RESEARCH ARTICLE

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

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Abstract

Breast cancer remains one of the most challenging cancers to treat, often due to evolving resistance to conventional therapies. This article presents a conceptual framework for differentiation therapy that exploits the EDAR and XEDAR signaling pathways. A two-phase therapeutic strategy involving epigenetic restoration of XEDAR expression and synthetic ligands to activate these pathways is described. The proposed approach targets patient subgroups with aggressive breast cancer subtypes, such as triple-negative breast cancer (TNBC), and those exhibiting high XEDAR promoter methylation. By focusing on cellular differentiation rather than cytotoxicity, this therapy could transform aggressive malignancies into more manageable chronic conditions. Potential technical, biological, and clinical challenges are discussed alongside proposed solutions to overcome them.

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Introduction

Breast cancer remains one of the most challenging malignancies despite significant advances in treatment options[1][2]. While current therapies focus primarily on killing cancer cells directly, an alternative approach involves inducing the differentiation of malignant cells, potentially transforming aggressive cancer into a more manageable chronic condition. This concept paper explores the theoretical framework for utilizing Ectodysplasin A receptor (EDAR) and X-linked Ectodysplasin-A2 receptor (XEDAR) signaling pathways to develop a differentiation-based therapy for breast cancer. **Fig. 1.**

