopy the transport of endocrine disruptors in the cell as well as their action on nuclear receptor mobility and interaction with other nuclear components important for gene regulation, and (ii) further dissecting at the tissue and molecular levels the actions of endocrine disruptors that interfere with PPAR pathways during *Xenopus* development and metamorphosis.