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Research project J3-8212

The importance of the intracrine estrogen action in hormone dependent diseases – impact on therapy

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Project group: [SICRIS](#)

Project description:

Hormone dependent cancers as breast cancer (BC), endometrial cancer (EC) and ovarian cancer (OC) **represent 35% of all cancers in women.** Worldwide, these cancers occur in more than 2.2 million of women/year and comprise 21% of cancer-related deaths/year. **Hormone-dependent cancers develop mainly in the postmenopausal women** and thus **rely on the local formation of active steroid hormones.** However, the altered mechanisms of steroid hormone actions in these diseases are still not completely understood. In target organs, **active estrogens can be formed from precursor steroid hormones,** mainly dehydroepiandrosterone-sulfate (DHEA-S), and estrone-sulfate (E1-S) after their uptake into cells through the transporter proteins of the organic anion-transporting polypeptide (OATP) and organic anion-transporter (OAT) families and further activation to the most potent estrogen, estradiol by a series of enzymes. On the other hand, the ATP Binding Cassette (ABC) transporters are responsible for active transport of E1-S and DHEA-S from the cells. The combination of **altered uptake of steroid precursors, changed intracrine action, in concert with changes in the metabolism and excretion may have major roles in the development of hormone-dependent cancers.** Although the importance of estrogens in development of BC have been investigated and partially explained, **much less is known about the mechanisms of estrogen action in EC and OC.** In particular, **the uptake and excretion of precursor steroids and estrogen metabolites via the transporter proteins of the OATP, OAT and ABC families have so far deserved no attention in these two diseases.**

Menopause is associated with increased incidence of hormone-dependent cancers, but also with increased risk for osteoporosis, cardiovascular diseases and with characteristic vasomotor symptoms. **A large number of women use different phytochemicals as “natural” hormone replacement therapy (HRT)** to treat the symptoms and conditions associated with menopause. However, **these phytochemicals may interfere with their hormone system, and may thus also affect the risks of EC and OC.** Although “natural” HRT including red clover and soy extracts have been widely studied, **less is known about black cohosh extracts,** especially about their interplay with the uptake of steroid precursors, estrogen biosynthesis and action.

The objectives of the proposed project are 1) **to examine the uptake of steroid precursors, biosynthesis, metabolism and action of estrogens** in model endometrial and ovarian cell lines and corresponding tissues; 2) **to explore the effects of “natural” HRT on the uptake of steroid precursors and the intracrine estrogen action** in ovarian and endometrial cell lines and 3) **to evaluate the systemic effects of “natural” HRT** by measuring concentrations of estrogens and estrogen metabolites in blood from postmenopausal women before and after use of “natural” HRT. The aims of this project will be achieved by targeted transcriptomics, proteomics and metabolomics approaches and further modeling studies. **The unique aspects of the proposal** are 1) **use of LC-HMRS** which allows simultaneous quantification of steroid precursors, active estrogens and their conjugates; 2) **availability of unique OC cell lines** as models of sensitive/resistant tumors, and 3) assessment of **local and systemic effects of phytochemicals** followed by **mathematical modelling**. The project aims to advance 1) understanding of intracrine estrogen action in development of EC and OC; 2) identification of novel targets for treatment of these diseases and 3) recognition of molecular effects of »natural« HRT. The proposed project will be performed jointly by **Faculty of Medicine, University of Ljubljana, University Medical Centre Ljubljana** and **Faculty of Natural Sciences, University of Vienna** and will combine expertise on steroid hormones (Ljubljana), transporter proteins (Vienna) and hormone dependent diseases (Ljubljana).

Bibliography: SICRIS