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REVIEW

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Topoisomerase Induced DNA Damage Coupled Diseases and Therapeutic Potential

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Topoisomerase is an essential enzyme which regulates the topological state of DNA supercoils during replication and transcription. Topoisomerases cleave either one or two DNA strands and then re-join the cleaved strands after passing the intact strand or a double strand through the gap respectively. During relaxation of supercoiled DNA, if topoisomerase is trapped by drugs or alteration of DNA structure, they stabilize topoisomerase-DNA cleavage complex which leads to DNA damage. If Topoisomerase cleavage complex is trapped by any anticancer or others drug, exogenous and endogenous DNA lesion involving mismatches, abasic sites, oxidative damage etc. it may cause DNA damage. DNA damages leads to several diseases such as tumorigenesis, autoimmune disease, Angelman syndrome, SCAN1, SCAR23, Papillary Thyroid Cancer (PTC), cancer therapy-related acute myeloid leukemia. Topoisomerase uses as a potential drug target to manage infectious diseases like leishmaniasis, Chagas disease, pneumococcal, dengue, yellow fever, corona virus, gastrointestinal infection. Here we review the recent information about the topoisomerase mediated DNA damage, related diseases, role of topoisomerase in heterochromatin structure and uses of topoisomerase as drug target in many diseases.

Key words: Camptothecin, etoposide, doxorubicin, xenotoxic, non-Hodgkin's lymphoma

Topoisomerase catalyzes the changes in topological state of DNA by interconverting relaxed the supercoiled DNA (Pommier *et al.*, 2006). Topoisomerases cleave either one or two DNA strands and then re-join the cleaved strands after passing the intact strand or a double strand through the gap respectively. The active site tyrosine residue attacks a phosphodiester bond in the backbone of the target DNA generating a break in the strand and remains attached covalently to the 5' broken end via a phosphotyrosine linkage. The other broken end with terminal OH group is also held tightly by the enzyme. The unbroken strand of DNA duplex is passed through this gap to release one supercoiling (Watson *et al.*, 2013). The topoisomerase then reseals the broken strands by reversing the original reaction. According to number of strand break topoisomerases are of two types – type I topoisomerase which is responsible for single strand break and subsequent release of one negative supercoil in the same DNA duplex and type II topoisomerase is responsible for double strand break and catenation or decatenation (Pommier *et al.*, 2006).

Type I Topoisomerase

Topoisomerase I (Top1) creates a single strand break by formation of phosphotyrosine linkage at the 5' end of the cut end of the target DNA strand. Top1 religates the break by reversing the reaction of phosphotyrosine bond formation. Relaxation of DNA supercoiling is achieved by allowing rotation of the broken strand around the Top1 bound DNA strand (Stewart *et al.*, 1998; Lesher *et al.*, 2002; Staker *et al.*, 2002). Religation of the DNA 5' end requires hydroxyl group to be aligned with the tyrosine DNA phosphoester bond (Pommier *et al.*, 2006). No ATP is required for this reaction rather, the energy from breaking the phosphodiester bond is stored in the phosphotyrosine linkage and is utilized for religation (Stewart *et al.*, 1998; Lesher *et al.*, 2002; Staker *et al.*, 2002). Both the type 1A and 1B are present in Mammalian system. Top1A are of two types such Top3α and Top3β. The Top1B is subdivided into Top1 nuclear in nucleus and Top1mt in mitochondria. Top 3α is responsible for resolution of post replicative hemicatenes and recombination intermediates (Wu & Hickson, 2003; Harmon *et al.*, 2003). Top3β reduces the frequency of chromosomal translocation (Barthelmes, 2000). Top1 Mt couples mitochondrial functions that is translation, mtDNA expansion, ATP generation and biogenesis (Dalla Rosa *et al.*, 2014; Dalla Rosa *et al.*, 2017). Top1 nuclear is responsible for releases of supercoiling during DNA replication and transcription in nucleus (Pommier *et al.*, 2006).

Type II topoisomerase

DNA Topoisomerase II (Top2) introduces an enzyme bridged DNA double strand break (DSB) where each 5' end of the cleaved DNA are covalently attached to the enzyme active sites by tyrosine phosphodiester linkage (Swan *et al.*, 2022). This enzyme bridged DSB is induced by nucleophilic attack of the phosphate backbone of DNA by the Top2 active site tyrosine which creates breaks forming covalent 5' phosphotyrosyl linkage between Top2 and the 5' end of the DNA (Swan *et al.*, 2022). Enzyme then passes a second DNA duplex through the DNA break, religates the cut ends and dissociate from the DNA. Topoisomerase II (Top2) requires divalent cation such as Mg^{2+} and ATP for double strand passage reaction (Osheroff, 1986; Lindsley & Wang, 1993; Osheroff *et al.*, 1983; Lindsley & Wang, 1991). There are three types of Top2 such as, Top 2α; Mainly implicated in DNA relaxation/decatenation and segregation (Grue *et al.*, 1998) Top2β; Mostly associated to transcription (Ju et. al., 2006) and Spo11; which expression is limited in germ cell (Swan *et al.*, 2022). Primary structure of Top2α & Top2β are very similar and divided into three domains based on sequence homology with the bacterial type II enzyme, DNA gyrase (Wang, 1996; Nitiss, 1998; Fortune & Osheroff, 2000; Austin & Marsh, 1998; Berger *et al.*, 1996). The N-terminal domain of Topoisomerase II which is the ATP binding site of the enzyme, homologous to the B subunit of DNA gyrase (Champoux, 2001; Velez-Cruz & Osheroff, 2004; Berger *et al.*, 1998). The central portion of the enzyme contains active site of tyrosine which is homologous to the A subunit of DNA gyrase (Champoux, 2001; Velez-Cruz & Osheroff, 2004; Worland & Wang, 1989). The C-terminal domain is highly variable among species and

between the two human isoforms top2α and top2β (McClendon & Osheroff, 2007). Top2α plays an important role during formation of replication fork and remains tightly associated with chromosome during mitosis. (Nitiss, 1998; Bauman *et al.*, 1997). In contrast Top2β dissociates from chromosome during mitosis (Nitiss, 1998; Austin & Marsh, 1998; Woessner *et al.*,, 1991; Isaacs *et al.*, 1998).

Top1 mediated DNA damage

The key step in the catalytic cycle of Top1 is the formation of a transient covalent bond between the Top1 active site tyrosine and the phosphate group of DNA strand and their by a Top1 DNA cleavage complex (Top1cc) intermediate is formed (Wang, 2002). Under certain conditions before relegation of the DNA strand this intermediate Top1cc is stabilized that triggers a DNA damage response including DNA lesion and single strand breaks (SSBs). Stabilization of Top1cc results from misalignment of the 5' OH end of DNA. These misalignments may be generated by any drug like camptothecin bound at the interface of the enzyme and broken DNA (Pommier & Cherfils, 2005; Pommier & Marchand, 2005). Camptothecin and Top1cc binds reversibly. The ternary drug-enzyme-DNA complex and the dissociated complex establish a rapid equilibrium in pharmacological conditions. Hence, cleavage complex reverse rapidly due to dilution of camptothecin (Covey, 1989). Camptothecin traps only a subset of the existing Top1cc that contain a guanine at the 5' end of the break (+1 position) (Jaxel *et al.*, 1991; Tanizawa *et al.*, 1995). Alternatively, Indenoisoquinolines stabilize those cleavage complexes which contain a cytosine at the 3' end of the breaks (-1 position) (Antony *et al.*, 2003).

Endogenous and frequent DNA lesions such as abasic sites, mismatches, oxidized bases, nicks at carcinogenic DNA adducts may lead to trapping of Top1cc irreversibly (Pommier *et al.*, 2006). DNA modifications due to oxidative damage can produce Top1cc (Pourquier *et al.*, 1999). The abasic site or DNA break causes irreversible misalignments of the 5' end of the DNA and thus the Top1cc induced by such lesions are irreversible (Pourquier *et al.*, 1997; Pourquier *et al.*, 1997a). Reactive oxygen species mediated chromatin modifications have also been reported to trap Top1cc during apoptosis (Pommier *et al.*, 2006). The irreversible Top1cc referred as 'suicide complexes' are composed of DNA lesion where the large Top1 remains covalently bound to the 3' end of the broken DNA (Burgin *et al.*, 1995; Shuman, 1989). The resulting disruption of the DNA backbone may lead to SSB or double strand breaks (DSBS) (Pommier *et al.*, 2006).

Reversible Top1cc may be converted into irreversible strand breaks after the DNA or RNA polymerase collide them on the leading strand during replication and on the transcribed strand during transcription respectively (Bendixen *et al.*, 1990; Wu & Liu, 1997). Thus, both DNA & RNA synthesis convert reversible cleavage complex into permanent DNA damage. In cancer cells replication induced DNA damaged contributes to most of the cytotoxicity at low dose camptothecin while, during transcription higher dose is generally required to induce DNA damage and cytotoxicity (Holm *et al.*, 1989; Hsiang *et al.*, 1989). Camptothecin-induced Top1cc may be readily converted into replication DSBs. The trapped Top1cc may also inhibit transcription by blocking elongation and this is a high probability event considering that Top1 is associated with transcription complexes (Pommier *et al.*, 1998). Single strand breaks accumulate in the DNA due to irreversible cleavage by Top1 adjacent to a misincorporated ribonucleotide (Kim *et al.*, 2011).

