The effect of loss of p27 and Cdk2 on cell cycle progression in response to ultra-violet irradiation in mouse embryo fibroblasts

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Abstract: Solar ultraviolet (UV) irradiation is the most important environmental carcinogen leading to the development of skin cancer. UVC causes predominantly DNA damage to cells. However, the molecular mechanisms underlying the cellular UV response remains to be elucidated. It has been previously reported that UV radiation results in cell cycle arrest in the G1 phase, which may or may not be p53-dependent. Other proteins involved in DNA damage pathways induced by UV radiation include AKT and ERK. Cyclin-dependent kinases (Cdks) and some of their inhibitors regulate not only cell cycle progression but play also a role in apoptosisand DNA damage repair. We have previously demonstrated that Cdk2 is required for Myc-induced apoptosis and for cytotoxicity induced by cisplatin in kidney cells. However, the role of Cdk2 during UV irradiation has not been elucidated. Recently, $p16^{INC4a}$ and $p27^{KIP1}$have been suggested to be key targets in the ATR-dependent signaling pathway in response to UV damage. However, how p27 regulates the response to UV irradiation is not fully understood. Therefore, the aim of the present study is to investigate the role of Cdk2 and p27 in UV-induced cell cycle arrest. To achieve this goal genetically modified mouse embryo fibroblasts (MEFs) lacking Cdk2 or p27 were used in the present study and three processes were investigated (1) The effect of UV irradiation on unsynchronized MEFs, (2) The effect of UV irradiation on cell cycle progression after synchronization by serum starvation, and (3) protein expression and activity after UV irradiation of unsynchronized MEFs. It was found that p27 and cdk2 are required for apoptosis induced by UV. The molecular mechanism underlying this may be due to the increased expression, phosphorylation and activation of AKT (a survival factor) in the *p27-/-* and *cdk2-/-* MEFs in comparison to wild type (WT) MEFs. Similarly, the inhibitory tyrosine 15 phosphorylation of Cdk1 was upregulated in the *p27-/-* and *cdk2-/-* MEFs in comparison to wild type (WT) MEFs. The overall data from the present study provide clues towards understanding the role of p27 and cdk2 in inducing growth arrest and apoptosis by UV radiation.
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