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# Research and Advances on RecQ5 Helicase in the Pathogenesis of Bone Tumors

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**Abstract:** ***RecQ5 is a member of the conserved RecQ helicase family and represents the newest member of the human RecQ helicase family. Five RecQ homologs have been identified: RecQL/RecQ1, BLM/RecQ2, WRN/RecQ3, RecQ4, and RecQ5. Dysregulation of RecQ5 has emerged as a significant clinical issue, implicated in cancer susceptibility, cardiovascular disease, and inflammation. Research has progressed from studies on the correlation between RecQ5 expression and osteosarcoma tissue malignancy, to the preliminary application of the anti-RecQ helicase monoclonal antibody 6H5 in several tumor cell lines, and further to the identification of RecQ5 as a potential therapeutic target in Janus family cytoplasmic non-receptor tyrosine kinase 617 (JAK2) in myeloproliferative neoplasms (MPN) patients harboring V2F mutations. Over the past 25 years, extensive research has elucidated RecQ5's complex functions in DNA repair and transcriptional regulation, which are critical for maintaining chromosomal integrity and controlling cell growth. However, substantial clinical research remains needed to establish RecQ5 as a therapeutic target in the clinical management of bone tumors.***

**Keywords:** RecQ5, Osteosarcoma, Bone Tumors**.**

## 1. Introduction

RecQ5 is the newest member of the human RecQ helicase family, with no known association to specific clinical syndromes. However, mounting evidence indicates that RecQ5 plays a unique role in protecting genomic integrity and preventing various diseases, including cancer, cardiovascular disease, and inflammation [1]. This article summarizes current understanding of the clinical significance of RecQ5 polymorphisms or mutations. By linking these genetic variations to RecQ5's biochemical properties and cellular functions, potential mechanisms underlying RecQ5-associated pathologies are elucidated. Research into RecQ5's mechanisms of action not only sheds light on nucleic acid metabolism processes but also helps reveal certain mechanisms related to cancer pathogenesis. It provides a solid foundation for further investigation into RecQ5-related therapies and potential targeted interventions in bone tumors.

## 2. RecQ Helicase and Clinically Relevant Diseases

The RecQ helicase subfamily, part of the second largest helicase family, plays a crucial role in nucleic acid metabolism. This family participates in replication, repair, recombination, transcription, and even telomere stabilization mechanisms [2]. Research has identified five RecQ family members in humans: RecQ1, BLM, WRN, RecQ4, and RecQ5 [3]. In 1998, RecQ4 and RecQ5 genes (designated RecQL4 and RecQL5, respectively) were successfully isolated through sequence homology searches targeting known RecQ family helicases [4]. Defects in the BLM, WRN, and RecQ4 encoding genes cause corresponding human diseases: Bloom syndrome, Werner syndrome, Rothmund-Thomson syndrome, Rapadilino syndrome, and Baller-Gerold syndrome, respectively [5]. Although these disorders are extremely rare recessive genetic diseases in humans, they all manifest at the molecular level as high genomic instability, chromosomal abnormalities (chromosomal breaks, deletions, rearrangements, sister chromatid exchanges, etc.), and increased sensitivity to DNA-damaging agents. Clinically, they present with premature aging, type 2 diabetes, osteoporosis, atherosclerosis, and an extreme predisposition to cancer. The majority of patients ultimately succumb to various cancers, a shared clinical phenomenon that has sparked significant attention and research [6].

## 3. Study on the Correlation Between RecQ5 Helicase and Malignancy Grade in Osteosarcoma Tissue

RecQ5 plays a unique role in the pathogenesis of cancer, cardiovascular disease, and inflammation. To investigate the correlation between RecQ5 and the malignancy grade of osteosarcoma tissue, Zhi Liqiang, Tongzhi Chao, Yao Shuxin et al. selected 35 osteosarcoma specimens, 20 para-tumoral tissue specimens, and 20 normal bone tissue specimens. They detected RecQ5 expression in different tissues using immunohistochemical staining and further analyzed the relationship between its expression levels and osteosarcoma staging. The results showed that RecQ5 was lowly expressed in human osteosarcoma tissues. In normal bone tissue, the RecQ5 expression positivity rate was 100% (20/20). In peritumoral tissue, the positivity rate was 90% (18/20). In osteosarcoma tissue, the RecQ5 expression positivity rate was 68.5% (24/35). The difference in RecQ5 expression rates between normal bone tissue, peritumoral tissue, and osteosarcoma tissue was statistically significant ($P=0.004$), while the difference between normal bone tissue and peritumoral tissue was not statistically significant ($P>0.05$). The intensity of RecQ5 expression progressively decreased with increasing tissue malignancy, showing a statistically significant difference ($P<0.05$). Furthermore, within osteosarcoma tissues, expression intensity also gradually diminished with advancing tumor stage ($P<0.05$), demonstrating statistical significance. Analysis of the relationship between RecQ5 expression intensity and osteosarcoma staging revealed a progressive decrease in RecQ5 expression with increasing tumor stage, indicating a trend toward reduced expression as tumor malignancy

increases. However, whether the decline or loss of RecQ5 expression contributes to osteosarcoma development, or whether osteosarcoma development causes such reduction or loss, requires further investigation to establish a causal relationship. Reduced RecQ5 expression is observed in osteosarcoma, particularly in advanced-stage or low-grade tumors. The precise mechanism by which RecQ5 regulates bone metastasis in this context remains to be elucidated [7].