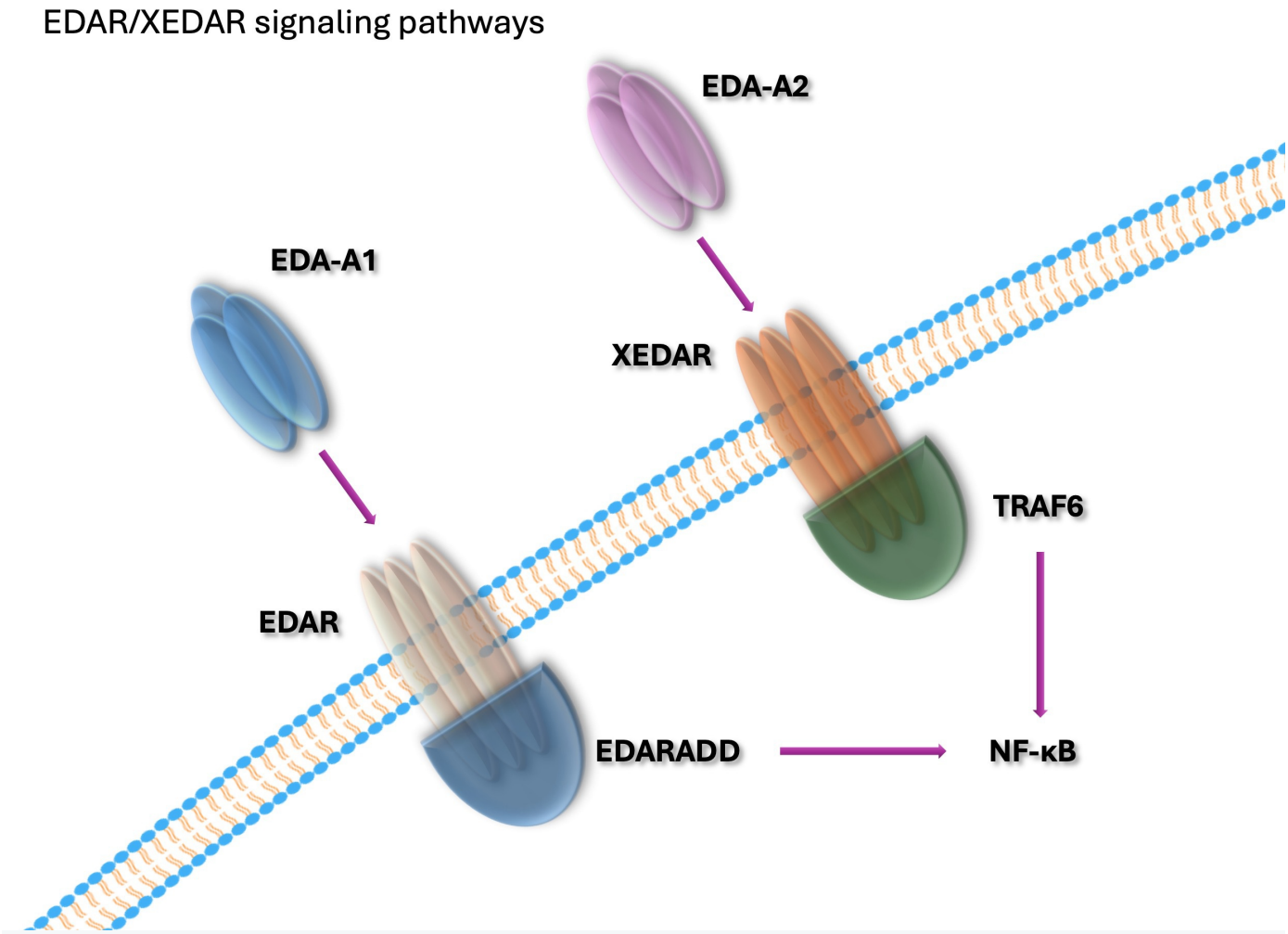

Figure 1. EDAR/XEDAR pathway diagram: Showing the mechanism of XEDAR receptor activation and key points such as TRAF6 and NF-κB.

Current State of Knowledge

Recent research has revealed critical insights into EDAR/XEDAR signaling pathways:

1. The XEDAR gene functions as a tumor suppressor in breast cancer, with its expression frequently silenced through promoter methylation[3].
2. EDAR and XEDAR demonstrate distinct developmental time expression patterns, suggesting their role in cell fate determination[4].
3. The EDAR/XEDAR pathways control epithelial cell differentiation through specific molecular mechanisms, including a two-amino acid molecular switch that determines receptor binding specificity[5].
4. TRAF6 is a key mediator of XEDAR signaling, linking receptor activation to downstream effects[6].

Therapeutic Need

Despite available treatments, breast cancer often develops resistance to conventional therapies[2], leading to disease progression. A differentiation-based approach could offer several advantages:

- Reduced risk of developing drug resistance
- Lower toxicity compared to conventional chemotherapy
- Potential for long-term disease management
- Possibility of combination with existing therapies

Research Question

Can the EDAR/XEDAR signaling pathways be therapeutically manipulated to induce differentiation in breast cancer cells, potentially converting aggressive malignancy into a more manageable chronic condition?

Hypothesis: that dual targeting of EDAR/XEDAR pathways through

1. DNA demethylating agents to restore XEDAR expression
2. Synthetic ligands to activate pathway signaling

could induce differentiation in breast cancer cells, reducing malignancy and improving patient outcomes.

Objectives

1. To develop a theoretical framework for targeting EDAR/XEDAR pathways in breast cancer therapy
2. To propose strategies for synthetic ligand design based on existing structural knowledge
3. To outline potential therapeutic protocols incorporating both pathway restoration and activation
4. To identify potential biomarkers for monitoring treatment response
5. 5. approach

Significance

This conceptual framework could provide the foundation for developing novel differentiation-based therapies in breast cancer treatment. By focusing on cellular differentiation rather than cytotoxicity, this approach might offer a less toxic alternative or complement to existing treatments, potentially improving long-term outcomes for breast cancer patients[7].

Current Understanding of EDAR and XEDAR Signalling Pathways in Development and Cancer

The EDAR and XEDAR signaling pathways have gained prominence in recent years in cancer biology[8][9][10], particularly in breast cancer, where XEDAR seems to play a key tumor suppressor role. Studies indicate that in most cases of breast cancer, XEDAR gene expression is significantly reduced due to hypermethylation of its promoter. For example, clinical analyses have shown that as many as 60-70% of breast cancer samples are characterized by XEDAR silencing due to

epigenetic changes[3][11]. Importantly, restoration of this gene expression by demethylating epigenetic agents such as 5-aza-2'-deoxycytidine led to inhibition of tumor cell proliferation and induction of differentiation mechanisms, as confirmed by preclinical studies[12].

The molecular mechanism of action of the XEDAR pathway is distinguished by its remarkable precision. A key element is the specificity of the EDA-A2 ligand binding to the XEDAR receptor due to the difference of only two amino acids in the structure of the EDA-A1 and EDA-A2 ligands. This specificity enables selective activation of the receptors and minimizes the side effects associated with interaction with the EDAR receptor[5]. XEDAR activation, in turn, is transduced into intracellular signaling pathways, such as NF-κB, via the key mediator TRAF6[6]. The differentiation process initiated by XEDAR activation involves multiple molecular steps. Upon ligand binding, XEDAR recruits TRAF6 through its cytoplasmic domain, leading to the assembly of a signaling complex. This complex triggers several downstream pathways, including NF-κB activation through IKK complex phosphorylation. The role of TRAF6 in XEDAR signaling extends beyond simple adapter functions[6]. Upon recruitment to the receptor complex, TRAF6 undergoes K63-linked auto-ubiquitination, creating a scaffold for downstream effector proteins. Additionally, TRAF6 facilitates the recruitment of TAK1 and TAB2/3 complexes[13].

