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The Key Role of Telomerase in The Initiation and Treatment of Colon Cancer: New Advances and Prospects

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Abstract: Telomeres are important regions for maintaining genome stability, and their dysfunction is closely related to the occurrence of colon cancer. This article reviews the recent progress in the study of telomeres and telomerase in colon cancer, and highlights the key role of telomerase in inducing telomere dysfunction and immortalization of cancer cells. Modulating telomerase activity has become a potential strategy to inhibit the proliferation of cancer cells, including immunotherapy, telomerase inhibitors and TERT gene targeted therapy, which provides prospects for the treatment of colon cancer. Finally, recommendations are made regarding the development of therapeutic strategies targeting telomerase.

Keywords: Telomeres; Colon Cancer; Enzyme Activity; Targeted Therapy; Immunity

Colon cancer (COC) is one of the most common cancers of the digestive tract worldwide and has become the second leading cause of cancer-related death [1]. Especially in China, the incidence of COCs and the burden of cancer are increasing rapidly [2]. Although improvements in colonoscopy and treatment have significantly improved survival in patients with COC [3,4], the prognosis for patients with advanced stages remains poor [5]. Telomeres are critical protective regions at the ends of chromosomes and are essential for maintaining chromosomal stability [6]. Activation of telomerase causes telomeres to lengthen, allowing cancer cells to emerge from a crisis state and become immortal [7]. Studies have shown that chromosomal instability (CIN) is closely related to the pathogenesis of COC [8], so telomeres and telomerase have become the focus of COC treatment and research [9,10]. This article reviews the latest research progress on telomeres and telomerase in COC, and provides valuable suggestions for future therapeutic strategies for telomeres and telomerase.

1 Structure And Function Of Telomeres And Telomerase

Telomeres are composed of continuously repeating TTAGGG DNA sequences located in the protective protein complex region at the end of chromosomes, which include six core protein members, namely telomere repeat binding factor (TRF) 1, TRF2, inhibitor/activation protein 1 (RAP1), TRF1 interacting nucleoprotein 2 (TIN2), telomere protection 1 (POT1), and POT1 and TIN2 hitabin (TPP1) (see Fig.1). A lasso-like T-ring configuration is formed at the single-stranded telomere end at the 3' end, which protects the chromosome end by wrapping the end of the DNA inside [11]. During the S phase of the cell cycle, phosphorylation of TRF2 regulates the unwinding and winding of the T-ring, thereby protecting telomeres from replication stress and DNA damage responses [12]. Normal cells gradually shorten the posterior granules with each division because DNA polymerase cannot fully synthesize the 3' end of chromosome, which is a normal physiological phenomenon. When telomeres become very short, uncapped telomeres trigger DNA damage signals, leading to arrest cell growth. This growth arrest, caused by shorter telomere length, is a protective mechanism for clearing aging cells and a protective barrier that hinders the initial proliferation of cancer cells [13,14]. If this protective mechanism is compromised, cells will continue to proliferate, telomeres will further shorten, exacerbating the accumulation of DNA damage, increasing instability at chromosomal ends, ultimately leading to cell death or aging, and contributing to the development of cancer [15].

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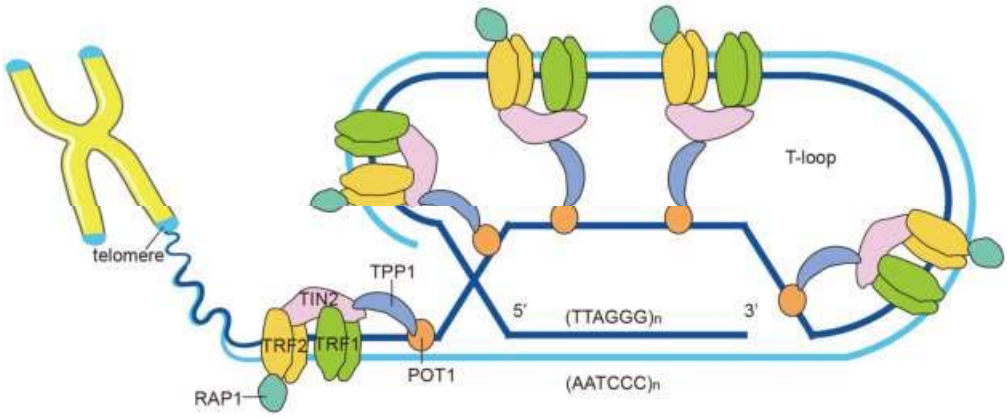