Top2 mediated DNA damage

Top2 cuts scissile bonds on the two strands of double helix which is staggered and located across the major groove. Then enzyme form cleaved DNA molecules which contain 4 base single stranded ends at their 5'-termini (Liu & Wang, 1983; Sander & Hsieh, 1983). Thus Top2 covalently joins to these newly formed 5'-termini (Worland & Wang, 1989; Liu & Wang, 1983; Zechiedrich *et al.*,, 1989). This covalently attach enzyme-cleave DNA complex is referred to as "cleavage complex" (Top2cc) (McClendon & Osheroff, 2007). Chemotherapeutic drugs such as etoposide and doxorubicin, Xenotoxic chemicals like benzene, dietary factors (bioflavonoids) and endogenous stressor like base mismatches and apurinic sites are common Top2 poisons (Loike, 1982; Tewey, *et al.*, 1984; Chen & Eastmond, 1995; Frantz *et al.*, 1996; Strick *et al.*, 2000;

Kingma *et al.*, 1997; Sabourin & Osheroff, 2000). These types of Top2 poisons stabilize the Top2cc and generate DSBs formation (Long & Stringfellow, 1988). The Top2 poison separates the DNA broken ends and prevents the relegation of the DNA which is cut by Top2 (Pommier *et al.*, 2015). Many Top2 poisons which are termed as interfacial inhibitors (Marchand & Pommier, 2011) bind at the interface between the enzyme and DNA and then form a drug-enzyme-DNA ternary complex. Anti-tumour drugs such as doxorubicin and etoposide generate high level of Top2 mediated DNA breakage. These drugs target and trap the Top2cc by stacking between the base pairs flanking the scission site and displacing the 5'phophotyrosl group from the 3'-OH group thereby preventing relegation. Thus a drug-enzyme-DNA ternary complex is formed leading to DNA damage (Capranico *et al.*, 1990; Marchand & Pommier, 2011; Pommier *et al.*, 1991).

Top2 poisons selectively trap Top2 at different sites like upstream and downstream nucleobase pairs which flank the cleavage sites where the enzymes cleave (Chen *et al.*, 1984; Tewey *et al.*, 1984a; Capranico *et al.*, 1990a; Pommier *et al.*, 1991a; Capranico *et al.*, 1993). In mammalian cells the two isoforms of Top2 areTop2α & Top2β. Top2 poisons the anticancer drug such as Idarubicin and Etoposide target both the isoforms and stabilize Top2cc preventing religation of the broken ends. Etoposide, a Top2 poison, stacks between the cytosine at -1 of the break site and guanine at +5 of the break site to trap the Top2βcc (Marchand & Pommier, 2011).

In Top2α-DNA –drug ternary complex amino acids in the etoposide-binding pocket of Top2α distinguished from Top2β by Met 762 and Ser 800 in Top2α while Gln 778 and Ala 816 in Top2β (Nitiss & Beck, 1996). This drug stabilized Top2αcc are reversible, however, their persistence leads to DSB formation (Mao *et al.*, 2001).Top2 mediated DSBs formation in the promoter region of some stimulus responsive genes in a variety of cell types and systems that are induced upon exposure to insulin, estrogen, progesterone etc. have also been reported (Ju *et al.*, 2006).

Human diseases caused by Top1 induced DNA damage

Top1 in tumorigenesis

Negatively supercoiled DNA facilitates RNA: DNA hybrid or R loops formation during transcription. If remains unresolved, the coiling R Loop prevents further RNA transcription & replication, leading to DSB formation (Aguilera & García-Muse, 2012). Top1 interact with RNA polymerase II (RNAPII) localized at transcriptionally active region (TARs) of the genome (Aguilera & García-Muse, 2012; Gilmour *et al.*, 1986). During RNAPII dependent transcription Top1 supresses R loop formation by removing supercoiled DNA. The Top1 holds RNAPII at the promoter proximal P site and RNAPII pauses at initiation (Khobta *et al.*, 2006). Top1 promotes recruitment and assembly of spliceosome at TARs which phosphorylates splicing factor (Tuduri *et al.*, 2009). For coupling of RNA processing factors to TARs is critical for continuous production of full-length mature mRNA. During Topoisomerase reaction with DNA, Top1 covalently link with the 5'phosphate group of DNA and accidentally form Top1cc which generate DNA lesion (Li & Liu, 2016). Presence of these Top1cc may generate DNA damage leading to cell death or mutagenesis which is a precursor for tumorigenesis. Top1 adjoining to a misincorporated ribonucleotide generally form irreversible Top1cc that results into SSBs deposition (Kim *et al.*, 2011). In human cells novel SUMO modification at the lysine residue K391 & K436 supress the topoisomerase activity of Top1 at TARs, thereby reducingTop1 induced DNA damage. Any defect in the SUMOylation on K391 & K436 against Top1 induced DNA damaged during transcription may turn to genome instability, mutagenesis and cancer (Li & Liu, 2016).

Top1 in autoimmune disease

Top1 autoimmune antibodies are most common features of scleroderma and associated with a poor prognosis (Hu *et al.* 2004; Mahler *et al.*, 2010). Sclerodermal disease is hardening of the skin and connective tissue which is caused by production of autoimmune antibodies against nuclear constituents (Li & Liu, 2016). Catalytic domain of αTop1 autoantibodies are highly reactive (Li & Liu, 2016). Patients with

autoimmune antibodies against RNAPII are also frequently positive for αTop1 autoantibodies (Harvey *et al.*, 1996). In many tissues of Scleroderma patients Top1 SUMOylationis increased but Top1 catalytic activity is decreased (Li & Liu, 2016). K391 & K436 residue of Top1 SUMOylation supresses the activity of Transcription associated Top1 while facilitate the Top1-RNAPII interaction. Therefore the Top1 K391/K436 SUMOylation may lead to DNA damage and genome instability (Li & Liu, 2016). Hyper K391/K436 SUMOylation improve the level of Top1-RNAPII complexes in cells which alter the transcriptional stress and increased programmed cell death (Li & Liu, 2016). The increased cell death due to apoptosis is expected to increase presentation of the Top1-RNAPII complex to the immune system resulting into autoimmunity (Li & Liu, 2016).

Top1 in autism

Top1 poisons are shown to alleviate Angelman syndrome, an autism spectrum disorders (ASD) by supressing the exceptionally long antisense RNA transcribed UBE3A-ATS (King *et al.*, 2013). UB3-ATS prevents the expression of its sense gene UB3A that is important for the disease to prevent (King *et al.*, 2013).Top1 recruits spliceosome assembly at TARS to promote efficient transcriptional progression. Top1 Poison (CPT & Topotecan) reduce the expression of exceptionally long and highly transcribed gene with median gene length of 66kb. This Top1 poisons up-regulate the expression of shorter gene that are normally expressed at low level. Top1 poison possibly influences the spliceosome assembly to inhibit gene expression in an intron dependent manner (Li & Liu, 2016). Spliceosome represses the R loop in the newly synthesized mRNA (Li & Liu, 2016). Top1 poison spliceosome stabilizes R loop formation and thereby inhibit the expression of UBE3A-ATS (Li & Liu, 2016).

TOP1cc in Ataxia with Axonal Neuropathy

Accumulation of Top1cc can contribute to the development of Spinocerebellar ataxia with axonal neuropathy (SCAN1) (Takashima *et al.*, 2002; El-Khamisy *et al.*, 2005; El-Khamisy *et al.*, 2007; Walton *et al.*, 2010). SCAN1 is a neurodegenerative disease (Takashima *et al.*, 2002). A particular mutation (H493R) in TDP1 has been identified to be the underlying cause of SCAN1 (Takashima *et al.*, 2002; Interthal *et al.*, 2001; Katyal *et al.*, 2007). This mutated TDP1 was observed to be unable to resolve endogenous TOP1ccs and as a result SCAN1 cells accumulate Top1ccs. The mutation in TDP1 actually inhibits the second step of TDP1 mediated DNA damage repair pathway leading to accumulation of TDP1-DNA catalytic intermediate or TDP1cc in addition to Top1cc. The accumulation of TDP1cc may block the alternative mechanisms for resolution of DNA lesions that typically respond to Top1cc formation (Interthal *et al.*, 2005; He *et al.*, 2007). Endogenous accumulation of Top1cc in TDP1 deficient cell is prevented by treatment with transcription inhibitor (Katyal *et al.* 2014). Therefore transcription and oxidative stress are major contributors to steady state levels of Top1cc that become pathological in SCAN1.

