Brief communication

Presumptive implications of epidermal growth factors in inflammation

Implicaciones presumibles del factor de crecimiento epidérmico en la inflamación

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ABSTRACT

Epidermal Growth Factor is a protein of only 53 amino acids, with considerable thermodynamic stability, provided by its three disulfide bridges. It has structural homology with a wide series of growth factors, distinguishing its typical motif from this family of proteins. The known function of this molecule is closely related to the heterodimerization of Epidermal growth factor receptor and its activation with implications in cell metabolism and cell division. Although the role of Epidermal growth factor receptor is well documented in the inflammatory context, information regarding the participation of its ligand is scarce. Evidence suggests that this molecule could be a promising marker of inflammation. A better understanding of the role of Epidermal Growth Factor in inflammation opens new therapeutic opportunities in the Cuban scenario based on the positioning of CIMAvax-EGF, a serum Epidermal Growth Factor depletion therapy with consolidated safety.

Keywords: serum biomarkers/inflammation; epidermal growth factor; CIMAvax - EGF.

RESUMEN

El Factor de Crecimiento Epidérmico es una proteína de apenas 53 aminoácidos, con una considerable estabilidad termodinámica, proporcionada por sus tres puentes disulfuro. Tiene homología estructural con una amplia serie de factores de crecimiento, distinguiendo su motivo típico de esta familia de proteínas. La función conocida de esta molécula está

estrechamente relacionada con la heterodimerización del receptor del factor de crecimiento epidérmico y su activación con implicaciones en el metabolismo celular y la división celular. Aunque el papel del receptor del factor de crecimiento epidérmico está bien documentado en el contexto inflamatorio, la información sobre la participación de su ligando es escasa. La evidencia sugiere que esta molécula podría ser un marcador prometedor de inflamación. Una mejor comprensión del papel del Factor de Crecimiento Epidérmico en la inflamación abre nuevas oportunidades terapéuticas en el escenario cubano a partir del posicionamiento de CIMAvax-EGF, una terapia de agotamiento del Factor de Crecimiento Epidérmico sérico con seguridad consolidada.

Palabras clave: biomarcadores séricos/inflamación; factor de crecimiento epidérmico; CIMAvax - EGF.

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Introduction

Epidermal Growth Factor (EGF)is a polypeptide of 53 amino acids with a molecular weight of 6045 Dalton (Da), proteolytically derived from the transmembrane proteinprepro - EGFof about 1207 aa encoded on the long arm of chromosome four (4q25).[1]

Discovered and characterized by Stanley Cohen;[2] and studied in subsequent years, with approaches to its role in the physiology of growth, with special emphasis on its role as a mediator of growth. During the early stages of its study, when only the murine polypeptide had been characterized, the structural homologue in humans was known as Urogastrone,polypeptide with antigastric secretory activity isolated from human urine.[3]

The human EGF gene is approximately (approx.) 110 kilobase pairs and has 24 exons, where several domains of the EGF precursor are encoded by individual exons and in addition 15 of the 24 exons encode protein segments that are homologous to sequences in other proteins, such as transferrin and LDL receptors respectively.[4],[5] However, the highest degree of

homology is shared with transforming growth factor (TGF)-α, amphiregulin (AREG) and epiregulin (EREG).

Signaling through EGFR is involved in the regulation of multiple biological processes, including cell proliferation, metabolism, differentiation, and survival,[6] where downstream intracellular signaling through the EGFR-activating protein kinase pathway mitogenesis (MAPK) they are crucial,[7] and constitute links between the processes of growth, inflammation and damage repair. However, the information available regarding the role beyond EGFR homodimerization is limited, as well as the estimation of the value of its serum concentrations both as a biomarker of inflammation or predictors of evolution or therapeutic response, depending on the context, therefore which we intend to argue based on the available evidence, the presumed implications of epidermal growth factor in inflammation.

