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The increasing role of amphiregulin in non-small cell lung cancer
Le rôle grandissant de l'amphiréguline dans le cancer du poumon non-à petites cellules

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Abstract

Non-small cell lung cancers present a 5-year survival rate below 12%. Such a poor prognosis may be explained by non small cell lung cancer cells evasion to apoptosis and resistance to treatments. Amphiregulin, an epidermal growth factor-related growth factor is secreted by non-small cell lung cancer cells in an autocrine/paracrine manner to promote autonomous growth of tumor cells and to provide resistance to apoptosis. Furthermore, amphiregulin is involved in non-small cell lung cancers resistance to epidermal growth factor receptor targeted therapy. This editorial underlines the increasing role of amphiregulin in non-small cell lung cancer cells resistance mechanisms and suggests the use of amphiregulin as a marker for drug sensitivity and/or as a prognostic marker to identify patients that may respond to epidermal growth factor receptor-tyrosine kinase inhibitors.

Résumé

Les cancers bronchiques non-à petites cellules présentent une survie à 5 ans inférieure à 12%. Un tel pronostic s'explique par la capacité des cellules cancéreuses pulmonaires à échapper à l'apoptose et à résister aux traitements. L'amphiréguline est un facteur de croissance de la famille de l'Epidermal Growth Factor (EGF) sécrété par les cellules de cancer bronchique de façon autocrine/paracrine, afin de permettre une croissance tumorale autonome et la survie cellulaire. De plus, l'amphiréguline est impliquée dans la résistance du cancer bronchique non-à petites cellules aux inhibiteurs de la tyrosine kinase du récepteur de l'EGF. Cet éditorial met en évidence le rôle de plus en plus important de l'amphiréguline dans les cancers bronchiques non-à petites cellules, et son implication dans les mécanismes de résistance à l'apoptose et aux traitements. Ceci suggère une utilisation potentielle de l'amphiréguline comme marqueur de sensibilité au traitement et/ou comme marqueur pronostique dans les cancers bronchiques non-à petites cellules afin d'identifier les patients susceptibles de répondre à un traitement à base d'inhibiteurs de tyrosine kinase du récepteur à l'EGF.

Keywords : amphiregulin; non-small cell lung cancer; gefitinib; growth factor; apoptosis; drug resistance; EGFR, targeted therapy; tyrosine-kinase inhibitors

Mots clés : amphiréguline; cancer bronchique non-à petites cellules; gefitinib; facteur de croissance; apoptose; résistance aux traitements; EGFR; thérapie ciblée, inhibiteurs de tyrosine kinase

Amphiregulin (AREG) is an 84-aminoacid glycoprotein discovered in the late 80's by M. Shoyab *et al*. AREG was originally isolated from the conditioned medium of phorbol 12-myristate 13-acetate (PMA)-stimulated MCF-7 human breast carcinoma cell line. The human AREG gene (GeneID 374) is located on the q13-q21 region of chromosome 4, and is composed of 6 exons encoding the preprotein mRNA transcript. AREG is thus synthesized as a 252-amino acid transmembrane precursor, named pro-AREG. Pro-AREG is subjected to sequential proteolytic cleavage at the plasma membrane within the ectodomain that leads to realeased N-glycosylated soluble AREG forms. This shedding is essentially mediated by tumor-necrosis factor-alpha converting enzyme (TACE), a member of the disintegrin and metalloproteinase (ADAM) family also known as ADAM-17.

The AREG gene expression profile indicates that AREG is constitutively expressed in various tissues, mainly in the genito-urinary and reproductive systems, as well as in the gastrointestinal tract, but also in bone marrow, liver and in the respiratory tract.

AREG is a member of the Epidermal Growth Factor (EGF) family of proteins, which include EGF itself, transforming growth factor alpha, heparin-binding EGF-like growth factor, betacellulin, and neuregulin. AREG binds to and activates the EGF receptor (EGFR or ErbB1) through autocrine, paracrine and juxtacrine mechanisms. The EGFR is widely expressed on epithelial cell membranes. The binding of AREG to EGFR induces autophosphorylation of the EGFR intracellular tyrosine kinase domain, which in turn activates two major intracellular pathways, i.e. the MEK/ERK1/2 and the PI3K/AKT pathways. EGFR is for instance involved in cell proliferation and

differentiation, cell metabolism, cell migration and survival, as well as in the control of cell cycle. Furthermore, the EGFR was the first tyrosine-kinase receptor to be directly linked to several human tumors. AREG possesses a mitogenic activity for cells and plays a role in several biological processes including nerve generation, bone formation, mammary duct formation, as well as the outgrowth and branching of several tissues such as lung, kidney and prostate. AREG is also expressed in several cancers, inducing cellular responses such as growth, proliferation, migration or invasiveness after the activation of EGFR.

