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Estrogens and alkylphenols promote proliferation of the seminoma-like TCam-2 cell line through ERα36-dependent pathways.

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Background

Seminoma, originated from carcinoma in situ cells (CIS), is one of the main causes of cancer in young men. Postpubertal development of these testicular germ cell tumors suggests a hormone-sensitive way of CIS cell proliferation induction probably stimulated by lifelong exposure to endocrine disruptors. In a first step to understand the mechanisms underlying the deleterious effects of endocrine disrupting compounds on germ cells, we aimed to decipher the estrogen-dependent transduction pathways in TCam2 cells. Then, we began to assess the effects of a [4tert-octyl + 4-nonylphenol] mix on testicular germ cell tumors in vitro and in vivo.

Material and methods

In this study, we used the unique seminoma TCam-2 cell line which do not express the canonical ERα66 estrogen receptor but ERα36, a truncated isoform retaining the DNA-binding, partial dimerisation and ligand-binding domains and a specific C-term 27 aa sequence. Cells were exposed to either estradiol at concentrations in the range of those detected in an adult human testis or to a [4tert-octyl + 4-nonylphenol] mix used at low doses - i.e. those found in food and drinking water. In vitro, we performed cell proliferation assays, siRNA- or shRNA-directed knockdown, microarray-directed gene targeting and signaling pathways identification after short term (1h) or mid-term (24h or 48h) treatment. We also addressed the question of TCam-2 derived tumor growth in xenografted Nude mice treated with the [4tert-octyl + 4-nonylphenol] mix.

Results

We demonstrate in vitro that estradiol and the alkylphenol mix trigger TCam-2 cell proliferation through ERα36-dependent pathways. We establish that estradiol can activate GPER-cAMP/PKA signaling pathway. Stable ERα36 knockdown indicates that ERα36 is (i) necessary for cell proliferation (ii) a downstream target of estradiol-activated GPER/PKA/CREB pathway, (iii) required for estradiol-dependent EGFR expression. The [4tert-octyl + 4-nonylphenol] mix signaling pathway is clearly ERα36 dependent but seems to be partially non-estrogenic. Finally, we show that the [4tert-octyl + 4-nonylphenol] mix stimulates tumor growth in TCam-2 xenografted Nude mice.

Conclusions

Our results highlight the functional role of ERα36 in context of seminoma cell proliferation and the importance of testing ERα36 in vivo as a possible marker for endocrine disruptor susceptibility.

Références Bibliographiques : Wallacides et al. (2012) Mol. Cell. Endocrinol. 350(1):61-71.

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