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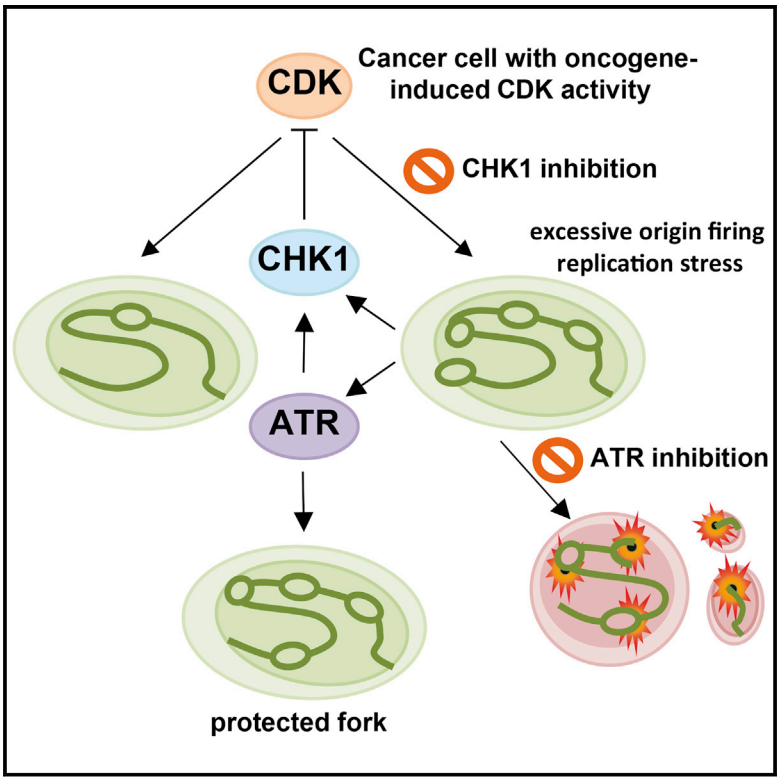
Cancer-Specific Synthetic Lethality between ATR and CHK1 Kinase Activities

Graphical Abstract



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In Brief

Sanjiv et al. report synthetic lethality in cancer cells induced by the inhibition of two kinases, ATR and CHK1, operating in the same signaling pathway. This combination therapy could potentially be used for the treatment of various cancer types due to cancer-specific cytotoxicity.

Highlights

- Synthetic lethality within the same pathway is via the induction of replication catastrophe
- New origin firing and replication stress induced by CHK1 inhibitor reliance on ATR
- ATR and CHK1 inhibitor combination results in cancer-specific cytotoxicity
- ATR and CHK1 inhibitor combination could be used broadly across cancer indications

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Cancer-Specific Synthetic Lethality between ATR and CHK1 Kinase Activities

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SUMMARY

ATR and CHK1 maintain cancer cell survival under replication stress and inhibitors of both kinases are currently undergoing clinical trials. As ATR activity is increased after CHK1 inhibition, we hypothesized that this may indicate an increased reliance on ATR for survival. Indeed, we observe that replication stress induced by the CHK1 inhibitor AZD7762 results in replication catastrophe and apoptosis, when combined with the ATR inhibitor VE-821 specifically in cancer cells. Combined treatment with ATR and CHK1 inhibitors leads to replication fork arrest, ssDNA accumulation, replication collapse, and synergistic cell death in cancer cells in vitro and in vivo. Inhibition of CDK reversed replication stress and synthetic lethality, demonstrating that regulation of origin firing by ATR and CHK1 explains the synthetic lethality. In conclusion, this study exemplifies cancer-specific synthetic lethality between two proteins in the same pathway and raises the prospect of combining ATR and CHK1 inhibitors as promising cancer therapy.

INTRODUCTION

Cancer is a disease of uncontrolled cellular proliferation, driven by oncogenes, leading to unfaithful and uncoordinated DNA replication, genomic instability, and DNA double-strand breaks (DSBs) (Alexandrov et al., 2013; Bartkova et al., 2006; Di Micco et al., 2006). DSBs activate the ATM kinase, which in turn mediates p53-dependent cell-cycle arrest and apoptosis, working as a tumor barrier to cancer development (Bartkova et al., 2005; Gorgoulis et al., 2005; Halazonetis et al., 2008). In contrast, the ATR kinase is activated by single-stranded DNA (ssDNA) present at stalled replication forks (Hekmat-Nejad et al., 2000; Zou and Elledge, 2003). ATR phosphorylates the checkpoint kinase CHK1, which plays a crucial role in preventing origin firing (Feijoo et al., 2001), avoiding premature chromosome condensation and facilitating RAD51-mediated homologus recombination (Cimprich and Cortez, 2008; Sørensen et al., 2005).

Since cancer cells often harbor some degree of replication stress, they upregulate ATR and CHK1 activity to mediate survival (Choi et al., 2011; Toledo et al., 2011). For example, B cell lymphomas are sensitive to CHK1 inhibitors as they have a high degree of MYC-induced replication stress (Höglund et al., 2011; Murga et al., 2011). Cancer cells also commonly lack compensatory DNA damage response proteins that are synthetic lethal with the ATR pathway, including ATM and p53 (Ding et al., 2008; Jiang et al., 2009), which further increases reliance on ATR and CHK1 in damaged tumor cells (Choi et al., 2011; Murga et al., 2009; Reaper et al., 2011). In addition, the cytotoxic mechanism of action of many anti-cancer drugs is to induce replication stress and replication-associated DNA damage. Taken together, ATR or CHK1 inhibition is a promising strategy, and selective inhibitors are undergoing clinical trials in combination with DNA-damaging chemotherapy and ionizing radiation (Brooks et al., 2013; Fokas et al., 2012; Foote et al., 2013, 2015; Jossé et al., 2014; Ma et al., 2011; Mitchell et al., 2010; Tang et al., 2012).

Although the ATR and CHK1 kinases function in the same pathway, they also may exert unique functions. For example, the ATR protein appears to have a more important role than CHK1 in preventing replication collapse after UV damage (Elvers et al., 2012), which is likely related to a unique role of ATR in supplying RPA to protect replication forks (Toledo et al., 2013). We and others previously have found that inhibition or depletion of CHK1 causes replication stress and activation of ATR, which is explained by the role of CHK1 in suppressing replication origin firing (Choi et al., 2011; Gagou et al., 2010; Petermann et al., 2010a; Syljuåsen et al., 2005). Since ATR is critical for replication fork stability under conditions of replication stress (Toledo et al., 2013), which may be independent of CHK1 (Elvers et al., 2012), we hypothesized that ATR may be critical for survival upon CHK1 inhibition in cancer cells. In line with this hypothesis, we demonstrate that sub-toxic concentrations of both the ATR inhibitor VE-821 and the CHK1 inhibitor AZD7762 combine synergistically to induce complete replication collapse and apoptosis specifically in cancer cells. In addition, the combination of the ATR inhibitor VX-970 and AZD7762