Original Article

Leveraging the htsFLT01/MiRGD Complex to Enhance Apoptosis and Suppress Angiogenesis in MCF7 Breast Cancer Cells

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What's Known

- htsFLT01 is a novel fusion protein that targets and neutralizes both vascular endothelial growth factor (VEGF) and placenta growth factor, showing potential for advanced anti-angiogenic cancer therapies.
- MiRGD nano carrier is an innovative nanoparticle-based system that has shown significant potential in delivering nucleic acids for gene therapy.
- The htsFLT01/MiRGD nano complex was effectively delivered to MCF7 breast cancer cells via iRGD targeting.

What's New

- Gene therapy introduces therapeutic genes into cancer cells to inhibit tumor growth or induce apoptosis. The *htsFLT01* gene, a novel anti-angiogenic construct, encodes the sFLT01 protein, which functions as a VEGF decoy receptor, impeding pathological angiogenesis. When combined with the MiRGD nanocarrier—a versatile peptide-based delivery system optimized for specificity, biocompatibility, and low toxicity—the htsFLT01/MiRGD complex offers a potent strategy against breast cancer. This study evaluated the effect of this complex on apoptosis induction in MCF7 cells via the extrinsic apoptotic pathway, revealing increased expression of *FADD*, *caspase-8*, and *p53* genes. These findings highlight a synergistic relationship between anti-angiogenic and pro-apoptotic mechanisms, offering promising avenues for future breast cancer therapies.

Abstract

Background: Gene therapy introduces therapeutic genes into cancer cells to inhibit tumor growth or induce apoptosis. The *htsFLT01* gene, a novel anti-angiogenic construct, encodes the sFLT01 protein that functions as a Vascular Endothelial Growth Factor (VEGF) decoy receptor, impeding pathological angiogenesis. When combined with the MiRGD nanocarrier—a versatile peptide-based delivery system optimized for specificity, biocompatibility, and low toxicity—the htsFLT01/MiRGD complex offers a potent strategy against breast cancer.

Methods: The *htsFLT01* gene was designed and constructed in previous studies. The MiRGD peptide was expressed and purified using Ni-NTA affinity chromatography in the *E. coli* C41 (DE3) expression strain. The potency of this peptide, along with the cell viability and toxicity of the nanoparticles, was previously evaluated in MCF7 cell culture. After transfection with the htsFLT01/MiRGD nanocomplex at a nitrogen-to-phosphorus (N/P) ratio of 14, cell lysates were collected, and expression analysis of the key genes, including Fas-Associated Death Domain Protein (*FADD*), Caspase-8 (*CASP8*), and Tumor Protein P53 (*TP53*), was conducted based on findings from prior research. Statistical analyses were conducted using IBM SPSS Statistics version 22 (IBM, USA) and REST 2009 software.

Results: The *htsFLT01* gene was previously designed and constructed, and the MiRGD nanocarrier was successfully produced and purified. This nanocarrier exhibited the best performance at an N/P ratio of 14. This study evaluated the effect of this complex on apoptosis induction in MCF7 cells via the extrinsic apoptotic pathway, revealing increased expression of *FADD*, *CASP8*, and *p53* genes.

Conclusion: These findings highlight a synergistic relationship between anti-angiogenic and pro-apoptotic mechanisms, offering promising avenues for future breast cancer therapies.

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Keywords ● CASP8 and FADD-like apoptosis regulating protein ● Tumor suppressor protein p53 ● Breast neoplasms ● Apoptosis ● Angiogenesis inhibitors

Introduction

Breast cancer continues to be the primary cause of death among women globally.[1] Traditional treatments often face challenges such as drug resistance and unintended side effects. Anti-angiogenic

strategies, which disrupt the blood supply critical to tumor survival, have emerged as an effective therapeutic approach.[2, 3] The *htsFLT01* gene, designed to encode the sFLT01 protein, which inhibits Vascular Endothelial Growth Factor (VEGF), an important regulator of angiogenesis. By integrating this gene into tumor cells, angiogenesis can be suppressed, depriving the tumor of nutrients and hindering its growth.[4, 5]