Disease caused by Topoisomerase II induced DNA damage

Cancer therapy-related acute myeloid leukemia

Top2 poisons, used in cancer treatment, induces apoptosis of the cancer cells by the DNA fork collapsing and unresolved DSBs. The DSBs produced may cause mutations that promote to secondary malignancies, such as therapy-related acute myeloid leukemia (t-AML). Breast cancer and non-Hodgkin's lymphoma (NHL) patients treated with the Top2 poisons like daunorubicin, etoposide, and doxorubicin, have the highest risk of being diagnosed with t-AML (Beadle *et al.*, 2009; Morton *et al.*, 2013; Leone, *et al.*, 2002). The majority of t-AML cases have been diagnosed with mutation due to translocation at chromosome 11 specifically the KMT2A or MLL gene (Pedersen-Bjergaard & Philip 1991; Broeker, *et al.*, 1996; Felix, 1998; Meyer *et al.*, 2018). It has been observed that the MLL gene fuse with either AF9, ENL, ELL, or AF4 (Meyer *et al.*, 2018). Some work on human hematopoietic stem cell and progenitor cells (HSPCs) demonstrated that treatment with low-dose, non-cytotoxic levels of etoposide and doxorubicin increase DNA break frequency within the therapy-related breakpoint cluster region (BCR) of MLL gene (Thys *et al.*, 2015). It has also been reported that the Top2 poison etoposide may induce chromosome breakage and translocations involving MLL, AF9, AF4,

AF6, and ENL in human HSPCs and lymphoblastoid cells (Gothe *et al.*, 2019). Altogether, the Top2 and its poisons may facilitate the mutagenic process which leads to t-AML in breast cancer and NHL patients.

Papillary Thyroid Cancer (PTC)

Some evidence suggests that the TOP2 also facilitates the formation of oncogenic translocations in solid tumours. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database Papillary thyroid cancer (PTC) increased dramatically since the 1970s (Chen *et al.*, 2005; Davies & Welch, 2006; Enewold *et al.*, 2009). PTC is increased by exposure of environmental chemicals and chemotherapeutic agents. Sporadic rearrangement-positive PTC cases are predominantly due to chemical exposure which possess the RET/PTC1 rearrangement (Nikiforov *et al.*, 1997; Finn *et al.*, 2003; Fenton *et al.*, 2000). The genes RET, CCDC6, and NCOA4 involved in the RET/PTC1 and RET/PTC3 rearrangements are located within known fragile sites indicating that they are more prone to DNA breaks than non-fragile sites of the genome (Burrow *et al.*, 2009). The chemical exposure-associated PTC cases have been found to be triggered by the benzene and/or chemotherapeutic agents, like Top1 and Top2 inhibitors/poisons. Benzene is a carcinogen consisting of anti-Top2 properties which is found in cigarette smoke, gasoline, and industrial emissions (National Toxicology Program, 2011; Eastmond *et al.*, 2005). For fragile site induction, low-dose exposure from these sources is sufficient (National Toxicology Program, 2011; Yunis *et al.*, 1987; Dillon *et al.*, 2012). PTC has been reported in some secondary cancer patients treated with fragile site-inducing chemotherapeutic agents for cancers such as Hodgkin's lymphoma, osteosarcoma, pediatric rhabdomyosarcoma, and others (Boffetta & Kaldor, 1994, Swerdlow *et al.*, 1992; Goto *et al.*, 1996; Jimenez *et al.*, 1995; Tsuchiya *et al.*, 1991; Verneris *et al.*, 2001; Yen *et al.*, 1993; Venkitaraman *et al.*, 2008; De Vathaire *et al.*, 1999; Gow *et al.*, 2003; Froelich-Ammon *et al.*, 1994; Jonstrup *et al.*, 2008). HTori-3 cells when treated with low-dose, non-cytotoxic level of benzene, etoposide, and doxorubicin a significant increase of the frequency of DNA breaks within the RET-BCR in intron 11 was observed (Lehman *et al.*, 2017). This suggests translocation process of PTC is regulated by Top2. Further studies shown that HTori-3 cells treated with fragile site-inducing chemicals or Top1/Top2 poisons generate DNA breaks within RET intron 11 which are predominantly distributed around predicted Top1 and Top2 cleavage sites (Dillon *et al.*, 2013). As topoisomerase enzymatic activity is enhanced by DNA secondary structures, the fragility associated with RET intron 11 increase by activity of topoisomerases at the DNA secondary structures (Froelich-Ammon *et al.*, 1994; Jonstrup *et al.*, 2008; Mills *et al.*, 2018).

Spinocerebellar Ataxia Autosomal Recessive23 (SCAR23)

The deficiency of DSB repair lead to the development of neurological abnormalities like SCAR23 (Alt & Schwer, 2018). This indicated that topoisomerase induced DNA damaged may be an important relevant lesion for neurological abnormalities. SCAR23 is an autosomal recessive syndrome that is characterized by treatment resistant epilepsy, progressive ataxia, and cerebellar degeneration (Gómez-Herreros *et al.*, 2013; Gómez-Herreros *et al.*, 2014). SCAR23 is also a degenerative rather than developmental disorder because SCAR23 patients also display a later age onset than other inherited ataxias, with symptoms which increases during older age (Gómez-Herreros *et al.*, 2013; Gómez-Herreros *et al.*, 2014). The cause of SCAR23 are mutations with TDP2 and SCAR23 cells are deficient for the resolution within TDP2. SCAR23 cells are insufficient for resolve the stalled Top2cc and are hypersensitive to ETP (epipolythiodioxopiperazine are a class of secondary metabolic toxin) (Gómez-Herreros *et al.*, 2014). TDP2 mutation results in shortened mRNA expression and nonsense mediated decay (Gómez-Herreros *et al.*, 2014). During transcription Top2cc is resolved by TDP2 when TDP2 insufficient in neurons show significant delay in recovery of transcription with treatment of ETP (Gómez-Herreros *et al.*, 2014). Wide expression of Genome profiling show over 100 genes which `are regulated in TDP2 deficient neurons than WT neurons and half of these genes are known to be epilepsy, ataxia and cognitive development (Gómez-Herreros *et al.*, 2014). Different expressions of

long genes in TDP2 insufficient cells specify inhibition of topoisomerase which result in a length dependent impairment in gene expression in post mitotic stage neurons (Zylka *et al.*, 2015).

Topoisomerase in Heterochromatin, aging and disease

Role of Top1 in Heterochromatin

Heterochromatin plays critical role in transcriptional silencing of transposons (SanMiguel *et al.*, 1996; Lander *et al.*, 2001; Waterston *et al.*, 2002). Aging and premature aging syndrome is caused by loss of heterochromatin (Villeponteau, 1997). Loss of heterochromatin and alteration of heterochromatin structure leads to cancer risk and neurological disease respectively (Feinberg *et al.*, 2016; Janssen *et al.*, 2018; Tenreiro *et al.*, 2014). Top1 plays important role for heterochromatin structure and histone modification. Heterochromatin in *Trypanosoma cruzi* is unpacked by Top1 inhibitors, camptothecin (CPT) and rebeccamycin (Zuma *et al.*, 2011). Decompression of heterochromatin with altered histone modifications is induced by the CPT treatment of human HCT16 cells (Baranello *et al.*, 2010). Inactivation of Top1 disrupts transcriptional silencing of transposons (Dinh *et al.*, 2015). Excess RNA-DNA hybrid or R-loop formation in heterochromatin domains was observed in Top1 depleted HEK293 cells. This observation indicate important role of Top1 in regulating R-loop homeostasis in heterochromatin (Manzo *et al.*, 2018).

Role of Top2 in heterochromatin

Transcriptional silencing in heterochromatinis regulated by Top2 as displacement of Top2 from satellite III in heterochromatin or chemical inhibition of Top2 activity which can disrupt heterochromatic silencing of a reporter gene (Blattes *et al.*, 2006). Top2 and chromatin remodelling complexes such as BAF (multisubunit of chromatin remodelers) which make accessory heterochromatin more accessible to transcription factors (Miller *et al.*, 2017). BAF complexes are ATP dependent chromatin remodelling complexes that modify chromatin structure and make the DNA more accessible to machinery of transcription, replication, repair (Clapier & Cairns, 2009; Kadoch *et al.*, 2013; Kadoch *et al.*, 2017). DNA entanglement during mitosis is prevented by BAF complex associated with Top2α (Kadoch *et al.*, 2013; Kadoch *et al.*, 2017). Top2α is identified by chromatin indicator assay (CIA) during BAF mediated chromatin remodelling of facultative heterochromatin. This process is specifically dependent on Top2α because it resolves the topological state of catenated facultative heterochromatin (Lee & Wang, 2019). Decatenation of DNA by Top2α makes the facultative heterochromatin more accessible for chromatin remodelers as well as transcription factors (Miller *et al.*, 2017).

Topoisomerase as target for treatment of diseases

By binding Topoisomerase with DNA strand create a break and passing another DNA strand through the break and releasing DNA. During cleavage process a covalent bond formed between the tyrosine residue of topoisomerase and phosphate group of breaking end of the DNA strand. Topoisomerase cleaves one or both strand of the DNA double helix. The Top1cc is a vulnerable intermediate that can lead to cell death if trapped by any anticancer drug or biomolecule (Seddek *et al.*, 2021). This property of topoisomerase may be utilizing for treatment of both infectious and noninfectious diseases (Seddek *et al.*, 2021).

