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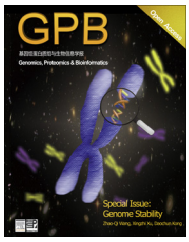

REVIEW

Topoisomerase I in Human Disease Pathogenesis and Treatments

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Abstract Mammalian **topoisomerase 1** (TOP1) is an essential enzyme for normal development. TOP1 relaxes supercoiled DNA to remove helical constraints that can otherwise hinder **DNA replication** and **transcription** and thus block cell growth. Unfortunately, this exact activity can covalently trap TOP1 on the DNA that could lead to cell death or mutagenesis, a precursor for tumorigenesis. It is therefore important for cells to find a proper balance between the utilization of the TOP1 catalytic activity to maintain DNA topology and the risk of accumulating the toxic DNA damages due to TOP1 trapping that prevents normal cell growth. In an apparent contradiction to the negative attribute of the TOP1 activity to genome stability, the detrimental effect of the TOP1-induced DNA lesions on cell survival has made this enzyme a prime target for **cancer** therapies to kill fast-growing **cancer** cells. In addition, cumulative evidence supports a direct role of TOP1 in promoting transcriptional progression independent of its topoisomerase activity. The involvement of TOP1 in transcriptional regulation has recently become a focus in developing potential new treatments for a subtype of **autism** spectrum disorders. Clearly, the impact of TOP1 on human health is multifold. In this review, we will summarize our current understandings on how TOP1 contributes to human diseases and how its activity is targeted for disease treatments.

Introduction

Topoisomerase 1 (TOP1) is a highly conserved enzyme that can be found in both prokaryotes and eukaryotes. In the mammalian system, TOP1 is an essential enzyme for normal development [1]. A major function of TOP1 is to relax supercoiled DNA and alleviate the DNA helical constraints [2,3]. This is achieved by the binding of TOP1 to the supercoiled DNA, followed by the cleavage of one strand of the duplex DNA to create a nick, allowing the duplex DNA to untwist and relax (**Figure 1**) [4]. DNA supercoiling is a naturally-occurring biological process when a DNA replisome or an RNA polymerase (RNAP) unwinds and translocates on the DNA to synthesize DNA or RNA. If not removed, these supercoiled DNA can hinder the progression of the replication fork or RNAP. In addition, negatively supercoiled DNA can

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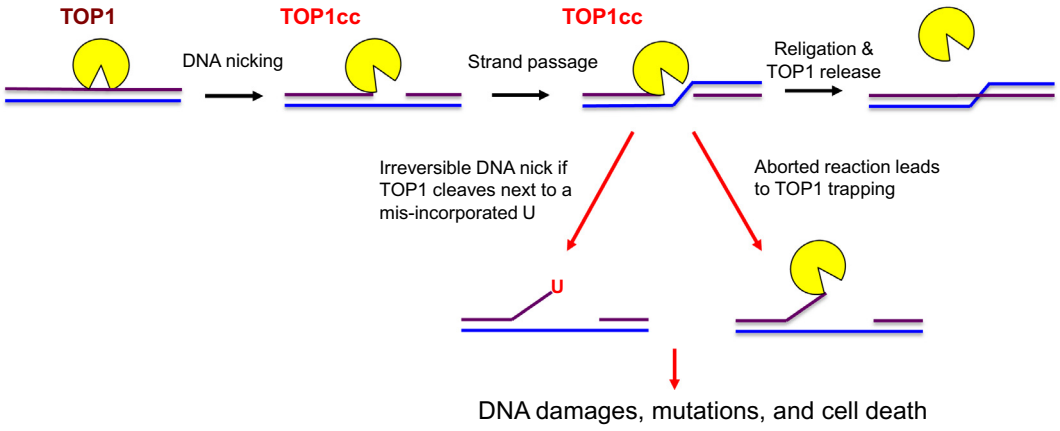