The primary reason for cancer-related deaths is metastasis, resulting from malignant tumor cells' capability to infiltrate nearby tissues and spread to remote locations.[6] A hallmark of cancer progression is the disruption of the balance between cell proliferation and apoptosis.[7] To sustain uncontrolled growth, cancer cells evade apoptotic mechanisms, thereby promoting survival and expansion. Consequently, the dysregulated expression of specific genes plays a crucial role in the development and progression of cancer.[8] Enhancing the susceptibility of cancer cells to apoptosis could significantly improve the efficacy of breast cancer therapies, offering a promising approach for targeted treatment strategies.[9]

To enhance the delivery and efficacy of therapeutic genes, the MiRGD nanocarrier system was employed. This carrier is composed of histone H1 motifs for DNA compression, a Gp41 sequence for endosomal escape, and an NLS motif for nuclear transport.[10] Additionally, the iRGD motif ensures selective targeting of endothelial cells overexpressing its receptor.[11]

Apoptosis, or programmed cell death, is a fundamental process that regulates cell growth, homeostasis, and survival.[12] It serves as a natural mechanism for eliminating damaged, dysfunctional, or unnecessary cells, thereby maintaining tissue integrity. However, in breast cancer, apoptosis is often deregulated, leading to uncontrolled proliferation and tumor progression.[13] Apoptosis is primarily regulated through three key pathways: the intrinsic (mitochondrial) pathway, the extrinsic (death receptor) pathway, and the non-caspase-dependent pathway.[14] The extrinsic apoptotic pathway is mediated by the Fas receptor (Fas) and its ligand (FasL). Upon activation, death signaling molecules interact with the Fas-associated death domain (FADD) and procaspase-8, forming the death-inducing signaling complex (DISC) at the inner side of the plasma membrane. This interaction initiates a cascade of caspase activation, ultimately leading to cell death.[15] Activated caspase-8 triggers the apoptotic process by activating downstream caspases, including caspase-3, which executes cell death by degrading essential cellular components.[16] Additionally, apoptotic signaling triggers the release of cytochrome c from the intermembrane space of the mitochondria, a key event in apoptosis regulation.[17] In response to Fas activation, caspase-8 cleaves Bid into its truncated form (tBid), which subsequently translocates to the mitochondria and activates Bak and Bax. This leads to the disruption of the mitochondrial membrane, causing the release of cytochrome c, which is a strong pro-apoptotic agent.[18]

A critical regulator of apoptosis is the tumor suppressor protein p53, which governs cell cycle arrest, DNA repair, and programmed cell death in response to cellular stress.[19] p53 directly influences the release of cytochrome c from mitochondria and enhances Fas-mediated apoptotic signaling, reinforcing its pivotal role in cancer suppression.[20] However, dysregulation or mutation of p53 in breast cancer impairs apoptosis, contributing to tumor progression and treatment resistance.[21]

This research examines the synergistic impact of htsFLT01 and MiRGD on apoptotic gene expression and angiogenesis inhibition, emphasizing its potential as a dual-targeting therapeutic strategy.

Materials and Methods

This study was conducted at the National Institute of Genetic Engineering and Biotechnology (NIGEB), Iran, between 2022 and 2024. All experimental protocols were approved by the institutional ethical review committee (Approval Code: IR.NIGEB.EC.1402.11.29.C).

Expression and Purification of htsFLT01/MiRGD Complex

The MiRGD complex was expressed using the pET28a plasmid system and purified based on established protocols.[10, 22-24] The *htsFLT01* gene was integrated with the MiRGD carrier at an optimal N/P ratio of 14:1.

Cell Culture and Transfection

MCF7 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS) and antibiotics under standard conditions. Cells were treated with either htsFLT01 alone or the htsFLT01/MiRGD complex. Transfection efficiency and subsequent gene expression were analyzed.