Data from animal model studies provide further compelling evidence for the importance of temporal regulation of EDAR/XEDAR signaling[14]. In a mouse model, peak XEDAR expression was observed during the early stages of follicle development, highlighting the key role of this pathway in epithelial differentiation processes[4]. In contrast, in the rat model, XEDAR expression remained stable, indicating important species differences in regulating this pathway – **Fig. 2.** These observations suggest that temporal control of XEDAR activation may be a key element in therapeutic strategies.

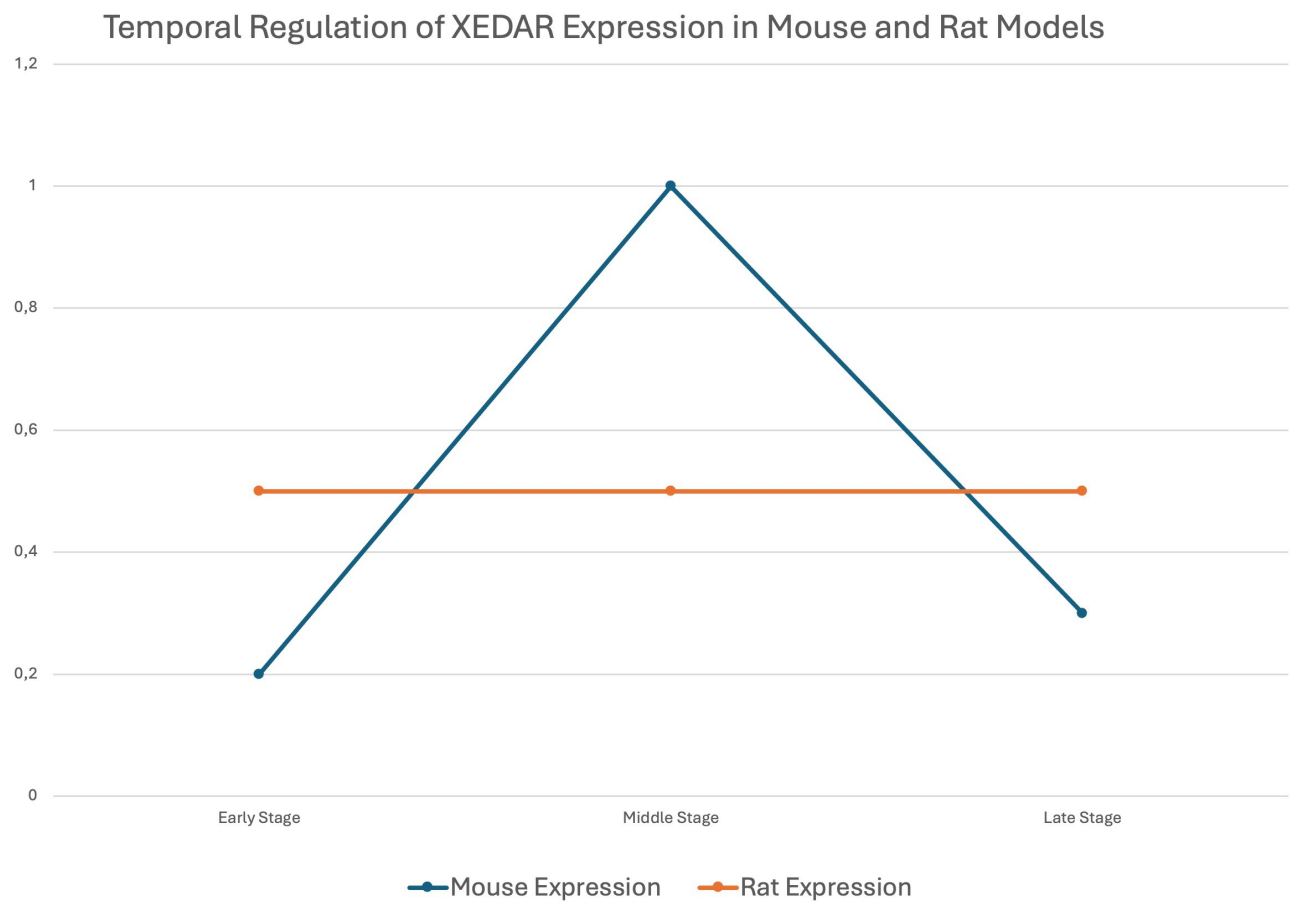

Figure 2. Temporal regulation of the pathway: Graphic representation of variation in XEDAR expression in mouse and rat models. Changes in XEDAR expression over time in mouse and rat models showing differences in peak activation of the pathway during epithelial development. Data are presented as relative mRNA expression obtained by RT-qPCR (Based on Wisniewski[4])

