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Targeting TOP2B as a vulnerability in aging and aging-related diseases

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ABSTRACT

The ongoing trend of rapid aging of the global population has unavoidably resulted in an increase in aging-related diseases. There is an immense amount of interest in the scientific community for the identification of molecular targets that may effectively mitigate the process of aging and aging-related diseases. The enzyme Topoisomerase IIβ (TOP2B) plays a crucial role in resolving the topological challenges that occur during DNA-related processes. It is believed that the disruption of TOP2B function contributes to the aging of cells and tissues, as well as the development of age-related diseases. Consequently, targeting TOP2B appears to be a promising approach for interventions aimed at mitigating the effects of aging. This review focuses on recent advancements in the understanding of the role of TOP2B in the processing of aging and aging-related disorders, thus providing a novel avenue for the development of anti-aging strategies.

1. Introduction

The World Population Prospects 2022 report predicts that the proportion of the global population aged ≥65 years will increase from 9.7 % in 2022 to 16.4 % in 2050 [1]. Aging is a complex biological phenomenon characterized by a progressive and irreversible decline in physical activity and physiological capabilities throughout life [2]. Aging is associated with an increased susceptibility to aging-related diseases. Although aging has traditionally been viewed as an irreversible pathophysiological phenomenon, numerous studies have been conducted to understand its characteristics. The objective of these investigations was to identify prospective therapeutic targets that could postpone or potentially reverse the process of aging and aging-related disorders [2].

Aging is commonly associated with 12 distinct hallmarks [2], each characterized by a specific feature: (1) genomic instability, (2) telomere attrition, (3) epigenetic alterations, (4) loss of proteostasis, (5) impaired macroautophagy, (6) deregulated nutrient-sensing, (7) mitochondrial dysfunction, (8) cellular senescence, (9) stem cell exhaustion, (10) altered intercellular communication, (11) chronic inflammation, and (12) dysbiosis. Genomic instability is recognized as the main contributor to aging [2]. The integrity of the genome is compromised by a diverse array of external and internal factors within cells, resulting in numerous types of cellular damage such as DNA mutations, translocations, and other molecular alterations. Cells have developed intricate mechanisms to maintain their genomic integrity and stability.

Topoisomerases are essential enzymes involved in regulating DNA topology. They can be classified into two main families: Topoisomerase I (TOP1, including TOP1 and TOP1MT) and Topoisomerase II (TOP2, including TOP2A and TOP2B). Although topoisomerases have similar roles in DNA topology, TOP2 possesses distinct characteristics in DNA-related processes in comparison to other members: (1) TOP2 can create breaks in both strands of DNA and then thread an unbroken DNA double helix through the break, allowing for a greater degree of control over the structure of DNA (Fig. 1). (2) The protein TOP2 creates homodimers, meaning that it pairs with another identical protein. This dimeric structure is crucial for protein activity. Dimers are formed to enable TOP2 to thread one DNA double helix through another, which is a crucial step in untangling DNA during replication and chromosomal segregation [3]. (3) TOP2 exhibits DNA gyrase activity, which involves the induction of negative supercoils in DNA. This activity is crucial for regulating the overall supercoiling state of the genome [4]. (4) The function of TOP2 is closely controlled during the cell cycle and is essential for several DNA-related activities, such as gene transcription, DNA replication and repair, recombination, chromosomal condensation, and chromatin remodeling [3]. Lower eukaryotic organisms such as *Saccharomyces cerevisiae*, *Drosophila*, and *Caenorhabditis elegans* have a solitary type II topoisomerase called TOP2. On the other hand, vertebrate species have two different forms of TOP2, specifically TOP2A and TOP2B. The proteins TOP2A and TOP2B exhibit a significant degree of amino acid sequence similarity of approximately 70 %, with closely

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related N-terminal ATPase and central core domains [5]. TOP2A is primarily detected in cells that are actively undergoing division, and it plays a vital role in several cellular activities, including DNA replication, chromosome condensation, and segregation during the cell cycle [5]. In contrast, TOP2B exhibits a substantial increase in post-mitotic mammalian cells [5].

TOP2B was highly expressed in a wide variety of tissues (Fig. 2a-p) [6] and cell types (Fig. 2q). It plays a vital role in regulating embryonic development and ensuring the proper functioning of tissues and organs. A recent proposal suggested that dysregulation of TOP2B may have an impact on the mechanisms of senescence and the regulation of longevity [7–9]. This review aimed to investigate the involvement of TOP2B in the aging process and age-related diseases. In addition, we offer a thorough examination of TOP2B's role in modulating the fundamental characteristics of aging with specific attention to genomic instability. Gaining a comprehensive understanding of the functions of TOP2B in the aging process is of great significance for the development of novel treatment approaches that aim to prolong lifespan and combat age-related diseases.

2. The role of TOP2B in the aging process

TOP2B is a double-stranded DNA topoisomerase. Its main function is to control the DNA structure by cutting, rotating, and reconnecting its strands [7]. Recent studies have shown that TOP2B plays a crucial role in maintaining chromosome structure, repairing DNA, replicating genes, and regulating transcriptional activity [5,7]. It plays a vital role in organisms, encompassing not only the regulation of the normal cell cycle and development, but also the pathogenesis and treatment of cancer and other aging-related diseases, as well as the regulation of normal aging

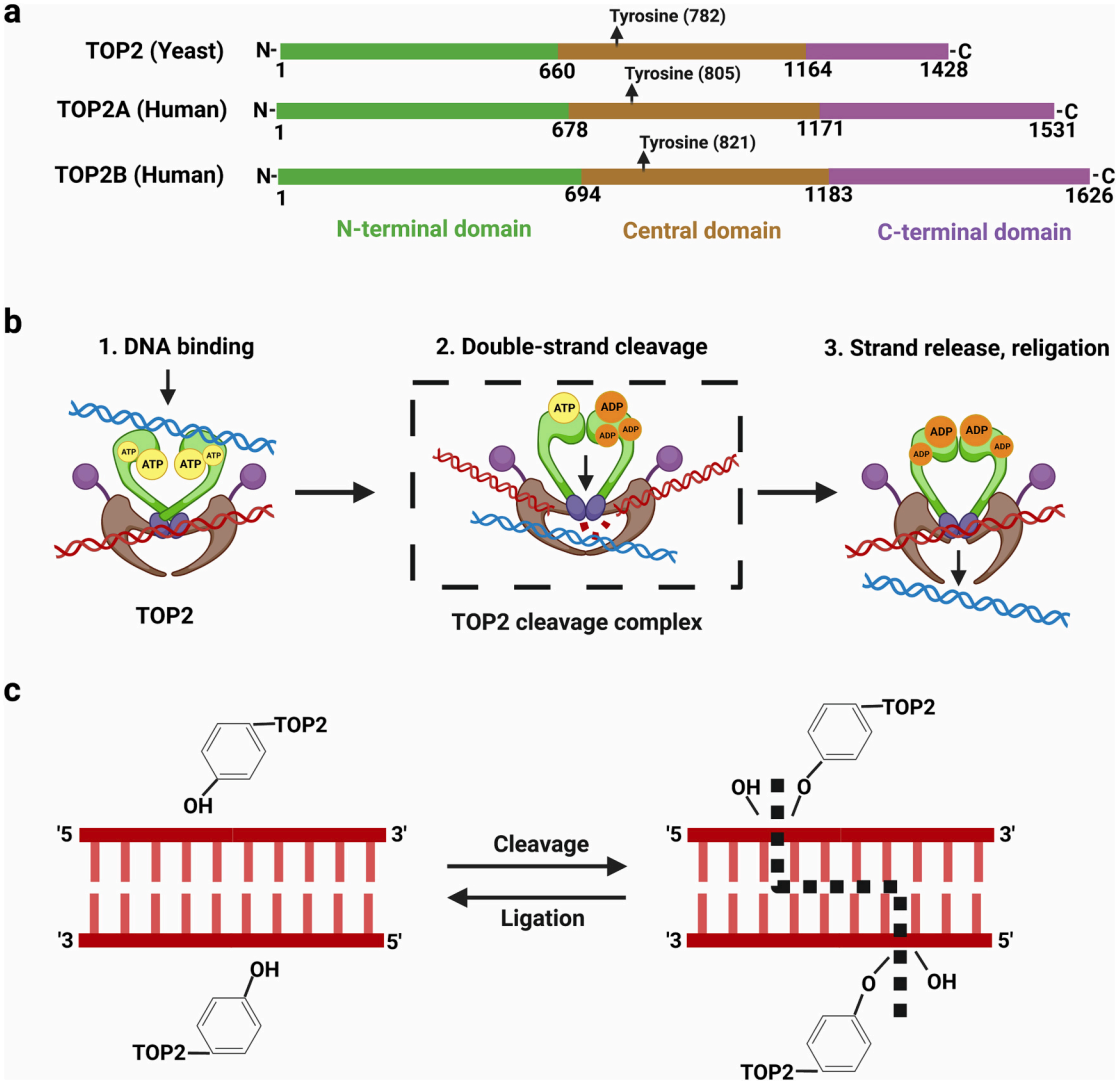

Fig. 1. Schematic diagram illustrating the process of TOP2 relieving DNA supercoiling. (a) The yeast and human TOP2 enzymes possess protein function domains that are conserved. The N-terminal domain is responsible for ATP binding and hydrolysis. The center domain contains tyrosine (Tyr) active sites that are responsible for forming covalent connections with DNA, enabling the breakage and reconnection of the DNA helix. The C-terminal domain displays considerable evolutionary diversity and is involved in the interaction between TOP2 and DNA, including its association and dissociation. The colors in the picture represent homologous areas in these enzymes. (b) TOP2-mediated DNA topology resolving. 1. The process of homodimerization of TOP2 enables the DNA concatenate to bind. 2. The formation of TOP2 cleavage complex (TOP2cc) occurs as a result of its DNA cleaving activity, which creates an interlocking connection between helices in the DNA structure. 3. The TOP2cc complex promotes the movement of whole helices and allows for the seamless rejoining of DNA breaks. (c) TOP2-mediated DNA resection and ligation. During cleavage, the tyrosine residue in the active site of each TOP2 unit forms a covalent bond with the newly created phosphate end on both DNA strands. This bond maintains the structural integrity of the DNA backbone. During ligation, the newly formed 3′-hydroxyl group interacts with TOP2 through non-covalent interactions, without making a covalent bond. This interaction leads to the DNA molecule returning to its original structure. The illustration was created by BioRender (https://www.biorender.com/).

