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Regulation of Cyclooxygenase-2, Mapkinases and Apoptotic Proteins by Estrogen, Isoflavones and the Combination of Estrogen and Isoflavones

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Cyclooxygenases (COXs) are key enzymes in the conversion of arachidonic acid into prostanoids which are involved in apoptosis in inflammation. Two distinct COXs have been identified: COX-1 which is constitutively expressed and COX-2 which is induced by different products such as tumor promoters or growth factors. In this study, 48 week old female Sprague-Dawly rats were fed high fat and high cholesterol diet with low concentration (300 *u*g/kg diet) and high concentration (1,200 *u*g/kg diet) of estrogen and the combination of estrogen (300 ug/kg) and isoflavones (1%). The combination treatment of estrogen and isoflavones induced the marked down-regulation of COX-2 protein and the decrease in PGE_2 production, and this was followed by the down-regulation of p38 among Mapkinases. The combined treatments of estrogen and isoflavones caused the down-regulation of bax and up-regulation of bcl-2. In the second system of ovariectomized female rats fed estrogen, low concentration of genistein containing polysaccharide (GCP) (0.08%) and the high concentration of GCP (0.4%), COX-2 expression was down-regulated by high concentration of GCP. This down-regulation was accompanied by the reduced expression of pERK1/2 Bcl-2 expression was down-regulated in high concentration of genistein. These results indicate that COX-2 down-regulation may occur at the high concentration of genistein and the combination of estrogen and genistein (isoflavones). The two different mapkinases are involved in the down-regulation of COX-2 depending on the presence of estrogen. COX-2 down-regulation appeared to be related to the down-regulation of bcl-2 only in high genistein supplemented rats. Estrogen seems to demolish this relationship between COX-2 and bcl-2 protein. Further investigations on the relationship between COX-2 and apoptosis by estrogen, genistein or the combination of the two compounds are required to establish tumorigenesis, apoptosis and COX-2 expression in *in vivo* system of female rats.