FIG. 1 TELOMERE STRUCTURE

On the one hand, the development of cancer requires telomere shortening, which triggers genomic instability, and on the other hand, cancer cells need to maintain long telomeres to achieve infinite proliferation. Most cancer cells overcome cell proliferation limits by enhancing the expression activity of telomerase. Telomerase is a ribonucleoprotein complex consisting of catalytic subunit telomerase reverse transcriptase (TERT) and RNA subunit telomerase RNA as a replication template, as shown in Figure 2. TERT is a rate-limiting step in telomerase complexes, while its expression is inhibited in normal somatic cells. However, in tumor cells, telomerase can directly lengthen telomeres through TERT reverse transcription RNA, or selective telomere elongation through homologous recombination to avoid DNA damage signaling and maintain cell immortality, and this ability to lengthen telomeres is known as the telomere maintenance mechanism [16-18]. Studies have shown that approximately 75 percent of tumors express TERT, with 31 percent of the samples having TERT promoter mutations (TPMs) and 53 percent having methylation in the promoter region of the TERT [19].

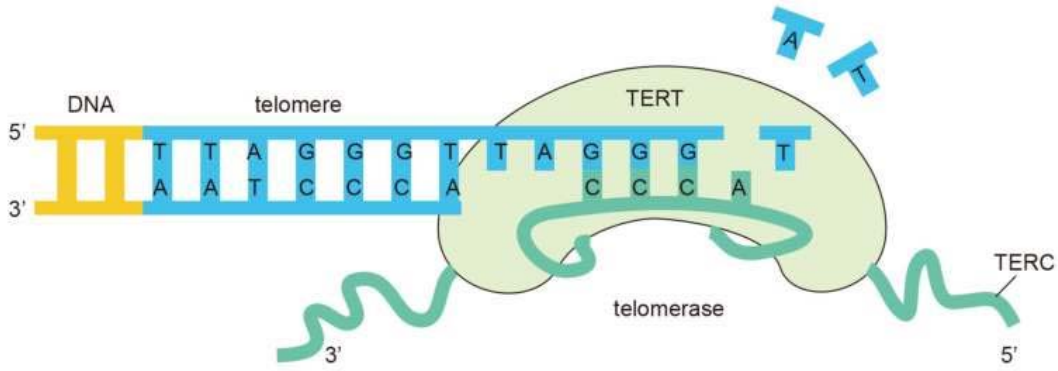

FIG. 2 TELOMERASE STRUCTURE

In addition to the typical role of telomere maintenance mechanisms, telomerase also has atypical cancer-promoting functions. These atypical functions include regulation of chromatin state, DNA damage response, oxidative stress protection, and proliferative gene activity [20-22]. For example, telomerase can promote MYC-driven tumorigenesis independently of its reverse transcriptase activity [22]. Short-term depletion of endogenous TERT can destabilize the telomere-protective complex, which includes the nucleases Snm1B/Apollo and TRF2, which are telomere dysfunction mediated independently of telomere erosion [22].

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In summary, telomeres influence the development of cancer in two different ways: on the one hand, the shortening of telomeres may lead to widespread genomic instability, thereby promoting cancer progression; on the other hand, cancer cells extend

telomere length by activating telomere maintenance mechanisms, achieving sustained and unlimited proliferation. By combining telomere maintenance mechanisms with abnormal DNA damage responses triggered by telomere erosion, cancer cells can break through the limits of cell division and accumulate irreparable genomic mutations through replication stress.