EDAR and XEDAR pathways do not function in isolation but integrate with other signaling systems, further enhancing their therapeutic potential. For example, activation of NF-κB by XEDAR is essential for differentiation and can also affect cell survival, highlighting the need to modulate this signaling precisely. The NF-κB pathway represents a primary downstream effector, but XEDAR activation also influences Notch signaling. Furthermore, crosstalk with the Wnt pathway occurs. These interactions create a complex signaling network that ultimately determines cell fate decisions[15]. In addition, XEDAR's ability to induce apoptosis via caspase-8 introduces an additional dimension in controlling tumor proliferation[16].

In conclusion, the study indicates significant therapeutic potential associated with modulating the EDAR/XEDAR pathway in treating breast cancer. In particular, the patient group that could benefit from this approach are those with aggressive cancer subtypes where XEDAR expression has been silenced, and current therapies have proven ineffective. The proposed combination of epigenetic unblocking of XEDAR with synthetic ligands could open new treatment options, focusing on restoring differentiation rather than solely on cytotoxicity[17].

Conceptual Framework for Differentiation-Based Therapy

Theoretical Basis for Therapeutic Intervention

The proposed therapeutic approach builds upon several key developmental biology and cancer research observations. The striking patterns of EDAR and XEDAR expression during normal development, particularly the dramatic peak in XEDAR expression during critical differentiation periods in mice, suggest that temporal control of these pathways may be crucial for inducing differentiation. Furthermore, the finding that XEDAR silencing through promoter methylation is common in breast cancer provides a clear rationale for therapeutic intervention.

Proposed Two-Phase Therapeutic Strategy – Fig. 3

Phase 1: Pathway Restoration The initial phase focuses on restoring XEDAR expression through epigenetic modulation. This approach is supported by previous studies showing successful re-expression of XEDAR in breast cancer cells following treatment with DNA demethylating agents. The restoration phase aims to re-establish the cellular machinery necessary for differentiation signaling.

Phase 2: Pathway Activation Following restoration of receptor expression, the second phase involves controlled pathway activation using synthetic ligands. This phase draws inspiration from the temporal patterns observed in developmental studies, particularly the distinct expression profiles seen in mouse models during appendage development.