Lung cancer is the leading cause of cancer mortality in the world, both in males and females. Non-Small Cell Lung Cancer (NSCLC) accounts for 80% of lung cancers. Once diagnosed, NSCLC 5-year survival rate hardly reaches 12% despite different treatments such as chemotherapy, radiotherapy, and surgery. Such a poor prognosis is partially explained by NSCLC ability to resist apoptosis and treatments. In this editorial, we report the roles of AREG in such resistance mechanisms leading to NSCLC progression.

1. Implication of AREG in NSCLC apoptosis resistance

The ability to evade apoptosis is a hallmark of almost all types of cancers. Cancer cells can acquire resistance to apoptosis through a variety of strategies, including the inactivation of the well-known protein p53. Another way to circumvent programmed cell death is to transmit antiapoptotic survival signals, essentially through autonomous production of growth factors by the tumor. Cancer cells produce growth factors that

can be secreted, thus binding to cell surface receptors and stimulating their own growth and apoptosis resistance in an autocrine manner. The autocrine roles of EGF-like growth factors in lung cancer pathogenesis and in apoptosis resistance have been extensively studied. The involvement of AREG in autocrine loops of activation is well described in several human malignancies and AREG antiapoptotic activity is already demonstrated in breast, lung and hepatocarcinomas. In NSCLC, AREG presence is correlated with tumor size, illustrating its functional activity as a growth factor enhancing cell proliferation. AREG is also an indicator of reduced overall survival for NSCLC, suggesting an interesting role as a prognostic marker [1]. AREG, in collaboration with Insulin-like Growth Factor Type-1 (IGF-1), inhibits serum deprivation-induced apoptosis in NSCLC cell lines [2]. AREG is able to activate the IGF1-receptor independently of its own EGF receptor. IGF1-receptor activation is in turn inducing the secretion of AREG and IGF1 in an autocrine loop. The combination of AREG and IGF1 and the subsequent receptor activation stimulate an original protein kinase C-dependant MAPK and PI3K-independant pathway that leads to NSCLC apoptosis resistance [3].

2. Implication of AREG in NSCLC resistance to treatment

Since autocrine-stimulated mitogenesis and apoptosis resistance contribute significantly to cancer progression, clinical development of anticancer treatments interrupting autocrine loops are under evaluation. In lung cancer, the use of EGFR-tyrosine kinase inhibitors (EGFR-TKI) such as gefitinib and erlotinib can block such autocrine EGFR activation is to use. Gefitinib showed potent anti-tumor effects in

clinical trials for NSCLC treatment after previous chemotherapy, but failed to improve overall survival benefit in an unselected population. Predictive markers of EGFR-TKI sensitivity have thus been investigated to identify patients likely to benefit from such a targeted therapy.

As a matter of fact, AREG is involved in NSCLC resistance to EGFR-TKI. Gefitinib responders and non-responders present a differential expression of AREG gene in biopsy samples obtained from gefitinib-treated NSCLC patients. These data are confirmed by RT-PCR, immunohistochemistry, and serologic ELISA assays : AREG is indeed significantly overexpressed in gefitinib non-responders but undetectable in responders. Moreover, NSCLC patients with the worst prognosis and a shorter survival time present high levels of seric AREG, which is correlated with gefitinib resistance [4]. This subset of gefitinib non responders patients contains principally males, smokers with non-adenocarcinomas NSCLC. Interestingly, independent studies showed that most of gefitinib sensitive patients are principally females, non-smokers with NSCLC adenocarcinomas [5], and with EGFR mutations.

Altogether these data suggest that seric AREG might be an important predictor of gefitinib resistance among advanced NSCLC patients. In other malignancies, AREG is also responsible of resistance to conventional chemotherapeutic drug, such as cisplatin, and to hormonal antitumor treatments such as exemestane, an oral steroidal aromatase inhibitor.

Conclusion

The implication of EGF-related growth factors in cancer progression is indisputable. AREG is already involved in various malignancies and we reported several oncogenic roles for AREG in NSCLC progression. AREG is secreted by tumor cells in an autocrine/paracrine manner, leading to present AREG as a prognostic marker in NSCLC. Furthermore, AREG allows resistance to apoptosis in NSCLC. Anti-AREG antibodies restored an apoptotic activity in NSCLC cells [2], suggesting that AREG might be an interesting target to overcome apoptosis resistance. In addition, AREG is involved in therapeutic resistance in breast cancer and NSCLC, thus suggesting the interest of AREG as a biological marker of sensitivity to both conventional and EGFR-targeted therapy. The use of AREG as a biomarker should be encouraged since AREG is correlated with a poor prognosis, resistance to treatments and to apoptosis.

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