2 Telomeres And Colon Cancer Development Mechanism

2.1 Genomic Instability Due To Telomere Dysfunction Induces Colon Cancer

The phenomenon of chromosomal instability (CIN) is present in approximately 65–70% of tissues of colorectal cancer (COC) patients [8], forming the basis of most COCs, while other COC tissues exhibit microsatellite instability (MSI) phenotypes. CIN is characterized by mutations such as chromosomal locus alleles, chromosomal amplification and translocation, resulting in the inactivation of tumor suppressor genes (such as APC, p53, etc.), the activation of oncogenes (such as KRAS, BRAF, etc.), and the loss of heterozygosity of the long arm of chromosome 18, thereby promoting the occurrence of COC [24]. In the genome, microsatellites (tandem nucleotide repeats) are prone to slip mismatch errors during replication. DNA mismatch repair (MMR) proteins identify and correct mismatch errors during DNA replication. Thus, defects in the MMR gene affect microsatellite repair, resulting in the MSI phenotype. In particular, promoter methylation of the MMR gene MLH1 is one of the most common mechanisms for silencing the MMR gene in episodic COCs [25].

Telomere shortening has been shown to be associated with MSI in mitochondria in COC tissues [26]. In addition, in COC patients with wild-type p53, telomere length is significantly shorter in patients presenting with the MSI phenotype than in microsatellite stabilized patients [27]. However, it is unclear exactly what telomere function alterations mean in MSI. Nevertheless, telomere dysfunction is thought to be the main driver of CIN. When the telomere terminal protection mechanism is impaired, the chromosome ends enter a breakage-fusion-bridge (BFB) cycle, which leads to significant genome rearrangements. At the same time, telomere dysfunction and BFB circulation contribute to a large increase in genomic amplification and deletion in tumors, leading to higher levels of CIN [28]. Telomere length in normal cells primarily reflects cell proliferation, but in COC cells, it reflects both telomere shortening due to cell proliferation and de novo synthesis of telomere sequence due to telomerase activation. In mouse models, mice lacking TERC exhibit telomere shortening, leading to gastrointestinal tumorigenesis and increased incidence of microadenomas [29]. Telomere length is shorter in COC cells relative to normal cells, and this trend is more pronounced in COC cells with high copy number variation and high somatic mutation number [30]. Telomeres in healthy tissue adjacent to the tumor are shorter than in healthy tissue away from the site of cancerous lesions [31]. In addition, reductions in telomere length in COC tissues were associated with worsening disease status, accelerated disease progression, and reduced survival [32], with patients with the greatest variation in telomere length having the highest risk of death [33]. However, increased telomerase activity has also been reported in COCs [34]. This is because although telomere shortening is promoted

Chromosomal instability leads to early carcinogenesis, but in later stages, activation of telomerase immortalizes tumor cells, i.e., an increase in telomere length is associated with an increase in the depth of tumor invasion [35]. These findings strongly support that telomere erosion-induced CIN is a key mechanism for COC occurrence.

2.2 Telomere Dysfunction, Inflammatory Bowel Disease And Colitis-Related Cancer

The inflammatory process is considered to be one of the important factors in the occurrence and progression of some cancers, especially COCs. The inflammatory process usually begins with the release of biomolecules in damaged tissue, followed by migration of white blood cells to the injured tissue to rebuild the tissue and assist in repairing the injury, which is the physiological response to healing of the injured tissue. However, chronic inflammation is not stimulated by injury, but the relevant signaling pathways are activated, and it plays a role in the various processes of tumor cell transformation, survival, proliferation, invasion, angiogenesis, and metastasis of COCs [36]. Patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are also at increased risk of developing COC [37]. In studies of patients with long-term UC, the cumulative incidence of colitis-associated cancer (CAC) after 10, 20, and 30 years has been 0.1 percent, 2.9 percent, and 6.7 percent, respectively [38]. The risk of CAC in patients with CD is not fully understood, but studies suggest that the incidence of COC in patients with CD is 2.9 percent, 5.6 percent, and 8.3 percent after 10, 20, and 30 years, respectively [39]. A recent cohort study also showed a poorer prognosis for COCs in patients with CD, who are associated with an increased risk of death compared with healthy individuals diagnosed with COCs [40].