Quantitative Real-Time PCR (qRT-PCR)

Total RNA was extracted using Trizol reagent (Yekta Tajhiz Azma Company, Iran) and

Table 1: Gene names, sequences, sizes, and accession numbers of the primers used in the study

Accession No	Genes	Reverse transcriptase reaction primer (5' to 3')	Product length (bp)
NM_001276696.3	*P53*	TTGTTGAGGGCAGGGGAGT	117
NM_001080125.2	*Cas8*	GAATGTAGTCCAGGCTCAGG	168
NM_003824.4	*FADD*	GATTCTCAGTGACTCCCGC	168
NM_001289746.2	*GAPDH*	GCCCAATACGACCAAATCC	93

converted to cDNA. Gene expression levels of *FADD*, *CASP8*, and *TP53* were quantified using SYBR Green qRT-PCR, normalized to *GAPDH*, and analyzed using the 2^-ΔΔCt method and specific primers (table 1).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22 (IBM, USA) and REST 2009 software (QIAGEN Corporation, Germany). Data are presented as mean±SD from three independent experiments, and a *t* test (two groups) was employed for data analysis. P values less than 0.05 were considered statistically significant.

Results

Gene Expression Analysis

The htsFLT01/MiRGD complex significantly enhanced the expression of *FADD, CASP8*, and *p53* genes compared to the control and htsFLT01-alone treatments (P<0.05). This upregulation underscores its pro-apoptotic impact, mediated via the extrinsic apoptosis pathway (figure 1).

Angiogenesis Inhibition

By targeting VEGF, the htsFLT01 protein suppressed angiogenesis effectively. This dual action—angiogenesis inhibition and apoptosis induction—demonstrates the therapeutic versatility of the htsFLT01/MiRGD complex.

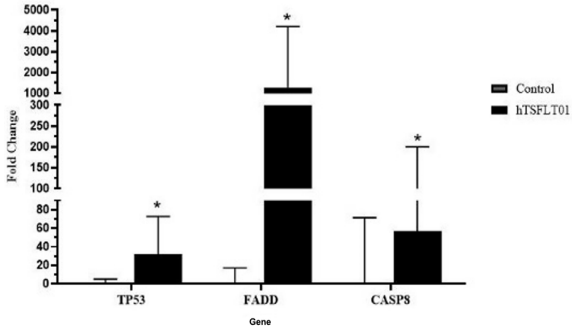

Figure 1: The effect of htsFLT01/MiRGD complex on the expression of *FADD, Cas8,* and *P53* genes in MCF7 cells treated with htsFLT01/MiRGD complex was compared with the control group using RT-qPCR. *Indicates P values less than 0.05, which were considered statistically significant. Gene expression analysis indicated increased expression of the *FADD*, *CASP8*, and *p53* genes.

Discussion

Gene therapy holds significant promise as an innovative approach to cancer treatment. However, before it can be integrated into routine clinical practice, several critical factors must be thoroughly evaluated, including the method of gene delivery, the efficacy of the delivery vector, and the overall therapeutic impact in preclinical models. This study explores the potential of a dual-targeting strategy, combining anti-angiogenic and pro-apoptotic mechanisms via the htsFLT01/MiRGD complex.

htsFLT01 is a novel fusion protein designed to neutralize both VEGF and placental growth factor (PlGF), key regulators of tumor angiogenesis. By inhibiting these pathways, htsFLT01 serves as a promising candidate for advanced anti-angiogenic cancer therapies. Previous studies have demonstrated its efficacy in ocular diseases that rely on anti-angiogenic drugs.[4] Moreover, research has indicated that htsFLT01 modulates invasion and metastasis in DU145 prostate cancer cells by targeting the *VEGF/GRP78/MMP2&9* axis.[25] Given that tumorigenesis is driven by an imbalance between proliferation and apoptosis, restoring apoptotic mechanisms is a fundamental strategy for cancer therapy.[15]

While htsFLT01 disrupts VEGF-mediated angiogenesis, the MiRGD complex enhances gene delivery efficiency in tumor cells. MiRGD consists of histone H1 motifs, Gp41 motif, and NLS motif,[10] with the addition of the iRGD peptide, which targets endothelial cells expressing the corresponding receptor.[22] Similar gene delivery motifs have previously demonstrated efficacy in facilitating gene transfer into eukaryotic cells.[10] Our findings confirm that the MiRGD complex effectively transports the *htsFLT01* gene into the nucleus of cancer cells, underscoring its potential for targeted gene therapy.