Rationale for targeting Topoisomerase as drug target

Topoisomerases being a major factor for impacting cell viability, have widely been targeted for clinical treatment of cancer and infectious disease. According to mechanism Topoisomerase inhibitors are classified as poison inhibitors and catalytic inhibitors (Pommier *et al.*, 2010). Poison inhibitors stabilize the topoisomerase covalent complex which forms during catalysis. Catalytic inhibitors interfere with the catalytic cycle of the enzyme inhibiting initial substrate binding of the cleavage complexes. In current clinical studies poison inhibitors against Top1B and Top2αare being used as Topoisomerase targeting drugs (Pommier *et al.*, 2010; Liu, 1989; Pham & Ziora, 2019). Topoisomerase poison inhibitors cause loss of cellular viability through accumulation of breaks in chromosome and thereby triggering apoptosis in cancer cells (Solary, *et al.*, 1994).

Bacterial Top1A as target for novel antibiotics

In thermophilic bacteria Top1 & Top3 are found (Seddek *et al.*, 2021). During transcription Top1 is responsible for relaxation of negative supercoiling and Top3 helps in resolving replication and recombination intermediates (Terekhova *et al.*, 2012; Terekhova *et al.*, 2014). Endogenous inhibitors of Top1 such as, overexpressed Tn5 transposase, T4 gp55.2 and toxin YJhX have been reported to inhibit cell growth and loss of viability of bacterial cell (Seddek *et al.*, 2021). Top1A poison inhibitors generate DNA lesion in bacteria and thereby exhibit bactericidal property (Seddek *et al.*, 2021). The mutated bacterial Top1including mutations in the conserved sequence D111, D113 and E115 triad that bind Mg^{2+} required for DNA relegation are unable to re-join the DNA (Cheng *et al.*, 2009). Effect of these Top1 mutations is expected to mimic the action of Top1A poison inhibitors. Overexpression of YjhX in E. coli leads to death even through YjhX has been shown to have no poison inhibitory effect of Top1. Some bacterial pathogens such as *Mycobacterium tuberculosis* (Ravishankar *et al.*, 2015) *Streptococcus pneumoniae* (Liu *et al.*, 2017), *P. aeruginosa* (Yan *et al.*, 2019) need Top1 for cellular viability. Bacteria have only Top1A to overcome DNA topological barrier during cellular processes and thus it is important for their survival. Catalytic inhibitors of Top1 have antibacterial adequacy of the mechanism of topoisomerase inhibition. Hence bacterial Top1A represents a valid target for novel antibiotics to overcome antimicrobial resistance (Wang, 2002).

Eukaryotic Top1A as potential target for infectious disease treatment

Top3 has two isoforms Top3α and Top3β (Forterre & Gadelle, 2009). In mice embryo development Top3α plays an important role. Top3β knockout mice have been reported to develop maturity but with shorter life span (Kwan & Wang, 2001). Both DNA and RNA Topoisomerase activities are found in human Top3β (Stoll *et al.*, 2013). During transcription it relaxes negatively supercoiled DNA and prevents R loop accumulation (Zhang *et al.*, 2019). Tudor domain containing 3 protein (TDRD3) stabilize Human Top3β which identified as a host protein needed for replication of Flavivirus such as dengue and yellow fever virus (Barrows *et al.*, 2019). Study on role of TDRD3 in viral replication have revealed that Top3β is essential for replication of all single stranded DNA virus and TDRD3 helps in stabilization of Top3β (Prasanth *et al.*, 2020). Therefore inhibitors specific to Top3β could be used successfully as broad spectrum antiviral drugs for management of flavivirus and corona virus including SARS-COV2 infections (Prasanth *et al.*, 2020).

Topoisomerase as a drug target in protozoa

Camptothecin is a Top1 poison which stabilizes the DNA-enzyme complex and induces slow religation (Das, 2004). Camptothecin inhibits the enzyme action in kinetoplast of *L. donovani*, *T. cruzi*, *T. bruci*. Camptothecin also induces programmed cell death of amastigote and promastigote stage of *Leishmania*. Camptothecin induces oxidative stress decrease the GSH level and increased the lipid peroxidation which leads to calcium elevation from intracellular or extracellular sources (Sen *et al.*, 2004, 2004a). The elevated Ca^{2+} loss of membrane potential in mitochondria of the *Leishmania* cells. Decrease in transmembrane K^{+} level of the cell leads to apoptosis (Sen *et al.*, 2004, 2004a). Loss of cell membrane potential, release of cytochrome c and activation of caspase-like proteases result in apoptosis and death of parasites (Kosec *et al.*, 2006).

CONCLUSION

Topoisomerases play an important role in maintaining the topological structure of DNA in all the organisms that used DNA as hereditary material. Any malfunctioning of topoisomerase results into DNA topoisomerase covalent cleavage complex, DSB and SSB which in turn causes mutations in DNA. This mutations lead to pathogenic conditions. Topoisomerase induced changes in DNA are localized in different tissues that trigger disease condition. So far the diseases reported the malfunctioning of topoisomerase has been reviewed here. However, it seems many diseases caused by topoisomerase are yet to be discovered. The topoisomerase induced DNA damaged may be a potential tool to kill harmful pathogens.

Therefore attempts are being made to design drugs targeting topoisomerase of pathogens. The probability of inducing topoisomerase mediated cytotoxicity in cancers cells are also being explored by different researchers.

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CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

REFERENCES

Aguilera, A., & García-Muse, T. (2012). R loops: from transcription byproducts to threats to genome stability. *Molecular cell*, *46*(2), 115-124.

Alt, F. W., & Schwer, B. (2018). DNA double-strand breaks as drivers of neural genomic change, function, and disease. *DNA repair*, *71*, 158-163.

Antony, S., Jayaraman, M., Laco, G., Kohlhagen, G., Kohn, K. W., Cushman, M., & Pommier, Y. (2003). Differential induction of topoisomerase I-DNA cleavage complexes by the indenoisoquinoline MJ-III-65 (NSC 706744) and camptothecin: base sequence analysis and activity against camptothecin-resistant topoisomerases I. *Cancer Research*, *63*(21), 7428-7435.

Austin, C. A., & Marsh, K. L. (1998). Eukaryotic DNA topoisomerase IIβ. *Bioessays*, *20*(3), 215-226.

Baranello, L., Bertozzi, D., Fogli, M. V., Pommier, Y., & Capranico, G. (2010). DNA topoisomerase I inhibition by camptothecin induces escape of RNA polymerase II from promoter-proximal pause site, antisense transcription and histone acetylation at the human HIF-1α gene locus. *Nucleic acids research*, *38*(1), 159-171.

Barrows, N. J., Anglero-Rodriguez, Y., Kim, B., Jamison, S. F., Le Sommer, C., McGee, C. E., ... & Garcia-Blanco, M. A. (2019). Dual roles for the ER membrane protein complex in flavivirus infection: viral entry and protein biogenesis. *Scientific reports*, *9*(1), 9711.

Barthelmes, H. U., Grue, P., Feineis, S., Straub, T., & Boege, F. (2000). Active DNA topoisomerase IIα is a component of the salt-stable centrosome core. *Journal of Biological Chemistry*, *275*(49), 38823-38830.

Bauman, M. E., Holden, J. A., Brown, K. A., Harker, W. G., & Perkins, S. L. (1997). Differential immunohistochemical staining for DNA topoisomerase II alpha and beta in human tissues and for DNA topoisomerase II beta in non-Hodgkin's lymphomas. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc*, *10*(3), 168-175.

Beadle, G., Baade, P., & Fritschi, L. (2009). Acute myeloid leukemia after breast cancer: a population-based comparison with hematological malignancies and other cancers. *Annals of oncology*, *20*(1), 103-109.

Bendixen, C., Thomsen, B., Alsner, J., & Westergaard, O. (1990). Camptothecin-stabilized topoisomerase I-DNA adducts cause premature termination of transcription. *Biochemistry*, *29*(23), 5613-5619.

Berger, J. M., Fass, D., Wang, J. C., & Harrison, S. C. (1998). Structural similarities between topoisomerases that cleave one or both DNA strands. *Proceedings of the National Academy of Sciences*, *95*(14), 7876-7881.

Berger, J. M., Gamblin, S. J., Harrison, S. C., & Wang, J. C. (1996). Structure and mechanism of DNA topoisomerase II. *Nature*, *379*(6562), 225-232.

Blattes, R., Monod, C., Susbielle, G., Cuvier, O., Wu, J. H., Hsieh, T. S., ... & Käs, E. (2006). Displacement of D1, HP1 and topoisomerase II from satellite heterochromatin by a specific polyamide. *The EMBO journal*, *25*(11), 2397-2408.

Boffetta, P., & Kaldor, J. M. (1994). Secondary malignancies following cancer chemotherapy. *Acta Oncologica*, *33*(6), 591-598.

Broeker, P. L., Super, H. G., Thirman, M. J., Pomykala, H., Yonebayashi, Y., Tanabe, S., ... & Rowley, J. D. (1996). Distribution of 11q23 breakpoints within the MLL breakpoint cluster region in de novo acute

leukemia and in treatment-related acute myeloid leukemia: correlation with scaffold attachment regions and topoisomerase II consensus binding sites. *Blood, 87*(5), 1912–1922.

Burgin Jr, A. B., Huizenga, B. N., & Nash, H. A. (1995). A novel suicide substrate for DNA topoisomerases and site-specific recombinases. *Nucleic acids research*, *23*(15), 2973-2979.