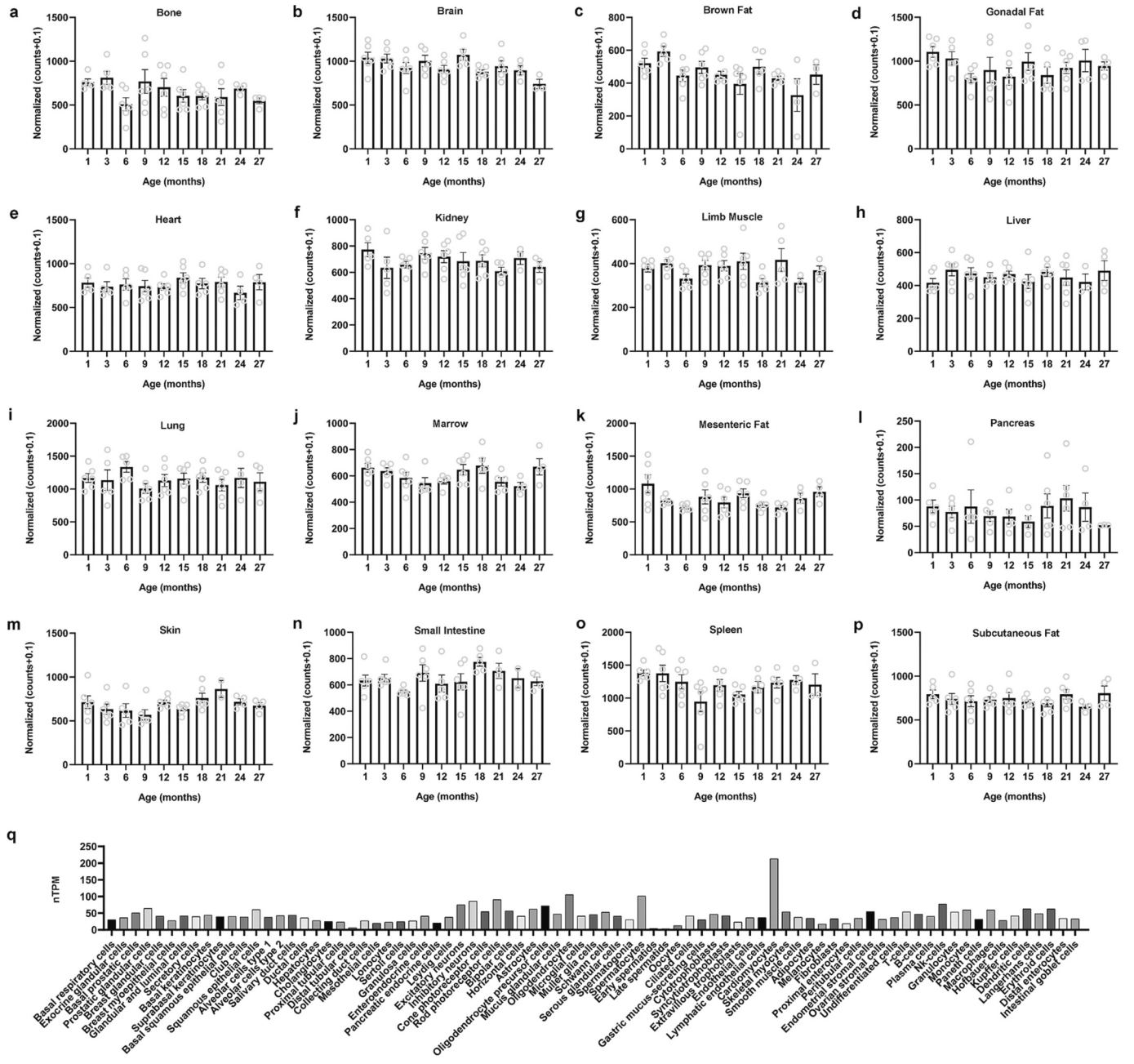

Fig. 2. The expression profiles of TOP2B in several mice tissues and certain human cell types. The mRNA levels of TOP2B in various mouse tissues were examined during the aging process. (a) Bone; (b) Brain; (c) Brown fat; (d) Gonadal fat; (e) Heart; (f) Kidney; (g) Limb muscle; (h) Liver; (i) Lung; (j) Marrow; (k) Mesenteric fat; (l) Pancreas; (m) Skin; (n) Small intestine; (o) Spleen; (p) Subcutaneous fat. The age of the mice is displayed on the X-axis, while the adjusted TOP2B expression level is represented on the Y-axis. The data was acquired from the Tabula Muris Senis database (https://twc-stanford.shinyapps.io/maca/). (q) The expression profiles of TOP2B in several human cell types. The X-axis displays the different cellular types, while the Y-axis indicates the normalized expression levels of TOP2B in individual cells, expressed as normalized single cell RNA (nTPM). The data was obtained from the Human Protein Atlas database (https://www.proteinatlas.org/).

processes.

While TOP2B is widely expressed in various regions of the central nervous system, a reduction in TOP2B expression was observed in the cerebellum of adult rats compared to young rats [8]. Likewise, a decline in TOP2B activity has been observed in aging sheep neuronal cells [10]. Animal models lacking TOP2B display numerous signs of accelerated aging, including retinopathies [11], Hoffman syndrome characterized by defective NK cells [12], autism [13], and hearing loss [14]. These occurrences are linked to a simultaneous reduction in lifespan. Moreover, it has been established that mutations or abnormal expression of yeast TOP2 (also known as yTop2) are associated with the process of replicative aging [7]. Senescence in yeast is facilitated by a decline in genome maintenance due to age-related factors. This decrease hindered the ability of yTop2 to detect or repair DNA damage. Hence, covalent bonding occurs between TOP2 and DNA. Blocking yTop2 results in the elongation of the replicative lifespan (RLS) [7]. This finding suggests that TOP2 may be a favorable target for anti-aging intervention. Caloric restriction has the potential to extend longevity and reduce the probability of age-related diseases. For example, caloric restriction, specifically by using a 5 % fetal bovine serum, might cause the down-regulation of TOP2B in RAW 264.7 cells [15]. Importantly, topoisomerase inhibitors such as camptothecin, irinotecan, and daunorubicin may act as drugs that promote aging [16]. Collectively, TOP2B exhibits multifaceted and dynamic functions in the pathophysiology of aging

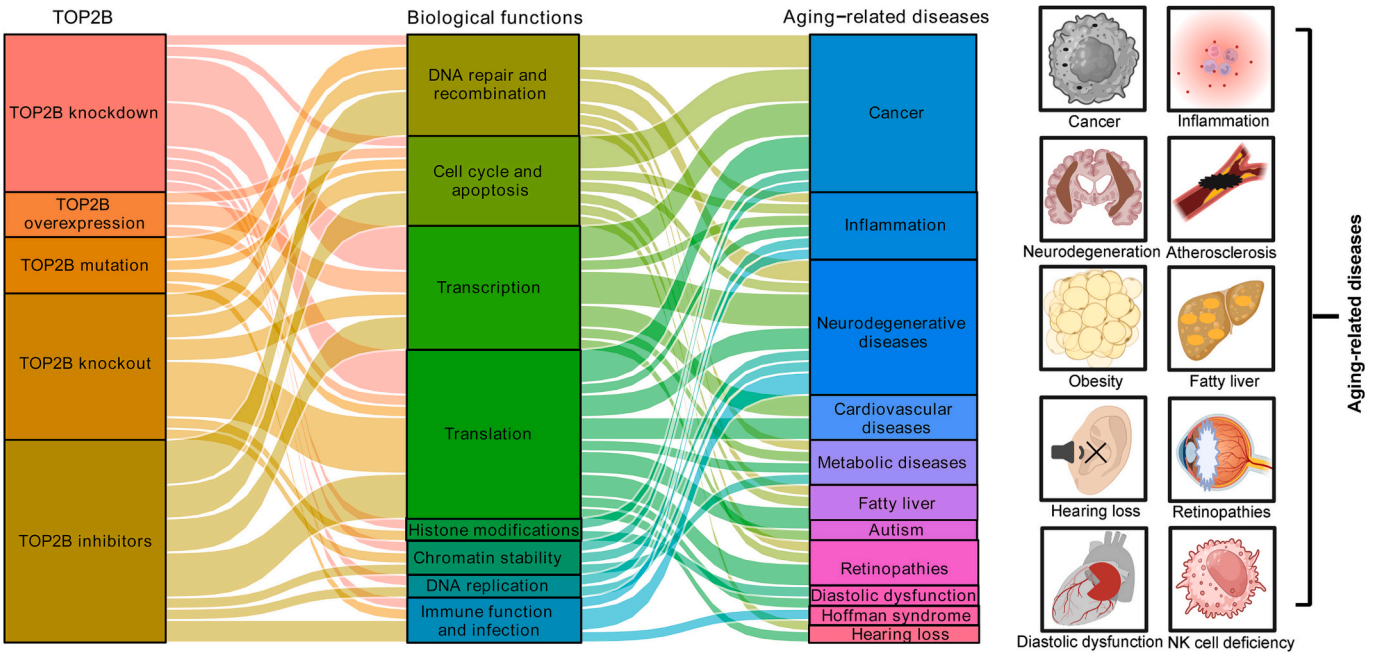

Fig. 3. TOP2B plays a crucial role in the control of age-related illnesses by carrying out many biological processes. The biological functions of TOP2B involve various processes relevant to the regulation of aging-related diseases, including DNA replication, transcription, chromatin stability, histone modifications, translation, DNA repair and recombination, cell cycle and apoptosis, and immune function and infection. This review encompasses a variety of age-related ailments, including inflammation, cancer, neurodegenerative diseases, cardiovascular diseases, metabolic diseases, fatty liver, autism, retinopathies, diastolic dysfunction, Hoffman syndrome, and hearing loss. The illustration was created by BioRender (https://www.biorender.com/).

