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Biochemistry and Molecular Biology Brown Bag Series

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"ATR kinase inhibition sensitizes non-replicating human cells to the lethal effects of the anti-cancer drug cisplatin and enhances mutagenesis"

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11:00 AM

145 Medical Sciences Building

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ATR kinase inhibition sensitizes non-replicating human cells to the lethal effects of the anti-cancer drug cisplatin and enhances mutagenesis

The ATR protein kinase protects human cells from the lethal and potentially genome-destabilizing effects of DNA damage during the DNA synthesis phase of the cell cycle. This property has led to the development of small molecule inhibitors of ATR for use in cancer chemotherapy regimens to improve the effectiveness of anti-cancer drugs that generate DNA damage. However, little is known about ATR kinase function in cells that are not actively synthesizing DNA, which includes both normal and cancer stem cells that reside in a quiescent, non-replicating state. We therefore used confluent, growth factor-deprived HaCaT keratinocytes and U2OS osteosarcoma cells to examine ATR function in response to the widely used anti-cancer drug cisplatin. We find that ATR is activated in non-replicating, quiescent cells treated with cisplatin in a manner dependent on the DNA translocase protein XPB, which is required for nucleotide excision repair. Importantly, ATR kinase inhibition sensitizes such cells to the acute, lethal effects of cisplatin and results in higher levels of apoptosis. Though ATR inhibition does not significantly impact the rate of removal of cisplatin-DNA adducts from the genome, our data suggests that ATR kinase inhibition alters the gap filling step of DNA repair and results in a greater utilization of mutagenic DNA polymerases. Consistent with this hypothesis, we observe that ATR kinase inhibition results in more mutagenesis at the HPRT locus in non-replicating cells treated with cisplatin. Thus, though clinically relevant ATR kinase inhibitors may be useful for killing both replicating and non-replicating cancer cells, the loss of ATR kinase activity may result in increased mutagenesis, which could promote future carcinogenesis.