Telomere dysfunction can induce the development of IBD, and the inflammatory microenvironment formed can further increase the risk of cancer. Intestinal epithelial cells of mice engineered with telomere dysfunction express the upregulated interleukin 18 precursor (pro-IL-18), exhibiting an IBD-like inflammatory state, suggesting that telomere dysfunction can drive the inflammatory process [41]. pro-IL-18 is one of the major factors that trigger IBD [42,43], and germline variants associated with impaired telomere maintenance exhibit activation of this pathway [41]. Germline mutations in TERC or TERT are associated with an increased risk of fibrosis, inflammatory disease, and cancer [44]. At the pathological level, individuals with germline mutations in the telomerase component present with progressive villi atrophy, enterocolitis, and intraepithelial lymphocytosis [45]. At the same time, the shorter telomere length in the UC intestinal epithelium may lead

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to genomic instability and exacerbate the increased incidence of cancer in these patients [46].

In addition, studies have also shown that telomere erosion or dysfunction can be a key trigger not only for the inflammatory process in IBD, but also a consequence of chronic inflammation. Inflammation increases epithelial damage, resulting in high local reactive oxygen species production by intestinal epithelial cells, neutrophils, and macrophages [47], and the resulting oxidative stress accelerates telomere shortening [48]. Even a low degree of chronic inflammation is sufficient to induce telomere erosion [49]. TERT is capable of regulating multiple signaling pathways, including Wnt/β-catenin, and modulates inflammatory signaling by binding to an NF-kB promoter capable of leading to transcription of genes such as IL-6 or TNFα [50]. NF-kB is a major driver of inflammatory signaling, a pathway that in turn regulates telomerase activity [51]. The expression of many immune cytokines, including IL-7, IL-8, and IL-10, has been reported to upregulate telomerase activity and correlate with telomere length in cancer [52]. This suggests that the accumulation of these cytokines in the tumor microenvironment may have an effect on the telomeres of tumor cells.

3 Research Progress On Anti-Cancer Strategies Targeting Telomerase

Cancer cells achieve their immortality by reactivating telomerase to extend telomeres. In addition, telomerase is ubiquitous upregulated in cancerous cells and is highly specific, so strategies targeting telomerase may have broad therapeutic applicability for all types of cancer.

3.1 *Immunotherapy*

Endogenous TERT peptides produced by cancer cells can be recognized by major histocompatibility complex class I or II molecules and trigger adaptive immune responses. Several early clinical trials of TERT peptide vaccines have been conducted. Therapeutic TERT peptide vaccines can elicit specific T cell responses in a high proportion of cancer patients. As an example, in one clinical trial, the TERT peptide vaccine UV1 was able to stimulate an internal immune response in 86 percent of patients with metastatic hormonal prostate cancer [53]. However, the immune response to the TERT vaccine alone is often insufficient to control disease progression [54]. Therefore, people began to combine the TERT vaccine with immune checkpoint inhibitors to improve the therapeutic effect. Studies have shown that a synthetic TERT DNA vaccine works synergistically with anti-CTLA-4 therapy to inhibit tumor growth and prolong survival in mouse models that have a weak response to a single immune checkpoint inhibitor, which provides a strong theoretical basis for immunotherapy combining the TERT vaccine with immune checkpoint inhibitors [55].

3.2 *Telomerase Inhibitors*

Telomerase inhibitors can impede the telomere maintenance mechanism of cells, resulting in a gradual shortening of telomeres, triggering DNA damage responses and subsequent apoptosis. Imetelstat is a drug that directly inhibits telomerase and inhibits cancer cell survival and tumor growth by competitively inhibiting telomerase activity [56]. In clinical trials, Imestim elicits a high response rate [57], however, in phase II trials in patients with advanced non-small cell lung cancer, overall survival improvement was not significant despite improved survival of shortest telomeres [58]. This may be because trace amounts of residual telomerase activity still maintain and protect the shortest telomeres, thus preserving the proliferation of tumor cells. Therefore, more efficient telomerase inhibitors are needed to completely eliminate telomerase activity. BIBR1532 is a non-competitive small molecule telomerase inhibitor. Although its pharmacokinetics are poor, limiting its clinical use, there is evidence that high doses of BIBR1532 can rapidly induce acute telomere dysfunction independent of telomere shortening, thereby rapidly initiating cytotoxicity [59]. This ability to quickly trigger an anti-cancer response indicates its potential developmental value.