(Fig. 3). Nevertheless, the precise mechanism by which TOP2B regulates aging is not well understood. Acquiring a more comprehensive understanding of the effects of abnormal TOP2B levels on the process of aging and aging-related diseases may be beneficial in promoting innovative therapeutic approaches and the exploration of drugs for anti-aging purposes.

2.1. *The impact of TOP2B on DNA replication during the aging process*

DNA replication is an essential process that occurs during the cell cycle and involves the unwinding of DNA, topological alterations, and DNA synthesis. TOP2B is important in the process of DNA replication because it facilitates the relaxation of the tightly compacted double-stranded supercoiled DNA structure. This allows DNA polymerase to effectively perform replication [17]. DNA replication involves unwinding of the DNA double helix, which usually results in the formation of a Y-shaped structure called the replication fork [17]. The upregulation of FOB1, a gene responsible for causing replication fork arrest at rDNA repeats, has been observed to have a negative impact on replicative lifespan in yeast [18]. Notably, growing evidence highlights the essential role of TOP2B in the regulation of replication forks [17]. The TOP2B enzyme can identify and cleave tangled single-stranded DNA molecules. This action contributes to maintaining the integrity and stability of the replication fork, thereby allowing proper progression of the replication process [17]. Moreover, it should be noted that Top1 and yTOP2 in *S. cerevisiae* exhibit capabilities that extend beyond resolving DNA entanglement and topological issues that arise during DNA replication. Instead, they play an active role in regulating the cell cycle, taking on an unexpected responsibility in assuring the temporary pause of replication forks at specified locations. Furthermore, TOP2 can alleviate the negative consequences of Top1 deficits in the DNA replication process [17].

2.2. *The influence of TOP2B on the regulation of transcription and translation during the aging process*

Transcriptional regulation refers to molecular processes that govern the adjustment of cellular gene expression in response to specific environmental conditions. TOP2B plays a crucial role in the regulation of DNA topological configuration and maintenance of chromatin stability during transcription [19]. This is accomplished by alleviating DNA supercoiling structures, facilitating seamless RNA polymerase transcription, assisting transcription factors in DNA binding, and preserving chromatin stability to avoid unnecessary damage during transcription [20]. TOP2B facilitates gene expression activation through site-specific transient double-strand breaks initiated by nuclear hormone receptors. Furthermore, it has been noted that the regulation of TOP2B transcription is associated with the DNA repair protein Ku-70 [21]. The decrease in Ku-70 levels with age is an important biomarker of testicular aging [21], suggesting that TOP2B may play a role in transcription-dependent aging development.

A challenging aspect of topoisomerase studies is comprehending the potential impact of mRNA metabolism on the generation of topological stress, necessitating the participation of topoisomerase for resolution. Regulation of both translation and protein degradation is generally recognized as a common mechanism that promotes longevity by maintaining protein homeostasis [22]. The maintenance of protein homeostasis is influenced by factors involved in mRNA metabolism. Dysfunction of processing bodies responsible for mRNA storage and degradation has been shown to adversely affect longevity [22]. Remarkably, studies have demonstrated that processing bodies in yeast have a crucial function in ensuring prolonged viability of cells in the stationary phase [23]. TOP2B plays a critical role in regulating the topology of mRNA, which in turn affects the efficiency and accuracy of translation [22]. TOP2B can alleviate the positive supercoiling structure of mRNA, which helps it interface with the ribosome more easily and speeds up the translation process [24]. Furthermore, TOP2B plays a role in controlling mRNA stability, thereby restricting its breakdown [22]. The absence or mutation of TOP2B has been found to have adverse effects on protein synthesis, which can subsequently have detrimental effects on the development and function of normal organisms [25].

2.3. The role of TOP2B in maintaining chromatin integrity and facilitating DNA repair and recombination during the aging process

Abnormal levels of TOP2B can alter chromosome structure and function, consequently affecting chromatin stability. Instability of chromatin is a characteristic feature of the aging process. Specifically, TOP2B deficiency or mutations may lead to chromosomal abnormalities such as breakage, loss, and chromosome inversion [22]. TOP2B is also involved in the formation of topological-associated domains (TADs) and chromatin looping by resolving topological issues in cis-regulatory elements. It is consistently present at TAD boundaries identified by CTCF/cohesin binding sites [19].

Furthermore, the gradual decrease in the ability of genome to repair itself is a notable cause and outcome of aging [26,27]. TOP2B participates in many DNA repair and recombination pathways such as homologous recombination (HR) [27] and non-homologous end joining (NHEJ) [26]. In the HR pathway, TOP2B induces transitory DNA double-strand breaks (DSBs), leading to DNA damage. This triggers the activation of cellular damage recognition systems, specifically BRCA1 and BRCA2, which then initiate the HR process [27]. A comprehensive analysis of the genetic landscape of different races has shown that there are more significant mutations in BRCA2 and TOP2B genes in both Caucasian and Asian pancreatic carcinoma patients with HR deficiency in various cancers [27]. In the NHEJ pathway, Ku70 and Ku80 recognize and position the broken ends, while XRCC4, DNA ligase IV, Werner's helicase, and pol-β-dependent pathways are responsible for subsequent ligation [26]. A previous study has demonstrated that TOP2B participates in the NHEJ process. Specifically, TOP2B facilitates DSB repair by interacting with Ku70, Werner helicase, and pol-β-dependent pathways. Additionally, TOP2B is essential for the repair of DSBs through Ku70-dependent and PARP-1-dependent pathways in primary cerebellar granule neurons [28].

TOP2B has been shown to interact with many proteins involved in DNA repair and recombination, such as DNA polymerases, helicases, and checkpoint kinases [29]. These interactions enable TOP2B to contribute to the coordination of DNA repair and recombination activities. Deficiencies in TOP2B result in genomic instability and the development of cancer, emphasizing its crucial role in protecting the integrity of the genome. TOP2B is a crucial target for DNA repair inhibitors prior to the specific cleavage of DNA repair. Furthermore, TOP2B has been recognized as a crucial factor in the formation of Melphalan-induced DNA cross-links, in contrast to TOP2A [30]. TOP2B conditional knockout mice exhibit DNA damage accumulation, follicular atresia, and reduced ovulation in the ovarian granulosa cells [29]. The absence of TOP2B heightened the vulnerability of NCH421k glioma stem cells to replication stress-inducing drugs such as cisplatin, temozolomide, hydrogen peroxide, and temozolomide. Additionally, it led to the accumulation of DNA damage within the cells [31].

In yeast, Tombline et al. [7] proposed an important hypothesis that the aging process is exacerbated by a decrease in genomic maintenance caused by yTop2's inability to detect or rectify DNA damage. LS1, a weak TOP2 poison that induces stable TOP2-DNA covalent complexes, accelerates yeast aging without affecting proliferative growth or survival. The yeast lifespan was extended by approximately 20 %–30 % when the levels of yTop2 were lowered by nearly 70 % [7]. This study indicated that intrinsic yTop2-mediated DNA damage may contribute to the aging process in yeast. This finding provides more evidence to support the concept that yTop2 activity is necessary for the proliferation of young cells but becomes harmful at later stages of life. The effect of yTop2 on lifespan depends on the decline in genomic maintenance capacity associated with aging, which eventually triggers the onset of aging and aging-related diseases.

2.4. The involvement of TOP2B in histone modifications during aging

Epigenetic modifications have recently been recognized as a novel and important characteristic of aging. TOP2B has been shown to participate in the control of gene expression through its interaction with histone modifications [32]. Within neurons, TOP2B exhibits a distinct preference for regions that contain a high concentration of H3K4 methylation, a widely recognized characteristic of actively transcribed chromatin [33]. The absence of H3K4me in yeast, caused by deficiencies in any of the three COMPASS subunits (Set1, Spp1, and Bre2), has been linked to a reduced chronological lifespan, suggesting its possible involvement in the aging process [34]. The role of H3K4me3 in regulating dynamic changes in gene transcription associated with aging has been confirmed [32]. A correlation has been discovered between H3K4me3 and selective activation of a certain group of genes that are known to exhibit increased expression during aging in animals. This observation highlights the direct involvement of H3K4me3 in preserving the optimal function of several genes throughout the lifespan of an organism. Modifications in age-related H3K4me3 dynamics in *C. elegans* are strongly linked to changes in mRNA expression of genes widely involved in the biology of aging [35].

