

Editorial

FROM PHYTOESTROGENS TO OBESITY AND THE METABOLIC SYNDROME: HEALTH FROM FOOD AND FOOD FOR HEALTH

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Phytoestrogens are defined as naturally occurring molecules of plant origin, capable of acting as estrogen hormone mimetics or antagonists, but also as endocrine disruptors (Committee on Toxicity of Chemicals in Food 2003). Public research and industry have posed increasing interest in these plant-derived substances in the last decade. Many of them have been marketed as dietary supplements or nutraceuticals with health claims, leading to significant increase in phytoestrogen consumption levels in the Western population (Davis et al. 1999). Even though several reports are available suggesting health-promoting effects for these compounds in preventing age-related diseases such as atherosclerosis, hormone-dependent cancers, and osteoporosis (Davis et al. 1999; Adlercreutz 2002), the mechanistic aspects of their activity have not been fully clarified and a wide consensus of the *pros* and *cons* of their use in humans has not been reached by the scientific community. It is clear however that, similarly to natural estrogens, these dietary compounds act on cellular responses through binding to the estrogen receptors (ERs): their beneficial or adverse effect is unpredictable, because it depends on their capacity to act as agonist or antagonist in each cell type, on the tissue and cell-specific expression of ER-coregulators, and also on the endogenous estrogen levels. Such interactions have been reported for both the “genomic” mode of action of ERs, based on binding of the activated receptors with the Estrogen Responsive Elements (EREs), or interacting with other transcription factors, such as AP-1 and SP-1, as well as for the fast “non genomic” effects that proceed through kinase-mediated signal transduction pathways such as ERK/MAPK, PI3K/AKT and PKC (Harris et al. 2005; Waring & Harris 2005).

Besides isoflavones, the most common and studied polyphenols, other molecules have been reported to interact with steroid receptors, among which flavonoids, tannins, stilbenes, lignans, tocotrienols. It might appear somehow surprising that so many different molecules share the ability to regulate a signaling pathway, especially considering that specificity, which is the ability to discriminate between different ligands, is the most important and typical feature of cellular signaling mediated by nuclear receptors (Vasudevan et al. 2002; Smith & O'Malley 2004).

One of the most intriguing hypothesis to justify the existence of so many naturally occurring molecules capable of interacting with, and modulating estrogen-dependent pathways, was built on the basis of studies dealing with the origin and evolution of steroid receptors. These studies elegantly demonstrated that ligand binding is an evolutionary late event for steroid receptors, including ERs, from a single original ancestor. It is intriguing to hypothesize that this ancestral membrane protein could act as “xenobiotic sensor” (McLachlan 2001; Thornton et al. 2003). Starting from this original receptor progenitor, evolution proceeded by ligand exploitation and serial genome expansion, but the ability to interact with the environment was maintained both in plants and plant-eaters, in a classical example of co-evolution. The ability of a plant to disrupt estrogen-mediated response in herbivorous represents, in fact, an expedient strategy aimed at discouraging from being eaten (Wynne-Edwards 2001). If this hypothesis is true, the conceptual distance between specific endogenous hormones and exogenous environmental molecules able to either mimic or modulate nuclear receptor-mediated signaling is probably closer than previously thought. This perspective opens new avenues of research and understanding of the mechanism of action of ERs and, at the same time, of the complex interplay between the environment, including diet, human health and disease. Identification of the most relevant dietary sources of bioactive compounds interfering with the endocrine system, as well as the definition of the variety of underlying mechanisms at molecular, cellular and physiological level, are among the priority targets for the scientific community in the future.

Endocrine disruption is a topic which will undoubtedly continue to receive attention throughout all sectors of the society, and the debate is likely to intensify between pharmaceutical companies and public health organisms. Both parts will call for urgent need of more research. Assessment of the impact of long-term, low-dose exposure to such chemicals on human health remains a difficult task to achieve and so does a full understanding of the synergistic effects of the copious number of chemicals to which we are exposed. Most estrogenic compounds, and in particular those present in the normal diet, are likely to have low

potency. The majority of available studies focused on the effects of single molecules, thus providing a picture which is probably not adherent to reality. In “real life”, we are exposed to mixtures of chemicals often acting in concert, yielding an entangled network of effects which inevitably differ from those reported for single, isolated chemicals.