Burrow, A. A., Williams, L. E., Pierce, L. C., & Wang, Y. H. (2009). Over half of breakpoints in gene pairs involved in cancer-specific recurrent translocations are mapped to human chromosomal fragile sites. *BMC genomics*, *10*, 1-11.

Capranico, G., De Isabella, P., Tinelli, S., Bigioni, M., & Zunino, F. (1993). Similar sequence specificity of mitoxantrone and VM-26 stimulation of in vitro DNA cleavage by mammalian DNA topoisomerase II. *Biochemistry*, *32*(12), 3038-3046.

Capranico, G., Kohn, K. W., & Pommier, Y. (1990). Local sequence requirements for DNA cleavage by mammalian topoisomerase II in the presence of doxorubicin. *Nucleic acids research*, *18*(22), 6611-6619.

Capranico, G., Zunino, F., Kohn, K. W., & Pommier, Y. (1990a). Sequence-selective topoisomerase II inhibition by anthracycline derivatives in SV40 DNA: relationship with DNA binding affinity and cytotoxicity. *Biochemistry*, *29*(2), 562-569.

Champoux, J. J. (2001). DNA topoisomerases: structure, function, and mechanism. *Annual review of biochemistry*, *70*(1), 369-413.

Chen, A. Y., Jemal, A., & Ward, E. M. (2009). Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *115*(16), 3801-3807.

Chen, G. L. Yang, L., Rowe, T. C., Halligan, B. D., Tewey, K. M., Liu L. F., (1984). Nonintercalative antitumor drugs interfere with the breakage-reunion reaction of mammalian DNA topoisomerase II. *J Biol Chem*, *259*, 13560-13566.

Chen, H., & Eastmond, D. A. (1995). Topoisomerase inhibition by phenolic metabolites: a potential mechanism for benzene's clastogenic effects. *Carcinogenesis*, *16*(10), 2301-2307.

Cheng, B., Annamalai, T., Sorokin, E., Abrenica, M., Aedo, S., & Tse-Dinh, Y. C. (2009). Asp-to-Asn substitution at the first position of the DxD TOPRIM motif of recombinant bacterial topoisomerase I is extremely lethal to E. coli. *Journal of molecular biology*, *385*(2), 558-567.

Clapier, C.R., and B.R Cairns. 2009. "The biology of chromatin remodeling complexes." *Annu. Rev. Biochem*. 78: 273–304.

Covey, J. M., Jaxel, C., Kohn, K. W., & Pommier, Y. (1989). Protein-linked DNA strand breaks induced in mammalian cells by camptothecin, an inhibitor of topoisomerase I. *Cancer research*, *49*(18), 5016-5022.

Dalla Rosa, I., Shar-yin, N. H., Agama, K., Khiati, S., Zhang, H., & Pommier, Y. (2014). Mapping topoisomerase sites in mitochondrial DNA with a poisonous mitochondrial topoisomerase I (Top1mt). *Journal of Biological Chemistry*, *289*(26), 18595-18602.

Dalla Rosa, I., Zhang, H., Khiati, S., Wu, X., & Pommier, Y. (2017). Transcription profiling suggests that mitochondrial topoisomerase IB acts as a topological barrier and regulator of mitochondrial DNA transcription. *Journal of Biological Chemistry*, *292*(49), 20162-20172.

Das, B. B., Sen, N., Ganguly, A., & Majumder, H. K. (2004). Reconstitution and functional characterization of the unusual bi-subunit type I DNA topoisomerase from Leishmania donovani. *FEBS letters*, *565*(1-3), 81-88.

Davies, L., & Welch, H. G. (2006). Increasing incidence of thyroid cancer in the United States, 1973-2002. *Jama*, *295*(18), 2164-2167.

De Vathaire, F., Hawkins, M., Campbell, S., Oberlin, O., Raquin, M. A., Schlienger, J. Y., ... & Lemerle, J. (1999). Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *British journal of cancer*, *79*(11), 1884-1893.

Dillon, L. W., Lehman, C. E., & Wang, Y. H. (2012). The

role of fragile sites in sporadic papillary thyroid carcinoma. *Journal of Thyroid Research*, *2012*.

Dillon, L. W., Pierce, L. C., Lehman, C. E., Nikiforov, Y. E., & Wang, Y. H. (2013). DNA topoisomerases participate in fragility of the oncogene RET. *PloS one*, *8*(9), e75741.

Dinh, T. T., Gao, L., Liu, X., Li, D., Li, S., Zhao, Y., ... & Chen, X. (2015). Correction: DNA Topoisomerase 1α Promotes Transcriptional Silencing of Transposable Elements through DNA Methylation and Histone Lysine 9 Dimethylation in Arabidopsis. *Plos Genetics*, *11*(9), e1005452.

Eastmond, D. A., Mondrala, S. T., & Hasegawa, L. (2005). Topoisomerase II inhibition by myeloperoxidase-activated hydroquinone: a potential mechanism underlying the genotoxic and carcinogenic effects of benzene. *Chemico-biological interactions*, *153*, 207-216.

El-Khamisy, S. F., & Caldecott, K. W. (2007). DNA single-strand break repair and spinocerebellar ataxia with axonal neuropathy-1. *Neuroscience*, *145*(4), 1260-1266.

El-Khamisy, S. F., Saifi, G. M., Weinfeld, M., Johansson, F., Helleday, T., Lupski, J. R., & Caldecott, K. W. (2005). Defective DNA single-strand break repair in spinocerebellar ataxia with axonal neuropathy-1. *Nature*, *434*(7029), 108-113.

Enewold, L., Zhu, K., Ron, E., Marrogi, A. J., Stojadinovic, A., Peoples, G. E., & Devesa, S. S. (2009). Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiology Biomarkers & Prevention*, *18*(3), 784-791.

Feinberg, A. P., Koldobskiy, M. A., & Göndör, A. (2016). Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. *Nature Reviews Genetics*, *17*(5), 284-299.

Felix, C. A. (1998). Secondary leukemias induced by topoisomerase-targeted drugs. *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, *1400*(1-3), 233-255.

Fenton, C. L., Lukes, Y., Nicholson, D., Dinauer, C. A., Francis, G. L., & Tuttle, R. M. (2000). The ret/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. *The Journal of Clinical Endocrinology & Metabolism*, *85*(3), 1170-1175.

Finn, S. P., Smyth, P., O'Leary, J., Sweeney, E. C., & Sheils, O. (2003). Ret/PTC chimeric transcripts in an Irish cohort of sporadic papillary thyroid carcinoma. *The Journal of Clinical Endocrinology & Metabolism*, *88*(2), 938-941.

Forterre, P., & Gadelle, D. (2009). Phylogenomics of DNA topoisomerases: their origin and putative roles in the emergence of modern organisms. *Nucleic Acids Research*, *37*(3), 679-692.

Fortune, J. M., & Osheroff, N. (2000). Topoisomerase II as a target for anticancer drugs: when enzymes stop being nice. *Progress in Nucleic Acid Research and Molecular Biology, 64*, 2221-253

Frantz, C. E., Chen, H., & Eastmond, D. A. (1996). Inhibition of human topoisomerase II in vitro by bioactive benzene metabolites. *Environmental health perspectives*, *104*(suppl 6), 1319-1323.

Froelich-Ammon, S. J., Gale, K. C., & Osheroff, N. (1994). Site-specific cleavage of a DNA hairpin by topoisomerase II. DNA secondary structure as a determinant of enzyme recognition/cleavage. *Journal of Biological Chemistry*, *269*(10), 7719-7725.

Gilmour, D. S., Pflugfelder, G., Wang, J. C., & Lis, J. T. (1986). Topoisomerase I interacts with transcribed regions in Drosophila cells. *Cell*, *44*(3), 401-407.

Gómez-Herreros, F., Romero-Granados, R., Zeng, Z., Alvarez-Quilon, A., Quintero, C., Ju, L., ... & Cortés-Ledesma, F. (2013). TDP2–dependent non-homologous end-joining protects against topoisomerase II–induced DNA breaks and genome instability in cells and in vivo. *PLoS genetics*, *9*(3), e1003226.

Gómez-Herreros, F., Schuurs-Hoeijmakers, J. H., McCormack, M., Greally, M. T., Rulten, S., Romero-Granados, R., ... & Caldecott, K. W. (2014). TDP2 protects transcription from abortive topoisomerase activity and is required for normal neural function. *Nature genetics*, *46*(5), 516-521.

Gothe, H. J., Bouwman, B. A. M., Gusmao, E. G.,

Piccinno, R., Petrosino, G., Sayols, S., ... & Roukos, V. (2019). Spatial chromosome folding and active transcription drive DNA fragility and formation of oncogenic MLL translocations. *Molecular cell*, *75*(2), 267-283.

Goto, M., Miller, R. W., Ishikawa, Y., & Sugano, H. (1996). Excess of rare cancers in Werner syndrome (adult progeria). *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, *5*(4), 239-246.

Gow, K. W., Lensing, S., Hill, D. A., Krasin, M. J., McCarville, M. B., Rai, S. N., ... & Hudson, M. M. (2003). Thyroid carcinoma presenting in childhood or after treatment of childhood malignancies: an institutional experience and review of the literature. *Journal of pediatric surgery*, *38*(11), 1574-1580.

