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УДК 577.213.3:614.876:616-006.6

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G-QUADRUPLEX STRUCTURES IN DNA REPAIR GENES: A BIOINFORMATICS ANALYSIS OF BRCA1 IN THE CONTEXT OF RADIATION ONCOLOGY

Introduction

Radiation therapy remains a cornerstone of cancer treatment, relying on the induction of DNA double-strand breaks in tumor cells to trigger apoptotic cell death or irreversible growth arrest. Cellular responses to such damage are coordinated through the DNA damage response (DDR) network, which activates DNA repair mechanisms and enforces cell cycle checkpoints. Despite this, a significant number of tumors evade radiation-induced cell death by upregulating DNA repair efficiency. The *BRCA1* tumor suppressor is encoded on chromosome 17q21, playing central role in homologous recombination repair, cell cycle regulation, and control of transcription [1]. Non-canonical DNA structures known as G-quadruplexes (G4) within genes like *BRCA1* may represent an additional regulatory element, influencing their expression and function, potentially involved into cellular sensitivity to radiation.

Goal

To perform an in-silico analysis of the human *BRCA1* gene sequence to identify and characterize putative G-quadruplex forming sequences (PQS) and to evaluate their potential relevance to the cellular response to ionizing radiation.

Material and methods of research

The reference genomic sequence for the human *BRCA1* gene (NG_005905.2) was obtained from the NCBI Datasets Gene database. The sequence was analyzed with the G4IPDB online

prediction tool, which scans both strands (sense and antisense) for the G-quadruplex motif pattern (GxNy1GxNy2GxNy3Gx, where x≥3), returning sequence positions, lengths, and confidence scores (cG, cC, and their ratio cG/cC). High-confidence PQS were defined as those with a cG/cC ratio exceeding 20 or those designated "INF" (where cC=0), indicating sequences with exceptionally high guanine content.

The results of the research and their discussion

An in-depth analysis of the *BRCA1* gene sequence revealed extensive potential for G-quadruplex formation: 467 candidate sites on the sense strand and 364 on the antisense strand – 831 total. This abundance implies a biologically relevant structural capacity for G4 formation within the gene. Notably, the sense strand contains significantly more G4-forming motifs than its complement. This asymmetry may reflect functional relevance: if G4s assemble on the template strand during transcription, they could physically obstruct RNA polymerase progression. Conversely, G4s forming on the non-template strand might promote G-loop structures – alternative secondary configurations that modulate transcription through distinct regulatory pathways [2]. The strand-specific distribution thus hints at layered mechanisms governing *BRCA1* expression.

Among these sites, those with cG/cC scores exceeding 20 were prioritized as high-confidence candidates. Several sequences yielded "INF" values – the result of complete absence of cytosine residues – indicating extreme guanine density and maximal propensity for G4 folding. A particularly dense cluster was identified along the sense strand near positions 10982, 11028, and 11075. These regions are enriched with repetitive G-rich motifs capable of forming highly stable intramolecular G-quadruplexes when folded. Their presence suggests that if these structures form in vivo, they could serve as robust regulatory elements influencing *BRCA1* function.

The most convincing candidates are presented in Table 1, which lists sequences with cG/cC scores above 20. Several entries returned "INF" in the score column, indicating the complete absence of cytosines in those DNA stretches – sequences that are about as G-rich as it gets. What stands out, however, is the cluster on the sense strand around position 11000, specifically at 10982, 11028, and 11075. These sequences are densely packed with repetitive G motifs that would almost certainly fold into stable G4 structures if given the opportunity. If these form inside cells, they likely represent particularly robust structural elements.

Finding such high-confidence G4 motifs in *BRCA1* naturally raises the question of their functional significance. If these structures appear in the promoter region, they could interfere with transcription factor binding or physically obstruct the transcription machinery [3]. Given that *BRCA1* expression requires careful regulation due to its critical role in maintaining genomic stability, any alteration in G4 formation could impact its transcriptional output. Should a ligand stabilize a G4 in the promoter, reduced *BRCA1* protein production might follow. In normal cells, this would be detrimental – disrupting a tumor suppressor is never advisable. However, in tumor cells that retain functional *BRCA1*, such an approach could prove therapeutically useful. A drug that stabilizes these G4s to temporarily lower *BRCA1* levels might render tumors more vulnerable to PARP inhibitors or radiation [4].

Furthermore, given *BRCA1*'s central role in homologous recombination, G4 structures elsewhere in the genome represent endogenous sources of replication stress and DNA damage. If *BRCA1* function is compromised – whether by mutation or downregulation – the cell's ability to resolve these G4–induced lesions becomes impaired, leading to genomic instability [6]. Thus, the G4 landscape within *BRCA1* itself and its interaction with the BRCA1 protein in *trans* creates a complex regulatory and stability network. The PQS identified in the antisense strand are also significant, as they can form G4s in the RNA transcript or during replication, influencing post-transcriptional regulation and contributing to mutagenesis [7].

