Amphiregulin (AREG)

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Amphiregulin (AREG) is a **transmembrane glycoprotein** and a member of the **epidermal growth factor (EGF) family**. It functions primarily as a **ligand for the epidermal growth factor receptor (EGFR)**.

General Characteristics

- **Protein type:** Transmembrane, EGF-like growth factor
- **Gene:** AREG (Chromosome 4q13.3)
- **Activation:** Cleaved by metalloproteases (e.g., ADAM17) to release soluble form
- **Receptor binding:** Binds EGFR (ErbB1/HER1)

Biological Functions

- Promotes **cell proliferation**, **survival**, and **migration**
- Involved in **organ development** (lung, mammary gland)
- Key role in **wound healing** and **epithelial regeneration**
- Modulates **immune responses** and **inflammation**

Role in Cancer

AREG is frequently upregulated in various cancers and is associated with:

- Tumor growth and progression
- Metastasis induction
- Resistance to **EGFR-targeted therapies**
- **Immunosuppressive tumor microenvironment**

Key Finding (Nature, 2025)

- **Reference:** Nature, 2025 May 14. Piffkó et al.

[1)]

- **Title:** Radiation-induced amphiregulin drives tumour metastasis
- **Main result:** Radiotherapy induces AREG expression in tumor cells, which activates EGFR on myeloid cells → **immunosuppression** and **reduced phagocytosis**, facilitating **distant metastasis**.
- **Therapeutic implication:** Combining radiotherapy with **AREG/EGFR inhibitor** may improve metastatic control.

Signaling Pathways

- **EGFR → RAS/RAF/MEK/ERK** → Proliferation
- **EGFR → PI3K/AKT/mTOR** → Survival
- **EGFR → JAK/STAT** → Immune modulation

Clinical Relevance

- **Biomarker** for aggressiveness and therapy resistance
- **Target** for combination therapy with radiotherapy
- May guide **patient stratification** for EGFR blockade

Background

Radiotherapy (RT) is a key modality in cancer treatment, traditionally associated with local tumor control and systemic immune activation (e.g., the **abscopal effect**). However, the **pro-metastatic potential** of RT is underexplored.

This study identifies **amphiregulin (AREG)** as a critical factor induced by RT that **promotes distant metastasis** by reprogramming **EGFR-positive myeloid cells** into an **immunosuppressive phenotype**.

Key Findings

- RT induces expression of **AREG** in tumor cells.
- AREG acts on **EGFR-expressing myeloid cells**, inhibiting phagocytosis.
- This **reprogramming suppresses immune surveillance** and supports **distant metastatic**

outgrowth.
- Inhibition of AREG or EGFR reduces metastasis in preclinical models.

Strengths

- **Mechanistic insight**: RT → AREG → EGFR+ myeloid cells → immunosuppression → metastasis.
- **Multimodal design**: Combines in vitro, in vivo, and clinical observations.
- **Translational relevance**: Suggests therapeutic potential of **AREG or EGFR blockade** post-RT.
- **Paradigm shift**: Challenges the assumption that RT is solely antitumoral.

Limitations

- **Tumor heterogeneity not addressed**: Unclear whether the mechanism is universal across tumor types.
- **Simplified immunological view**: Focuses on myeloid cells; limited analysis of T-cell responses.
- **Lacks clinical trial data**: Proposes interventions not yet validated in humans.
- **Short-term perspective**: No data on long-term effects of AREG inhibition (e.g., on wound healing).
- **Potential oversimplification**: Other radiation-induced cytokines may also contribute to metastasis.

Clinical Implications

- Reframes RT as a **double-edged sword**: antitumoral locally, potentially **protumoral systemically**.
- Encourages exploration of **RT + anti-EGFR/anti-AREG combinations**.
- Reinforces the importance of **immune monitoring** during radiotherapy.

Conclusion

This study presents robust evidence that **RT can promote metastasis via radiation-induced AREG**, which suppresses innate immunity. It introduces a compelling mechanism with **therapeutic and conceptual implications**, though **further clinical validation is needed**.

Related Topics

- Amphiregulin (AREG)
- EGFR Pathway
- Immune Evasion
- Radiotherapy
- Combination Therapy

1)

Piffkó A, Yang K, Panda A, Heide J, Tesak K, Wen C, Zawieracz K, Wang L, Naccasha EZ, Bugno J, Fu Y, Chen D, Donle L, Lengyel E, Tilley DG, Mack M, Rock RS, Chmura SJ, Vokes EE, He C, Pitroda SP, Liang

HL, Weichselbaum RR. Radiation-induced amphiregulin drives tumour metastasis. Nature. 2025 May 14. doi: 10.1038/s41586-025-08994-0. Epub ahead of print. PMID: 40369065.