[S3-1] [10/22/2004(Fri) 09:30-10:10/Room 202]

p53 Restrains Genomic and Non-genomic Action of Estrogen in Mammary Epithelial Cells

Keon Wook Kang[1] and Eva Y.H.P. Lee[2]

[1]College of Pharmacy, Chosun University, Gwangju 501-759, [2]Department of Biological Chemistry, University of California Irvine, CA92697, USA

p53 is a transcription factor which controls cellular stress response. Defect in the function of p53 is the most frequent genetic alteration in human tumors. Germ-line mutations of p53 have been linked to 70% of families with Li-Fraumeni syndrome. These patients have a high risk of early-onset breast cancers as well as other tumors. In fact, mutation of p53 gene is frequently found in human breast carcinomas (>50%) and about 30-50% of breast cancers carry a mutant p53 gene. Ovarian steroid hormones including estrogen are critical not only in mammary gland development but also in breast carcinogenesis. We examined the impact of p53 on estrogen signaling to the proliferation of primary cultured mammary epithelial cells (MECs). MECs showed a rapid activation of extracellular signal-regulated kinase (ERK) in response to estradiol (E2), which was substantially potentiated and sustained in p53-inactivated MECs. In contrast, activities of other MAP kinases including p38 kinase and c-Jun N-terminal kinase were not affected by p53 inactivation. The genomic action of estogen was assessed by luciferase reporter activity using five repeated ERE sequences and confirmed by pS2 expression levels. p53 inactivation significantly increased both the basal luciferase reporter gene activity and pS2 level, which were completely blocked in cells treated with an ERK specific inhibitor, U0126. In order to further reveal the mechanism of the potentiated ERK activation in p53 inactivated MECs, we determined the expression levels of ERK-specific phosphatases, dual specific phosphatase (Dusp) 2, Dusp3 and PP2A. The expression level of Dusp3 in p53-inactivated MECs was obviously decreased, while the levels of other phosphatases including Dusp2 and PP2A were not affected. Our results support a notion that p53 restains genomic and non-genomic action of estrogen in MECs and this novel linkage may be associated with the regulation of cellular functions such as cell proliferation and cancer formation by p53.

This work was supported by the KOSEF grant (R05-2004-000-10361-0).