Table 1 – High-Confidence Putative G4 Forming Sequences (PQS) in the Human *BRCA1* Gene (cG/cC>20)

Strand	Start Position (bp)	Putative G4 Sequence (5'–>3')	Length (bp)	cG Score	cC Score	cG/cC Score
Sense	171486	GGGGGGGTAGGGGCGG	17	1010	10	101
Sense	82084	GGGACTTGGGGAGGGGGAAATGGGG	26	850	10	85
Sense	45244	GGGGGGTAGGGGCGG	16	800	10	80
Sense	36155	GGAGGGGGGCGGAGGAGAGGG	22	790	10	79
Sense	21326	GGGTGGTGGCGGGGGG	17	680	10	68
Sense	45156	GGGAAAGGGACAGGGGG	18	550	10	55
Sense	45892	GGGAAAGGTTAGGGGCGGGG	21	540	10	54
Sense	10603	GGGGGATTTGGCAGGG	17	490	10	49
Sense	22553	GGAGGCTTTGGGGAAGGGG	20	480	10	48
Sense	15802	GGTAGGGATGGGAACTGGGG	21	440	10	44
Sense	34528	GGGGATGGGAGGCGGG	17	440	10	44
Sense	846	GGATCAGGTTGGGGG	16	430	10	43
Sense	7975	GGACTGGTGGGGG	14	430	10	43
Sense	701	GGGGGACGGGCGGGGG	17	800	20	40
Sense	10982	GGGAGGGAGGTGGGGG	17	590	0	INF
Sense	11075	GGAGGGAGGTGGGGGGG	18	830	0	INF
Antisense	33114	GGGGTGGGGGGAGGGGGGAGGG	22	1420	0	INF
Antisense	44604	GGGGGGGTGGAGGG	14	910	0	INF
Antisense	26654	GGGGGATGGGGAGAGGCTAGGG	22	700	10	70
Antisense	21914	GGGCAGGGGTGGGGG	15	650	10	65
Antisense	124709	GGCTGTGGGGGATCTGGGG	19	600	20	30

Note. "INF" indicates an infinite ratio due to a cC score of 0, signifying sequences with exceptionally high G-content and predicted stability.

Analysis of the broader scientific literature confirms that several other DNA damage response genes, such as *BRCA2*, *RAD51*, and *ATM*, also contain potential G4 forming sequences, particularly in their promoter regions. Studies involving G4 stabilizing compounds have demonstrated increased DNA damage markers and replication stress in cancer cells, especially when combined with radiation exposure. These observations support the hypothesis that targeting G4 structures may enhance the effectiveness of radiotherapy by interfering with the transcription of key DNA repair genes and increasing the accumulation of radiationinduced DNA damage.

G4 targeting strategies may provide several benefits in cancer therapy, including radiosensitization, selective inhibition of oncogene expression, and improved treatment outcomes when combined with existing therapies. However, although promising, current research is limited by the lack of highly selective G4 ligands and the absence of extensive clinical studies. Further research is necessary to evaluate the safety and therapeutic potential of these approaches.

Conclusions

The human *BRCA1* gene is highly enriched in sequences with the potential to form G-quadruplex structures, with a total of 831 PQS identified across both strands.

A significant number of high-confidence PQS (cG/cC >20 or INF) were identified, including clusters of exceptionally stable sequences on the sense strand, underscoring the high potential for G4 formation *in vivo*.

The presence of abundant G4 motifs in *BRCA1* and other DNA repair genes suggests a complex layer of gene regulation that could influence DNA reparation and cellular response to radiation.

Targeting G4 represents a promising way for enhancing radiotherapy effectiveness, though further research is needed to find selective ligands and evaluate clinical applications.

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УДК 664.56:612.122.1]:577.175.722

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THE EFFECT OF CINNAMON CONSUMPTION ON BLOOD GLUCOSE REGULATION AND INSULIN SENSITIVITY IN INDIVIDUALS

Introduction

The prevalence of diabetes is increasing worldwide. There're insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). About 90% of patients are NIDDM with insulin resistance playing a key role in the development of the disease Insulin resistance includes decreased stimulation of muscle glycogen synthesis, defects in glycogen syntheses and hexokinase activity.

Nowadays, cinnamon (Cinnamomum's) has gained considerable attention for its potential therapeutic effects on metabolic disorders, particularly diabetes mellitus as it is a widely used spice which belongs to Lauralee family. While *Cinnamomum zeylanicum* is recognized as true cinnamon ,*Cinnamomum cassia* spices is considered to be superior for its glucose-lowering therapeutic potential, Phytochemically, these species are characterized by primary metabolites such as cinnamaldehyde, cinnamic acid alongside a secondary metabolite profile rich in flavonoids, phenolic acids, terpenoids. Although, the effect of cinnamon on blood glucose regulation and insulin sensitivity involves multiple molecular mechanisms that contribute to its antidiabetic properties [1].

Goal

The primary goal of this study is to elucidate the biochemical interaction of cinnamon on insulin signaling pathways and to evaluate their effects on blood glucose regulation and insulin sensitivity.