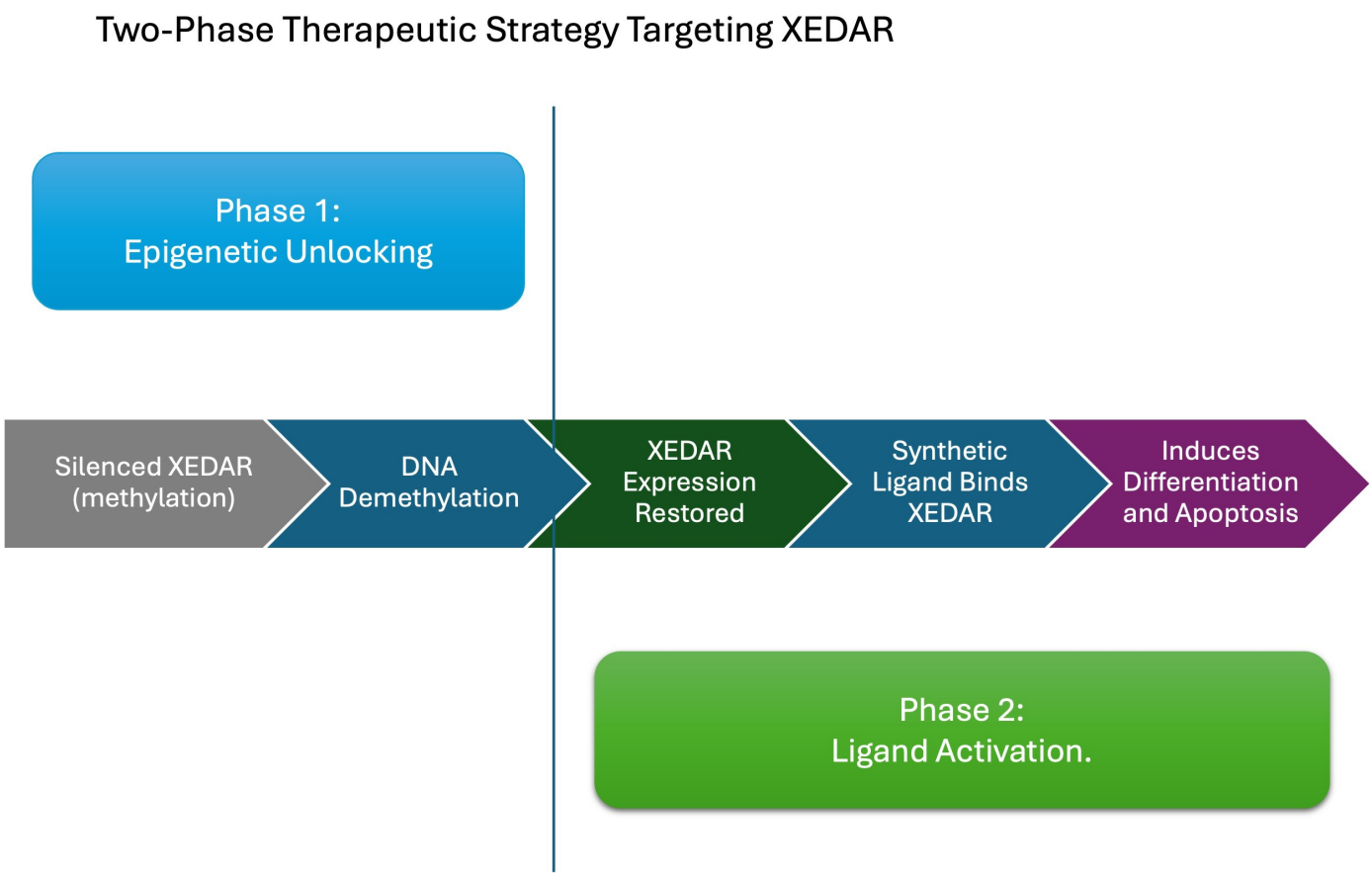

Figure 3. Diagram of the biphasic therapeutic strategy: Illustrating the process of epigenetic unblocking of XEDAR and its activation by synthetic ligands.

For Whom? - Anticipated Groups of Patients

In treating breast cancer, differentiation therapies based on the EDAR and XEDAR pathways may be of particular interest to selected groups of patients whose disease is characterized by specific molecular and clinical features. Current evidence suggests that therapies targeting these pathways could be beneficial in cases where existing treatments prove inadequate[18].

One potential target group is patients with a subtype of hormone receptor negative (ER- and PR-) breast cancer. This subtype, known as Triple Negative Breast Cancer (TNBC), is characterized by an aggressive course and limited therapeutic options, as it does not respond to standard hormonal therapies or drugs targeting the HER2 receptor[19]. The absence of hormone receptors and HER2 often goes hand in hand with other molecular abnormalities, including XEDAR silencing, making this group of patients an ideal candidate for differentiation therapy. Restoring XEDAR signaling in this group could improve control of tumor proliferation through induction of differentiation and apoptosis.

An equally promising application is the treatment of breast cancer patients exhibiting high XEDAR promoter methylation,

regardless of molecular subtype. With the increasing availability of epigenetic analysis methods, such as DNA methylation analysis in biopsy samples or circulating tumor DNA (ctDNA), it is possible to quickly and accurately identify these patients[20][21]. Incorporating such epigenetic markers into clinical practice could support selecting patients who best respond to a combination of demethylation and XEDAR-activating synthetic ligands.

Another group of potential beneficiaries is patients whose breast cancer shows resistance to standard therapies, including chemotherapy[22]. This resistance is often due to dynamic changes in tumor cells that contribute to an evasive immune or cytotoxic response. Differential therapy could work in synergy with existing treatments, lowering the rate of tumor adaptation by reducing cellular plasticity and increasing their susceptibility to other therapies.

Also, the use of EDAR/XEDAR therapy cannot be ruled out in patients with HER2+ subtypes, which, while often responding to targeted therapy (e.g., trastuzumab), in some cases exhibit escape mechanisms. Restoring differentiation in these tumors could enhance the efficacy of combination therapy by reducing tumor cell heterogeneity.

