

TITLE: The Development of Differentiation-Based Therapy for Breast Cancer Using Edar and Xedar Signaling 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 involves epigenetic restoration of XEDAR expression and synthetic ligands to activate these pathways. 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 diseases. Potential technical, biological, and clinical challenges are discussed, along with proposed solutions to overcome them.

Keywords: breast cancer, EDAR, XEDAR, differentiation therapy, epigenetics, synthetic ligands, personalized medicine, biomarkers.

INTRODUCTION

Breast cancer remains one of the most challenging malignancies despite significant advances in treatment options (Hanahan and Weinberg, 2011; Vasan et al., 2019). Although current therapies focus primarily on killing cancer cells directly, an alternative approach involves inducing malignant cell differentiation, potentially transforming aggressive cancer into a more manageable chronic disease. This concept paper explores the theoretical framework for using the Ectodysplasin A receptor (EDAR) and X-linked Ectodysplasin-A2 receptor (XEDAR) signaling pathways to develop a differentiation-based therapy for breast cancer (**Fig. 1**).

Current State of Knowledge:

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

1. The XEDAR gene functions as a tumor suppressor in breast cancer, with its expression frequently silenced by promoter methylation (Punj et al., 2010).
2. EDAR and XEDAR demonstrate different expression patterns at developmental time, suggesting their role in determining cell fate (Wisniewski, 2024).
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 (Yan et al., 2000).
4. TRAF6 is a key mediator of XEDAR signaling, linking receptor activation to downstream effects (Naito et al., 2002).

Therapeutic Need:

Despite available treatments, breast cancer often develops resistance to conventional therapies (Vasan et al., 2019), 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 EDAR / XEDAR signaling pathways be therapeutically manipulated to induce differentiation in breast cancer cells, potentially converting aggressive malignancy into a more manageable chronic disease?

Hypothesis: that dual targeting of EDAR/XEDAR pathways through:

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

It could induce differentiation in breast cancer cells, reduce malignancy, and improve 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 to monitor treatment response.
5. To anticipate and address potential challenges in implementing this therapeutic approach.

Significance:

This conceptual framework could provide the foundation for developing new differentiation-based therapies in breast cancer treatment. By focusing on cellular differentiation rather than cytotoxicity, this approach could offer a less toxic alternative or complement to existing treatments, potentially improving long-term outcomes for patients with breast cancer (Safa, 2019).

CURRENT UNDERSTANDING OF EDAR AND XEDAR SIGNALING PATHWAYS IN DEVELOPMENT AND CANCER

The EDAR and XEDAR signaling pathways have gained prominence in recent years in cancer biology (Wark et al., 2023; Kowalczyk-Quintas and Schneider, 2014; Sadier et al., 2014), 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 up to 60-70% of breast cancer samples are characterized by silencing of XEDAR due to epigenetic changes (Punj et al., 2010; Tsai and Baylin, 2011). 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 (Chang et al., 2007).

The molecular mechanism of action of the XEDAR pathway is distinguished by its remarkable precision. A key element is the specificity of the binding of the EDA-A2 ligand 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 receptors and minimizes the side effects associated with interaction with the EDAR receptor (Yan et al., 2000). XEDAR activation, in turn, is transduced into intracellular signaling pathways, such as NF- κ B, via the key mediator TRAF6 (Naito et al., 2002). The differentiation process initiated by XEDAR activation involves multiple molecular steps. Upon ligand binding, XEDAR recruits TRAF6 through its cytoplasmic domain, assembling a signaling complex. This complex triggers several downstream pathways, including NF- κ B activation of NF- κ B through phosphorylation of the

IKK complex. The role of TRAF6 in XEDAR signaling extends beyond simple adapter functions (Naito et al., 2002). Upon recruitment to the receptor complex, TRAF6 undergoes K63-linked autoubiquitination, creating a scaffold for downstream effector proteins. Additionally, TRAF6 facilitates the recruitment of TAK1 and TAB2/3 complexes (Chen and Greene, 2004).

Data from animal model studies provide further compelling evidence for the importance of temporal regulation of EDAR/XEDAR signaling (Lefebvre & Mikkola, 2014). In a mouse model, peak expression of XEDAR was observed during the early stages of follicle development, highlighting the key role of this pathway in epithelial differentiation processes (Wisniewski, 2024). In contrast, in the rat model, the expression of XEDAR remained stable, indicating important species differences in regulating this pathway – Fig. 3. These observations suggest that temporal control of XEDAR activation may be a key element in therapeutic strategies.

The EDAR and XEDAR pathways do not function in isolation but integrate with other signaling systems, further enhancing their therapeutic potential. For example, XEDAR-induced activation of NF- κ B by XEDAR is essential for differentiation and can also affect cell survival, highlighting the need to modulate this signaling precisely. The NF- κ B 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 (Biswas and Longhi, 2020). Additionally, the ability of XEDAR to induce apoptosis through caspase-8 introduces an additional dimension in controlling tumor proliferation (Tanikawa et al., 2009).

In conclusion, the study indicates a 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 is 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 cytotoxicity (Lund et al., 2020).

CONCEPTUAL FRAMEWORK FOR DIFFERENTIATION-BASED THERAPY

Theoretical basis for therapeutic intervention.

The proposed therapeutic approach builds on 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. 2.

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 the 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.

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 characteristics. Current evidence suggests that therapies targeting these pathways could be beneficial in cases where existing treatments prove inadequate (Rodon et al., 2019).

