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DNA double-strand breaks induced by transcription-blocking topoisomerase I lesions

Topoisomerase I (Top1) relaxes DNA supercoiling generated during transcription by producing transient Top1-DNA cleavage complexes (Top1cc). These Top1cc intermediates can be stabilized under a broad range of physiological conditions including oxidative base damage, alkylation by carcinogenic compounds and nicks, and by ribonucleotide misincorporation. Stabilized Top1cc are potent transcription-blocking lesions and our observations indicate that they can be converted into DNA double-strand breaks (1-4). We will discuss the mechanism of production of these co-transcriptional DNA double-strand breaks and their potential relevance in the pathogenesis of neurodegenerative diseases.

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