Development

In the context of the biological response against external noxas, inflammation plays a crucial role. The basic function of this non-specific response mechanism of our immune system is to defend ourselves, contain aggression and thereby allow a return to homeostasis. A sustained inflammatory response over time is a potential health risk.[8]

Beyond the classic considerations regarding the clinical inflammatory response, inflammation is essentially a molecular process with endothelial dysfunction, which may not always be clinically evident. For its effective monitoring, inflammatory biomarkers are crucial tools.[8]

Classically, certain cell populations, proteins and molecules have been very useful in identifying the inflammatory status. The discovery and positioning of new inflammatory biomarkers is a growing area of knowledge applied to clinical practice.[8]

It has been observed that, in the inflammatory environment, EGFR is overexpressed, with a direct relationship to the presence of TNF-a, interleukin 1 (IL-1) and interleukin 6 (IL-6),[9],[10] the latter associated with the development of severe/critical forms of multiple diseases where inflammation is the critical pathophysiological basis. The activation of EGFR itself stimulates the positive regulation of pro-inflammatory cytokines.[11]

Intertwining inflammation with pulmonary fibrosis, a critical cell in its progression is fibroblasts. Myofibroblastic transformation is a crucial process in aberrant tissue remodeling,[9] classic in the etiopathogenesis of interstitial lung disease, such as idiopathic fibrosis, but it also constitutes a mechanism for generating resistance in many tumors, including lung tumors. Another point of confluence is also the association between myofibroblast activity and tumor necrosis factor α (TNF-α). TNF-α has been shown to lead to a striking increase in EGFR expression on the cell surface of myofibroblasts; In this context, studies reflect that the subsequent binding of EGF to EGFR is associated with greater tyrosine kinase activity of EGFR, with prolonged activation of ERK and a significant increase in the expression of cyclooxygenase-2 (COX-2), this It kills a very important enzyme in the production of inflammatory mediators, making this a dangerous positive feedback loop.[12]

Recent studies in the context of COVID-19 have reported positive correlates between the plasma concentration of EGF and several cytokines, particularly with classic pro-inflammatory cytokines such as IL-1β, IL-8, MIP-1a (CCL3), as well as cytokines associated with Th2 (IL-4, IL-5 and IL-13) and Th17 (IL-17A, IL-17F, IL-17E / IL-25 and IL-22) polarization. Plasma levels of EGF are reported to positively correlate with both CRP levels (r>0.5) and lung injury due to pneumonia characterized by computed tomography (CT) (r>0.4) and to a lesser extent but notably with platelet concentration (r>0.3), which in turn were significantly related to important inflammatory cells and cytokines, highlighting the positive correlates with monocytes and neutrophils (r>0.6) and to a lesser extent with lymphocytes, similar to the correlate of EGF with CRP; a negative correlation with IL-10 concentrations is notable.[13]

In a proteomics study that explored the relationship of certain molecules and their contribution to the severity of the disease, comparatively with sepsis and influenza as an alternative model of pneumoinflammation, on a nodal network analysis model, a relationship between values of Higher serum EGF in patients with severe COVID-19; although the differences were in the shared circulating proteomic response, specific differences involved the EGF values.[14]

The plausible relationship that this evidence provides on the potential of EGF as a biomarker of inflammation is of great academic interest, taking into account that in relation to the action of disintegrin and metalloprotease 17 (ADAM17), which is responsible for proteolytically

cleaving both TNFα , both TNF receptors, ligands for EGFR and the interleukin-6 receptor; taken into account in the particular case of the latter the relevance in the modulation of the signaling pathway mediated by IL-6R, since the generation of the soluble interleukin-6 receptor (sIL-6R) is necessary for trans signaling, which It has been identified as critical in the pro-inflammatory activity of this cytokine. In contrast, interleukin-6 signaling through the membrane-bound interleukin-6 receptor is primarily regenerative and protective. Despite this dual role, ADAM17 is essential for life and most of the few human individuals identified with ADAM17 genetic defects died at a young age.[15]