## 4. Molecular Mechanisms of RecQ5 in Bone Tumor Pathogenesis

Numerous RecQ5-associated single nucleotide polymorphisms (SNPs) have been identified and linked to susceptibility across various cancer types. These SNPs, including rs820200, rs4789223, rs142406301, and rs74632503 [8], reside within introns. The impact of these SNPs on RecQ5 protein structure and expression levels remains unclear. Nevertheless, rs4789223 is associated with colorectal cancer and osteosarcoma [9], while rs820200 is linked to increased breast cancer incidence [10]. Notably, rs142406301 exhibits high recurrence rates in NUT RAS-mutated adenocarcinoma, an aggressive and lethal malignancy for which no effective treatment has yet been established. Conversely, the rs74632503 variant exhibits protective effects against head and neck cancers. On the other hand, rs820196 involves a single nucleotide substitution within the RecQ5 coding sequence, resulting in the replacement of the negatively charged aspartic acid (D) side chain at position 480 with a nonpolar glycine (G) or valine (V) residue. This D480G/V mutation has been associated with several cancer types [11], including breast, colon, laryngeal, and bone cancers. This residue is located between the SFII-RQC and KIX domains, a region critical for TRIM28 SUMO E3 ligase interaction, SUMO2-PCNA conjugation, and TRC resolution. Given the predicted disordered secondary structure of this region, the effects of the D480G/V mutation on RecQ5 biochemical activity, interaction with TRIM28, or potential post-translational modifications (e.g., phosphorylation of nearby Y484) remain undetermined. Junlong Wu, Zhiqiang Zhi, Xin Dai, Qingchun Cai, Wei Ma et al. investigated the relationship between RecQ5 expression and osteosarcoma disease progression, further examining RecQ5's role in MG-63 cell proliferation and apoptosis [12]. Immunohistochemical analysis, qRT-PCR, and Western blot revealed downregulated RecQ5 expression in osteosarcoma tissues and cells. Patients with advanced tumor stages and low-grade tumors exhibited lower RecQ5 expression. To establish a stable RecQ5-overexpressing osteosarcoma cell line (MG-63-RecQ5), the RecQL1 gene was inserted into the human AAVS9 safe harbor using the CRISPR/Cas5 system. Overexpression of RecQ5 was validated via qRT-PCR and Western blot. Cell proliferation, cell cycle, and apoptosis assays demonstrated that RecQ5 overexpression inhibited MG-63 cell proliferation, induced G63 phase arrest, and promoted apoptosis.

## 5. Preliminary Application of Anti-RecQ Helicase Monoclonal Antibody 6H5 in Several Tumor Cell Lines

Zhang Ronghong, Lian Fang, Zhou Meng et al. collected ascites fluid from Baib/e mice after intraperitoneal inoculation with hybridoma cells 6H5. The 6H5 antibody in ascites was identified by ELISA [13]. Indirect immunofluorescence detected binding of the 6H5 antibody to BLM, RecQ4, and RecQ5 in breast cancer cells MDA. MB-435, human renal carcinoma cells GRC-1, and human tongue carcinoma cells Tca8113. Using 6H5 antibody as the primary antibody, immunohistochemical staining analyzed the expression levels of RecQ helicases in Jurkat, MDA-MB-435 tumor cells, and tumor stem cells. The 6H5 antibody was identified as positive in mouse ascites fluid. This antibody recognizes BLM, RecQ4, and RecQ5 helicases in various tumor cell lines and sensitively detects RecQ helicase expression in Jurkat, MDA-MB-435 tumor cells, and tumor stem cells. RecQ helicase expression levels were significantly higher in Jurkat tumor stem cells than in Jurkat tumor cells, while MDA-MB-435 tumor stem cells exhibited lower expression levels than MDA-MB-435 tumor cells, with statistically significant differences ($P<0.05$). RecQ helicase expression will undoubtedly provide new research directions and therapeutic targets for tumor diagnosis and treatment.