3.3 *TERT Gene Targeted Therapy*

Most cancers acquire the ability to immortalize replication through the reexpression of TERT, which is reactivated by TPM [60]. Recent studies have begun to focus on cancer cells where TPM occurs. GABPβ1L (β1L) is a tetramer-forming GABP subtype whose knockout has no effect on normal cell development but results in TPM-dependent TERT silencing, so cancer cells that treat TPM can be targeted by inhibiting transcription of β1L-driven ETS-binding sites [61]. A key issue with TPM-targeted therapies lies in distinguishing between normal and transformed telomerase-expressing cells. However, the incidence and nature of TPM in different types of cancer vary widely, and the underlying causes of this phenomenon remain an important question, as understanding its mode of occurrence may reveal important regulatory dynamics of TERT in cancer cells with TPM versus cells without these mutations.

3.4 *Challenges And Obstacles*

Although telomerase has many desirable advantages as a cancer therapeutic target, the development of its clinical therapeutic application faces significant challenges. Because treatment relies on gradual wear out of each dividing telomere, therapies based on inhibition of telomerase reverse transcriptase activity take a longer period of time to exert anticancer effects, which may make them unsuitable for first-line treatment, so the search for drugs that do not rely on telomere shortening to induce acute telomere dysfunction needs to be developed. At the same time, due to the expression of telomerase in both stem cells and precursor cells, telomerase-targeted therapy may have certain side effects. In addition, telomerase activity may be at a low level due to limitations in the telomere maintenance mechanism in tumor cells and the ability to maintain tumor cell proliferation, which may limit the efficacy of telomerase inhibitors, suggesting the need for more efficient inhibitors to ensure therapeutic efficacy. At the same time, the structure and composition of human telomerase holases remain unclear due to

the low cellular abundance of telomerase, which makes active telomerase difficult to purify and crystallize, which also hinders the progress of drug design and mechanism analysis [10].

4 Conclusion

Genomic instability caused by telomere disorders is a key factor in inducing colon cancer. In addition, telomere dysfunction can also lead to the occurrence of inflammatory bowel disease, and the inflammatory environment further promotes telomere erosion and increases the risk of cancer. Because cancer cells extend telomeres for immortality, telomerase has long been an attractive target for cancer treatment. Despite significant challenges, anti-cancer strategies targeting telomerase, such as immunotherapy, telomerase inhibitors, and TERT gene-targeted therapy, remain promising cancer treatments. To achieve better clinical outcomes, further research into acute induction of telomere dysfunction and identification of potential synergies between TERT vaccines and immune checkpoint inhibitors are needed.

References

[1]SIEGEL R L, MILLER K D, FUCHS H E, et al.Cancer statistics, 2022[J].CA: a Cancer Journal For Clinicians,2022, 72 (1).

[2]WU C, LI M, MENG H, et al.Analysis of status and countermeasures of cancer incidence and mortality in China[J].Science China. Life Sciences,2019, 62 (5): 640-647.

[3]FENG R-M, ZONG Y-N, CAO S-M, et al.Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics?[J].Cancer Communications (London, England),2019, 39 (1): 22.

[4]XIA C, DONG X, LI H, et al.Cancer statistics in China and United States, 2022: profiles, trends, and determinants[J].Chinese Medical Journal,2022, 135 (5): 584-590.

[5]MILLER K D, NOGUEIRA L, DEVASIA T, et al.Cancer treatment and survivorship statistics, 2022[J].CA: a Cancer Journal For Clinicians,2022, 72 (5): 409-436.

[6]VICTORELLI S, PASSOS J F.Telomeres and Cell Senescence - Size Matters Not[J].EBioMedicine,2017, 21: 14-20.

