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Research project J3-2535

The importance of androgens in hormone dependent diseases: impact on diagnostics and therapy

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Project group: SICRIS

Project description:

Hormone dependent cancers as breast cancer (BC), endometrial cancer (EC) and ovarian cancer (OC) affect more than 2.7 million of women/year and cause 22% of cancer-related deaths/year. EC represents the most common gynaecological cancer and OC the most deadly of hormone dependent cancers. In developed countries, the number of new cases of EC and OC is still increasing every year. These cancers predominately affect post-menopausal women and thus rely on the local formation of active steroid hormones. However, the altered mechanisms of local steroid biosynthesis and actions are not completely understood and there is a significant lack of knowledge about the involvement of androgens in these diseases. The published data on the roles of androgens in EC and OC seems contradictory; while epidemiological studies associate elevated levels of androgens with increased risk of EC, studies in cell lines suggest that androgens may have anti-proliferative actions. For OC recent epidemiological data revealed difference in associations between androgens and individual histotypes, with inverse correlations seen for high grade serous OC. In contrast, cell based studies indicate that androgens stimulate proliferation and chemoresistance of OC. These inconclusive data call for further investigation of local androgen formation and actions in EC and OC.

In post-menopausal women androgens are formed in the ovary, adrenal gland and in different peripheral tissues. Androgens can also be formed in cancer tissue from androgen precursors dehydroepiandrosterone-sulfate (DHEA-S), DHEA and androstenedione via classical and alternate pathways by the consecutive actions of a series of enzymes, sulfatase (STS), 3beta-hydroxysteroid dehydrogenases (HSD3B1/HSD3B2), aldo-keto reductase 1C3 (AKR1C3) and 5alpha-reductases (SRD5A1, SRD5A2 and SRD5A3). In addition to the classical androgens adrenal gland forms 11-oxygenated androgens, which can be activated in the peripheral tissue to potent 11-ketotestosterone and 11-keto-dihydrotestosterone by the actions of 11beta-hydroxysteroid dehydrogenase (HSD11B2), AKR1C3 and SRD5A enzymes. The formation of these androgen metabolites has not yet been studied in cancerous tissue.

The proposed project has the following aims i) to examine biosynthesis, metabolism and actions of androgens in endometrial and ovarian control cell lines and tissues and corresponding cancer cell lines and tissues and ii) to evaluate diagnostic and/or prognostic potential of 11-oxyandrogens by determining concentrations of these androgens in blood/tissue samples from patients with EC and OC and in control patients. The aims of the project will be achieved by nontargeted and targeted transcriptomics and targeted metabolomics followed by modelling studies. The unique aspects of the proposed project comprise; i) androgen profiling in EC and OC, focusing on 11-oxygenated androgens, ii) nontargeted transcriptomics to illuminate interplay between androgen action and chemoresistance, and iii) evaluation of diagnostic/prognostic potential of 11-oxygenated androgens. The project aims to advance understanding of androgens' action in EC and OC and the mechanisms of chemoresistance in OC; and may thus contribute to identification of novel targets for treatment and diagnostic/ prognostic biomarkers of these diseases. The proposed project will be performed in collaboration between Faculty of Medicine, University of Ljubljana, University Medical Centre Ljubljana, and University of Birmingham, UK.

Bibliography: SICRIS