Metabolic network of estrogen metabolism in human mammary gland: Validation and influence of soy isoflavones

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A contributing factor to breast cancer development is the female sex hormone 17β-estradiol (E2), which can be converted to reactive metabolites known to form adducts with the DNA. Intake of soy isoflavones (IF, for example soy-based food) is known to reduce the risk of breast cancer in Asian women, whereas in Western women no association has been observed. Hence, the influence of IF on the activation of E2 to genotoxic metabolites in female mammary gland tissue was investigated using computational based metabolic network modelling. Based on tissue levels of E2 and estrone quantified by means of GC-MS/MS and on transcript levels of 22 E2 metabolizing enzymes determined by quantitative TaqMan PCR, the metabolic flux of DNA adducts of 45 mammary gland tissues, of women on soy-rich or soy-deficient diet or taking an IF-rich extract, were modelled. In addition to 159 reactions of the E2 metabolism the network model also contained 66 reactions of energy metabolism, using published microarray data from human platelets as constraints. Furthermore, tissue levels of genistein and daidzein, their conjugates and their bacterial metabolites were quantified by means of UHPLC-MS/MS. Then, linear regression models with metabolic flux of estrogen DNA adducts as dependent variable and age, body mass index, number of pregnancies, smoking habits, intake of estrogen active drugs and IF tissue levels (all as explanatory variables) were examined. 17 reasonable combinations of tissue levels of IF aglyca, conjugates and biotransformation products were used as explanatory variables in 17 individual models. No IF-related explanatory variable significantly influenced the metabolic flux of DNA adducts, whereas both age (negative relationship) and intake of E2-releasing drugs (positive correlation) had a significant influence. DFG, Le-1329/10-1.

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