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8-Hydroxydeoxyguanosine induces G₁ cell cycle arrest in KG-1, a human acute leukemia cells, by up-regulating p21 and blocking the Ras to ERK signaling pathway

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We previously reported that KG-1, a human acute leukemia cell line, had mutational loss of 8-oxoguanine (8-hydroxyguanine; oh8Gua) glycosylase 1 (OGG1) activity and its viability was disturbed by 8-hydroxydeoxyguanosine (8-oxodeoxyguanosine; oh8dG). In the present study, the nature of this cell viability affected by oh8dG was investigated. Here we demonstrate that oh8dG treated KG-1 cells show G₁ cell cycle arrest and that this is linked to the inactivation of cdk4 and cdk2, which this is associated with the up-regulation of p21, independently of cellular p53 status. Moreover, Rb protein, a substrate of cdk4 and cdk2, remains hypo-phosphorylated, which results in the inactivation of the E2F function. Furthermore, oh8dG treatment blocked the Ras-to-ERK pathway and this induced G₁ cycle arrest, as was shown by the effects of the specific MEK inhibitors, PD98059 or U0126. Our results demonstrate for the first time that in addition to apoptosis, cell disturbance of oh8Gua in DNA may be induced by arrest of cell cycle.

Keyword : KG-1; 8-hydroxyguanine; cell cycle; OGG1