Figure 1 Illustration of TOP1 DNA cleavage reaction
The TOP1 DNA cleavage reaction is initiated by the binding and DNA nicking (purple line) of TOP1 to form a TOP1cc complex that covalently links TOP1 to the DNA. The intact DNA strand (blue line) passes through the DNA nick before the nick is religated, followed by the release of TOP1 from the DNA. TOP1 DNA cleavage next to a misincorporated ribonucleotide U or an aborted TOP1cc reaction can lead to mutations and cell death. TOP1 is shown in yellow and the two DNA strands are shown in purple and blue, respectively. TOP1, topoisomerase 1; TOP1cc, TOP1–DNA cleavage complex; U, uridine.

facilitate the formation of RNA:DNA hybrids, or R-loops, between DNA template and the newly-synthesized RNA. If not resolved, R-loops can stall further transcription and DNA replication forks, leading to DNA double-strand break (DSB) formation [5]. TOP1 is known to interact directly with the active form of RNAPII and localize to transcriptionally-active regions (TARs) of the genome [2,3]. It has been suggested that TOP1 may aid to suppress R-loop formation by removing supercoiled DNA during RNAPII-dependent transcription [4,5].

In addition to its function in relaxing supercoiled DNA, cumulative evidence supports a direct role of TOP1 in transcriptional regulation. For example, during transcription, RNAPII pauses at initiation and splice sites [6], while TOP1 has been proposed to hold RNAPII at the promoter-proximal pause site [7]. Nonetheless, the exact molecular mechanism by which TOP1 pauses RNAPII at the initiation site remains to be defined. Furthermore, TOP1 has been shown to promote the recruitment and assembly of spliceosome at TARs [8–10], and this function may be contributed by a potential TOP1-associated kinase activity to phosphorylate splicing factors [9]. Efficient recruitment and coupling of RNA processing factors to the TARs are critical for ensuring uninterrupted production of full-length mature mRNA. In addition, spliceosome assembly onto nascent RNA transcript has important implications for genome stability as well, because the binding of RNA processing factors to the newly-transcribed RNAs can also prevent these RNA strands from invading the DNA template to generate R-loops [5,9,11]. The involvement of TOP1 in spliceosome assembly may explain why TOP1 is important for transcriptional progression and R-loop suppression. Nonetheless, whether TOP1 functions as a protein kinase for the spliceosome assembly remains in great debate, as evidence also suggests that TOP1 is unlikely the only or the primary kinase that phosphorylates splicing factors [12,13].

The dynamic functions of TOP1 in DNA replication and transcription provide important clues to why TOP1 is essential for development in the mammalian system. However, because TOP1 forms a covalent link intermediate, known as TOP1–DNA cleavage complex (TOP1cc), with the 5′ phosphate group of the DNA during the topoisomerase reaction, the TOP1 activity can generate toxic DNA lesions due to a naturally-aborted topoisomerase reaction, leaving the TOP1 covalently trapped on the DNA (Figure 1) [14]. Alternatively, single-strand breaks (SSBs) accumulate due to irreversible DNA cleavage by TOP1 adjacent to a misincorporated ribonucleotide [15]. The presence of these TOP1cc and DNA lesions may lead to cell death or mutagenesis, a precursor for tumorigenesis. Therefore, the topoisomerase activity of TOP1 is a double-edged sword and can have both positive and negative consequences on genome integrity and normal cell growth.

In addition, the potential direct involvement of TOP1 in transcriptional regulation [7–10] suggests that TOP1 dysfunction may alter transcriptional landscape, leading to abnormal cellular functions. It is therefore not surprising that several human diseases have been linked to TOP1 regulation and activity. In this review, we will discuss the human diseases that may be linked to TOP1 and the mechanism by which the TOP1 activity may contribute to the etiologies of these diseases (**Figure 2**). In addition, we will also overview how the poisonous effect of TOP1cc on cell growth has benefited cancer treatments and how the ability in changing the transcriptional landscape by TOP1 has become a focus for developing possible novel strategy to treat genetic diseases.

TOP1 in tumorigenesis

In yeast, TARs are prone to mutations that arise as erroneous repair of TOP1cc created by TOP1-mediated removal of supercoiled DNA or irreversible DNA nick generated by the TOP1 cleavage next to a misincorporated ribonucleotide [14,15]. The mutagenic potential of the TOP1 activity demonstrated in yeast suggests that if the same activity was to exist in humans,