It is also worth noting that integrating differentiation biomarkers, such as XEDAR expression levels, DNA methylation levels, and NF-κB pathway activation, could enable personalized therapy[23]. This approach could tailor treatment to each patient's tumor characteristics, increasing the likelihood of therapeutic success.

In conclusion, EDAR/XEDAR-based differentiation therapy has the potential to revolutionize the treatment of specific groups of breast cancer patients. The most significant benefit can be expected in patients with aggressive or refractory cancers where other therapies have failed and in cases showing specific epigenetic abnormalities[11]. This targeted approach increases the effectiveness of treatment and opens the door to more precise and less toxic cancer therapy.

Anticipated Challenges and Proposed Solutions

Implementing differential therapy based on the EDAR and XEDAR pathways in clinical practice poses several challenges that involve technical and biological aspects and methods of monitoring treatment efficacy. Understanding and resolving these difficulties is crucial to the success of the proposed approach.

Technical challenges

The most complex technical challenge is to develop suitable synthetic ligands that activate XEDAR while maintaining high specificity and optimal pharmacological properties[24]. Based on a two-membered amino acid arrangement, the structural differences between EDAR and XEDAR receptors provide a starting point for designing such ligands. However, maintaining protein stability and bioavailability in vivo remains challenging. Developing delivery systems for these ligands to penetrate tumor tissue efficiently without adverse effects in healthy tissues is also important.

Another technical difficulty is the introduction of epigenetic inhibitors[25], such as 5-aza-2'-deoxycytidine, into the clinical breast cancer treatment protocol. While effective in restoring the expression of genes silenced by methylation, these drugs

may have nonspecific effects that affect other genes. Therefore, developing strategies for precisely delivering demethylation to target sites is necessary to minimize side effects. The use of epigenetic modulators, such as DNA demethylating agents, also introduces unique challenges. These compounds, while effective in restoring XEDAR expression, carry the risk of off-target effects, including the reactivation of unintended genes. Such effects could inadvertently promote oncogenic pathways or cause systemic toxicity, such as myelosuppression. To mitigate these risks, strategies should include the development of targeted delivery systems, such as antibody-drug conjugates, to concentrate the effects of these modulators within tumor tissues. Furthermore, dosing protocols should be carefully optimized to achieve therapeutic outcomes with minimal systemic exposure, potentially through low-dose or intermittent regimens. Treatment may trigger various systemic responses through release of damage-associated molecular patterns[26]. Preclinical studies using tumor organoids and animal models will be instrumental in evaluating these strategies and minimizing unintended consequences.

One significant challenge lies in the immunogenicity of synthetic ligands designed to activate XEDAR. These molecules, while tailored to engage specific receptors, may inadvertently trigger immune responses[27], including the production of neutralizing antibodies or hypersensitivity reactions. Such responses could reduce therapeutic efficacy or, in severe cases, lead to adverse systemic effects. To address this, future efforts should focus on designing ligands that closely mimic endogenous proteins, thereby minimizing recognition by the immune system. Preclinical evaluations, including in vitro and in vivo assessments, will play a pivotal role in identifying potential immunogenic epitopes and refining ligand structures. Additionally, the use of advanced drug delivery technologies, such as nanoparticles or liposomal carriers, could protect synthetic ligands from immune surveillance, enhancing their bioavailability while reducing the risk of immunogenicity.

Biological challenges

The biological complexities of EDAR/XEDAR signaling also present significant challenges. These pathways integrate with other systems, such as NF-κB, which have multiple functions in cancer cells, from regulating survival to controlling inflammation. Excessive activation of NF-κB can paradoxically promote tumor growth, so it is crucial to precisely monitor and modulate the activity of this pathway during therapy. Moreover, the temporal regulation of XEDAR signaling, which is important in cellular differentiation processes, requires carefully planned therapeutic regimens that include periodic administration of ligands in a manner that mimics the natural activation patterns of the receptor.

Determining how XEDAR signaling affects healthy tissues, especially those involving stem cells or with a high degree of proliferation, such as glandular epithelium or the immune system, is also a challenge. In this context, therapy must be as selective as possible, requiring precise ligand design and dosage adjustments.

Another area of concern is the potential impact of XEDAR activation on healthy tissues, particularly those with a high degree of cellular turnover, such as glandular epithelium or components of the immune system. While differentiation therapy is designed to target cancer cells, unintended activation of XEDAR in normal tissues could lead to hyperplasia or other disruptions in cellular homeostasis. Addressing this issue will require designing synthetic ligands with high specificity

for XEDAR isoforms predominantly expressed in tumor cells. Monitoring biomarkers, such as NF-κB activity or proliferation markers in healthy tissues, can also provide early indications of off-target effects, enabling timely adjustments to therapy.