[7]NEIDLE S, PARKINSON G.Telomere maintenance as a target for anticancer drug discovery[J].Nature Reviews. Drug Discovery,2002, 1 (5): 383-393.

[8]LENGAUER C, KINZLER K W, VOGELSTEIN B.Genetic instabilities in human cancers[J].Nature,1998, 396 (6712): 643- 649.

[9]MIZUKOSHI E, KANEKO S.Telomerase-Targeted Cancer Immunotherapy[J].International Journal of Molecular Sciences,2019, 20 (8).

[10]GUTERRES A N, VILLANUEVA J.Targeting telomerase for cancer therapy[J].Oncogene,2020, 39 (36): 5811-5824.

[11]DOKSANI Y, WU J Y, DE LANGE T, et al.Super-resolution fluorescence imaging of telomeres reveals TRF2-dependent T-loop formation[J].Cell,2013, 155 (2): 345-356.

[12]SAREK G, KOTSANTIS P, RUIS P, et al.CDK phosphorylation of TRF2 controls t-loop dynamics during the cell cycle[J].Nature,2019, 575 (7783): 523-527.

[13]MACIEJOWSKI J, DE LANGE T.Telomeres in cancer: tumour suppression and genome instability[J].Nature Reviews. Molecular Cell Biology,2017, 18 (3): 175-186.

[14]SHAY J W.Role of Telomeres and Telomerase in Aging and Cancer[J].Cancer Discovery,2016, 6 (6): 584-593.

[15]HACKETT J A, GREIDER C W.Balancing instability: dual roles for telomerase and telomere dysfunction in tumorigenesis[J].Oncogene,2002, 21 (4): 619-626.

[16]EBATA H, LOO T M, TAKAHASHI A.Telomere Maintenance and the cGAS-STING Pathway in Cancer[J].Cells,2022, 11 (12).

[17]BORGES G, CRIQUI M, HARRINGTON L.Tieing together loose ends: telomere instability in cancer and aging[J].Molecular Oncology,2022, 16 (18): 3380-3396.

[18]GAO J, PICKETT H A.Targeting telomeres: advances in telomere maintenance mechanism-specific cancer therapies[J].Nature Reviews. Cancer,2022, 22 (9): 515-532.

[19]BARTHEL F P, WEI W, TANG M, et al.Systematic analysis of telomere length and somatic alterations in 31 cancer types[J].Nature Genetics,2017, 49 (3): 349-357.

[20]MASUTOMI K, POSSEMATO R, WONG J M Y, et al.The telomerase reverse transcriptase regulates chromatin state and DNA damage responses[J].Proceedings of the National Academy of Sciences of the United States of America,2005, 102 (23): 8222-8227.

[21]NITTA E, YAMASHITA M, HOSOKAWA K, et al.Telomerase reverse transcriptase protects ATM-deficient hematopoietic stem cells from ROS-induced apoptosis through a telomere-independent mechanism[J].Blood,2011, 117 (16): 4169-4180.

[22]KOH C M, KHATTAR E, LEOW S C, et al.Telomerase regulates MYC-driven oncogenesis independent of its reverse transcriptase activity[J].The Journal of Clinical Investigation,2015, 125 (5): 2109-2122.

[23]GRONROOS E, LóPEZ-GARCíA C.Tolerance of Chromosomal Instability in Cancer: Mechanisms and Therapeutic Opportunities[J].Cancer Research,2018, 78 (23): 6529-6535.

[24]MALKI A, ELRUZ R A, GUPTA I, et al.Molecular Mechanisms of Colon Cancer Progression and Metastasis: Recent Insights and Advancements[J].International Journal of Molecular Sciences,2020, 22 (1).

[25]DE' ANGELIS G L, BOTTARELLI L, AZZONI C, et al.Microsatellite instability in colorectal cancer[J].Acta Bio-medica : Atenei Parmensis,2018, 89 (9-S).

[26]PARK W-J, BAE S U, HEO Y-R, et al.Telomere shortening in non-tumorous and tumor mucosa is independently related to colorectal carcinogenesis in precancerous lesions[J].International Journal of Molecular Epidemiology and Genetics,2017, 8 (5): 53-58.