2.5. The role of TOP2B in cell cycle regulation and apoptosis

TOP2B is closely linked to the cell cycle and apoptosis [36]. TOP2B plays an important role in essential cellular activities such as DNA replication, chromosome segregation, and mitosis during cell division [37]. During the non-dividing stage of cells, TOP2B is also involved in fundamental biological functions such as maintaining genome stability and transcriptional regulation [36]. Previous studies have demonstrated a direct relationship between the expression level of TOP2B and susceptibility of peripheral blood lymphocytes to anthracycline treatment [38,39]. Gieseler et al. [39] discovered a notable correlation between the expression levels of TOP2B and the sensitivity of leukemia cell lines to anthracene drugs. Kersting et al. [36] found that TOP2B also mediates the apoptotic response of normal peripheral blood lymphocytes to anthracycline. In addition, Zhang et al. [29] demonstrated that ovarian granulosa cells in mice with a conditional knockout of TOP2B gene are more sensitive to low-dose genotoxic agents, such as bleomycin and VP-16, in comparison to animals with the wild-type gene. Moreover, this pathway responds to DNA damage by activating DNA damage checkpoints and inducing p53-dependent apoptosis. Studies have also revealed that the activity and function of TOP2B in cell cycle regulation are affected by its phosphorylated state [37,40]. TOP2B phosphorylation levels change across several stages of the cell cycle, thereby influencing its subcellular localization, enzymatic activity, and interactions with other proteins. Ultimately, this can affect drug resistance in human leukemia CCRF-CEM cells [40]. Additionally, Wang et al. [37] emphasized the role of E2F1-TOP2B signaling in regulating cell cycle exit and neuronal differentiation.

2.6. The correlation of TOP2B in immune and infection regulation during aging

Chronic inflammation is a well-established characteristic of aging. Aging is characterized by significant changes in the immune system, such as a reduced capacity to combat infections, increased vulnerability to cancer, and a higher incidence of autoimmune disorders. There has been a recent increase in attention paid to the involvement of TOP2B in the immune system [41,42]. The $TOP2B^{A485P}$ mutation can impair the maturation of early B cells and is associated with specific B cell dysmorphism [41]. The absence of mouse $CD19^{+}$ B cell precursors was a result of TOP2B loss, underscoring the crucial involvement of TOP2B in the initial stages of B cell lineage development [41]. Furthermore, TOP2B is involved in the regulation of NK cell stability. A $TOP2B^{1/EE587E}$ heterozygous mouse model demonstrated that the presence of a TOP2B mutation resulted in impaired NK cell functionality, characterized by a decrease in the number of mature NK cells and a reduction in their cytotoxicity against target cell lines [12]. This mutation has been linked

to the occurrence of Hoffman syndrome in humans, specifically affecting the functionality of NK cells [12]. Moreover, several studies have provided evidence indicating the involvement of TOP2 in the reverse transcription of HIV [42]. During HIV infection, TOP2B is upregulated and undergoes phosphorylation. This leads to an increase in TOP2B activity, which in turn enhances HIV replication [42].

In summary, although there is disagreement on the molecular and physiological processes by which TOP2B influences the aging process, it is clear that TOP2B plays a role in controlling essential traits linked to aging.

3. Aberrant TOP2B in aging-related diseases

Dysregulation of gene expression and epigenetic alterations, as well as the accumulation of DNA DSBs and abnormal chromosomal structures, can result from the disruption or aberrant expression of TOP2B [33]. These molecular events ultimately contribute to cellular aging and onset of age-related diseases. Here, we provide a comprehensive summary of the current discoveries regarding the involvement of TOP2B in aging-related diseases. Our primary focus was on its implications in cancer, inflammation, neurodegenerative diseases, cardiovascular diseases, and metabolic diseases (Fig. 4). Aberrant TOP2B alterations in human aging and aging-related diseases are summarized in Table 1.

3.1. The occurrence of aberrant TOP2B expression and its association with cancer

Cancer is a group of malignant diseases that is strongly linked to age in terms of morbidity. TOP2B has been found to be expressed abnormally in various forms of cancer, including blood cancer [38,43–47], reproductive system cancer [20,29,48–52], glioma [53,54], digestive system cancer [55–58], and lung cancer [24,59–61]. Dysregulation of TOP2B expression may lead to an aberrant topological structure of DNA, thereby impacting DNA replication and repair and promoting the growth and proliferation of cancer cells. Owing to its substantial involvement in the development of cancer cells, TOP2B has become a prospective target for anti-cancer therapy. Several anti-cancer drugs, including TOP2B inhibitors, can restrict the replication of DNA and impede the repair mechanisms of cancer cells, ultimately resulting in a decrease in their ability to spread to other parts of the body. It is crucial to recognize that current research on the correlation between TOP2B and cancer is still in its preliminary stages, and additional examination is required to gain a complete understanding of the specific functions and mechanisms of TOP2B in cancer development.

3.1.1. Blood cancer

The aberrant expression of TOP2B and its correlation with acute myeloid leukemia (AML) have been extensively documented [38,44,45]. Individuals with AML who have elevated levels of TOP2B transcripts experience improved disease-free survival and overall survival, with increases of 64 % and 65 %, respectively [38]. In contrast, patients with AML who had low levels of TOP2B mRNA expression in their mononuclear cells taken from peripheral blood were more likely to have resistance to cytarabine, be in a relapsed/refractory stage of AML, and have inferior event-free and overall survival rates [44]. Interestingly, the increased expression of TOP2B in the bone marrow of AML patients coincided with elevated expression levels of CD4, CD7, CD11a, CD11b, CD11c, CDw14, CD15, CD16, CD34, CD54, and HLA-DR [45]. This discovery implies that TOP2B is involved in regulating the dynamic biology of highly proliferative diseases and diverse immunophenotypes

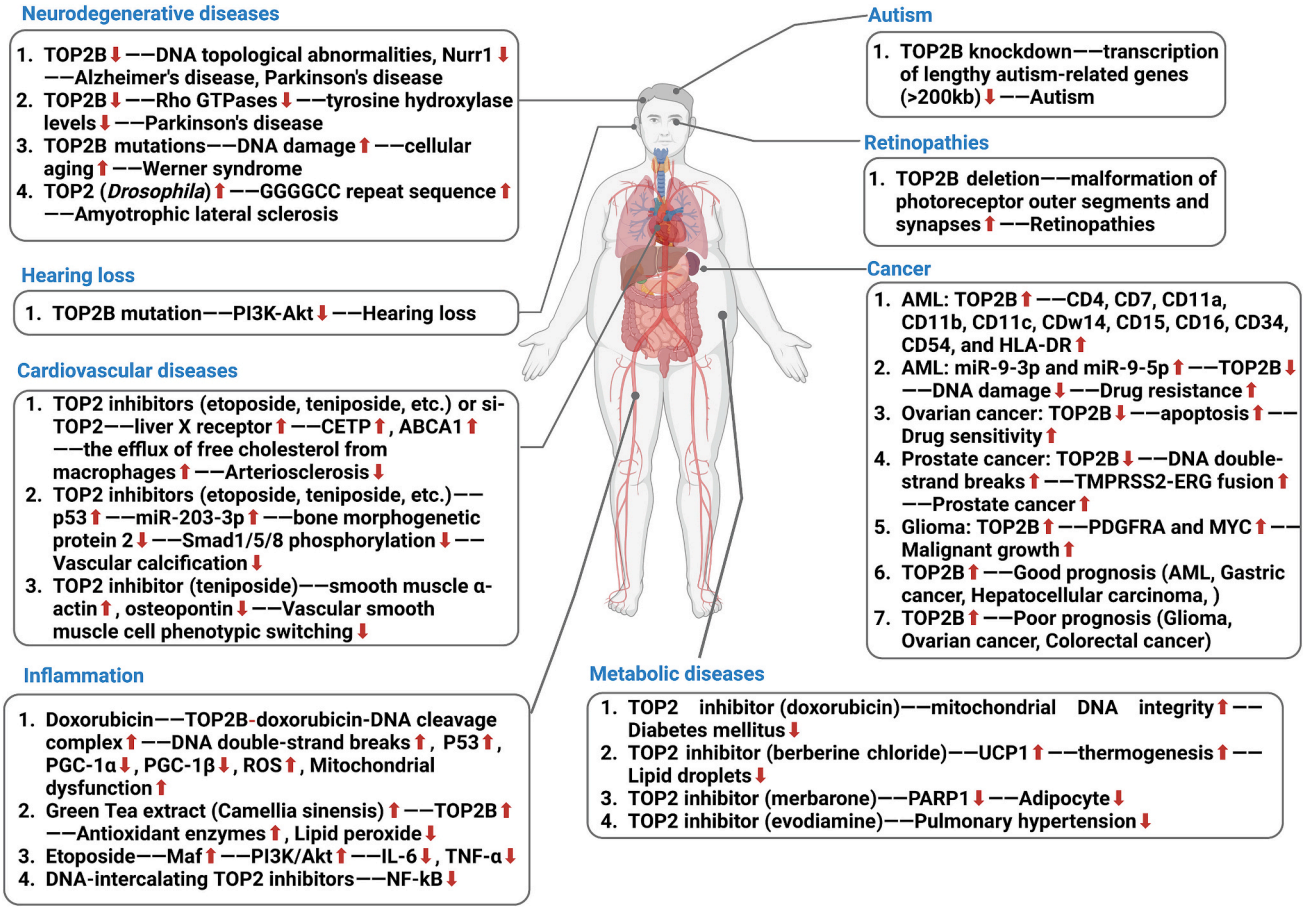

Fig. 4. The regulatory mechanisms of TOP2B in aging-related disease pathogenesis. The illustration was created by BioRender (https://www.biorender.com/).

Table 1
TOP2B alterations in aging and aging-related diseases.

