

NRP Endocrine Disruptors

Final Summary

Original project title Biological activity of complex mixtures of endocrine disruptors
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Disruption of endocrine-mediated gene expression

The vast majority of biological responses to hormones, natural compounds or man-made chemicals with estrogenic activity culminate in the reprogramming of gene expression in target tissues.

Research questions

Previous epidemiologic studies have linked prolonged estrogen exposure to an increased risk for breast or endometrial cancer. There is also widespread concern that synthetic chemicals with estrogenic activity may pose a threat to human health. In contrast, plant-derived estrogens (phytoestrogens) are thought to confer beneficial health effects, for example by protecting from breast and prostate cancer. These different findings prompted a large-scale molecular analysis to compare the global changes of gene expression in human cells in culture exposed to diverse estrogenic stimuli.

Results

- We found that by monitoring a broad molecular fingerprint involving multiple endpoints, as opposed to the determination of a single parameter, the detection of cellular reactions becomes more specific and sensitive
- A large-scale analysis is particularly useful for the evaluation of mixture effects because it provides a suitable method to detect simultaneously the activation or repression of separate pathways
- Complex mixtures of estrogenic compounds act in an additive manner by increasing both the amplitude of gene expression changes and the range of affected human genes

- Estrogenic mixtures extracted from biological samples (breast milk, soy beans, animal adipose tissue, cow milk) induce identical gene expression profiles in human breast cancer cells
- These gene expression profiles depend on the particular pattern of estrogen receptor subtypes in the target cells
- Phytoestrogens seem to exert tumor-suppressive effects through an estrogen receptor subtype beta-mediated attenuation of growth-promoting signals. However, this beneficial activity is abrogated when, during the course of tumor development, the estrogen receptor subtype beta is gradually lost.

Perspectives

Based on our findings, a recommendation to reduce the intake of estrogenic chemicals (including phytoestrogens) in the particular age groups at highest risk for breast and prostate cancer should be further evaluated. In collaboration with an industrial partner, we are developing a focussed low-density microarray chip, which displays the sequences of selected estrogen-dependent genes, for the high-throughput analysis of food, breast milk, animal tissues, water or environmental samples.