

NRP Endocrine Disruptors

Final Summary

Original project title Environmental disruptor actions in living cells and animals : elucidating molecular mechanisms of PPAR pathway alterations.
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Disrupted receptor action in cultured cells, embryos and whole organisms

Hormones and pollutants modulate the activity of nuclear receptors, which control gene expression. We studied the activity of receptors in the cell nucleus under the influence of compounds used as fragrances or plasticizers and also analyzed these compounds in whole body physiology in the mouse and embryonic development of amphibians.

Research questions

The ability of pollutants to affect human health is a major concern, justified by the wide demonstration that reproductive functions are altered when these compounds act as endocrine disruptors. Toxicology approaches have demonstrated that different xenobiotics like fragrances and phthalate plasticizers can directly influence estrogen receptor and peroxisome proliferator-activated receptor activity, respectively. What is missing is a molecular understanding of these events that will give a key fundamental basis to the concept of endocrine disruption. Using compounds as the ones mentioned above as a model, the project aimed at characterizing their molecular mechanisms of disturbance within the cell nucleus and the developmental and physiological consequences of their disruption of receptor pathways.

Results

The project led to significant progress in the technological live-cell imaging analyses and in the understanding of the molecular mode of nuclear receptor action. We discovered ligand-specific mobility patterns of human estrogen receptor in living breast cancer and found that this receptor forms a limited number of distinct complexes with other nuclear components. In a library of 250 representative compounds used as fragrances, we found a number of molecules with xenoestrogenic activities. Additional nuclear imaging analyses highlighted key mechanisms in metabolic disruption that are also instrumental in the context of selective peroxisome proliferator-activated receptor (PPAR) modulation, a promising field for new therapeutic development based on tuning the activity of PPAR. While some cellular observations suggested that exposure to phthalates could have detrimental effects leading to obesity, results in mouse models actually demonstrate that exposure to the phthalate plasticizer DEHP protects from diet-induced obesity. This observation suggests counterbalancing effects of two PPAR isotypes on energy expenditure and adipogenesis.



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Investigating the mechanism of action of PPAR during frog development validated the concept that PPAR can be disrupted by exogenous ligands in early embryonic development.

Perspectives

Our findings open up new routes to elucidate gene expression regulation and to detect and distinguish pharmacologically and toxicologically active, as well as endocrine disrupting compounds in vivo. Technologies developed within this project might become of broad applicability in screening biochemical networks for fundamental research and in particular for fast environmental analytical screening