[P-7]

G1 CELL CYCLE ARREST OF KG-1, A HUMAN ACUTE LEUKEMIA CELLS, BY 8-HYDROXYDEOXYGUANOSINE OCCURS THROUGH BLOCKADE OF THE EXTRACELLULAR SIGNAL REGULATED KINASE PATHWAY

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8-hydroxydeoxyguanosine (oh8dG) potently inhibits proliferation of KG-1, a human leukemia cell line in vitro, but little is known regarding to molecular mechanisms mediating this effect. Here we demonstrate that treatment of KG-1, deficient in 8-oxo-guanine glycosylase (OGG1) activity, with oh8dG lead to G1 arrest associated with a dramatic decrease in the levels of cyclin D3 and cyclin-dependent kinase 4 (cdk4) and accompanied by an increase in the expression of p21. We further show that these effects occur independent of cellular p53 status, for which KG-1 is mutated. The decline in cyclin D3 and cdk4 protein levels correlated with loss in cdk4 kinase activity. Cdk2 activity is also significantly inhibited in oh8dG treated cells, an effect closely associated with the up-regulation of p21. Immuno-precipitation experiments verified that p21 was indeed complex with cdk2 in oh8dG treated cells. Furthermore, the retinoblatoma protein (Rb), a substrate of cdk4 and cdk2 whose phosphorylation is necessary for cell cycle progression, remains hypophosphorylated in oh8dG treated cells. The oh8dG treated KG-1 showed the blockade of RAS-to-ERK pathway and this inhibition of the ERK pathway induced the G1cycle arrest as shown in the result using the specific MEK inhibitors, PD98059 and U0126. Our results demonstrate first that oh8Gua in DNA is able to regulate cell cycle.

Keyword : G1 cell cycle arrest, 8-hydroxydeoxyguanosine