One of the key regulators of apoptosis is FADD, which plays a crucial role in multiple cellular processes, including cell growth, apoptosis, immune responses, and drug resistance.[26] Elevated FADD levels have been implicated in the progression of prostate cancer (PC), oral squamous cell carcinoma (OSCC), head and neck squamous cell carcinoma

(HNSCC), and breast cancer (BC), suggesting an oncogenic function.[26] Conversely, low FADD expression has been observed in thymic lymphoma, acute myeloid leukemia (AML), and glioblastoma multiforme (GBM), where it may act as a tumor suppressor.[27] The regulation of FADD expression in cancer remains complex, with both overexpression and downregulation observed across different malignancies. Post-translational modifications further contribute to FADD modulation, influencing its function in tumor progression.[28] Consequently, therapeutic strategies aimed at restoring FADD expression may provide a novel approach to cancer treatment, warranting further investigation.

Caspase-8, initially identified as a zymogen protease essential for death receptor (DR)-mediated apoptosis,[29] has since been recognized as a multifunctional protein involved in diverse signaling pathways. Given its dual role in apoptosis and tumor survival, interpreting caspase-8 solely as a pro-apoptotic factor requires caution.[30] Our findings suggest that treatment with the htsFLT01/MiRGD complex enhances caspase-8 activity, reinforcing the apoptotic response. However, the precise regulatory mechanisms governing caspase-8 function in different tumor types remain an area of ongoing research, highlighting the need for further studies.

One of the hallmark mechanisms by which cancer cells evade apoptosis is through upregulation of apoptotic regulators, such as *FADD, CASP8*, and *p53*, which can inhibit external apoptotic signals and prevent activation of the apoptotic cascade. Our findings indicate that increased expression of *FADD, CASP8*, and *p53* upon treatment suggests activation of the extrinsic apoptotic pathway, reinforcing tumor suppression mechanisms.[31] While previous studies have established the roles of FADD and caspase-8 in apoptosis,[29] their regulatory dynamics are tumor-dependent, with overexpression exhibiting contrasting effects across cancer types (figure 1).[28] Similarly, p53, a well-known tumor suppressor, orchestrates cell cycle arrest and apoptosis in response to cellular stress.[31] By modulating these key proteins, the htsFLT01/MiRGD complex demonstrates potential as an effective breast cancer therapeutic. Despite promising findings, this study has several limitations. Further protein-level validation and *in vivo* studies are required to confirm the therapeutic potential of the htsFLT01/MiRGD complex. Additionally, preclinical studies and clinical trials will be essential to determine its efficacy, optimize dosing strategies, and assess safety in human applications.

Conclusion

The htsFLT01/MiRGD complex integrates anti-angiogenic and pro-apoptotic mechanisms, offering a targeted approach for breast cancer therapy. By combining efficient gene delivery with robust therapeutic effects, this strategy represents a significant step toward personalized cancer treatment. Future research will focus on scaling this approach for clinical applications and exploring its utility across different cancer types.

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Authors' Contribution

M.Kh: Conceptualization, study design, visualization, validation, resources, review, formal analysis, data collection, fundraising, and drafting; ZS.S: Conceptualization, study design, visualization, validation, resources, review, formal analysis, data collection, fundraising, and drafting; S.H: Conceptualization, formal analysis, reviewing and editing; Sh.S: Study design, formal analysis, fundraising, supervision, and drafting; H.LN: formal analysis, and reviewing the manuscript; N.K: Study design, formal analysis, and reviewing; H.S: Study design and reviewing; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Conflict of Interest: None declared.

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