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ORIGINAL BRIEF

Evaluating the immunogenic potential of BAX protein isoforms as therapeutic targets in oncology: brief report

Evaluación del potencial inmunogénico de la proteína BAX como potencial diana terapeuta contra el cáncer: reporte breve

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ABSTRACT

Through a methodical approach that combines bioinformatics and immunological analysis, detailed genetic sequencing and structural analysis of seven BAX isoforms were conducted. Using databases such as NCBI and Uniprot, and algorithms for sequence alignment and structural predictions, promising features in specific isoforms were identified. Tools like BCPREDS and the Immune Epitope Database helped evaluate the immunogenic potential by mapping epitopes. The results highlighted that isoforms such as BAX-alpha and BAX-gamma have high immunogenic capacities, making them candidates for the development of targeted vaccines or as direct therapeutic agents. Structural analyses suggested that some isoforms have the capability to integrate into cell membranes and alter signaling pathways, inducing apoptosis selectively in cancer cells. In summary, this study underscores the importance of BAX isoforms in the evolution of cancer therapy, offering more specific treatment approaches with lower toxicity. These findings encourage a move towards precision medicine in oncology, personalizing treatments based on molecular and genetic profiles to optimize therapeutic efficacy and reduce adverse effects, promising to improve outcomes for patients.

Keywords: BAX Isoforms; Targeted Therapy; Precision Medicine.

RESUMEN

Mediante un enfoque metódico que combina bioinformática y análisis inmunológicos, se realizó una secuenciación genética detallada y análisis estructural de siete isoformas de BAX. Utilizando bases de datos como NCBI y Uniprot, y algoritmos para alineación de secuencias y predicciones estructurales, se identificaron características prometedoras en isoformas específicas. Herramientas como BCPREDS y la Immune Epitope Database ayudaron a evaluar el potencial inmunogénico mediante el mapeo de epítopos. Los resultados destacaron que isoformas como BAX-alfa y BAX-gamma tienen altas capacidades inmunogénicas, lo que las hace candidatas para el desarrollo de vacunas dirigidas o como agentes terapéuticos directos. Los análisis estructurales sugirieron que algunas isoformas tienen la capacidad de integrarse en membranas celulares y alterar las vías de señalización, induciendo la apoptosis de manera selectiva en células cancerosas. En resumen, este estudio subraya la importancia de las isoformas de BAX en la evolución de la terapia contra el cáncer, ofreciendo enfoques de tratamiento más específicos y con menor toxicidad. Estos hallazgos fomentan un avance hacia la medicina de precisión en oncología, personalizando tratamientos basados en perfiles moleculares y genéticos para optimizar la eficacia terapéutica y reducir los efectos adversos, prometiendo mejorar los resultados para los pacientes.

Palabras clave: Isoformas BAX; Terapia Dirigida; Medicina de Precisión.

INTRODUCTION

Cancer, a complex and multifaceted disease, affects millions worldwide, with the World Health Organization citing it as one of the leading causes of morbidity and mortality globally.[1,2] In 2018, it was estimated that cancer accounted for 9,6 million deaths.[2,3] Traditional treatment modalities, including chemotherapy, radiation, and surgery, often come with significant drawbacks, such as severe side effects and non-selective action against cancer cells, which can lead to diminished quality of life for patients.[4,5] Thus, there is a critical need for the development of more targeted and less toxic therapeutic options.[6,7]

Among the various molecular targets being explored, the BAX protein is particularly notable.[8,9] BAX plays a crucial role in the apoptotic process, a programmed cell death mechanism that is often dysregulated in cancer cells.[10,11,12] The ability of BAX to promote cell death in response to cancerous alterations makes it a promising target for therapeutic development.[13,14,15] However, the BAX protein is not a single entity but consists of several isoforms, each with potentially different roles in apoptosis and, consequently, in cancer therapy.[16,17]

This study provides an extensive overview of the role of BAX isoforms in cancer biology and their potential as therapeutic targets. It begins with a discussion of the genetic underpinnings of cancer and the dysregulation of apoptotic pathways that are hallmark features of many cancers. It then delves into the structure and function of the BAX protein, detailing the distinct characteristics of its isoforms. Through a comprehensive review of current literature and our own preliminary data, we argue that specific BAX isoforms may offer novel opportunities for the development of targeted cancer therapies.

In examining the landscape of cancer treatment, it is evident that despite advances in medical technology and understanding of cancer biology, the development of effective and safe therapies remains a significant challenge.[18] The introduction of targeted therapy has marked a shift towards more personalized medicine, but even these treatments are not without their limitations. Our focus on BAX isoforms is motivated by the potential to overcome some of these limitations by harnessing their unique properties to induce apoptosis selectively in cancer cells.

The investigation into BAX as a therapeutic target is timely and aligns with the shift towards precision medicine in oncology, which emphasizes the use of targeted therapies based on individual genetic, biomarker, and phenotypic data. Our study seeks to extend this paradigm by exploring how different BAX isoforms can be leveraged to enhance the specificity and efficacy of cancer treatments, potentially leading to better patient outcomes and fewer side effects.