Grue P, Grasser A, Sehested M, Jensen PB, Uhse A, *et al.* (1998). Essential mitotic functions of DNA topoisomerase IIa are not adopted by topoisomerase IIb in human H69 cells. *J Biol Chem, 273*, 33660–33666.

Harmon, F. G., Brockman, J. P., & Kowalczykowski, S. C. (2003). RecQ helicase stimulates both DNA catenation and changes in DNA topology by topoisomerase III. *Journal of Biological Chemistry*, *278*(43), 42668-42678.

Harvey, G. R., Rands, A. L., & McHugh, N. J. (1996). Anti-RNA polymerase antibodies in systemic sclerosis (SSc): association with anti-topoisomerase I antibodies and identification of autoreactive subunits of RNA polymerase II. *Clinical & Experimental Immunology*, *105*(3), 468-474.

He, X., van Waardenburg, R. C. A. M., Babaoglu, K., Price, A. C., Nitiss, K. C.,He, X., van Waardenburg, R. C. A. M., Babaoglu, K., Price, A. C., Nitiss, K. C.,. (2007). Mutation of a conserved active site residue converts Tyrosyl-DNA phosphodiesterase I into a DNA topoisomerase I-dependent poison. *Mol. Biol. 372*, 1070–1081.

Holm, C., Covey, J. M., Kerrigan, D., & Pommier, Y. (1989). Differential requirement of DNA replication for the cytotoxicity of DNA topoisomerase I and II inhibitors in Chinese hamster DC3F cells. *Cancer research*, *49*(22), 6365-6368.

Hsiang, Y. H., Lihou, M. G., & Liu, L. F. (1989). Arrest of replication forks by drug-stabilized topoisomerase I-DNA cleavable complexes as a mechanism of cell killing by camptothecin. *Cancer research*, *49*(18), 5077-5082.

Hu, P. Q., Fertig, N., Medsger, T. A., & Wright, T. M. (2004). Molecular recognition patterns of serum anti-DNA topoisomerase I antibody in systemic sclerosis. *The Journal of Immunology*, *173*(4), 2834-2841.

Interthal, H., Chen, H. J., & Champoux, J. J. (2005). Human Tdp1 cleaves a broad spectrum of substrates, including phosphoamide linkages. *Journal of Biological Chemistry*, *280*(43), 36518-36528.

Interthal, H., Pouliot, J. J., & Champoux, J. J. (2001). The tyrosyl-DNA phosphodiesterase Tdp1 is a member of the phospholipase D superfamily. *Proceedings of the National Academy of Sciences*, *98*(21), 12009-12014.

Isaacs, R. J., Davies, S. L., Sandri, M. I., Redwood, C., Wells, N. J., & Hickson, I. D. (1998). Physiological regulation of eukaryotic topoisomerase II. *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, *1400*(1-3), 121-137.

Janssen, A., Colmenares, S. U., & Karpen, G. H. (2018). Heterochromatin: guardian of the genome. *Annual review of cell and developmental biology*, *34*, 265-288.

Jaxel, C., Capranico, G., Kerrigan, D., Kohn, K. W., & Pommier, Y. (1991). Effect of local DNA sequence on topoisomerase I cleavage in the presence or absence of camptothecin. *Journal of Biological Chemistry*, *266*(30), 20418-20423.

Jimenez, M., Leon, P., Castro, L., Azcona, C., & Sierrasesumaga, L. (1995). Second tumors in pediatric oncologic patients. Report of 5 cases. *Revista de medicina de la Universidad de Navarra*, *40*(2), 72-77.

Jonstrup, A. T., Thomsen, T., Wang, Y., Knudsen, B. R., Koch, J., & Andersen, A. H. (2008). Hairpin structures formed by alpha satellite DNA of human centromeres are cleaved by human topoisomerase IIα. *Nucleic acids research*, *36*(19), 6165-6174.

Ju, B. G., Lunyak, V. V., Perissi, V., Garcia-Bassets, I., Rose, D. W., Glass, C. K., & Rosenfeld, M. G. (2006). A topoisomerase IIß-mediated dsDNA break required for regulated transcription. *Science*, *312*(5781), 1798-1802.

Kadoch, C., Hargreaves, D. C., Hodges, C., Elias, L., Ho, L., Ranish, J., & Crabtree, G. R. (2013). Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nature genetics*, *45*(6), 592-601.

Kadoch, C., Williams, R. T., Calarco, J. P., Miller, E. L., Weber, C. M., Braun, S. M., ... & Crabtree, G. R. (2017). Dynamics of BAF–Polycomb complex opposition on heterochromatin in normal and oncogenic states. *Nature genetics*, *49*(2), 213-222.

Katyal, S., El-Khamisy, S. F., Russell, H. R., Li, Y., Ju, L., Caldecott, K. W., & McKinnon, P. J. (2007). TDP1 facilitates chromosomal single-strand break repair in neurons and is neuroprotective in vivo. *The EMBO journal*, *26*(22), 4720-4731.

Katyal, S., Lee, Y., Nitiss, K. C., Downing, S. M., Li, Y., Shimada, M., ... & McKinnon, P. J. (2014). Aberrant topoisomerase-1 DNA lesions are pathogenic in neurodegenerative genome instability syndromes. *Nature neuroscience*, *17*(6), 813-821.

Khobta, A., Ferri, F., Lotito, L., Montecucco, A., Rossi, R., & Capranico, G. (2006). Early effects of topoisomerase I inhibition on RNA polymerase II along transcribed genes in human cells. *Journal of molecular biology*, *357*(1), 127-138.

Kim, N., Huang, S. Y. N., Williams, J. S., Li, Y. C., Clark, A. B., Cho, J. E., ... & Jinks-Robertson, S. (2011). Mutagenic processing of ribonucleotides in DNA by yeast topoisomerase I. *Science*, *332*(6037), 1561-1564.

King, I. F., Yandava, C. N., Mabb, A. M., Hsiao, J. S., Huang, H. S., Pearson, B. L., ... & Zylka, M. J. (2013). Topoisomerases facilitate transcription of long genes linked to autism. *Nature*, *501*(7465), 58-62.

Kingma, P. S., Greider, C. A., & Osheroff, N. (1997). Spontaneous DNA lesions poison human topoisomerase IIα and stimulate cleavage proximal to leukemic 11q23 chromosomal breakpoints. *Biochemistry*, *36*(20), 5934-5939.

Kosec, G., Alvarez, V. E., Agüero, F., Sánchez, D., Dolinar, M., Turk, B., ... & Cazzulo, J. J. (2006). Metacaspases of Trypanosoma cruzi: possible candidates for programmed cell death mediators. *Molecular and biochemical parasitology*, *145*(1), 18-28.

Kwan, K. Y., & Wang, J. C. (2001). Mice lacking DNA topoisomerase IIIβ develop to maturity but show a reduced mean lifespan. *Proceedings of the National Academy of Sciences*, *98*(10), 5717-5721.

Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., Devon, K., Dewar, K., and Doyle M. (2001). Initial sequencing and analysis of the human genome. *Nature*, *409*, 860-921.

Lee, S. K., & Wang, W. (2019). Roles of topoisomerases in heterochromatin, aging, and diseases. *Genes*, *10*(11), 884.

Lehman, C. E., Dillon, L. W., Nikiforov, Y. E., & Wang, Y. H. (2017). DNA fragile site breakage as a measure of chemical exposure and predictor of individual susceptibility to form oncogenic rearrangements. *Carcinogenesis*, *38*(3), 293-301.

Leone, G., Teofili, L., Voso, M. T., & Lubbert, M. (2002). DNA methylation and demethylating drugs in myelodysplastic syndromes and secondary leukemias. *haematologica*, *87*(12), 1324-1341.

Lesher, D. T. T., Pommier, Y., Stewart, L., & Redinbo, M. R. (2002). 8-Oxoguanine rearranges the active site of human topoisomerase I. *Proceedings of the National Academy of Sciences*, *99*(19), 12102-12107.

Li, M., & Liu, Y. (2016). Topoisomerase I in human disease pathogenesis and treatments. *Genomics, Proteomics and Bioinformatics*, *14*(3), 166-171.

Lindsley, J. E., & Wang, J. C. (1991). Proteolysis patterns of epitopically labeled yeast DNA

topoisomerase II suggest an allosteric transition in the enzyme induced by ATP binding. *Proceedings of the National Academy of Sciences*, *88*(23), 10485-10489.

Liu, L. F. (1989). DNA topoisomerase poisons as antitumor drugs. *Annual review of biochemistry*, *58*(1), 351-375.

Liu, L. F., *& Wang*, J. C. (1983). DNA topoisomerases-enzymes that catalyse the breaking and rejoining of DNA. *Critical Reviews in Biochemistry*, *15*(1), 1-24.

Liu, X., Gallay, C., Kjos, M., Domenech, A., Slager, J., van Kessel, S. P., ... & Veening, J. W. (2017). High-throughput CRISPRi phenotyping identifies new essential genes in Streptococcus pneumoniae. *Molecular systems biology*, *13*(5), 931.