Finally, the integration of EDAR/XEDAR signaling into the broader network of cellular pathways presents a complex challenge. These pathways, particularly their interactions with Wnt and Notch signaling, could yield unpredictable outcomes, potentially enhancing or antagonizing the therapeutic effects[28]. Computational modeling offers a promising avenue for exploring these interactions and optimizing therapeutic protocols. Moreover, combining differentiation therapy with existing targeted treatments should be approached with caution to avoid unintended interactions, with preclinical studies guiding the rational design of combination regimens.

Biomarkers that monitor the effectiveness of therapy

Monitoring the efficacy of differentiation therapy requires the identification of appropriate biomarkers to assess EDAR/XEDAR pathway activation and the differentiation process. XEDAR expression at the mRNA and protein levels is one of the most apparent biomarkers that can be assessed using techniques such as RT-qPCR or immunohistochemistry.

Another key biomarker is the methylation level of the XEDAR promoter, which can be monitored by analyzing circulating tumor DNA (ctDNA) in patient plasma samples[29][30]. Such noninvasive methods allow real-time tracking of response to therapy and can be used to predict treatment efficacy.

Finally, the activity of NF-κB as an effector of EDAR/XEDAR signaling could be assessed by analyzing its phosphorylation level or the expression of target genes. Combining several biomarkers into a diagnostic panel could increase monitoring precision and allow more dynamic therapy adjustment to patient response[31][32].

Proposed solutions

Many of these challenges can be solved by using a multi-step approach. For example, structural optimization of synthetic ligands could be supported by advanced computer modeling to predict ligand-receptor interactions. At the same time, the development of nanotechnology-based delivery systems could significantly improve drug specificity and efficacy.

Integrating molecular and epigenetic methods into a monitoring system could provide a dynamic picture of therapeutic response in the context of biomarkers. An example would be using microarray technology or next-generation sequencing (NGS) to simultaneously analyze gene expression, methylation levels, and the activity of key signaling pathways[33].

Despite numerous technical and biological challenges, the development of EDAR/XEDAR differentiation therapy is enabled by precise drug design technologies and advanced efficacy monitoring methods. Integrating biomarkers such as XEDAR expression levels, promoter methylation, and NF-κB activity may enable personalized treatment to enhance therapy efficacy and tolerability[34]. Thus, the proposed approach may form the foundation of modern oncology, oriented to individual patient needs.

Future Directions and Research Priorities

Differential therapy based on the EDAR and XEDAR pathways has the potential to complement existing breast cancer treatments, offering new opportunities to improve treatment efficacy. However, integration with current approaches requires careful planning to maximize clinical benefit and minimize the risk of side effects.

Use of differential therapy in combination with chemotherapy

Chemotherapy, based on compounds such as taxanes and anthracyclines, remains one of the primary pillars of breast cancer treatment. However, the development of resistance to these drugs is a significant challenge, especially in aggressive subtypes such as triple-negative breast cancer (TNBC). Differential therapy could act as a "sensitizer" for cancer cells, reducing their plasticity and restoring their sensitivity to chemotherapy. For example:

- Epigenetic restoration of XEDAR expression can alter the growth dynamics of cancer cells, forcing them to differentiate and inhibiting proliferation[35].
- Synthetic ligands that activate XEDAR could enhance the effects of chemotherapy by making cancer cells more susceptible to DNA damage.

This combination could be particularly effective in neoadjuvant therapy regimens, where the goal is to reduce tumor size before surgery[1].

Integration with hormone therapy

In patients with hormone receptor-dependent breast cancer (ER+/PR+), differentiation therapy could support hormonal treatments such as tamoxifen or aromatase inhibitors. Hormones, such as estrogen, modulate tumor cell proliferation, and activation of the XEDAR pathway could support the differentiation process while reducing the potential risk of recurrence by reducing the reserve of stem-like tumor cells[36].

Combination with targeted therapies

Targeted therapies such as trastuzumab and pertuzumab have produced breakthrough results in the treatment of HER2+ breast cancer. However, resistance to these drugs can develop because of adaptive molecular changes in tumor cells[37]. Including therapy differentiation into therapeutic regimens for HER2+ patients could counteract these adaptations by reducing tumor heterogeneity and the population of resistant cells. XEDAR activation could further enhance tumor cell differentiation by reducing their proliferation ability under unfavorable conditions.