[27]RAMPAZZO E, BERTORELLE R, SERRA L, et al.Relationship between telomere shortening, genetic instability, and site of tumour origin in colorectal cancers[J].British Journal of Cancer,2010, 102 (8): 1300-1305.

[28]O'HAGAN R C, CHANG S, MASER R S, et al.Telomere dysfunction provokes regional amplification and deletion in cancer genomes[J].Cancer Cell,2002, 2 (2): 149-155.

[29]RUDOLPH K L, MILLARD M, BOSENBERG M W, et al.Telomere dysfunction and evolution of intestinal carcinoma in mice and humans[J].Nature Genetics,2001, 28 (2): 155-159.

[30]LOPEZ-DORIGA A, VALLE L, ALONSO M H, et al.Telomere length alterations in microsatellite stable colorectal cancer and association with the immune response[J].Biochimica Et Biophysica Acta. Molecular Basis of Disease,2018, 1864 (9 Pt B): 2992-3000.

[31]HEAPHY C M, GAONKAR G, PESKOE S B, et al.Prostate stromal cell telomere shortening is associated with risk of prostate cancer in the

placebo arm of the Prostate Cancer Prevention Trial[J].The Prostate,2015, 75 (11): 1160-1166.

[32]VALLS C, PIñOL C, REñé J M, et al.Telomere length is a prognostic factor for overall survival in colorectal cancer[J].Colorectal Disease : the Official Journal of the Association of Coloproctology of Great Britain and Ireland,2011, 13 (11): 1265-1272.

[33]HERRMANN M, PUSCEDDU I, MäRZ W, et al.Telomere biology and age-related diseases[J].Clinical Chemistry and Laboratory Medicine,2018, 56 (8): 1210-1222.

[34]GERTLER R, ROSENBERG R, STRICKER D, et al.Telomere length and human telomerase reverse transcriptase expression as markers for progression and prognosis of colorectal carcinoma[J].Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,2004, 22 (10): 1807-1814.

[35]PINO M S, CHUNG D C.The chromosomal instability pathway in colon cancer[J].Gastroenterology,2010, 138 (6): 2059- 2072.

[36]HIRANO T, HIRAYAMA D, WAGATSUMA K, et al.Immunological Mechanisms in Inflammation-Associated Colon Carcinogenesis[J].International Journal of Molecular Sciences,2020, 21 (9).

[37]WIJNANDS A M, DE JONG M E, LUTGENS M W M D, et al.Prognostic Factors for Advanced Colorectal Neoplasia in Inflammatory Bowel Disease: Systematic Review and Meta-analysis[J].Gastroenterology,2021, 160 (5): 1584-1598.

[38]CHOI C-H R, RUTTER M D, ASKARI A, et al.Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview[J].The American Journal of Gastroenterology,2015, 110 (7): 1022-1034.

[39]CANAVAN C, ABRAMS K R, MAYBERRY J.Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease[J].Alimentary Pharmacology & Therapeutics,2006, 23 (8): 1097-1104.

[40]OLéN O, ERICHSEN R, SACHS M C, et al.Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study[J].The Lancet. Gastroenterology & Hepatology,2020, 5 (5): 475-484.

[41]CHAKRAVARTI D, HU B, MAO X, et al.Telomere dysfunction activates YAP1 to drive tissue inflammation[J].Nature Communications,2020, 11 (1): 4766.

[42]MOKRY L E, ZHOU S, GUO C, et al.Interleukin-18 as a drug repositioning opportunity for inflammatory bowel disease: A Mendelian randomization study[J].Scientific Reports,2019, 9 (1): 9386.

[43]WILLIAMS M A, O'CALLAGHAN A, CORR S C.IL-33 and IL-18 in Inflammatory Bowel Disease Etiology and Microbial Interactions[J].Frontiers In Immunology,2019, 10: 1091.

