

Peer Review

Review of: "The Development of Differentiation-Based Therapy for Breast Cancer Using EDAR and XEDAR Signalling Pathways: A Conceptual Framework"

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This article presents a novel approach to breast cancer therapy by focusing on differentiation-based strategies targeting the EDAR and XEDAR signaling pathways. It offers an innovative perspective by aiming to restore normal cellular functions instead of relying solely on cytotoxic approaches. This strategy could address critical gaps in treating aggressive and therapy-resistant breast cancer subtypes, such as TNBC. By proposing a two-phase therapeutic framework, the paper also provides a practical roadmap for future preclinical and clinical research. Its emphasis on combining epigenetic reactivation and synthetic ligand activation is particularly significant for precision medicine.

The title is informative and accurately reflects the content of the article. However, it could be made more concise for better readability. Suggested alternative:

"Differentiation-Based Therapy for Breast Cancer via EDAR and XEDAR Pathways: A Conceptual Framework"

The abstract is comprehensive and effectively summarizes the key concepts of the paper, including the rationale, proposed therapeutic strategy, and target patient subgroups. However, the following suggestions could improve it:

- **Inclusion of Specific Challenges:** Briefly mention the technical, biological, or clinical challenges discussed in the paper to provide a balanced overview.

- **Quantitative Data:** If possible, include numerical estimates (e.g., prevalence of XEDAR promoter methylation) to give readers a clearer picture of the target population.
- **Focus on Outcomes:** Add a sentence emphasizing the potential clinical outcomes, such as improved survival rates or reduced toxicity compared to conventional therapies.

Introduction

The introduction effectively establishes the need for innovative breast cancer therapies, highlighting the challenges of treatment resistance and the limitations of conventional cytotoxic approaches. The conceptual proposal to leverage EDAR and XEDAR signaling pathways for differentiation therapy is presented clearly. The hypothesis that these pathways can induce differentiation and reduce malignancy is compelling and grounded in current scientific knowledge.

Strengths:

- Provides a solid rationale for exploring differentiation therapy.
- Sets a clear research question and hypothesis.

Areas for Improvement:

- The introduction could benefit from a concise overview of current therapeutic strategies and their limitations to provide a broader context for the novel approach.

Current State of Knowledge

This section offers an informative review of the EDAR/XEDAR pathways, detailing their roles in epithelial differentiation and their silencing in breast cancer via promoter methylation. The discussion of molecular mechanisms, such as TRAF6 and NF- κ B involvement, adds depth to the scientific foundation.

Strengths:

- Comprehensive explanation of the signaling pathways.
- Includes critical insights into the molecular biology underlying the proposed therapy.

Areas for Improvement:

- Could include more recent studies or data to reinforce the relevance of the pathways in breast cancer specifically.
- The section may benefit from a diagram summarizing the key molecular interactions for clarity.

Therapeutic Need

The manuscript makes a strong case for differentiation-based therapies as a less toxic alternative to cytotoxic treatments. It highlights the potential to overcome drug resistance and improve the chronic management of aggressive cancers.

Strengths:

- Effectively conveys the significance of targeting differentiation.
- Highlights the unique advantages of the proposed approach over existing therapies.

Areas for Improvement:

- The therapeutic need for specific breast cancer subtypes (e.g., TNBC) could be expanded with more epidemiological data or case studies to emphasize clinical relevance.

Proposed Solutions

The discussion of synthetic ligand design, nanotechnology-based drug delivery systems, and advanced biomarker monitoring is thorough and innovative. The integration of molecular and epigenetic methods for therapeutic response monitoring is particularly noteworthy.

Strengths:

- Proposes realistic and technically advanced solutions to challenges.
- Emphasizes the importance of precision medicine and personalized approaches.

Areas for Improvement:

- Details on how nanotechnology-based delivery would specifically target breast cancer cells could enhance this section.
- A brief mention of potential side effects or unintended consequences of these solutions would make the discussion more balanced.

Future Directions and Research Priorities

The paper outlines promising strategies for integrating differentiation therapy with existing modalities, including chemotherapy, hormone therapy, and targeted therapies. The emphasis on timing and sequencing of therapeutic interventions is well-thought-out.

Strengths:

- Strong focus on practical integration into current therapeutic frameworks.
- Highlights the importance of reducing toxicity and improving tolerability.

Areas for Improvement:

- Experimental data to support the proposed timing and sequencing strategies would strengthen this section.
- The role of patient stratification based on biomarkers in clinical trials could be discussed more extensively.

Impact on the Future of Breast Cancer Therapy

The concluding section effectively synthesizes the proposed framework, emphasizing its potential to revolutionize oncology by shifting from cytotoxicity to differentiation. The dual mechanism of action and personalization of treatment through biomarkers are highlighted as transformative innovations.

Strengths:

- Inspiring vision of how the approach could redefine breast cancer treatment.
- Balances scientific insight with clinical implications.

Areas for Improvement:

- The potential impact on health care systems (e.g., cost, accessibility) could be briefly discussed.
- Limitations of the current framework and areas requiring further validation should be acknowledged more explicitly.

The references in this article are appropriate and provide a solid foundation for the conceptual framework presented. They effectively support the discussion on EDAR/XEDAR signaling pathways, therapeutic strategies, and the proposed innovations in breast cancer treatment. However, incorporating more recent references, especially those highlighting the latest advancements in molecular biology, epigenetics, and nanotechnology, would enhance the manuscript's relevance and strengthen its scientific credibility.

Declarations

Potential competing interests: No potential competing interests to declare.