Time synchronization of therapy

A key element in integrating differential therapy with other approaches is precise management of the timing and sequence of drug administration. For example:

- **Pre-phase**: Administration of demethylation to restore XEDAR expression before chemotherapy can increase the susceptibility of cancer cells to cytotoxicity.
- **Activation phase**: Inclusion of XEDAR-activating ligands after chemotherapy or during hormonal therapy may promote differentiation and reduce the risk of recurrence.

However, this synchronization requires detailed monitoring of biomarkers such as XEDAR expression levels or NF-κB pathway activity to tailor therapy to the dynamic tumor response.

Toxicity reduction

One of the key advantages of integrating differentiation therapies is that they can reduce the toxicity of other treatments. Differential therapies, which promote natural differentiation processes, are less taxing on the body than chemotherapy or radiation therapy. As a result, doses of cytotoxic drugs can be reduced while maintaining treatment efficacy, which is particularly important for older patients or those with comorbidities.

The integration of EDAR/XEDAR differentiation therapy with existing breast cancer treatments offers the possibility of a synergistic approach that can significantly improve treatment efficacy and tolerability[38]. By reducing tumor cell plasticity and restoring differentiation mechanisms, this therapy can support chemotherapy, hormonal therapy, and targeted therapy. However, the key aspect remains appropriate timing and sequencing, which requires advanced biomarker monitoring and optimization of therapeutic protocols. Thus, the proposed approach represents an innovation in oncology and a potential foundation for more precise and effective treatment strategies for breast cancer.

Conclusions and Future Perspectives

Differential therapy based on the EDAR and XEDAR pathways is breaking new ground in the treatment of breast cancer, shifting attention from traditional cytotoxic approaches to more subtle modulation of tumor cell fate. The concept restores natural biological processes and introduces potential innovations that could revolutionize oncology practice. The findings below focus on key aspects of the proposed therapy and its potential impact on science and the clinic.

A new therapeutic perspective

The proposed approach focuses on restoring the ability of cancer cells to differentiate by modulating EDAR and XEDAR signaling pathways[39][10][40]. This strategy is based on a solid biological basis, indicating that epigenetic silencing of XEDAR is one of the mechanisms by which breast cancer cells avoid differentiation. By combining epigenetic agents with synthetic ligands that activate the XEDAR pathway, we can create a biphasic therapy that restores key molecular functions and promotes cancer cell differentiation.

Clinical potential

The use of this therapy can be particularly effective in:

- Subtypes of breast cancer are associated with an aggressive course and resistance to therapies, such as triple-negative breast cancer (TNBC).
- Breast cancer patients with high levels of XEDAR promoter methylation can be precisely monitored by epigenetic analysis.
- Situations where current therapies, such as chemotherapy, hormonal, or targeted treatments, become insufficient due to resistance or intolerance.

Relevance to science and innovation

EDAR/XEDAR differential therapy brings several key innovations:

- **Dual mechanism of action**: The proposal includes both epigenetic unblocking and targeted receptor activation, increasing the chances of successful restoration of differentiation.
- **Temporal control of pathway activation**: The therapy is based on precise management of the timing of receptor activation, mimicking natural biological processes, which minimizes the risk of adverse effects.
- **Personalization of treatment**: Including biomarkers such as DNA methylation levels or XEDAR expression allows personalization of therapy, which increases efficacy and reduces toxicity.

Key challenges and recommendations

The development of EDAR/XEDAR differential therapy requires further research to address the following questions:

- Optimizing the structure of synthetic ligands to ensure their specificity and stability.
- Developing drug delivery strategies to precisely activate receptors in tumor tissue without disrupting the function of healthy tissues.
- Further studies on interactions between the EDAR/XEDAR pathway and other signaling pathways in cancer cells[41].

Impact on the future of breast cancer therapy

The proposed concept could not only improve treatment outcomes for patients with resistant subtypes of breast cancer but also inspire the development of similar strategies to treat other cancers. Its clinical success could also influence the development of more advanced monitoring technologies, such as real-time ctDNA sequencing, contributing to more precise therapy management.

EDAR/XEDAR differentiation therapy represents an innovative approach that harmoniously combines biological research with practical clinical applications. Its development and implementation have the potential not only to improve the treatment of breast cancer but also to usher in a new era in oncology, focusing on the biological reprogramming of cancer cells instead of destroying them. However, this requires further investment in research and development to realize the

concept's full potential. With personalization and advanced monitoring technologies, this therapy has the potential to become a milestone in cancer treatment.

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