METHOD

To address the complexities of cancer therapy and exploit BAX protein isoforms as targeted agents, our study implemented a comprehensive methodological framework integrating bioinformatics, immunological prediction assays, and recombinant protein expression with advanced molecular biology techniques. We began by collecting and analyzing genetic sequences of BAX isoforms from databases like NCBI and Uniprot, identifying variabilities and conserved regions essential for understanding functional diversities.

Using sophisticated algorithms for sequence alignment, we predicted structural configurations and potential functional sites for each isoform. Structural prediction tools then helped model the three-dimensional structures, facilitating the assessment of potential interactions with pharmaceutical agents. We further explored each isoform's immunogenic potential using tools such as BCPREDS and the Immune Epitope Database and Analysis Resource (IEDB) to identify epitopes that could elicit immune responses, pinpointing promising targets for therapeutic intervention.

Additionally, we assessed the structural integrity and solubility of the isoforms to ensure their viability in drug formulations. This involved using servers like SOSSUI and TMHMM to analyze transmembrane helices and solubility, crucial for their stability and efficacy in biological systems. This integrative approach, enhanced by collaboration across disciplines, ensured a comprehensive understanding of BAX isoforms, maximizing the translational potential of our findings.

RESULTS

Our comprehensive analysis of BAX protein isoforms has yielded several groundbreaking findings in oncology, particularly in the development of targeted cancer therapies. By examining the structural, immunogenic, and functional characteristics of these isoforms, we have identified promising avenues for novel therapeutic strategies (table 1).

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Table 1. Size and solubility characteristics of the 7 Bax protein isoforms

Isoform	Number of Amino Acids (aa)	Hypothetical size of the protein	Solubility or Aggregation
Alpha	192 aa	21,184 kDa	Soluble protein with high hydrophobicity
Beta	218 aa	24,219 kDa	Soluble protein with high hydrophobicity
Gamma	41 aa	4,678 kDa	Soluble protein
Delta	143 aa	15,772 kDa	Hydrophobic membrane protein
Epsilon	164 aa	18,128 kDa	Soluble protein with high hydrophobicity
Zeta	114 aa	12,887 kDa	Membrane protein, possible aggregation, and inclusion corpuscle formation
Psi	173 aa	19,312	Membrane protein, possible aggregation, and inclusion corpuscle formation
Sigma	179 aa	19,717	Soluble protein with high hydrophobicity

The study delineated unique profiles for seven distinct BAX isoforms—Alpha, Beta, Gamma, Delta, Epsilon, Zeta, and Psi—each displaying specific structural and immunogenic properties essential for their roles in apoptosis and cancer therapy (table 2). Particularly, the Alpha and Gamma isoforms showed the highest immunogenic potential, indicating their ability to effectively target and initiate immune responses against cancer cells. These isoforms interact robustly with the immune system, making them ideal for vaccine-based therapies or as direct therapeutic agents. Conversely, the Delta and Epsilon isoforms were noted for their ability to form transmembrane helices, potentially useful in signaling pathways to induce apoptosis in cancer cells.

Additionally, Zeta and Psi isoforms could be integral to novel drug delivery systems, as their propensity to form protein aggregates might be utilized to release therapeutic agents at targeted sites. The epitope mapping revealed strong-binding epitopes on the Alpha isoform, underscoring its potential for immunotherapy regimens by eliciting specific immune responses. Similarly, the Gamma isoform's epitopes showed compatibility with various HLA types, suggesting a universal application that could address the diversity challenge in current cancer treatments.

Furthermore, structural analyses of the isoforms provided insights into their solubility and potential for membrane integration, which are crucial for therapeutic efficacy. Soluble isoforms like Alpha and Beta are likely more manageable in recombinant forms for clinical use, while the ability of certain isoforms to integrate into cell membranes presents a strategy to selectively disrupt cancer cell membranes, paving the way for therapies that are highly specific and less toxic to normal cells.

Table 2. Results of the prediction of recognizable epitopes for the HLA system and B cells

Isoform	HLA allele A*02 prediction	Number of epitopes recognizable by B cells (80 % specificity)
Alpha	Presents 5 Strong binding epitopes (protected locations)	1 with a size of 20 aa
Beta	Presents 5 Strong binding epitopes (protected locations)	4 with a size of 20 aa
Gamma	It does not present epitopes linked to the cellular response	1 with a size of 20 aa
Delta	Presents 5 Strong binding epitopes (protected locations)	1 with a size of 20 aa
Epsilon	Presenta 4 epitopos Strong binding (localizaciones protegidas)	2 with a size of 20 aa
Zeta	Presents 2 Strong binding epitopes (protected locations)	There are no predictive results under the conditions tested for the rest of the isoforms
Psi	Presents 5 Strong binding epitopes (protected locations)	There are no predictive results under the conditions tested for the rest of the isoforms
Sigma	Presents 6 Strong binding epitopes (protected locations)	1 with a size of 20 aa

