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Suppression of Mammary Tumorigenesis by Soy Peptide

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Epidemiological studies suggest that dietary factors play an important role in the etiology of different types of cancer. The high consumption of soybean and soybean-related products has been suggested to contribute to risk reduction in breast cancer (1). Many components of soy including isoflavones, protease inhibitors, saponins, and inositol hexaphosphate, have been investigated in the search for candidates responsible for the chemopreventive effects of soy (2). Among these, the predominant isoflavone, genistein has been reported to inhibit protein tyrosine kinase and topoisomerase II activities. Although the chemopreventive effects and mechanism of genistein are well documented, the effect of soy peptide, which is the most abundant component of soy product, is not as well studied. In our study, we initiated investigations into whether soy peptides prepared by hydrolysis with combination of endo- and exopeptidase have any effect on the chemoprevention and suppression of breast cancer development. Administration of genistein-deficient soy peptide to rats of 8 weeks of age before and after carcinogen treatment revealed significant chemopreventive and tumor suppressive effects on 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced rat mammary tumorigenesis. To our knowledge, this is the first report to show the tumor suppressive effect of genistein-deficient soy peptide *in vivo* and *in vitro*.

It has been demonstrated that the natural dietary intake of many phytochemicals can block or suppress multistage carcinogenesis and also confer cancer chemoprevention. For example, resveratrol suppressed DMBA-induced rat mammary carcinogenesis by inhibiting NF-κB activation and expression of cyclooxygenase 2 and MMP 9 proteins (3). Furthermore, recent findings suggest the involvement of common molecular targets for various chemopreventive phytochemicals (4). Numerous intracellular signal transduction pathways converge with the activation of the transcription factors. Among target genes, NF-κB is an ubiquitous eukaryotic transcription factor that mediates the expression of genes involved in tumor promotion, angiogenesis, and metastasis. Activation of NF-κB blocks apoptosis and promotes cell proliferation (5,6). Overexpression of NF-κB is linked to the phenotypic changes that are characteristic of neoplastic transformation. Thus, it is a prime target of diverse classes of chemopreventive phytochemicals (7). Consistent with this observation, our findings demonstrate that administration of soy peptide diet suppresses expression of NF-κB protein as well as inducing both activation of caspase 3 and expression of p21 protein *in vivo*. To further explore the mechanism of chemopreventive and tumor suppressive effect of soy peptide, we have searched for its target molecules. Our cDNA microarray profiling analysis of rat mammary gland tumors induced by DMBA has revealed a dramatic suppression of HSP90, cyclin dependent kinase 4 (cdk4), vascular endothelial growth factor (VEGF) mRNAs in tissues fed with soy peptide diet. cDNA microarray profiling analysis by Snyderwine's group also demonstrated that cdk4 was one of overexpressed genes in DMBA and PhIP-induced rat mammary gland carcinoma compared to normal mammary gland (8). Although the precise mechanism for the involvement of NF-κB in chemoprevention remains to be elucidated, the activation of NF-κB is known to be linked to decreased apoptosis and increased cellular resistance to chemotherapeutic drugs and radiation treatment (9). Taken together, soy peptide can inhibit many important biological processes involved in apoptosis, cell cycle progression, angiogenesis, tumor invasion, resulting in its

chemopreventive and tumor suppressive effect on mammary tumorigenesis *in vivo*.

In summary, one of major findings of this study is that soy peptide deprived of genistein can exert its chemopreventive and tumor suppressive effect by inhibition of apoptotic signaling pathway linking between intrinsic and extrinsic apoptotic pathway involving NF-κB and HSP90. Suppression of the major angiogenic factor, VEGF by soy peptide also suggests its potential anti-angiogenic effect mediated by suppression of NF-κB in breast tumorigenesis. Studies to explore effects of soy peptide on other processes involved in angiogenesis and metastasis as well as in drug resistance would provide further insight into understanding the mechanism of soy peptide in prevention and/or suppression of breast cancer with minimal side effects.

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