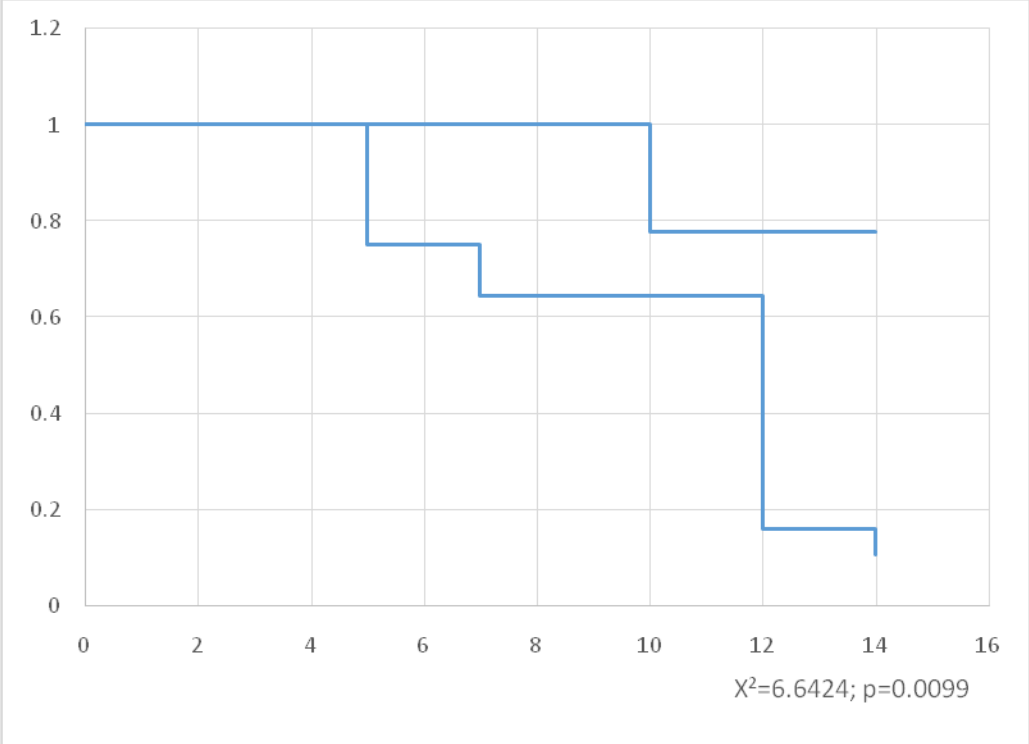
Among the few studies published regarding serum EGF concentrations, Jorge Monserrat and collaborators approach them in a referential manner, focusing their study on the first five critical days of admission to the hospital for patients who survived and non-survivors, observing that patients who survived COVID-19 show higher circulating levels of some growth factors associated with tissue repair, including EGF, as well as that these levels are higher than those observed in healthy controls, as well as that higher levels of growth factors, among They, EGF, had a significant predictive value for a good prognosis in patients with severe COVID-19, with EGF being premised on one of the most notable in the group of growth factors with an area under the ROC curve = 0.642, only behind, and without large differences in sVEGFR1, using values > 169.49 ng/ml as estimation criteria. The approach to the results was generally superficial, without particularizing details regarding the variability with respect to other parameters, despite being collected, as stated in the method.[16]

Among the preliminary results observed within the framework of the sector project: Role of the Epidermal Growth Factor in the etiopathogenesis and pathophysiology of inflammatory lung disease in the context of the SARSCoV-2 pandemic. (PS24SC1223), a notable case to point out is the complex implications of the interpretation of serum EGF levels in the context of COVID-19. Expanding Bayestheorem, based on the observations reported in the literature as well as the analysis of the behavior of the disease in the study's starting population, which supported the assumptions regarding: The probability of finding healthy subjects with high EGF (200 pg/mL) is approx. 98.9 %, with a probability of finding subjects with high EGF (200 pg/mL) is approx. 80 %, and the probability of developing severe COVID-19 is 20 %; These probabilities allowed us to wait a posteriori. The probability of finding seriously ill

patients with low EGF (200 pg/mL) is approx. 28 %. However, what was observed was that 78.94 % of severe COVID-19 had low EGF.

The analysis of the survival function based on the Kaplan-Meyer statistic reflected something contradictory with this observation; although differences were evident between the curves based on the value of serum EGF levels, it was in patients with high EGF that 71.42 % of deaths, while only 28.57 % of patients with low EGF progressed to a fatal outcome, as seen in figure 1

Fig. 1 Kaplan Meyer curve, severe COVID-19, based on serum EGF values



Source: Database

These observations, in principle clearly counterintuitive, partly reveal the depth of the theoretical problem in relation to the interpretation of the significance of serum EGF values in the context of the health-disease process in general, and inflammation in particular. In this sense, the results of Dülger and collaborators help us make sense of it, since in their study of the expression of EGFR in lung tissue affected by inflammation, of deceased patients with COVID-19, significantly higher levels were observed in 38 % of the deceased. higher protein

expression, in contrast to those observed in the remaining 62 % with mild or absent expression.[17]

In the Cuban context, there is extensive and documented evidence of the therapeutic effects, based on a solid safety profile, with the use of the CIMAvax-EGF therapeutic vaccine, accumulated in the more than 20 years since the first preclinical studies, which supports the ability of this immunogen to induce a humoral immune response against autologous Epidermal Growth Factor (EGF), with the consequent inhibition of the activation of its canonical receptor: the epidermal growth factor receptor (EGFR).[18],[19]

During the SARS-CoV-2 pandemic, in mid-June 2021, the clinical study: "Safety and effect of CIMAvax-EGF® in convalescents from SARS-CoV-2 infection with respiratory disorders / CORVAXCIM" (RPCEC00000375);[20] in the CIMAvax-EGF center, an innovative Cuban medicine, registered in 2008 (B-08-063-L03) by the Center for State Control of Medicines, Equipment and Medical Devices.