Aging and aging-related diseases	Human, animal, or cell models	TOP2B alterations	Impacts on the outcomes of aging or aging-related diseases	References
Aging	Wild-type Sprague-Dawley rat	Normal aging	The activity and protein levels of TOP2B in rat brains across various age groups, including E11 (Embryo day 11), E18 (Embryo day 18), post-natal day 1, young (<10 days), adult (<6 months), and old (>2 years), were tested. Notably, diminished levels of TOP2B activity were detected in the aging cerebellum.	Kondapi et al., 2004 [8]
	Cortical neurons from 60-day-old sheep embryos (primary cells)	Normal aging	The expression level of TOP2B in neurons decreases with age.	Lepore et al., 2013 [10]
	Saccharomyces cerevisiae (S. cerevisiae) strain BY4741	TOP2 knockdown	Knocking down yeast TOP2 (yTop2) expression led to an extension in the replicative lifespan of *S. cerevisiae*.	Tombline et al., 2017 [7]
	RAW 264.7 cell line (murine)	Normal aging	Caloric restriction (5 % fetal bovine serum) reduced TOP2B expression in RAW 264.7 cells.	Andrawus etal., 2020 [15]
Cancer	Wild-type athymic nude mice	TOP2B knockdown	The knockdown of TOP2B in human glioma intracranial implants resulted in prolonged survival ($P < 0.0001$).	Gonzalez-Buendia et al., 2021 [54]
	Glioma stem cell line NCH421k	TOP2B knockdown	TOP2B deficiency heightened the susceptibility of NCH421k glioma stem cells to replication stress-inducing drugs (*e.g.*, cisplatin, temozolomide, hydrogen peroxide) and intensified cellular DNA damage.	Kenig et al., 2016 [31]
	Acute myeloid leukemia cells from seventy-two patient bone marrow or blood samples	Normal aging	Cells from relapsed human acute myeloid leukemias after initial treatment with anthracycline-containing regimens exhibited significantly reduced TOP2B activity.	Gieseler et al., 1996 [39]
	Wild-type C57BL/6 mice	TOP2B knockout	In TOP2B knockout mice, ovarian granulosa cells exhibit increased susceptibility to low-dose genotoxic agents (bleomycin and etoposide) compared to wild-type mice.	Zhang et al., 2013 [29]
	54 bone marrow samples from patients diagnosed with M2-subtype acute myeloid leukemia	_	Patients with acute myeloid leukemia exhibiting elevated TOP2B transcript levels demonstrated significantly enhanced disease-free survival and overall survival compared to individuals with lower TOP2B levels, showcasing respective increases of 64 % and 65 %, highlighting this correlation.	Song et al., 2012 [38]
	Acute myeloid leukemia patients ($n = 154$)	_	Low TOP2B expression correlated with cytarabine resistance, relapsed/refractory AML, inferior event-free survival ($P = 0.002$), and overall survival ($P < 0.001$).	Hatzl et al., 2020 [44]
	Myeloma cell line MM.1S	TOP2B deletion	The authors employed whole-genome CRISPR screening to discover the involvement of TOP2B in the resistance of multiple myeloma patients to Thalidomide analogs. Deletion of TOP2B reinstated sensitivity to Thalidomide analogs in MM.1S resistant cells.	Costacurta et al., 2021 [43]
	Etoposide-resistant K562 cells (K/VP.5)	TOP2B knockdown	miR-9-3p and miR-9-5p contribute to the development of acquired resistance to etoposide by reducing TOP2B protein levels.	Carvajal-Moreno et al., 2023 [47]
	Epithelial ovarian cancer patients ($n = 1582$)	_	The expression of TOP2B, whether above or below the median in all epithelial ovarian cancer patients, did not result in significant differentiation of prognostic groups (n = 1582) with a hazard ratio of 1.14 [0.99–1.31] and a *p*-value of 0.061.	Bai et al., 2016 [48]
	Paired biopsies ($n = 33$) obtained during the initial and subsequent surgeries were chosen from patients diagnosed with stage III-IV epithelial ovarian cancer	TOP2B mutation	TOP2B mutations increased platinum-based chemotherapy resistance in stage III-IV epithelial ovarian cancer patients, and the rate of repeat surgery for cancer recurrence after initial surgery was significantly higher in TOP2B mutant patients ($P < 0.05$).	Beltrame et al., 2015 [49]
	Human ovarian cancer cell line RMG-1	TOP2B knockdown	Inhibiting Lewis (y) antigen downregulates TOP2B, promoting carboplatin-induced apoptosis through ovarian cancer cell adhesion and reducing drug resistance.	Wang et al., 2011 [50]
	Human prostate cancer cell lines LNCaP and LAPC4	_	The TMPRSS2-ERG gene fusion is frequently seen in prostate cancer. Researchers found that androgen signaling facilitates the binding of androgen receptor and TOP2B to the genomic breakpoints of TMPRSS2-ERG.	Haffner et al., 2010 [51]
	Prostate cancer patients (unable to obtain the number of cases from the authors)	_	In prostate cancer, a notably higher occurrence of co-expression between ERG and TOP2B was observed ($P = 0.028$). there was a statistically notable rise in the TOP2B H-index observed in locally advanced prostate cancer as opposed to localized tumors ($P = 0.046$). Authors discovered strong co-expression of ERG and	Kolar et al., 2014 [20]

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Table 1 (*continued*)

Aging and aging-related diseases	Human, animal, or cell models	TOP2B alterations	Impacts on the outcomes of aging or aging-related diseases	References
			TOP2B, which positively correlated with TMPRSS2-ERG fusion gene levels of prostate cancer.	
	SV-HUC-1 (non-malignant human urothelium), T24 (human bladder cancer), DU-145 (human prostate cancer), and RWPE-1 (non-malignant human prostate epithelium) cell lines	TOP2B knockdown	Ciprofloxacin and levofloxacin reduced TOP2B expression in cancer cells ($P < 0.05$) and had increased cytotoxic effects on cancer cell lines ($P < 0.05$).	Kloskowski et al., 2021 [52]
	Human proneural glioblastoma ($n = 339$); mouse proneural tumors ($n = 23$)	_	TOP2B transcript levels were higher in glioma cancer tissues than normal brain samples, and mouse glioma cells with elevated TOP2B transcription displayed increased sensitivity to etoposide.	Sonabend et al., 2014 [53]
	Gastric cancer patients ($n = 876$); gastric intestinal-type adenocarcinoma patients ($n = 320$); diffuse gastric adenocarcinoma patients ($n = 241$)	_	Elevated mRNA levels of TOP2B are associated with improved overall survival among patients with gastric cancer (Hazard Ratio: 0.51 [0.42–0.62], $P = 2.2e{-}12$). Furthermore, heightened TOP2B mRNA expression correlates with extended overall survival in patients with gastric intestinal-type adenocarcinoma (Hazard Ratio: 0.37 [0.27–0.51], $P = 1.4e{-}10$) and in those with diffuse gastric adenocarcinoma (Hazard Ratio: 0.62 [0.44–0.87], $P = 0.0051$).	Hou et al., 2020 [55]
	Hepatocellular carcinoma patients ($n = 19$)	_	Tumors exhibiting a complete response ($n = 13$) demonstrated a noteworthy elevation in pretreatment chemotherapy sensitivity and a substantial increase (approximately 72 %) in TOP2B mRNA expression compared to tumors with a partial response ($n = 6$), with a statistical significance at $P < 0.05$.	Gaba et al., 2015 [56]
	Human colorectal adenocarcinoma cell line DLD1	TOP2B knockdown	Girdin knockdown augments the chemosensitivity of colorectal cancer to oxaliplatin by down-regulating TOP2B.	Zhang et al., 2014 [57]
	Human hepatocellular carcinoma cell line HepG2	TOP2B knockdown	The anti-proliferative effects on hepatocellular carcinoma cells through the downregulation of TOP2B expression were demonstrated by the DHA ester of phloridzin.	Nair et al., 2014 [58]
	80 autopsy samples (40 primary tumors and 40 corresponding normal lung tissues)	_	TOP2B gene expression did not show notable variances between tumors and normal lung tissues, as well as between small cell lung cancer and non-small cell lung cancer.	Syahruddin et al., 1998 [24]
	Non-small cell lung cancer patients ($n = 1726$); lung adenocarcinoma patients ($n = 591$); lung squamous cell carcinoma patients ($n = 492$)	_	Elevated mRNA levels of TOP2B were correlated with a positive overall survival outcome in all non-small cell lung cancer patients (Hazard Ratio: 0.88 [0.77–1], $P = 0.059$). Furthermore, high expression of TOP2B mRNA was significantly linked to improved overall survival exclusively in patients with lung adenocarcinoma (Hazard Ratio: 0.53 [0.41–0.68], $P = 2.6e{-}07$), but not in those with lung squamous cell carcinoma (Hazard Ratio: 1.09 [0.85–1.4], $P = 0.48$).	Hou et al., 2017 [59]
	Human non-small cell lung cancer cell lines including NCI-H460, A549, and NCI-H1299; Four-week-old athymic male nude mice (BALB/c-nu/nu), $n = 20$	TOP2B knockdown	Berberine chloride inhibits human non-small cell lung cancer by disrupting the Sin3A/TOP2B pathway, inducing DNA damage, and promoting apoptosis both *in vitro* and *in vivo*.	Chen et al., 2020 [61]
Inflammation	Six-week-old male wild-type B6C3F1/J mice; Human primary cardiomyocytes (cat#6200)	_	TOP2B promotes inflammation in anthracycline drugs, particularly doxorubicin-induced cardiotoxicity.	Hasbullah et al., 2022 [67]; Jiang et al., 2018 [66]
	Wild-type rabbit model; SaOS2 (Cat# HTB-85, RRID:CVCL_0548), A549 (Cat# CCL-185, RRID:CVCL_0023), NCI-H1299 (Cat# CRL-5803, RRID:CVCL_0060), HCT-15 (Cat# CCL-225, RRID:CVCL_029), MDA-MB-231 (Cat# HTB-26, RRID:CVCL_0062), SkBR3 (Cat# HTB-30, RRID:CVCL_0033) and MDA-MB-468 (Cat# HTB-132, RRID:CVCL_0419)	_	Doxorubicin engages with TOP2B, forming a complex that induces the cleavage of DNA, resulting in the formation of double-strand breaks and DNA damage. This process activates p53, triggering cell death in cardiac myocytes.	Kollárová-Brázdová et al., 2021 [68]; Menendez et al., 2022 [69]
	Wild-type Wistar rats ($n = 60$)	–	Green tea mitigated cardiac remodeling triggered by Doxorubicin and was linked to upregulating TOP2B expression while reducing oxidative stress.	Modesto et al., 2021 [70]
	RAW264.7 macrophages (murine macrophage cell lines)	TOP2B inhibitor	Etoposide, a TOP2 inhibitor, induces the activation of Maf and the PI3K/Akt pathway, thereby inhibiting the production of pro-inflammatory cytokines (IL-6, TNF-α) in lipopolysaccharide (LPS)-stimulated macrophages.	Zhang et al., 2021 [71]
	Wild-type C57BL/6 J (B6) mice ($n = 12$)	TOP2B inhibitor	Dexrazoxane safeguards the heart against cardiac injury induced by TOP2B toxicity through the reduction of TOP2B levels.	Deng et al., 2014 [65]
	Skin-specific TOP2B-knockout (*K14-Cre TOP2B$^{flox/-}$*) mice	TOP2B knockout	Nitric oxide-activated TOP2 induces DNA cleavage and mutations, leading to inflammation-associated tumorigenesis.	Yang et al., 2013 [72]