This third issue of *Genes & Nutrition* hosts 3 papers addressing estrogen signaling-related matters. The first one is the result of a special working group of the European Union Thematic Network “*Phytohealth*” (see www.phytohealth.org). This network was built around a cluster of three EU-funded projects dealing with health effects of phytoestrogens (*Phytos*, *Phytoprevent* and *Isoearth*), and involved 44 partners belonging to nutrition and agro-industrial research institutes, academic institutions, leading food manufacturers and Small-Medium Enterprises in a total of twelve European Member States and one Associated State. The objective of *Phytohealth* was to coordinate and synergize the European expertise in the field of phytoestrogens. The overall objective of the network was to integrate, expand and exploit the results obtained by each specific project group. Among an impressive number of different kinds of deliverables addressed to industry, scientists and consumers, *Phytohealth* has provided “consensus papers” dealing with three of the major topics in phytoestrogen research which are still open to debate: safety of utilization, health effects in postmenopausal women, and an evaluation of the most commonly used *in vitro* and *in vivo* tests for assessment of the estrogenic potency of phytoestrogenic compounds, with a special attention to food-related compounds. This latter report is published in the present issue of G&N and it is introduced by a commentary by Gustafsson. It is obviously a privilege for us to publish this consensus paper, in light of the increasing importance of the topic and its relevance to the scopes of our Journal.

The second paper in the table of contents of this issue also deals with the interaction of ERs with flavonoids. Although to a lesser extent in comparison with the most active isoflavones, different flavonoids have been reported to bind to both ER α and ER β , significantly affecting both the nuclear and the cytoplasmic activity of these receptors. In some cases ER activity was enhanced and in other cases decreased. Galluzzo and Marino elegantly present an overview of the state of the art of the knowledge on the molecular mechanisms underlying the estrogen-like activity of flavonoids, dissecting between the effects on “genomic” nuclear activity and on “rapid” cell signaling responses mediated by phosphorylation, triggered in both cases by their ability to bind to ERs. The authors provide an original conceptual background for a deeper understanding of the beneficial role of flavonoid intake on human health, and in particular on cancer cell proliferation.

A third manuscript deals with the implications of estrogen-related response on the onset of the metabolic syndrome, one of the major health concerns in industrialized societies, as it parallels the increasing incidence of obesity. It is a complex pathologic profile characterized by central obesity, hypertension, raised fasting glucose and triglyceride levels. Starcke and Vollmer have produced an original interpretation of the available data, indicating a potential linkage between the metabolic mechanisms underlying

development of this complex syndrome and the regulatory features of estrogenic compounds. The authors propose different candidate molecules for this link, all interplaying and sensitive to estrogen levels, and describe their putative contribution to this metabolic dysfunction. Interestingly, the conclusions of this work drive us back to the previous paper, creating a cross-talk that further indicates the importance of phytoestrogens as possible means of intervention to improve human health.

The fourth paper in this issue of *Genes and Nutrition* focuses on the genetics aspects of obesity and reviews the complex relationships existing between white adipose tissue, central nervous system, endogenous microbiota, and nutrition. This paper deals with selected aspects of the regulation of energy homeostasis, which are summarized and discussed according to the evidence that obesity, and its numerous related disorders, are a major concern in industrialized societies. The authors take into consideration the links existing between the “brains” (*i.e.* the central nervous system and the enteric nervous system) and white adipose tissue, emphasizing the expression of specific genes controlling adipogenesis as well as their nutritional regulation. A very interesting aspect of this review is the role of intestinal commensal flora, whose functional food claims and perspectives are also considered and discussed.

In perfect coordination with the contents of this issue, the section of literature highlights “Sideways glance” focuses on recent reports that underline the importance of genetic polymorphisms in the perilipin gene, encoding a key protein in adipose lipid metabolism and in body weight reduction strategies based on low-energy diets.

We believe that our readers will find good “food for their mind” in this issue.

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