## 6. Applications of RecQ Helicase Somatic Alterations in Cancer

No clinical trials of therapies directly targeting RecQ helicases have been approved or are currently known. However, efforts are underway to identify small-molecule inhibitors for RECQL1, BLM, and WRN [14]. As further research explores the structures and biochemical interactions of these emerging biomolecular inhibitors, deeper insights into their inhibitory roles within DNA repair pathways may lead to the development of successful targeted therapies. Most conventional chemotherapy and radiotherapy methods for treating cancer induce double-strand breaks (DSBs) or other DNA damage, leading to subsequent cell death. When certain genes involved in DNA repair are altered through mutation or epigenetic silencing, cancer cells may rely on alternative repair pathways for survival. Synthetic lethality is a model where inhibiting two or more related pathways can trigger cell death. For example, loss of BRCA1 or BRCA2 reduces HR, forcing cancer cells to utilize poly (ADP-ribose) polymerase (PARP), an enzyme that promotes single-strand breaks and BER repair. When PARP is inhibited and single-strand breaks accumulate, stalled replication forks degrade into DSBs that cannot be repaired in BRCA-deficient cancer cells. This synthetic lethality model has driven the development of multiple PARP inhibitors, now approved for treating several cancers with peak efficacy in patients with germline BRCA alterations. Similar to PARP inhibitors, topoisomerase I (TOP1) inhibitors—including camptothecin (CPT)—block DNA repair by inducing replication-mediated DSBs and are used to treat various metastatic cancers. TOP1 inhibitors capture the TOP1 cleavage complex—a catalytic intermediate composed of TOP1 covalently linked to superhelical DNA—and subsequently convert it into replication-induced DSBs. Furthermore, low doses of TOP2003 inhibitors block replication, further impairing DNA repair. One unique feature of RecQL1 compared to other members of the RecQ enzyme family is its ability to drive recovery of the DNA replication fork after structural reversal, which occurs secondary to replication stress induced by TOP1 inhibition. A study demonstrated that PARP1 is required in this state to regulate

RecQL1 activity, thereby stabilizing the reverted fork. Combining PARP1 inhibition with TOP2003 inhibition induces replication-mediated DSBs even at low doses. This suggests that when PARP1 and TOP1 are suppressed in homologous recombination-depleted cells, further inhibition of RecQL1 may amplify outcomes via TOP2006 inhibition and significantly impair DNA repair. As previously reported, siRNA silencing of RecQL1 has demonstrated lethal effects in various HCC, ovarian cancer cell lines, and hypopharyngeal carcinoma, with in vivo activity in mice. This approach may also be effective against other cancers. The mechanism of anticancer activity involves mitotic catastrophe, even enhanced by the addition of chemotherapeutic agents. Research by Viziteu et al. indicates that RecQL1 depletion sensitizes multiple myeloma cells to PARPi-induced apoptosis [15]. Data suggest that future therapeutic targets for multiple myeloma could potentially combine DNA methyltransferase inhibitors (DNMTis), PARPIs, and inhibitors targeting the RECQL1 helicase to downregulate RecQL1 activity during replication stress and minimize resistance to chemotherapeutic agents. Cancer stem cells exhibit high proliferative capacity and resistance to DNA damage and cell death through constitutive checkpoint inhibitors and repair mechanisms. Review authors explain that RecQL4 expression may be critical for stemness, as evidenced by its positive correlation with several stem cell markers including Myc and CD133. They propose that RECQL4 represents a potential target for addressing these DNA damage-resistant cells, as its expression may contribute to the unlimited proliferative potential and survival of tumor stem cells [16]. Studies indicate elevated RecQL4 expression in glioblastoma stem cells, whose development is impaired upon RecQL4 inhibition. Furthermore, RecQL4 expression significantly correlates with its downstream target MAFB, a transcription factor whose inhibition impacts the invasiveness of ovarian cancer cells and osteosarcoma stem cells. Previous studies also revealed that the antibiotic spiramycin inhibits the replication function of numerous DNA helicases, including RecQL4. Future therapies may utilize compounds like spiramycin to suppress RecQL4-induced replication in cancer cells.

## 7. Conclusion

RecQ helicases are termed the “guardians” of the genome, playing roles in maintaining genomic stability and repairing DNA through multiple pathways. Biallelic germline mutations in BLM, WRN, and RECQL4 are associated with rare cancer susceptibility syndromes. Emerging research also implicates somatic alterations in RecQ helicases across multiple cancers, including hematologic malignancies, breast cancer, and osteosarcoma. Crucially, somatic alterations in RecQ5 helicase represent a novel therapeutic target in osteosarcoma-specific targeted therapies. However, the mechanisms underlying various targets remain unclear, continuing to hinder research. Therefore, close integration and translation between basic and clinical research are still required to achieve breakthroughs in targeted therapy for osteosarcoma. With emerging new biological studies and discoveries alongside novel technologies, greater understanding of RecQ5 helicase and significant progress in its therapeutic applications are anticipated. The molecular mechanisms and somatic alterations of RecQ5 helicases in osteosarcoma remain frontier topics requiring in-depth investigation. This review highlights that deciphering the genetic code of RecQ5 is pivotal for elucidating osteosarcoma pathogenesis and targeted applications. Much like assembling a complete map requires every small puzzle piece, understanding osteosarcoma mechanisms and advancing clinical treatments demands the collective effort of every healthcare professional.

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