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Table 1 (*continued*)

Aging and aging-related diseases	Human, animal, or cell models	TOP2B alterations	Impacts on the outcomes of aging or aging-related diseases	References
	Human osteosarcoma cell line U-2 OS	TOP2B inhibitor	DNA-intercalating TOP2 inhibitors inhibit NF-kB target genes, suppressing inflammation.	Campbell et al., 2006 [73]
Neurodegenerative diseases	Cerebellar granule neurons isolated from post-natal eight-day rats; neurally-differentiated human mesenchymal (hMSC) cell line	TOP2B knockdown	Reducing the expression of TOP2B results in DNA topological irregularities and changes in gene expression, exacerbating the progression of Alzheimer's disease.	Terzioglu-Usak et al., 2017 [74]
	$TOP2B^{\Delta1/\Delta1}$ knockout C57BL/6 mice	TOP2B knockout	Knockout of TOP2B in mice results in a notable reduction of dopaminergic neurons within the substantia nigra and disruptions in neural processes along the nigrostriatal pathway.	Heng et al., 2012 [75]
	Human neuroblastoma cell line SH-SY5Y	TOP2B knockdown	Silencing TOP2B expression in neuro-differentiated SH-SY5Y cells *in vitro* contributes to neurodegeneration in a Parkinson's disease cell model by reducing tyrosine hydroxylase levels through the Rho GTPases pathway.	Yeman & Isik, 2021 [76]
	Werner syndrome lymphoblast cell lines (KO375 and DJG), originally obtained from Dr. G.M. Martin (Seattle)	TOP2B inhibitor	In KO375 and DJG cells, the WRN protein mutation results in heightened misrepair rates upon TOP2B inhibition, likely due to compromised G2 phase processes associated with the WRN protein.	Pichierri et al., 2000 [78]
	Drosophila strains (including gmr-GAL4/UAS-GGGGCC30-EGFP, elav-GAL4/UAS-GGGGCC3-EGFP, elav-GAL4/UAS-GGGGCC30-EGFP, ok371-GAL4/UAS-GGGGCC3-EGFP, ok371-GAL4/UAS-GGGGCC3-EGFP and gmr-GAL4/UAS-CGG90-EGFP)	TOP2B knockdown	Specific modulation of GGGGCC-related neurodegeneration in the eye can be achieved by downregulating the TOP2 gene. Chemical inhibition or small interfering RNA (siRNA)-mediated downregulation of TOP2 can alleviate GGGGCC-induced neurotoxicity in *Drosophila*.	Jiao et al., 2021 [77]
Cardiovascular diseases	New Zealand White rabbits and wild-type C57/BL6 mice	TOP2B inhibitor	In hypercholesterolemic rabbits and mice, the use of TOP2 inhibitors (etoposide and teniposide) exhibits anti-atherosclerotic effects by mitigating atherosclerosis.	de la Llera-Moya et al., 1992 [85]; Tavares et al., 2011 [86]; Zhang et al., 2013 [87]
	$ApoE^{-/-}$ mice ($n = 45$)	TOP2B inhibitor	The administration of the TOP2 inhibitor (Teniposide) triggers the activation of the liver X receptor, leading to the promotion of cholesteryl ester transfer protein transcription. This, in turn, reverses cholesterol transport and inhibits the development of atherosclerosis and vascular calcification in $apoE^{-/-}$ (apoE deficient) mice.	Liu et al., 2018 [88]
	C57BL/6 wild type mice (~8 weeks, males); CETP transgenic (CETPtg) mice; human hepatic cell line HepG2	TOP2B inhibitor	The TOP2 inhibitor (teniposide) plays a crucial role in cholesterol metabolism by stimulating hepatic CETP expression and facilitating reverse cholesterol transport.	Liu et al., 2015 [91]
	Human aortic smooth muscle cells (purchased from ATCC); $ApoE^{-/-}$ mice	TOP2B inhibitor	Teniposide protects against vascular smooth muscle cell phenotypic switch in atherosclerosis by enhancing smooth muscle α-actin expression and reducing osteopontin expression in aortic plaques.	Han et al., 2018 [93]
Metabolic diseases	Type 1 diabetes mellitus patients ($n = 195$)	Anti-TOP2	Anti-TOP2 could serve as a more reliable marker for tracking the progression of type 1 diabetes mellitus in Chinese patients, particularly in those with a prolonged disease duration (exceeding 11 years). Late onset of the disease (>18 years) emerged as a risk factor (relative risk = 2.15; 95 % confidence interval: 1.02–4.53), contributing to the elevated incidence of anti-TOP2 as determined by multivariate analysis.	Shiau et al., 2000 [97]
	Male euglycemic Wistar and diabetic Goto-Kakizaki (GK) rats	TOP2B inhibitor	Doxorubicin enhanced mitochondrial DNA fragmentation, suggesting the importance of inhibiting mitochondrial TOP2 for preserving DNA integrity and suppressing diabetes.	Hicks et al., 2013 [95]
	Primary brown adipocytes	TOP2B inhibitor	Berberine chloride, a TOP2 inhibitor, upregulates UCP1 gene expression in brown adipocytes, inducing thermogenesis and reducing lipid droplets in fat cells.	Ferdous et al., 2023 [98]
	Mouse embryo fibroblasts (3 T3-L1 cell line)	TOP2B inhibitor	Merbarone, a potent inhibitor of TOP2, significantly reduces Poly (ADP-ribose) polymerase-1 (PARP1) activation and adipocyte function.	Erener et al., 2012 [96]
Other aging-related diseases	Dkk3-Cre;$Top2B^{flox2/flox2}$ mice	TOP2B knockout	Deleting TOP2B leads to malformation of photoreceptor outer segments (OSs) and synapses, causing significant loss of photoreceptor-differentiating cells.	Li et al., 2017 [11]
	α-MHC-MerCreMer $Top2b^{flox/flox}$ mice	TOP2B knockout	TOP2B knockout mice exhibited diastolic dysfunction in echocardiography.	Moudgil et al., 2020 [9]
	Peripheral blood leukocytes (cryopreserved) or primary skin fibroblasts from both Hoffman syndrome patients and sex-matched healthy controls; C57BL/6 J mice	TOP2B mutation	Mutations associated with Hoffman syndrome in TOP2B adversely affect the development and function of NK cells in both murine and human models.	Broderick et al., 2022 [12]
	Cortical neurons (from E13.5-E15.5 mouse embryos); Forebrain cortical neurons (from human induced pluripotent stem cells)	TOP2B knockdown	TOP2B promotes the transcription of extensive autism-related genes (>200 kb). However, reducing TOP2B specifically in neurons leads to a decreased	King et al., 2013 [13]

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Table 1 (*continued*)

Aging and aging-related diseases	Human, animal, or cell models	TOP2B alterations	Impacts on the outcomes of aging or aging-related diseases	References
			expression of long genes (>200 kb), contributing to the development of autism.	
	Autosomal-dominant nonsyndromic hearing loss patients ($n = 16$)	TOP2B mutation	Mutations in TOP2B can lead to autosomal-dominant nonsyndromic hearing impairment by inhibiting the PI3K-Akt signaling pathway.	Xia et al., 2019 [14]

within the bone marrow of patients with AML.

Moreover, TOP2B has been extensively studied as a promising target for anti-cancer treatments to overcome resistance to chemotherapy. Remarkably, it has shown significant promise in treating specific blood cancers such as AML and multiple myeloma [46,47]. Evidence indicates that the mechanisms of TOP2B-mediated resistance vary among different types of blood tumors. Co-administration of protein kinase C delta (PKC-δ) dramatically reduces the resistance of acute promyelocytic leukemia cell lines to retinoic acid, relying on the stability and catalytic activity of TOP2B [46]. TOP2B has been identified as a causative factor for resistance in multiple myeloma patients treated with thalidomide analogs [43]. Deletion of TOP2B confers resistance to thalidomide analogs in MM1.S cells. Additionally, Carvajal-Moreno et al. [47] noted that transfection of miR-9-3p/5p mimics into K562 cells led to a significant reduction in TOP2B levels. This decrease was associated with reduced XK469-induced DNA damage, which specifically targets TOP2B. Consequently, this modification at the molecular level increases the ability of K562 cells to withstand the effects of imatinib. Although the exact roles and mechanisms of TOP2B in blood malignancies are not fully understood, current research suggests that TOP2B plays a crucial role in the pathological processes of blood cancer. Consequently, it is a potentially valuable therapeutic target for the treatment of hematological disorders.