A potential target group are patients with a subtype of estrogen 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 (Andre et al., 2019). 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 who exhibit high methylation of the XEDAR promoter, regardless of the 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 (O'Leary et al., 2018; Wan et al., 2017). Incorporating such epigenetic markers into clinical practice could support selecting patients who respond best to a combination of demethylation and synthetic ligands activating XEDAR.

Another group of potential beneficiaries is patients whose breast cancer shows resistance to standard therapies, including chemotherapy (Sharma et al., 2010). 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. Furthermore, 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 the heterogeneity of tumor cells.

It is also worth noting that integrating differentiation biomarkers, such as XEDAR expression levels, DNA methylation levels, and NF- κ B pathway activation, could allow personalized therapy (Schenk and Brinkman, 2016). This approach could tailor treatment to the tumor characteristics of each patient, 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 (Tsai and Baylin, 2011). 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 (Jacobson & Müller, 2016). 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 a challenge. 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 (Stresemann and Lyko, 2008), 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, strategies for precisely delivering demethylation to target sites are necessary to minimize side effects. Using epigenetic modulators, such as DNA demethylating agents, also introduces unique challenges. Although effective in restoring XEDAR expression, these compounds carry the risk of off-target effects, including 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 developing 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 results with minimal systemic exposure, potentially through low-dose or intermittent regimens. Treatment can trigger systemic responses by releasing damage-associated molecular patterns (Krysko et al., 2011). 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. While tailored to engage specific receptors, these molecules may inadvertently trigger immune responses (Gentles et al., 2015), 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, thus minimizing recognition by the immune system. Preclinical evaluations, including *in vitro* and *in vivo* evaluations, will play a pivotal role in identifying potential immunogenic epitopes and refining ligand structures. Furthermore, using advanced drug delivery technologies, such as nanoparticles or liposomal carriers, could protect synthetic ligands from immune surveillance, enhancing their bioavailability and 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- κ B, which have multiple functions in cancer cells, from regulating survival to controlling inflammation. Excessive activation of NF- κ B 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 the glandular epithelium or the immune system, is also challenging. In this context, therapy must be as selective as possible, requiring precise ligand design and dosage adjustments.

Another concern is the potential impact of XEDAR activation on healthy tissues, particularly those with a high degree of cellular turnover, such as the glandular epithelium or immune system components. Although differentiation therapy targets cancer cells, unintended activation of XEDAR in normal tissues could lead to hyperplasia or other disruptions in cell homeostasis. Addressing this issue will require the design of synthetic ligands with high specificity for XEDAR isoforms predominantly expressed in tumor cells. Monitoring biomarkers, such as NF-

κ B activity or proliferation markers in healthy tissues, can also provide early indications of off-target effects, allowing timely adjustment to therapy.

Finally, integrating 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 produce unpredictable outcomes, potentially enhancing or antagonizing therapeutic effects (Purvis and Lahav, 2013). Computational modeling offers a promising avenue for exploring these interactions and optimizing therapeutic protocols. Furthermore, combining differentiation therapy with existing targeted treatments should be approached cautiously 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 the activation of the EDAR / XEDAR pathway 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 level of XEDAR promoter methylation, which can be monitored by analyzing circulating tumor DNA (ctDNA) in patient plasma samples (Tie and Gibbs, 2021; Dawson et al., 2015). Such noninvasive methods allow real-time tracking of response to therapy and can be used to predict treatment efficacy.

Finally, the activity of NF- κ B 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 (Best et al., 2019; Egger et al., 2004).

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 the 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 (Schwarzenbach et al., 2011).

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- κ B activity may enable personalized treatment to improve therapy efficacy and tolerability (Pollyea et al., 2017). 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 (Baylin and Jones, 2016).
- 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, which aim to reduce tumor size before surgery (Hanahan and Weinberg, 2011).

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 (Bonnet and Dick, 1997).

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 due to adaptive molecular changes in tumor cells (Dean et al., 2005). Including therapy differentiation in 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 its proliferation ability under unfavorable conditions.

Time synchronization of therapy

A key element in integrating differential therapy with other approaches is the 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- κ B pathway 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 promote natural differentiation processes and 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.

Integrating EDAR / XEDAR differentiation therapy with existing breast cancer treatments offers the possibility of a synergistic approach that can significantly improve treatment efficacy and tolerability (Kowalczyk-Quintas et al., 2015). By reducing tumor cell plasticity and restoring differentiation mechanisms, this therapy can support chemotherapy, hormonal therapy, and targeted therapy. However, the key aspect remains the appropriate timing and sequencing, which requires advanced biomarker monitoring and optimization of therapeutic protocols. Therefore, the proposed approach represents an innovation in oncology and a potential basis 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 following findings 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 cancer cells' ability to differentiate by modulating the EDAR and XEDAR signaling pathways (Lindfors et al., 2013; Sadier et al., 2014; Sadier et al., 2015). 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 in which 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:** 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 (Mikkola, 2011).

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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Figures

Fig. 1 Diagram of the EDAR / XEDAR pathway: Showing the activation mechanism of the XEDAR receptor and key points such as TRAF6 and NF- κ B.

Fig. 2 Diagram of the biphasic therapeutic strategy: Illustrating the epigenetic unblocking process of XEDAR and its activation by synthetic ligands.

Fig. 3 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 expression of mRNA obtained by RT-qPCR (based on Wisniewski 2024).