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E2F1-mediated DNA damage is implicated in 8-Cl-adenosine-induced chromosome missegregation and apoptosis in human lung cancer H1299 cells

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Abstract Although E2F1-mediated DNA double-stranded breaks (DSBs) and tetraploid have been extensively studied, the role of E2F1 in mitotic catastrophe is still unknown. We have previously shown that 8-chloro-adenosine (8-Cl-Ado) induces DNA DSBs and aberrant mitosis in human lung cancer cells, followed by delayed apoptosis. Here, we demonstrate that E2F1-mediated DNA damage is implicated in 8-Cl-Ado-induced chromosome missegregation and apoptosis in lung cancer H1299 cells. We showed that E2F1 was accumulated upon 8-Cl-Ado-induced DNA DSBs. Induction of E2F1 by 8-Cl-Ado caused DNA damage in cycling cells including M cells. In contrast, silencing of E2F1 expression decreased 8-Cl-Ado-induced DNA DSBs, particularly eliminated E2F1-mediated mitotic DNA damage. Over-expression of E2F1 and/or 8-Cl-Ado exposure resulted in aberrant mitotic spindles and chromosome segregation errors. Furthermore, over-expression of E2F1 expression enhanced 8-Cl-Ado-induced apoptosis. Together, our data indicate that E2F1-mediated DNA damage, in particular mitotic DNA damage, is an important fraction of 8-Cl-Ado-induced DNA damage, which is implicated in 8-Cl-Ado-induced mitotic catastrophe and delayed apoptosis. Induction of E2F1 by 8-Cl-Ado may contribute at least partly to the drug-inhibited proliferation of cancer cells.

Keywords E2F1 · DNA damage · Chromosome missegregation · Apoptosis · 8-Chloro-adenosine

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Introduction

E2F transcription factors regulate a very diverse array of genes and play roles in cell-cycle progression and other biological processes. Among E2F family members, E2F1 is unique in its induction upon DNA damage [1–3]. In normal cells, E2F1 is accumulated in the late G1 phase and rapidly degraded in the S/G2 phase. Down-regulation of E2F1 activity in S/G2 is linked to Skp2-dependent ubiquitination pathway [4]. In response to DNA damage, ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related) phosphorylate E2F1 at Ser31 [2]; E2F1 is also phosphorylated by CHK2 [3]. These phosphorylation events lead to stabilization and activation of E2F1 upon DNA damage. E2F1 regulates cellular growth in both positive and negative manners. E2F1 promotes cell-cycle progression [5, 6] and induces apoptosis [7–9]. A number of E2F-regulated genes are involved in DNA replication, DNA repair and mitosis [10]. Also, E2F1 mediates DNA double-stranded breaks (DSBs) with subsequent tetraploidy, even in the absence of exogenous DSB stimuli [11, 12]. The bimodal roles of E2F1 in tumor formation have been demonstrated in various cellular systems and animal models. E2F1 seems to act as an oncogene in lung, breast, thyroid, pancreatic tumors, and Burkitt's lymphoma [13, 14]. Also, E2F1 behaves as a tumor suppressor in large B cell