Invited commentary

Mechanistic explanations for the chemopreventive action of soyabean isoflavones: reducing the possibilities

There is increasing evidence in favour of a link between diets high in soybeans, a rich source of the isoflavones genistein and daidzein, and reduced incidence of colon cancer and hormone-dependent cancers, such as breast cancer and prostate cancer (for review, see Bingham et al. 1998). A number of studies in animal models demonstrate a chemopreventive effect of soyabean and/or genistein. For example, dietary soyabean and genistein inhibited the growth of transplantable tumours in rats (Schleicher et al. 1999; Zhou et al. 1999) and dietary isoflavones were shown to reduce the induction of tumours in rats by chemical carcinogens (Onozawa et al. 1999).

The isoflavones are polyphenolic compounds with structural similarity to mammalian oestradiol and belong, therefore, to a family of compounds referred to as phyto-oestrogens. The reported effects of genistein on cells are wide-ranging and numerous. Actions potentially involved in the chemopreventive effect of genistein include effects mediated through binding to oestrogen receptors (ER) (Kuiper et al. 1997), inhibition of DNA topoisomerase (Markovits et al. 1989), antioxidant action (Wei et al. 1999; Suzuki et al. 2002) and effects on cell signalling pathways. The latter include inhibition of tyrosine-specific protein kinases (Akiyama et al. 1987), inhibition of epidermal growth factor-induced phosphatidylinositol turnover (Imoto et al. 1988), inhibition of nuclear factor-κ B activation (Davis et al. 1999) and stimulation of transforming growth factor β synthesis and/or release (Kim et al. 2001). Induction of apoptosis, well established as a response of cancer cells to genistein (Balabhadrapathruni et al. 2000; Salti et al. 2000), is a potential link between a number of these cellular effects and anti-cancer action. Oestrogen promotes breast-cell proliferation, possibly through reduced apoptosis, and is considered a risk factor for breast cancer (Nenci et al. 1988). Therefore, genistein-induced apoptosis in breast-cancer cells may be the result of antagonism of oestrogen effects at ER. Po et al. (2002) address this possibility in a study reported in the present issue of the British Journal of Nutrition.

Po et al. (2002) show that genistein bound to the ER-α expressed heterologously in (ER-negative) HepG2 cells to increase expression of a reporter gene under the control of the oestrogen response element. They also demonstrate that genistein failed to antagonise stimulation by 17β-oestradiol of reporter gene expression. In other words, genistein is reported to show oestrogenic rather then anti-oestrogenic activity. In agreement with these observations, the paper reports induction by genistein in MCF-7 breast cancer cells of pS2 and Bcl-2 mRNA. Both are transcripts of genes well established as oestrogen-responsive (Ciocca & Ellerdge, 2000). Po et al. (2002) also demonstrate that, in MCF-7 cells, genistein increased expression of Bak, an apoptosis-promoting factor (Chittenden et al. 1995), and reduced expression of Bcl-xL, a factor that inhibits apoptosis (Cheng et al. 1996). All effects reported occurred at concentrations of genistein that were shown to induce apoptosis in MCF-7 cells. The evidence presented, therefore, does not support an anti-oestrogenic effect of genistein at ER-α in driving apoptosis. Commensurate with this new evidence is the finding that human breast-cancer cell lines did not differ in their apoptotic response to genistein, irrespective of whether or not they expressed ER (Shao et al. 1998).

It has been established that variants of MCF-7 cells differ in, among other features, their ER status. Some variants express no ER whilst others express ER-α or ER-α and -β (Burow et al. 2000; Jacobs et al. 2000). Po et al. (2002) do not confirm the ER status of the MCF-7 cells used in their study. The apoptotic response to genistein of the MCF-7 cells might, therefore, be ER-β-mediated. The results of reporter gene experiments like those presented by Po et al. (2002), but using ER-negative cells transfected with ER-β rather than ER-α, will establish unequivocally whether genistein antagonises the action of 17β-oestradiol at ER-β. Similarly, the study by Shao et al. (1998) reporting that ER-positive and -negative breast-cancer cell lines did not differ in their anti-proliferative response to genistein did not distinguish between expression of ER-α and/or -β. Studies comparing the effects of genistein in cell lines of precisely defined ER status will be of value in establishing the relative importance of genistein interaction with the respective receptor subtypes in chemopreventive action.

Studies on the biological action of genistein using cell line models offer advantages in terms of precise dosing and ease of molecular analysis. A limitation of such studies, however, is that they focus on the biological actions of the parent compound. Genistein is extensively metabolised in vivo to glucuronides (Adlercreutz et al. 1995) and by cytochrome P450 to hydroxylated derivatives (Roberts-Kirchoff et al. 1999; Kulling et al. 2001). Furthermore, halogenated and nitrated derivatives of genistein can be formed as a result of reaction with oxidants produced by inflammatory cells (Boersma et al. 2001). It
has been proposed that the anti-cancer effect of soyabean isoflavones may be attributable partly to competitive inhibition of carcinogen-activating enzymes (Setchell et al. 1984). Whilst metabolism of genistein by enzymes endogenous to breast-cancer cell lines has been reported (Peterson et al. 1996), systemic metabolism and metabolism at the target site that requires enzymes not expressed in cell line models is likely to modulate the biological effects.

There remain many possible mechanisms through which soyabean isoflavones may effect chemopreventive action. The activity of isoflavone metabolites requires elucidation and, through polymorphism in the relevant enzymes, may have implications with regard to inter-individual variation in chemopreventive response to dietary isoflavonoids. In addition to potential effects mediated through binding to ER-α, relevant actions may be ER-β-mediated or mediated through non-oestrogenic pathways and may be cell-type specific. The paper presented by Po et al. (2002) makes an important contribution to this field of research by adding to accumulating evidence (e.g. Shao et al. 1998) that, at least in breast-cancer cell lines, effects through binding to ER may not be of fundamental importance.

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References


