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COMMENTS TO THE PAPER "TOOLS TO EVALUATE ESTROGENIC POTENCY OF DIETARY PHYTOESTROGENS: A CONSENSUS PAPER FROM THE EU THEMATIC NETWORK "PHYTOHEALTH" (QLKI-2002-2453)"

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This paper brings up many important issues regarding plant-derived compounds with estrogenic activity. The authors correctly emphasize the need for control of estrogenicity of foods containing phytoestrogens in view of the significant health effects of various estrogenic derivatives. This is particularly essential in the light of the current wave of enthusiasm for vegetarian food in general and phytoestrogens in particular.

The authors give several examples of in vitro assays to test estrogenicity of foodstuff. Some in vivo assays are also described. Needless to say, the latter assays are very important since it is to be expected that many compounds in food do not become estrogenic until after metabolism in the body. Another important aspect that needs to be addressed is whether food derived estrogens primarily act on one or the other of the two ER isoforms.

It has been known since several years that certain phytoestrogens preferentially bind to ERβ rather than to ERα (Kuiper et al., 1998) but individual phytoestrogens may show the opposite specificity.

Our view on estrogen signaling has undergone dramatic changes since the discovery of ERβ in 1995 (Kuiper et al., 1996). Based on studies from our own laboratory and those of other workers in the field it seems as if the two ER isoforms in many cases have a yin-yang relationship where ERα often represents the "proactive" principle whereas ERβ counteracts the actions of ERα (Lindberg et al., 2003). Experiments involving mice with deleted ERα and/or ERβ genes as well as studies involving use of recently commercially available ER isoform specific chemical compounds (PPT for ERα, DPN for ERβ) have made it possible to start to delineate ERα- and ERβ-regulated signal transduction networks, respectively.

Examples of tissues that are especially rich in ERβ include the prostate gland, lungs, gastrointestinal tract, urinary tract and immune system. ERα predominates in the uterus and liver. The CNS, mammary gland and many other tissues contain both isoforms. Mice with deleted ERβ show a plethora of phenotypes, including lung fibrosis, prostate hyperplasia, and neuronal degeneration in the CNS, myeloproliferative disease and subfertility, indicating important roles of ERβ in physiology.

Administration of ERα and ERβ specific ligands, respectively, and subsequent analysis of gene expression data in several tissues using microarray, indicate that the two ER isoforms often appear to regulate the same genes but in opposite directions, in agreement with a yin/yang scenario. There are also exceptions to this rule. Anyway, it would seem as if the old definitions of "estrogenic" activity need to be replaced with a more modern nomenclature, in line with the discoveries of the recent ten years. The terms "α-estrogenic" and "β-estrogenic", respectively, referring to effects mediated by ERα and ERβ would appear to be adequate. This distinction is indeed quite important in view of e.g. the findings that ERα has a proliferative action whereas ERβ is antiproliferative in several hormone dependent tissues.

It should also be mentioned that many drug companies have extensive programs aimed at developing new drugs targeting ERβ for several indications, e.g. inflammatory bowel disease, rheumatoid arthritis, endometriosis, prostatic disease as well as depression. Some of these drugs are in Phase II clinical trials. This exciting development underlines the potential medical significance of the ERβ signaling pathway.

Finally, it should be pointed out that knowledge of whether certain phytoestrogens are mainly α-estrogenic or α-estrogenic might be of direct significance for our understanding as to how phytoestrogens might affect metabolic diseases. Activation of ERα in the liver has been reported to alleviate glucose intolerance (Bryzgalova et al., 2006) whereas activation of ERβ in skeletal muscle downregulates GLUT 4 (Barros et al., 2006) which should lead to decreased glucose tolerance.

Against the background described above it appears essential to complement available test batteries for estrogenicity of phytoestrogens by more modern approaches to allow distinction of ER signaling via the two ER isoforms. If the idea is to initiate a European program for systematic testing of biological activities of various phytoestrogens it would seem to be a good idea to first

develop new and up-to-date assays before embarking on such an important undertaking with its high potential impact for public health.

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