The main clinical site during the first year of execution of the study was the Saturnino Lora Provincial Hospital, with a consolidated track record in clinical research led by renowned doctors, highlighting the particular one of Dr. Soraida Cándida Acosta Brooks, who became authority on the matter on its own merit.[21]

The preliminary clinical results, based on the data generated at the Saturnino Lora Provincial Hospital, showed a solid safety profile, in the first intervention in humans without oncological pathologies reported to date with the product.

The clinical regression of all post-COVID-19 symptoms characterized all treated patients, where the clinical and spirometric benefit observed was correlated, with a recovery of forced vital capacity values in more than 60 % of those treated with an increase greater than 10 %, doubling the value that is considered clinically significant by consensus, with the presence of neutralizing antibody titers and serum castration of EGF values.

The promising preliminary results observed may contribute to the collection of essential biomedical data for carrying out subsequent studies, which could contribute to the development of sovereign therapeutic strategies, where the relationship between EGF-inflammation is a novel and promising target.

Conclusions

Epidermal growth factor could be a promising biomarker of inflammation, with implications beyond the heterodimerization of its receptor, with a plausible potential as a predictor of evolution and/or therapeutic response, despite which new studies are demanded in the framework of the health-disease process for an accurate understanding of its implications in the context of inflammation.

Bibliographic references

1. Carpenter G. Receptors for epidermal growth factor and other polypeptide mitogens. Annu Rev Biochem [Internet]. 1987 [cited 2023 Nov 30];56(1):881-914. Available from: https://pubmed.ncbi.nlm.nih.gov/3039909/

2. Shakhakarmi K, Seo JE, Lamichhane S, Thapa C, Lee S. EGF, a veteran of wound healing: highlights on its mode of action, clinical applications with focus on wound treatment, and recent drug delivery strategies. Arch Pharm Res [Internet]. 2023 [cited 2023 Nov 30];46(4):299-322. Available from: https://pubmed.ncbi.nlm.nih.gov/36928481/

3. Gray A, Dull TJ, Ullrich A. Nucleotide sequence of epidermal growth factor cDNA predicts a 128,000-molecular weight protein precursor. Nature [Internet]. 1983 [cited 2023 Nov 30];303(5919):722-5. Available from: https://pubmed.ncbi.nlm.nih.gov/6304537/

4. Bell GI, Fong NM, Stempien MM, Wormsted MA, Caput D, Ku L, et al. Human epidermal growth factor precursor: cDNA sequence, expression in vitro and gene organization. Nucleic Acids Res [Internet]. 1986 [cited 2023 Nov 30];14(21):8427-46. Available from: https://pubmed.ncbi.nlm.nih.gov/3491360/

5. Scott J, Patterson S, Rall L, Bell GI, Crawford R, Penschow J, et al. The structure and biosynthesis of epidermal growth factor precursor. J Cell Sci [Internet]. 1985 [cited 2023 Nov 30];1985(Supplement_3):19-28. Available from: https://pubmed.ncbi.nlm.nih.gov/3011823/

6. Venkataraman T, Frieman MB. The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis. Antiviral Res [Internet]. 2017 [cited 2023 Nov 30];143:142-50. Available from: http://dx.doi.org/10.1016/j.antiviral.2017.03.022

7. Roskoski R Jr. Small molecule inhibitors targeting the EGFR/ErbB family of protein-tyrosine kinases in human cancers. Pharmacol Res [Internet]. 2019 [cited 2023 Nov 30];139:395-411. Available from: https://pubmed.ncbi.nlm.nih.gov/30500458/

8. Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology. 10aed. Madrid: Elsevier; 2021.