3.1.2. Reproductive system cancer

The TOP2B gene is also known to have significant implications in the occurrence, progression, and chemotherapy responsiveness of reproductive system cancers [20,29,48–52]. Evidence indicates that patients with epithelial ovarian cancer (EOC) may experience a less favorable prognosis with high levels of TOP2B expression [48]. TOP2B mutations have been found to increase resistance to platinum-based chemotherapy in patients with stage III-IV EOC, along with an elevated likelihood of necessitating additional surgical interventions [49]. Inhibition of the Lewis (y) antigen can potentially decrease the expression of TOP2B, which in turn can promote carboplatin-induced apoptosis in ovarian cancer RMG-1 cells [50]. This mechanism can contribute to a reduction in drug resistance. Zhang et al. [29] established that TOP2B plays a crucial role in controlling the stability of the genome and degeneration of ovarian granulosa cells. Their study revealed that conditional knockout of the TOP2B gene in mice heightened ovarian sensitivity to low-dose genotoxic agents such as bleomycin and VP-16. This finding suggests that targeting the TOP2B gene could be a potential intervention strategy for patients with ovarian cancer who experience ovarian dysfunction after chemotherapy. This finding suggests that targeting TOP2B could be a promising approach to address ovarian dysfunction in patients with ovarian cancer after chemotherapy.

Furthermore, TOP2B plays an important role in the development and progression of prostate cancer. Androgen signaling promotes the recruitment of androgen receptor (AR) and TOP2B to the genomic breakpoints of TMPRSS2-ERG [51]. This reconfiguration is commonly observed in prostate cancer [62–64], and it triggers TOP2B-mediated DSBs for recombination. Moreover, a significant association was found between the co-expression of ERG, AR, and TOP2B and the expression levels of TMPRSS2-ERG fusion genes [20]. This finding suggests that identifying these genes has potential as a diagnostic indicator for prostate cancer and for detecting malignant transformations [20]. A recent study examined the effectiveness of ciprofloxacin and levofloxacin for the treatment of bladder cancer. The study found that fluoroquinolones were able to reduce the expression of TOP2B, indicating their potential as effective treatment options for bladder cancer [52].

In conclusion, TOP2B plays a crucial role in the progression of reproductive system cancers, impacting the incidence, malignancy, and prognosis of cancer, as well as regulating the response of cancer cells to chemotherapy and hormone-based therapeutic interventions.

3.1.3. Glioma

Glioma is a common type of cancer that affects the central nervous system [54]. Multiple studies have specifically examined the function of TOP2B in controlling the transcription of oncogenes in gliomas in the human brain [53,54]. TOP2B is detected in the enhancers, promoters, and introns of the PDGFRA and MYC genes [54]. Moreover, there was a direct relationship between the levels of TOP2B and the expression of PDGFRA and MYC in glioma samples. Additionally, mice implanted with human glioma xenografts and suppressed TOP2B showed an extended lifespan [54]. The sensitivity of mouse glioma cell lines to etoposide, a chemotherapeutic drug used in tumor treatment, is directly linked to increased levels of TOP2B transcription [53]. Further investigation is necessary to obtain a thorough understanding of the association between TOP2B and gliomas. Nevertheless, current research indicates that TOP2B promotes the transcription of many oncogenes in glioma cells, thereby contributing to cancer progression.

3.1.4. Digestive system cancer

TOP2B plays a role in the occurrence and progression of gastrointestinal cancers [55–58]. Research has revealed that increased mRNA levels of TOP2B are associated with improved overall survival, HER2-negative status, lower clinical stages, diminished lymph node involvement, and reduced distant metastasis in patients with gastric intestinal-type adenocarcinoma and diffuse gastric adenocarcinoma [55]. A study revealed that hepatocellular carcinoma exhibits elevated levels of TOP2B mRNA, which is associated with a distinct chemotherapy response. This indicated that elevated levels of TOP2B in cancerous tissues may reflect reduced susceptibility to chemotherapeutic inhibition [56]. However, the precise processes responsible for improved prognosis in patients with increased TOP2B expression are not completely understood. Furthermore, the significance of TOP2B in cancer therapy has attracted considerable interest. For instance, studies have shown that blocking girdin can potentially increase the effectiveness of oxaliplatin treatment in colorectal cancer cells by lowering the expression of TOP2B [57]. Likewise, the DHA ester of phloridzin has inhibitory effects on the growth of hepatocellular carcinoma cells by reducing the expression of TOP2B [58].

3.1.5. Lung cancer

The role of TOP2B in lung cancer remains unclear. Multiple studies have indicated that there is no significant difference in the levels of TOP2B expression between tumor tissues and normal lung tissues, as well as between lung cancer cell lines and normal lung epithelial cell lines [24]. However, the study of bioinformatic data has led to conflicting interpretations. The analysis using Oncomine and Kaplan-Meier plotter revealed a notable association between increased levels of TOP2B and improved overall survival rates among patients with non-

small cell lung cancer and lung adenocarcinoma [59]. Furthermore, berberine chloride can decrease the expression of TOP2B by reducing the regulatory effect of the Sin3A/TOP2B pathway. This results in the induction of apoptosis in non-small cell lung cancer cells [61].

Despite a substantial amount of evidence indicating the role of TOP2B in different forms of cancer, the connection between TOP2B and malignancies remains unclear. Therefore, further studies are necessary to clarify the precise chemical mechanisms involved.

3.2. TOP2B and chronic inflammation

Chronic inflammation plays an important role in aging. The immune system gradually declines in functionality as a result of the aging process, resulting in an uncontrolled and persistent low-level chronic inflammation, generally referred to as "immune aging" or "inflammaging" [65]. The presence of chronic inflammation during the aging process is commonly recognized as a common feature of many age-associated ailments.

Existing evidence suggests that TOP2B plays a pro-inflammatory role in anthracycline drugs, particularly in relation to doxorubicin-induced cardiotoxicity [66,67]. In adult cardiac myocytes, TOP2B is expressed exclusively, whereas TOP2A is not expressed at all [65]. The combination of doxorubicin and TOP2B results in the formation of a TOP2B-doxorubicin-DNA cleavage complex. This complex causes DNA DSB and subsequent DNA damage, which activates p53 and triggers cell death process in cardiomyocytes [68,69]. Nevertheless, Green tea effectively reduced cardiac remodeling caused by doxorubicin and was associated with an increase in TOP2B expression, while decreasing oxidative stress [70]. Etoposide, a TOP2 inhibitor, demonstrated the ability to increase the expression of the transcription factor Maf and stimulate the PI3K/Akt pathway. This results in the suppression of pro-inflammatory cytokines, such as IL-6 and TNF-α, in macrophages induced by LPS. These findings suggest that etoposide could be a potential therapeutic option for treating inflammatory diseases, particularly for patients experiencing the "cytokine release syndrome" caused by COVID-19 [71]. Dexrazoxane has demonstrated cardioprotective properties against heart damage caused by TOP2B by reducing TOP2B levels [65]. TOP2B is involved in controlling the expression of inflammation-related genes such as cytokines, inflammatory mediators, and immune-related genes [45]. The onset of tumor formation associated with inflammation is ascribed to DNA cleavage and mutations facilitated by nitric oxide-activated TOP2 [72]. Moreover, control of the inflammatory process is achieved by inhibiting NF-kB target genes with DNA-intercalating TOP2 inhibitors [73].

Further investigation is required to elucidate the exact relationship between TOP2B and inflammation as well as to unravel the intricate molecular pathways and regulatory networks involved in TOP2B.

3.3. The contribution of TOP2B in neurodegenerative diseases

Neurodegenerative diseases are a group of aging-related disorders that affect nervous system, including Alzheimer's disease (AD) [74], Parkinson's disease (PD) [75,76], amyotrophic lateral sclerosis [77], and Werner's syndrome [78]. The activation of neuronal genes by TOP2B at the transcriptional level is essential for neural differentiation and brain [33]. TOP2B is crucial for the activation of specific genes during terminal differentiation [79,80]. TOP2B knockout mice experience postnatal mortality due to the lack of TOP2B regulation of crucial genes involved in neurodevelopment, including neuromuscular junction formation, cerebral cortex development, and embryonic brain gene expression [81]. Brain-specific deletion of the TOP2B gene in mice results in cortical developmental defects during brain development [33]. These studies highlight the significant contribution of TOP2B in the development of the nervous system. Moreover, the inhibitory effect of TOP2B on axonal length and the decline in neuronal synapses are commonly observed in neurodegenerative diseases [11]. In summary, abnormal expression and dysfunction of TOP2B in the nervous system are associated with the pathogenesis of neurodegenerative diseases [74].

AD is characterized by neuronal degeneration and formation of amyloid plaques within the brain [82]. In a rat AD model, there was a significant drop in both mRNA and protein levels of TOP2B in cerebellar granule neurons. This decrease had a profound effect on the inhibition of nuclear receptor-related factor 1 (Nurr1) transcription, which ultimately worsened the course of AD [74]. Moreover, evodiamine, a well-established inhibitor of TOP2 [83], displays a broad spectrum of pharmacological activities and diverse biological effects, particularly its anti-Alzheimer capabilities. Further investigations are needed to determine the exact pharmacological processes and specific targets of its interaction with TOP2.