Loike, J. D. (1982). VP16-213 and podophyllotoxin: a study on the relationship between chemical structure and biological activity. *Cancer Chemotherapy and Pharmacology*, *7*, 103-111.

Long, B. H., & Stringfellow, D. A. (1988). Inhibitors of topoisomerase II: structure-activity relationships and mechanism of action of podophyllin congeners. *Advances in enzyme regulation*, *27*, 211-214.

Mahler, M., Silverman, E. D., Schulte-Pelkum, J., & Fritzler, M. J. (2010). Anti-Scl-70 (topo-I) antibodies in SLE: myth or reality?. *Autoimmunity reviews*, *9*(11), 756-760.

Manzo, S. G., Hartono, S. R., Sanz, L. A., Marinello, J., De Biasi, S., Cossarizza, A., ... & Chedin, F. (2018). DNA Topoisomerase I differentially modulates R-loops across the human genome. *Genome biology*, *19*, 1-18.

Mao, Y., Desai, S. D., Ting, C. Y., Hwang, J., & Liu, L. F. (2001). 26 S proteasome-mediated degradation of topoisomerase II cleavable complexes. *Journal of Biological Chemistry*, *276*(44), 40652-40658.

Marchand, C., & Pommier, Y. (2011). Topoisomerases inhibitors: a paradigm for interfacial inhibition. In *DNA Topoisomerases and Cancer* (pp. 175-184). New York, NY: Springer New York.

McClendon, A. K., & Osheroff, N. (2007). DNA topoisomerase II, genotoxicity, and cancer. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *623*(1-2), 83-97.

Meyer, C., Burmeister, T., Gröger, D., Tsaur, G., Fechina, L., Renneville, A., ... & Marschalek, R. (2018). The MLL recombinome of acute leukemias in 2017. *Leukemia*, *32*(2), 273-284.

Miller, E. L., Hargreaves, D. C., Kadoch, C., Chang, C. Y., Calarco, J. P., Hodges, C., ... & Crabtree, G. R. (2017). TOP2 synergizes with BAF chromatin remodeling for both resolution and formation of facultative heterochromatin. *Nature structural & molecular biology*, *24*(4), 344-352.

Mills, W. E., Spence, J. M., Fukagawa, T., & Farr, C. J. (2018). Site-Specific cleavage by topoisomerase 2: a mark of the core centromere. *International Journal of Molecular Sciences*, *19*(2), 534.

Morton, L. M., Dores, G. M., Tucker, M. A., Kim, C. J., Onel, K., Gilbert, E. S., ... & Curtis, R. E. (2013). Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. *Blood, The Journal of the American Society of Hematology*, *121*(15), 2996-3004.

National Toxicology Program. (2011). NTP 12th report on carcinogens. *Report on carcinogens: carcinogen profiles*, *12*, iii-499.

Nikiforov, Y. E., Rowland, J. M., Bove, K. E., Monforte-Munoz, H., & Fagin, J. A. (1997). Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. *Cancer Research*, *57*(9), 1690-1694.

Nitiss, J. L. (1998). Investigating the biological functions of DNA topoisomerases in eukaryotic cells. *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, *1400*(1-3), 63-81.

Nitiss, J. L., & Beck, W. T. (1996). Antitopoisomerase drug action and resistance. *European Journal of Cancer*, *32*(6), 958-966.

Osheroff, N. (1986). Eukaryotic topoisomerase II.

Characterization of enzyme turnover. *Journal of Biological Chemistry*, *261*(21), 9944-9950.

Osheroff, N., Shelton, E. R., & Brutlag, D. L. (1983). DNA topoisomerase II from Drosophila melanogaster. Relaxation of supercoiled DNA. *Journal of Biological Chemistry*, *258*(15), 9536-9543.

Pedersen-Bjergaard, J., & Philip, P. (1991). Balanced translocations involving chromosome bands 11q23 and 21q22 are highly characteristic of myelodysplasia and leukemia following therapy with cytostatic agents targeting at DNA-topoisomerase II.

Pham, T. D., Ziora, Z. M., & Blaskovich, M. A. (2019). Quinolone antibiotics. *Medchemcomm*, *10*(10), 1719-1739.

Pommier, Y., & Cherfils, J. (2005). Interfacial inhibition of macromolecular interactions: nature's paradigm for drug discovery. *Trends in pharmacological sciences*, *26*(3), 138-145.

Pommier, Y., & Marchand, C. (2005). Interfacial inhibitors of protein-nucleic acid interactions. *Current Medicinal Chemistry-Anti-Cancer Agents*, *5*(4), 421-429.

Pommier, Y., & Marchand, C. (2012). Interfacial inhibitors: targeting macromolecular complexes. *Nature reviews Drug discovery*, *11*(1), 25-36.

Pommier, Y., Barcelo, J. M., Rao, V. A., Sordet, O., Jobson, A. G., Thibaut, L., ... & Redon, C. (2006). Repair of topoisomerase I-mediated DNA damage. *Progress in nucleic acid research and molecular biology*, *81*, 179-229.

Pommier, Y., Capranico, G., Orr, A., & Kohn, K. W. (1991). Distribution of topoisomerase II cleavage sites in simian virus 40 DNA and the effects of drugs. *Journal of molecular biology*, *222*(4), 909-924.

Pommier, Y., Capranico, G., Orr, A., & Kohn, K. W. (1991a). Local base sequence preferences for DNA cleavage by mammalian topoisomerase II in the presence of amsacrine or teniposide. *Nucleic acids research*, *19*(21), 5973-5980.

Pommier, Y., Kiselev, E., & Marchand, C. (2015). Interfacial inhibitors. *Bioorganic & medicinal chemistry letters*, *25*(18), 3961-3965.

Pommier, Y., Leo, E., Zhang, H., & Marchand, C. (2010). DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. *Chemistry & biology*, *17*(5), 421-433.

Pommier, Y., Pourquier, P., Fan, Y. I., & Strumberg, D. (1998). Mechanism of action of eukaryotic DNA topoisomerase I and drugs targeted to the enzyme. *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, *1400*(1-3), 83-106.

Pourquier, P., Pilon, A. A., Kohlhagen, G., Mazumder, A., Sharma, A., & Pommier, Y. (1997). Trapping of mammalian topoisomerase I and recombinations induced by damaged DNA containing nicks or gaps: importance of DNA end phosphorylation and camptothecin effects. *Journal of Biological Chemistry*, *272*(42), 26441-26447.

Pourquier, P., Ueng, L. M., Fertala, J., Wang, D., Park, H. J., Essigmann, J. M., ... & Pommier, Y. (1999). Induction of reversible complexes between eukaryotic DNA topoisomerase I and DNA-containing oxidative base damages: 7, 8-dihydro-8-oxoguanine and 5-hydroxycytosine. *Journal of Biological Chemistry*, *274*(13), 8516-8523.

Pourquier, P., Ueng, L. M., Kohlhagen, G., Mazumder, A., Gupta, M., Kohn, K. W., & Pommier, Y. (1997a). Effects of uracil incorporation, DNA mismatches, and abasic sites on cleavage and religation activities of mammalian topoisomerase I. *Journal of Biological Chemistry*, *272*(12), 7792-7796.

Prasanth, K. R., Hirano, M., Fagg, W. S., McAnarney, E. T., Shan, C., Xie, X., ... & Garcia-Blanco, M. A. (2020). Topoisomerase III-β is required for efficient replication of positive-sense RNA viruses. *Antiviral research*, *182*, 104874.

Ravishankar, S., Ambady, A., Awasthy, D., Mudugal, N. V., Menasinakai, S., Jatheendranath, S., ... & Sharma, U. K. (2015). Genetic and chemical validation identifies Mycobacterium tuberculosis topoisomerase I as an attractive anti-tubercular target. *Tuberculosis*, *95*(5), 589-598.

Sabourin, M., & Osheroff, N. (2000). Sensitivity of

human type II topoisomerases to DNA damage: stimulation of enzyme-mediated DNA cleavage by abasic, oxidized and alkylated lesions. *Nucleic acids research*, *28*(9), 1947-1954.

Sander, M., & Hsieh, T. S. (1983). Double strand DNA cleavage by type II DNA topoisomerase from Drosophila melanogaster. *Journal of Biological Chemistry*, *258*(13), 8421-8428.

SanMiguel, P., Tikhonov, A., Jin, Y. K., Motchoulskaia, N., Zakharov, D., Melake-Berhan, A., ... & Bennetzen, J. L. (1996). Nested retrotransposons in the intergenic regions of the maize genome. *Science*, *274*(5288), 765-768.

Seddek, A., Annamalai, T., & Tse-Dinh, Y. C. (2021). Type IA topoisomerases as targets for infectious disease treatments. *Microorganisms*, *9*(1), 86.

Sen, N., Das, B. B., Ganguly, A., Mukherjee, T., Bandyopadhyay, S., & Majumder, H. K. (2004). Camptothecin-induced imbalance in intracellular cation homeostasis regulates programmed cell death in unicellular hemoflagellate Leishmania donovani. *Journal of Biological Chemistry*, *279*(50), 52366-52375.