9. Yoo J, Perez CER, Nie W, Edwards RA, Sinnett-Smith J, Rozengurt E. TNF-α induces upregulation of EGFR expression and signaling in human colonic myofibroblasts. Am J Physiol Gastrointest Liver Physiol [Internet]. 2012 [cited 2023 Nov 30];302(8):G805-14. Available from: https://pubmed.ncbi.nlm.nih.gov/22301110/

10. Yoo J, Rodriguez Perez CE, Nie W, Sinnett-Smith J, Rozengurt E. TNF-α and LPA promote synergistic expression of COX-2 in human colonic myofibroblasts: role of LPA-mediated transactivation of upregulated EGFR. BMC Gastroenterol [Internet]. 2013 [cited 2023 Nov 30];13(1). Available from: https://pubmed.ncbi.nlm.nih.gov/23688423/

11. Zhuang S, Liu N. EGFR signaling in renal fibrosis. Kidney Int Suppl (2011) [Internet]. 2014 [cited 2023 Nov 30];4(1):70-4. Available from: https://pubmed.ncbi.nlm.nih.gov/26312153/

12. Upagupta C, Shimbori C, Alsilmi R, Kolb M. Matrix abnormalities in pulmonary fibrosis. Eur Respir Rev [Internet]. 2018 [cited 2023 Nov 30];27(148):180033. Available from: https://pubmed.ncbi.nlm.nih.gov/29950306/

13. Kalinina O, Golovkin A, Zaikova E, Aquino A, Bezrukikh V, Melnik O, et al. Cytokine storm signature in patients with moderate and severe COVID-19. Int J Mol Sci [Internet]. 2022 [cited 2023 Nov 30];23(16):8879. Available from: https://pubmed.ncbi.nlm.nih.gov/36012146/

14. Ahern DJ, Ai Z, Ainsworth M, Allan C, Allcock A, Angus B, et al. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. Cell [Internet]. 2022 [cited 2023 Nov 30];185(5):916-938.e58. Available from: https://pubmed.ncbi.nlm.nih.gov/35216673/

15. Schumacher N, Rose-John S. ADAM17 orchestrates Interleukin-6, TNFα and EGF-R signaling in inflammation and cancer. Biochim Biophys Acta Mol Cell Res [Internet]. 2022 [cited 2023 Nov 30];1869(1):119141. Available from: https://pubmed.ncbi.nlm.nih.gov/34610348/

16. Monserrat J, Gómez-Lahoz A, Ortega M, Sanz J, Muñoz B, Arévalo-Serrano J, et al. Role of innate and adaptive cytokines in the survival of COVID-19 patients. Int J Mol Sci [Internet].

2022 [cited 2023 Nov 30];23(18):10344. Available from: https://pubmed.ncbi.nlm.nih.gov/36142255/

17. Dülger SU, Mutlu N, Ceylan İ, Özhan E. The relationship between lung fibrosis, the epidermal growth factor receptor, and disease outcomes in COVID-19 pneumonia: a postmortem evaluation. Clin Exp Med [Internet]. 2022;23(4):1181-8. Available from: http://dx.doi.org/10.1007/s10238-022-00872-7

18. Popa X, García B, Fuentes KP, Huerta V, Alvarez K, Viada CE, et al. Anti-EGF antibodies as surrogate biomarkers of clinical efficacy in stage IIIB/IV non-small-cell lung cancer patients treated with an optimized CIMAvax-EGF vaccination schedule. Oncoimmunology [Internet]. 2020 [cited 2023 Nov 30];9(1). Available from: https://pubmed.ncbi.nlm.nih.gov/32923124/

19. Crombet Ramos T, Santos Morales O, Dy GK, León Monzón K, Lage Dávila A. The position of EGF deprivation in the management of advanced non-small cell lung cancer. Front Oncol [Internet]. 2021 [cited 2023 Nov 30];11. Available from: https://pubmed.ncbi.nlm.nih.gov/34211836/

20. RPCEC [Internet]. Havana: Work Team of the Cuban Public Registry of Clinical Trials, National Coordinating Center for Clinical Trials - MINSAP. CIMAvax-EGF®-convalescents with post-COVID-19 respiratory disorders-adults-Phase II (CORVAXCIM); 2021 Dec 06 [cited 2021 Dec 13]; [7 screens]. Available from: https://www.rpcec.sld.cu/ensayos/RPCEC00000375-Sp

21. Crombet Ramos T, Ramos Susarte M & Lage Dávila A. Center for Molecular Immunology. Historical aspects of the clinical development of CIMAvax-EGF. Havana: Directorate of Clinical Research; 2023.23 p.

Interest conflict

The author declares that he has no conflict of interest