



**Karolinska
Institutet**

Institutet för Miljömedicin

Gender Differences in Chemical Carcinogenesis

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Karolinska Institutet offentligen försvaras i Atrium, Nobels väg 12, Solna Campus.

Tisdagen den 10 december, 2013, kl 09.15

av

Sandeep Kadekar

M.Sc.

Huvudhandledare:

Dr. Ilona Silins
Karolinska Institutet
Institute of Environmental Medicine

Bihandledare:

Professor Ulla Stenius
Karolinska Institutet
Institute of Environmental Medicine

Professor Johan Högberg
Karolinska Institutet
Institute of Environmental Medicine

Dr. Kristian Dreij
Karolinska Institutet
Institute of Environmental Medicine

Professor Ralf Morgenstern
Karolinska Institutet
Institute of Environmental Medicine

Fakultetsopponent:

Professor Kirsi Vähäkangas
University of Eastern Finland
School of Pharmacy/Toxicology
Faculty of Health Sciences

Betygsnämnd:

Docent Petra De Verdier
Karolinska Institutet
Department of Oncology-Pathology

Docent Annika Wallberg
Karolinska Institutet
Institute of Environmental Medicine

Professor Joseph DePierre
Stockholm University
Department of Biochemistry and Biophysics

Stockholm 2013

ABSTRACT

Gender differences in cancer incidence and mortality is a regular finding in epidemiological studies. In addition to reproductive organs this pattern is also seen in non-reproductive organs, with men being the most affected gender for the majority of cancer-sites. The underlying reasons for the observed disparity are not known, but can partly be explained by differences in exposures, lifestyle factors and biological factors such as hormones and metabolism. Exposure to carcinogenic chemicals is one of the risk factors for cancer, however little is known about gender-specific sensitivity to carcinogens. The overall aim of this thesis was to investigate gender differences in susceptibility to chemical carcinogens and the underlying mechanisms.

In the National Toxicology Program (NTP) database detailed technical reports from 2-year bioassays on male and female rats exposed to the same concentration of chemical in well-controlled environments is publicly available. In the first paper, 477 chemicals tested on rats were evaluated for possible gender differences in the carcinogenic effect. The analysis of NTP bioassays showed that male rats were more affected than females. In a total of 278 carcinogens, 201 showed statistically significant gender differences in at least one non-reproductive organ. 69 carcinogens induced male-specific tumors and 19 induced female-specific tumors. Male-specific tumors included for example mesothelioma, kidney-, skin- and pancreas tumors, while female-specific tumors included neoplasms in pituitary, bone marrow and lymphoid tissues, lung and urinary bladder. The study further showed that genotoxicity was more common among male-specific carcinogens, compared to female-specific carcinogens.

Based on the results from the NTP study eight male-specific pancreatic carcinogens were studied in more detail in the second study. To find common mechanisms that could clarify the male-specific effect of these carcinogens, the published literature on the eight chemicals was analyzed using a text-mining tool, CRAB. This analysis proposed inflammation as a common mechanism for these carcinogens. In *in vitro* studies it was found that all eight carcinogens increased the levels of the inflammatory protein Autotaxin (ATX), in parallel with increased invasiveness. Testosterone further increased ATX levels, alone and in combination with carcinogens. These data suggests that ATX may be a target for carcinogens that promote pancreatic tumor development.

In the third study, the role of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), Polychlorinated biphenyl (PCB) and estradiol on benzo(*a*)pyrene (BaP)-induced apoptosis and p53 signaling was investigated. The results showed that BaP induced apoptosis increased nuclear p53 and phosphorylation of FOXO3a. The apoptotic effect of BaP was attenuated by pretreatment of TCDD, PCB or estradiol, leading to a further increase in nuclear p53 and decreased levels of phosphorylated FOXO3a. FOXO3a dephosphorylation was further showed to be essential for the attenuated apoptosis and nuclear trapping of p53, which resulted in restoration of BaP-induced apoptosis. The data suggests an interaction between p53 and FOXO3a, which leads to an attenuated BaP-induced apoptosis in cells co-exposed to TCDD, PCB153 or estradiol. This study also reflects the effect of estradiol as a modulator of the toxic response caused by carcinogens.

In conclusion, the results of this thesis show that male rats are more sensitive to chemical carcinogens compared to female rats. The data further suggests interactions between hormones and carcinogens that could be important for the cellular response to carcinogens.