# When Transcription and Replication Collide: A BRD4-TopBP1 Interaction Controls Activation of the ATR-Chk1 Pathway During Transcription-Replication Collision Events in Oncogenic Cells

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The cellular response to replication stress-induced DNA damage occurs through the assembly of several factors on chromatin, culminating in the activation of the ATR-Chk1 checkpoint. Details of this chromatin assembly process and its regulation are incompletely understood. We recently reported a novel function for BRD4 in limiting DNA damage signaling following exposure of oncogenic cells to ionizing radiation, in part through recruitment of the condensin complex to open chromatin. In that study, we also observed that inhibition of BRD4 alone led to an increased endogenous DNA damage response in cells. We now show that this damage response involves formation of double strand DNA breaks as a result of increased replication stress as a consequence of increased collision between the transcription and replication machinery following inhibition of BRD4. Through an unbiased proteomic interaction screen, we identified a direct functional interaction between the DNA damage replication stress mediator TopBP1 and BRD4. Disruption of the BRD4-TopBP1 interaction leads to an inability to mount a robust ATR response to these collision events following bromodomain inhibition, leading to failed checkpoint activation, and apoptotic cell death. These findings identify novel crosstalk between an epigenetic chromatin reader that modulates transcription and the replication stress-induced DNA damage response.