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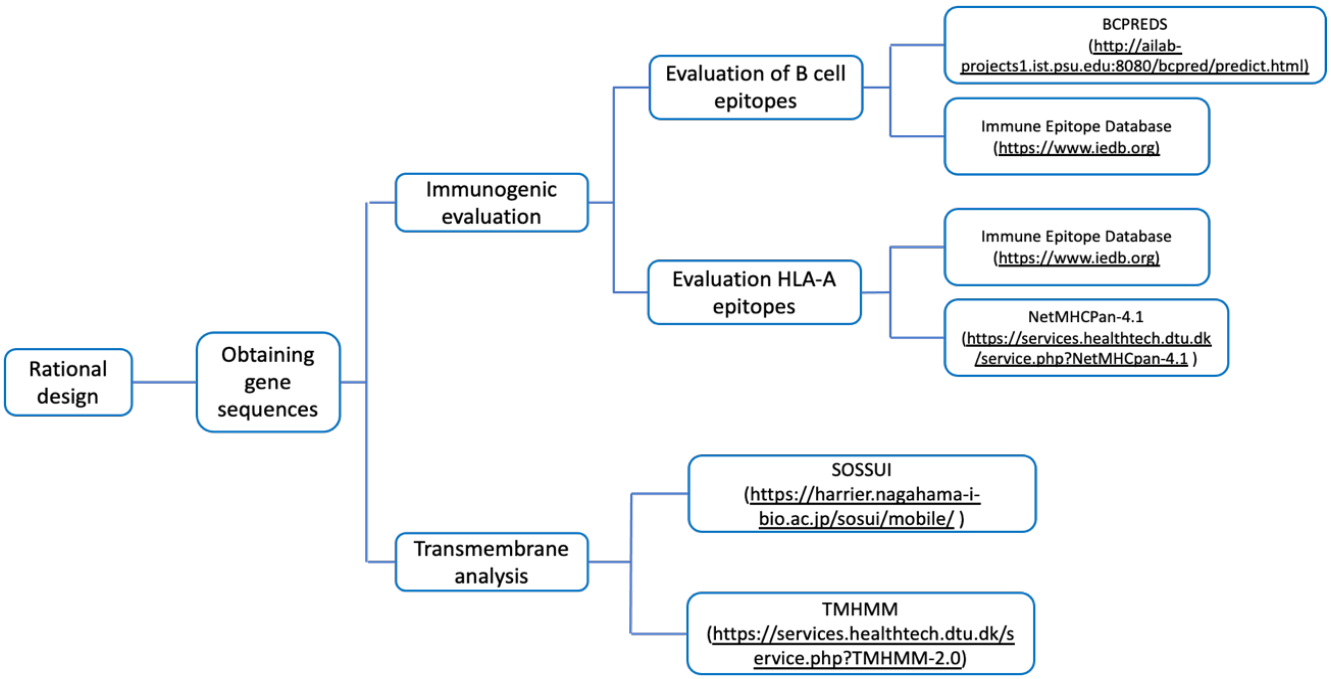

Figure 1. Rational design pipeline for the evaluation of the protein sequences of the isoforms of the Bax protein

DISCUSSION

This study provides pivotal insights into the roles of BAX protein isoforms in cancer apoptosis, significantly advancing oncology by identifying their unique immunogenic and structural properties.[19,20,21] This research suggests potential therapeutic applications and opens new paths for clinical application.[22,23] By differentiating the capabilities of isoforms like BAX-alpha and BAX-gamma, it allows for the development of targeted therapies that provoke strong immune responses specifically against cancer cells expressing these isoforms.[17,24,25] This approach minimizes damage to healthy cells and tackles the challenge of non-specificity in current cancer treatments.[9,19,23]

Targeted therapies could potentially reduce the dosage of chemotherapeutic agents, lessening the severe side effects associated with high-dose treatments, thus improving patient tolerance and overall health outcomes.[4,26,27] The study also enhances understanding of apoptotic mechanisms, crucial for developing drugs that selectively activate these pathways and address cancer cell resistance, a major hurdle in existing therapies.[10,14,28]

Moreover, the research explores the potential of BAX isoforms as biomarkers for diagnosing and monitoring cancer progression, which could lead to more precise prognostication and tailored treatment strategies.[29,30,31,32] The findings encourage further research, including clinical trials to test the efficacy and safety of isoform-targeted therapies and studies exploring interactions with other pathways, potentially unveiling new therapeutic targets.

Overall, the study advocates for adopting precision medicine principles in oncology, enhancing treatment effectiveness and reducing adverse effects, supported by interdisciplinary collaboration across fields such as bioinformatics, molecular biology, immunology, and clinical sciences.[4,7,33,34]

CONCLUSION

Our findings mark a promising advancement in personalized cancer therapy, with the potential to significantly improve patient outcomes through the application of isoform-specific cancer treatments. As we continue to unravel the complexities of BAX protein isoforms, the future of oncology looks poised for a paradigm shift towards more effective, less invasive, and highly personalized treatment strategies.

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CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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