PD is characterized by degeneration of dopaminergic neurons in the midbrain and a decline in dopamine levels [75]. In Nurr1 knockout mice, the expression of TOP2B is reduced in the nigrostriatal pathway. Additionally, the promoter region of TOP2B contains two functional Nurr1 binding sites [75]. Research conducted on mice with TOP2B gene deletion demonstrated a significant decrease in dopaminergic neurons in the substantia nigra, along with altered brain functions in the nigrostriatal pathway. These findings suggest that Nurr1 may affect the development of axons in dopaminergic neurons by controlling the expression of TOP2B. This could potentially play a role in PD progression. In a cellular model of PD created by reducing the activity of tyrosine hydroxylase, the expression of TOP2B was suppressed, which had a notable impact on the progression of neurodegeneration [76].

Hutchinson-Gilford Progeria Syndrome (HGPS), also known as Werner syndrome, is an additional neurodegenerative disorder linked to TOP2B [78]. This syndrome is a rare genetic disorder characterized by premature aging and the early onset of multiple age-related symptoms. Individuals with Werner syndrome often have genetic anomalies in the TOP2B gene, resulting in decreased functionality of TOP2B, which subsequently disrupts the processes of DNA damage repair and cellular aging [78].

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of motor neurons in the central nervous system [84]. The GGGGCC repeat sequence, which is found in the non-coding region of C9orf72, has been identified as a key genetic factor contributing to ALS [84]. It has been shown that expansion of the GGGGCC repeat sequence alone can cause neurodegeneration in *Drosophila* [84]. Furthermore, it has been observed that an expanded GGGGCC repeat sequence has the ability to modulate the transcriptomes of multiple genes [77]. Downregulation of TOP2 can specifically alter the progression of GGGGCC-related neurodegeneration in the eye [77]. In addition, it has been noted that the pharmacological inhibition of TOP2 or the downregulation induced by small interfering RNA (siRNA) can alleviate neurotoxicity caused by GGGGCC in *Drosophila* [77]. The results of this study provide initial evidence for the idea that higher levels of TOP2 may contribute to a common route involved in several pathological processes of ALS.

Although the correlation between TOP2B and neurodegenerative diseases has been established, further investigation is necessary to comprehensively understand the precise mechanisms and interactions underlying this association.

3.4. The involvement of TOP2B in cardiovascular diseases

As people age, the arterial wall gradually loses its flexibility, leading to an increase in stiffness [85]. This change in vascular properties increases the workload on the heart, thereby increasing the vulnerability to cardiovascular diseases [85]. Furthermore, the process of aging typically results in the accumulation of atherosclerotic plaques within blood vessel walls, which hampers normal blood flow [86]. The anti-atherosclerotic effects of two inhibitors, etoposide and teniposide, have been found in hypercholesterolemic rabbits [85–87]. Treatment

with TOP2 inhibitors or si-TOP2 has been shown to stimulate the activation of the liver X receptor, which subsequently initiates the transcriptional activation of cholesteryl ester transfer protein. This activation results in the reversal of cholesterol transport, thereby contributing to the prevention of atherosclerosis formation of atherosclerosis [88]. ATP-binding cassette transporter A1 (ABCA1) is responsible for promoting cholesterol efflux, thereby inhibiting foam cell formation and atherosclerosis caused by the accumulation of lipids [89]. The expression level of ABCA1 is regulated by liver X receptor (LXR) transcription [90]. Etoposide and teniposide have been shown to increase the ABCA1 expression in an LXR-dependent manner, resulting in the increased removal of free cholesterol from macrophages. This action exhibits features that are effective against atherosclerosis [87]. Teniposide, a TOP2 inhibitor, has a significant impact on cholesterol metabolism by stimulating hepatic CETP expression and facilitating reverse cholesterol transport [91]. Ultimately, these molecular events help to decrease atherosclerotic calcification and improve plaque stability. The transformation of muscle cells from a contractile to a proliferative phenotype is an important pathogenic characteristic of atherosclerotic plaque development [92]. The TOP2B inhibitor teniposide can protect against the phenotypic switch of vascular smooth muscle cells in the context of atherosclerosis by upregulating the production of smooth muscle α-actin and downregulating the production of osteopontin within aortic lesion plaques [93].

Hypertension is a prevalent cardiovascular disease with a high occurrence rate. Evodiamine, a known TOP2 inhibitor, has recently demonstrated potential in controlling pulmonary hypertension [94]. However, the precise chemical pathways underlying this action are still poorly understood.

3.5. The relationship between TOP2B and aging-related metabolic diseases

The incidence of metabolic diseases, particularly diabetes, obesity, and fatty liver disease, tends to increase in parallel with age progression. These disorders are characterized by disturbances in both energy metabolism and the endocrine system [95]. Recent research has revealed abnormal changes in TOP2B expression levels in individuals afflicted with metabolic diseases [95,96].

In the Goto-Kakizaki rat diabetes model, diabetes-induced oxidative stress altered the activity of mitochondrial TOP2B, leading to mutations in mitochondrial DNA and impaired mitochondrial function [95]. Furthermore, doxorubicin, a TOP2 inhibitor, greatly enhanced DNA fragmentation in the isolated mitochondrial extracts. This suggests that the inhibitory state of mitochondrial TOP2 plays a vital role in maintaining mitochondrial DNA integrity and preventing the onset of diabetes [95]. Furthermore, recent findings suggest that anti-TOP2 antibodies may serve as a more reliable biomarker for tracking the progression of type 1 diabetes mellitus in Chinese patients, especially those who have had the disease for >11 years. Late-onset disease (>18 years) has been identified as a risk factor (relative risk = 2.15) leading to an increased occurrence of anti-TOP2, as determined by multivariate analysis [97].

Obesity is a major cause of mortality, worldwide. Poly (ADP-ribose) polymerase-1 (PARP1) activation has been found to increase during adipocyte development [96]. However, it has been noted that the presence of the TOP2 inhibitor merbarone can substantially reduce PARP1 activity and hence hinder the functionality of adipocytes [96]. In addition, inhibition of TOP2 by Chloride has been found to have a notable effect on the upregulation of UCP1 in brown adipocytes, leading to thermogenesis and the reduction of lipid droplets in fat cells [98].

Fatty liver disease is characterized by abnormal accumulation of fat within the liver. Besides its role in lipid metabolism, TOP2B also plays a vital role in the pathogenesis of hepatic steatosis [58]. TOP2B can regulate the expression of genes involved in fatty acid synthesis and oxidative metabolism. TOP2B influences the control of fat storage and metabolism in the liver by adjusting the activity of important genes, such as fatty acid synthase and fatty acid oxidation-related genes. This modulation affects fatty acid synthesis and degradation. Additionally, it has been observed that TOP2B has a significant role in the regulation of cholesterol metabolism, a pivotal factor in the development and advancement of fatty liver [87]. TOP2B has been linked to biological processes such as inflammation and cell apoptosis [72]. These processes are significant in the development of fatty liver disease, and TOP2B can influence their extent by regulating the expression of key genes and activating apoptotic pathways.

4. TOP2 inhibitors

Accelerated aging of the global population inevitably leads to an increase in the incidence of aging-related diseases. There is significant interest in identifying molecular targets that can help fight aging and aging-related diseases [2]. TOP2 inhibitors can be divided into two categories: TOP2 poison inhibitors and TOP2 catalytic inhibitors. Etoposide, doxorubicin, epirubicin, berubicin, idarubicin, and other well-known TOP2 poison inhibitors have been shown to increase the stability of the cleavage complex formed by the enzyme during DNA replication (TOP2 enzyme-inhibitor-DNA cleavage complex) [87]. This intricate complex induces DSBs in DNA, hindering the accurate resealing of DNA strands, ultimately resulting in cell death [85,91]. As outlined in Supplemental Table S1, TOP2 poison inhibitors play a pivotal role in therapeutic strategies for diverse cancers. Furthermore, it is worth noting that a significant number of dietary items commonly ingested in the human diet naturally include TOP2 poison inhibitors. Genistein, which is abundantly present in soy, is believed to possess chemopreventive properties in adults, potentially reducing the incidence of breast and colorectal cancers [99]. In contrast, TOP2 catalytic inhibitors refer to substances that efficiently impede the enzymatic activity of TOP2. Several compounds have been identified, including novobiocin, merbarone, suramin, and aclarubicin [100]. Nevertheless, it should be noted that novobiocin, merbarone, suramin, and aclarubicin interact with several targets other than TOP2, thus constraining their potential for further investigation and development as anticancer drugs.

5. Conclusion and perspectives

Given the remarkable advancements in the understanding of the role of TOP2B in aging and aging-related diseases, it is crucial to further investigate the possibility of using TOP2B intervention as a therapeutic strategy for anti-aging purposes. Nevertheless, it is essential to determine the intricate molecular mechanisms responsible for the complex regulatory mechanisms involved. Further investigation is necessary to examine two important areas: (1) elucidating the similarities and differences in the contribution of TOP2B to aging in proliferating cells (replicative aging) and post-mitotic cells (chronological aging), and (2) establishing a comprehensive understanding of the regulatory network of TOP2B in aging-related diseases. Additional research is required to study the correlation between TOP2B and other important age-related diseases. Currently, various regulatory procedures related to TOP2B, including those using TOP2B inhibitors, have been investigated in animal and cellular models. However, only a few studies have focused on patients. It is recommended to select interventions with strong evidence of their effectiveness and conduct randomized controlled trials to confirm their therapeutic potential.

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CRediT authorship contribution statement

Man Zhu: Conceptualization, Writing – original draft, Visualization, Writing – review & editing. **Hao Li:** Conceptualization, Writing – review & editing. **Yi Zheng:** Conceptualization, Writing – review & editing. **Jing Yang:** Conceptualization, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

Data sharing not applicable to this manuscript as no datasets were created or analyzed during the current study.

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