Title:	Topoisomerase I Essentiality, DnaA-Independent Chromosomal Replication, and Transcription-Replication Conflict in Escherichia coli
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Abstract:	Topoisomerase I (Topo I) of Escherichia coli, encoded by topA, acts to relax negative supercoils in DNA. Topo I deficiency results in hypernegative supercoiling, formation of transcription-associated RNA-DNA hybrids (R-loops), and DnaA- and oriC-independent constitutive stable DNA replication (cSDR), but some uncertainty persists as to whether topA is essential for viability in E. coli and related enterobacteria. Here, we show that several topA alleles, including ΔtopA, confer lethality in derivatives of wild-type E. coli strain MG1655. Viability in the absence of Topo I was restored with two perturbations, neither of which reversed the hypernegative supercoiling phenotype: (i) in a reduced-genome strain (MDS42) or (ii) by an RNA polymerase (RNAP) mutation, rpoB*35, that has been reported to alleviate the deleterious consequences of RNAP backtracking and transcription-replication conflicts. Four phenotypes related to cSDR were identified for topA mutants: (i) one of the topA alleles rescued ΔdnaA lethality; (ii) in dnaA+ derivatives, Topo I deficiency generated a characteristic copy number peak in the terminus region of the chromosome; (iii) topA was synthetically lethal with rnhA (encoding RNase HI, whose deficiency also confers cSDR); and (iv) topA rnhA synthetic lethality was itself rescued by ΔdnaA. We propose that the terminal lethal consequence of hypernegative DNA supercoiling in E. coli topA mutants is RNAP backtracking during transcription elongation and associated R-loop formation, which in turn leads to transcription-replication conflicts and to cSDR.
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