[44]WATANABE S, HIBIYA S, KATSUKURA N, et al.Importance of Telomere Shortening in the Pathogenesis of Ulcerative Colitis: A New Treatment From the Aspect of Telomeres in Intestinal Epithelial Cells[J].Journal of Crohn's & Colitis,2022, 16 (1): 109-121.

[45]JONASSAINT N L, GUO N, CALIFANO J A, et al.The gastrointestinal manifestations of telomere-mediated disease[J].Aging Cell,2013, 12 (2): 319-323.

[46]O'SULLIVAN J N, BRONNER M P, BRENTNALL T A, et al.Chromosomal instability in ulcerative colitis is related to telomere shortening[J].Nature Genetics,2002, 32 (2): 280-284.

[47]AVIELLO G, KNAUS U G.ROS in gastrointestinal inflammation: Rescue Or Sabotage?[J].British Journal of Pharmacology,2017, 174 (12): 1704-1718.

[48]BARNES R P, FOUQUEREL E, OPRESKO P L.The impact of oxidative DNA damage and stress on telomere homeostasis[J].Mechanisms of Ageing and Development,2019, 177: 37-45.

[49]GRAHAM M K, MEEKER A.Telomeres and telomerase in prostate cancer development and therapy[J].Nature Reviews. Urology,2017, 14 (10): 607-619.

[50]GHOSH A, SAGINC G, LEOW S C, et al.Telomerase directly regulates NF-κB-dependent transcription[J].Nature Cell Biology,2012, 14 (12): 1270-1281.

[51]JURK D, WILSON C, PASSOS J F, et al.Chronic inflammation induces telomere dysfunction and accelerates ageing in mice[J].Nature Communications,2014, 2: 4172.

[52]SVENSON U, GRöNLUND E, SöDERSTRöM I, et al.Telomere length in relation to immunological parameters in patients with renal cell carcinoma[J].PloS One,2013, 8 (2): e55543.

[53]LILLEBY W, GAUDERNACK G, BRUNSVIG P F, et al.Phase I/IIa clinical trial of a novel hTERT peptide vaccine in men with metastatic hormone-naive prostate cancer[J].Cancer Immunology, Immunotherapy : CII,2017, 66 (7): 891-901.

[54]ZANETTI M.A second chance for telomerase reverse transcriptase in anticancer immunotherapy[J].Nature Reviews. Clinical Oncology,2017, 14 (2): 115-128.

[55]DUPERRET E K, WISE M C, TRAUTZ A, et al.Synergy of Immune Checkpoint Blockade with a Novel Synthetic Consensus DNA Vaccine Targeting TERT[J].Molecular Therapy : the Journal of the American Society of Gene Therapy,2018, 26 (2): 435-445.

[56]ASAI A, OSHIMA Y, YAMAMOTO Y, et al.A novel telomerase template antagonist (GRN163) as a potential anticancer agent[J].Cancer Research,2003, 63 (14): 3931-3939.

[57]BAERLOCHER G M, OPPLIGER LEIBUNDGUT E, OTTMANN O G, et al.Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocythemia[J].The New England Journal of Medicine,2015, 373 (10): 920-928.

[58]CHIAPPORI A A, KOLEVSKA T, SPIGEL D R, et al.A randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced non-small-cell lung cancer[J].Annals of Oncology : Official Journal of the European Society For Medical Oncology,2015, 26 (2): 354-362.

[59]EL-DALY H, KULL M, ZIMMERMANN S, et al.Selective cytotoxicity and telomere damage in leukemia cells using the telomerase inhibitor BIBR1532[J].Blood,2005, 105 (4): 1742-1749.

[60]PILSWORTH J A, COCHRANE D R, XIA Z, et al.TERT promoter mutation in adult granulosa cell tumor of the ovary[J].Modern Pathology : an Official Journal of the United States and Canadian Academy of Pathology, Inc,2018, 31 (7): 1107-1115.

[61]MANCINI A, XAVIER-MAGALHãES A, WOODS W S, et al.Disruption of the β1L Isoform of GABP Reverses Glioblastoma Replicative Immortality in a TERT Promoter Mutation-Dependent Manner[J].Cancer Cell,2018, 34 (3).