Sen, N., Das, B.B., Ganguly, A., Mukherjee, T., Tripathi, G., and Bandopadhyay, S., *et al.* (2004a) Camptothecin induced mitochondrial dysfunction and programmed cell death in unicellular hemoflagellate Leishmania donovani. *Cell Death Diff, 11*, 924–936.

Shuman, S. (1989). Vaccinia DNA topoisomerase I promotes illegitimate recombination in Escherichia coli. *Proceedings of the National Academy of Sciences*, *86*(10), 3489-3493.

Solary, E., Bertrand, R., & Pommier, Y. (1994). Apoptosis induced by DNA topoisomerase I and II inhibitors in human leukemic HL-60 cells. *Leukemia & lymphoma*, *15*(1-2), 21-32.

Staker, B. L., Hjerrild, K., Feese, M. D., Behnke, C. A., Burgin Jr, A. B., & Stewart, L. (2002). The mechanism of topoisomerase I poisoning by a camptothecin analog. *Proceedings of the National Academy of Sciences*, *99*(24), 15387-15392.

Stewart, L., Redinbo, M. R., Qiu, X., Hol, W. G., & Champoux, J. J. (1998). A model for the mechanism of human topoisomerase I. *Science*, *279*(5356), 1534-1541.

Stoll, G., Pietiläinen, O. P., Linder, B., Suvisaari, J., Brosi, C., Hennah, W., ... & Palotie, A. (2013). Deletion of TOP3β, a component of FMRP-containing mRNPs, contributes to neurodevelopmental disorders. *Nature neuroscience*, *16*(9), 1228-1237.

Strick, R., Strissel, P. L., Borgers, S., Smith, S. L., & Rowley, J. D. (2000). Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. *Proceedings of the National Academy of Sciences*, *97*(9), 4790-4795.

Swan, R. L., Cowell, I. G., & Austin, C. A. (2022). Mechanisms to repair stalled topoisomerase II-DNA covalent complexes. *Molecular Pharmacology*, *101*(1), 24-32.

Swerdlow, A. J., Douglas, A. J., Hudson, G. V., Hudson, B. V., Bennett, M. H., & MacLennan, K. A. (1992). Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. *British Medical Journal*, *304*(6835), 1137-1143.

Takashima, H., Boerkoel, C. F., John, J., Saifi, G. M., Salih, M. A., Armstrong, D., ... & Lupski, J. R. (2002). Mutation of TDP1, encoding a topoisomerase I–dependent DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. *Nature genetics*, *32*(2), 267-272.

Tanizawa, A., Kohn, K. W., Kohlhagen, G., Leteurtre, F., & Pommier, Y. (1995). Differential stabilization of eukaryotic DNA topoisomerase I cleavable complexes by camptothecin derivatives. *Biochemistry*, *34*(21), 7200-7206.

Tenreiro, S., Eckermann, K., & Outeiro, T. F. (2014). Protein phosphorylation in neurodegeneration: friend or foe?. *Frontiers in molecular neuroscience*, *7*, 42.

Terekhova, K., Gunn, K. H., Marko, J. F., & Mondragón, A. (2012). Bacterial topoisomerase I and topoisomerase III relax supercoiled DNA via

distinct pathways. *Nucleic acids research*, *40*(20), 10432-10440.

Terekhova, K., Marko, J. F., & Mondragon, A. (2014). Single-molecule analysis uncovers the difference between the kinetics of DNA decatenation by bacterial topoisomerases I and III. *Nucleic acids research*, *42*(18), 11657-11667.

Tewey, K. M., Chen, G. L., Nelson, E. M., & Liu, L. F. (1984). Intercalative antitumor drugs interfere with the breakage-reunion reaction of mammalian DNA topoisomerase II. *Journal of Biological Chemistry*, *259*(14), 9182-9187.

Tewey, K. M., Rowe, T. C., Yang, L., Halligan, B. D., & Liu, L. F. (1984a). Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II. *Science*, *226*(4673), 466-468.

Thys, R. G., Lehman, C. E., Pierce, L. C., & Wang, Y. H. (2015). Environmental and chemotherapeutic agents induce breakage at genes involved in leukemia-causing gene rearrangements in human hematopoietic stem/progenitor cells. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *779*, 86-95.

Tsuchiya, H., Tomita, K., Ohno, M., Inaoki, M., & Kawashima, A. (1991). Werner's syndrome combined with quintuplicate malignant tumors: a case report and review of literature data. *Japanese journal of clinical oncology*, *21*(2), 135-142.

Tuduri, S., Crabbé, L., Conti, C., Tourrière, H., Holtgreve-Grez, H., Jauch, A., ... & Pasero, P. (2010). Topoisomerase I suppresses genomic instability by preventing interference between replication and transcription. *Nature Cell Biology*, *12*(11), 1122.

Vélez-Cruz, R., & Osheroff, N. (2004). DNA topoisomerases: type II. in: *Encyclopedia of Biological Chemistry*." Elsevier Inc, p: 806-811.

Venkitaraman, R., Affolter, A., Ahmed, M., Thomas, V., Pritchard-Jones, K., Sharma, A. K., ... & Nutting, C. M. (2008). Childhood papillary thyroid cancer as second malignancy after successful treatment of rhabdomyosarcoma. *Acta Oncologica*, *47*(3), 469-472.

Verneris, M., McDougall, I. R., Becton, D., & Link, M. P. (2001). Thyroid carcinoma after successful treatment of osteosarcoma: a report of three patients. *Journal of pediatric hematology/oncology*, *23*(5), 312-315.

Villeponteau, B. (1997). The heterochromatin loss model of aging. *Experimental gerontology*, *32*(4-5), 383-394.

Walton, C., Interthal, H., Hirano, R., Salih, M. A., Takashima, H., & Boerkoel, C. F. (2010). Spinocerebellar ataxia with axonal neuropathy. *Diseases of DNA Repair*, 75-83.

Wang, J. C. (1996). DNA topoisomerases. *Annu Rev Biochem, 65*, 635–692.

Wang, J. C. (2002). Cellular roles of DNA topoisomerases: a molecular perspective. *Nature reviews Molecular cell biology*, *3*(6), 430-440.

Waterston, R. H., Lindblad-Toh, K., Birney, E., Rogers, J., Abril, J. F., Agarwal, P., ... & Bult, C. (2002). Initial sequencing and comparative analysis of the mouse genome: Mouse Genome Sequencing Consortium.

Watson, J. D., Baker, T. A., Bell, S. P., Gann, A., Levine, M., Losick R. (2013). Molecular biology of the gene. 7th edition., Pearson Education, 880 p.

Woessner, R. D., Mattern, M. R., Mirabelli, C. K., Johnson, R. K., & Drake, F. H. (1991). Proliferation-and cell cycle-dependent differences in expression of the 170 kilodalton and 180 kilodalton forms of topoisomerase II in NIH-3T3 cells. *Cell Growth Differ*, *2*(4), 209-214.

Worland, S. T., & Wang, J. C. (1989). Inducible overexpression, purification, and active site mapping of DNA topoisomerase II from the yeast Saccharomyces cerevisiae. *Journal of Biological Chemistry*, *264*(8), 4412-4416.

Wu, J., & Liu, L. F. (1997). Processing of topoisomerase I cleavable complexes into DNA damage by transcription. *Nucleic acids research*, *25*(21), 4181-4186.

Wu, L., & Hickson, I. D. (2003). The Bloom's syndrome helicase suppresses crossing over during homologous recombination. *Nature*, *426*(6968), 870-874.

Yan, R., Hu, S., Ma, N., Song, P., Liang, Q., Zhang, H., ... & Chen, L. (2019). Regulatory effect of DNA topoisomerase I on T3SS activity, antibiotic susceptibility and quorum-sensing-independent pyocyanin synthesis in Pseudomonas aeruginosa. *International journal of molecular sciences*, *20*(5), 1116.

Yen, B. C., Kahn, H., Schiller, A. L., Klein, M. J., Phelps, R. G., & Lebwohl, M. G. (1993). Multiple hamartoma syndrome with osteosarcoma. *Archives of pathology & laboratory medicine*, *117*(12), 1252-1254.

Yunis, J. J., Soreng, A. L., & Bowe, A. E. (1987). Fragile sites are targets of diverse mutagens and carcinogens. *Oncogene*, *1*(1), 59-69.

Zechiedrich, E. L., Christiansen, K., Andersen, A. H., Westergaard, O., & Osheroff, N. (1989). Double-stranded DNA cleavage/religation reaction of eukaryotic topoisomerase II: evidence for a nicked DNA intermediate. *Biochemistry*, *28*(15), 6229-6236.

Zhang, T., Wallis, M., Petrovic, V., Challis, J., Kalitsis, P., & Hudson, D. F. (2019). Loss of TOP3B leads to increased R-loop formation and genome instability. *Open Biology*, *9*(12), 190222.

Zuma, A. A., Cavalcanti, D. P., Maia, M. C., de Souza, W., & Motta, M. C. M. (2011). Effect of topoisomerase inhibitors and DNA-binding drugs on the cell proliferation and ultrastructure of Trypanosoma cruzi. *International journal of antimicrobial agents*, *37*(5), 449-456.

Zylka, M. J., Simon, J. M., & Philpot, B. D. (2015). Gene length matters in neurons. *Neuron*, *86*(2), 353-355.