Transgenerational effects of ERalpha36 over-expression on mammary gland development and molecular phenotype: clinical perspective for breast cancer risk and therapy.

Clémence Chamard-Jovenin, Amand Chesnel, Emmanuel Bresso, Chloé Morel, Charlène Thiébaut, Malika Smail-Tabbone, El-Hadi Djermoune, Marie-Dominique Devignes, Taha Boukhobza, Hélène Dumond

To cite this version:
Clémence Chamard-Jovenin, Amand Chesnel, Emmanuel Bresso, Chloé Morel, Charlène Thiébaut, et al. Transgenerational effects of ERalpha36 over-expression on mammary gland development and molecular phenotype: clinical perspective for breast cancer risk and therapy. 21st World Congress on Advances in Oncology and 19th International Symposium on Molecular Medicine, Oct 2016, Athens, Greece. hal-01416469

HAL Id: hal-01416469
https://hal.archives-ouvertes.fr/hal-01416469
Submitted on 26 Jan 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License
Transgenerational effects of ERalpha36 over-expression on mammary gland development and molecular phenotype: clinical perspective for breast cancer risk and therapy.

Clémence Chamard-Jovenin, Amand Chesnel, Emmanuel Bresso, Chloé Morel, Charlène Thiébaut, Malika Smail-Tabbone, El-Hadi Djermoune, Marie-Dominique Devignes, Taha Boukhobza and Hélène Dumond.

1CNRS-Université de Lorraine, UMR 7039, Centre de Recherche en Automatique de Nancy, BP70239, Vandœuvre-lès-Nancy, F-54506, France.
2LORIA, CNRS UMR 7503, INRIA, Villers les Nancy, France.
E-mail: clemence.jovenin@univ-lorraine.fr

Growing source of evidence suggests that exposure to estrogen mimicking agents is a risk factor for breast cancer onset and progression. Long chain alkylphenols are man-made compounds still present in household products, industrial and agricultural processes, leading to a global environmental and human contamination. These molecules are known to exert estrogen-like activities through binding to classical estrogen receptors. Recently, we have demonstrated that a realistic mixture of 4-tert-octylphenol and 4-nonylphenol can stimulate proliferation and modulate epigenetic status of testicular cancer germ cells through a rapid, Estrogen Receptor alpha 36 (ERα36)- dependent non genomic pathway (Ajj et al, 2013; doi: 10.1371/journal.pone.0061758). In a retrospective study of breast tumor samples, we also validated ERα36 expression as a reliable prognostic factor for cancer progression from an estrogen dependent proliferative tumor toward an estrogen dispensable metastatic disease (Chamard-Jovenin et al, 2015; doi: 10.1186/s12918-015-0178-7).

Since high ERα36 expression enhances expression of migration/invasion markers in breast tumors, we addressed the question of its involvement in response to alkylphenol exposure in vitro (MCF-10A mammary epithelial cell line and MCF-7 estrogen-sensitive cancer cells) and in vivo (C57BL mice).

A male inherited transgenerational model of exposure to environmentally relevant doses of an alkylphenol mix was set up in C57BL/6J mice to determine whether and how it impacts on mammary gland morphogenesis. Human mammary epithelial MCF-10A cells were exposed to similar doses to decipher the molecular mechanisms involved by a combination of transcriptomic study, cell phenotype analyses, functional and signaling network modeling. The relevance of mouse phenotype extrapolation to human risk is discussed.

Mouse mammary gland exposed transgenerationally to the alkylphenol mix displayed a neoplastic-like histology. This phenotype was correlated with the enhanced proliferation, migration ability and apoptosis resistance observed in vitro on human mammary epithelial cells and mediated by the estrogen receptor variant ERα36.

Since cellular phenotypes are similar in vivo and in vitro and involve the unique ERα36 human variant, such consequences of alkylphenol exposure could be extrapolated from mouse model to human. Low dose alkylphenol transgenerational exposure could promote abnormal mammary gland development and subsequently increase the risk of breast cancer at ageing.

This work is supported by ANSES (n°2012-2-014) and INSERM/Plan Cancer (2013-2016).