BASIC BIOMEDICAL SCIENCES
ORIGINAL ARTICLE

Reno-protective and reno-restorative effect of the Epidermal Growth Factor in the biomodel of Chronic Renal Failure

Efecto reno-protector y reno-reparador del Factor de Crecimiento Epidérmico en biomodelo de Insuficiencia Renal Crónica

Carlos Rafael Núñez Cairo

Universidad de Ciencias Médicas de La Habana. La Habana, Cuba.

How to cite this paper:
Núñez Cairo CR. Reno-protective and reno-restorative effect of the Epidermal Growth Factor in the biomodel of Chronic Renal Failure. Rev haban cienc méd [Internet]. [Cited];16(7):[1032-1043]. Available from: http://www.revhabanera.sld.cu/index.php/rhab/article/view/2333

Received: Novembre 14, 2016.
Approved: December 5, 2016.

This paper is a translation to English of its original version, available on:
http://www.revhabanera.sld.cu/index.php/rhab/article/view/1681/1542

ABSTRACT

Introduction: Kidney disease is a health problem worldwide. Epidermal Growth Factor acts as cytoprotector, and trophic restorative.

Objective: To evaluate the reno-protective and reno-restorative effect of the Epidermal Growth Factor in the biomodel of Chronic Renal Failure.

Material and Methods: 120 Wistar rats were studied in 6 groups: Negative and Positive Control, Saline Solution Single-Dose and Multiple-Dose, Epidermal Growth Factor Single-Dose and Multiple-Dose. A single dose was applied before the damage for the reno-protective effect, and multiple doses were applied after the damage for the reno-restorative effect,at a weight ratio of 100 µg/kg.

Results: Creatinine, urea, and uric acid diminished significantly in the experimental groups, with a higher decrease for experimental group with single dose; therefore, the reno-protective effect was higher than the reno-

restorative one for the treatment patterns used.
Conclusions: Epidermal Growth Factor showed reno-protective and reno-restorative effect by diminishing the hematological variables of kidney damage.

Keywords: Epidermal Growth Factor, reno-protective, reno-restorative, Chronic Renal Insufficiency, 5/6 renal ablation.

RESUMEN

Introducción: La Enfermedad Renal es un problema de salud mundial. El Factor de Crecimiento Epidérmico actúa como citoprotector y trófico reparador.
Objetivo: Evaluar el efecto reno-protector y reno-reparador del Factor de Crecimiento Epidérmico en biomodelo de Insuficiencia Renal Crónica.
Material y Métodos: Se estudiaron 120 ratas, Wistar, en 6 grupos: Control Negativo y positivo, Solución Salina Dosis Única y Múltiple, Factor de Crecimiento Epidérmico Dosis Única y Múltiple. Se aplicó para efecto reno-protector dosis única antes del daño, y para la reno-reparador dosis múltiple posterior al daño, a razón de 100 µg/kg de peso.
Resultados: La creatinina, urea y ácido úrico disminuyeron significativamente en los grupos experimentales, con mayor disminución para el grupo experimental dosis única, por lo que el efecto reno-protector fue mayor que el reno-reparador para los esquemas de tratamiento utilizados.
Conclusiones: El Factor de Crecimiento Epidérmico mostró efecto reno-protector y reno-reparador al disminuir las variables hematológicas de daño renal.

Palabras claves: Factor de Crecimiento Epidérmico, reno-protector, reno-reparador, Insuficiencia Renal Crónica, 5/6 ablación renal.

INTRODUCTION

Kidney Disease is the morphological and/or functional alteration of the kidney for more than 3 months, with implications for health. It has become a global health problem, both for its strictly sanitary implications, and for the implications of economic and social nature.[1]

Currently, Chronic Kidney Disease affects more than 50 million people worldwide; more than one million of all these patients stay with renal replacement therapy, and more than 250,000 new patients initiate these treatments every year.[1,2]

Chronic Renal Failure is characterized by a slow and progressive decrease in the glomerular filtration, which entails a variable affectation of the kidney function.[2]

At present, a great number of research studies are aimed at looking into factors or agents that slow the progression of the disease,[3-8] the so-called reno-protective or reno-restoratives; although the international scientific community state that, due to their great level of impact, they are the appropriate control of Arterial Hypertension and Diabetes Mellitus, as the principal risk factors.[9-11]

Among the agents to which a cytoprotective, and trophic restorative actions have been described we can find the Epidermal Growth Factor (EGF),

mitogenic polypeptide, motogenic and inducer of cell differentiation, which was described for the first time by Stanley Cohen and Rita Levi-Montalcini in 1959.[12-14]

The cytoprotective action appears very quickly, even after a single dose and the trophic restorative one appears with repeated administrations of the product and in a more or less prolonged way.[13,15-18]

The Center for Genetic Engineering and Biotechnology (CIGB) of Cuba produces recombinant human EGF since 1988, as a mixture of isoforms of 51 and 52 amino acids, being our country one of the pioneers in obtaining this protein by the application of genetic engineering techniques. This is the highest purity EGF of those that are marketed in injectable form.[12,14,15,19,20]

Many research studies have been carried out in this field all over the world,[21-26] and Cuba has not been exempt from it. The Laboratory of Kidney Physiology of "Victoria de Girón" Institute of Basic and Pre-clinical Sciences has been closely linked to the group of researchers of the CIGB for the evaluation of EGF since the very beginning. It developed a study to evaluate the antioxidant defense capacity in a model of ischemia / bilateral renal reperfusion, which prevented the morphological and functional deterioration of renal tissue.28 Other studies in which the product was evaluated in different models of acute and chronic kidney damage in the early stages were developed.[28-29]

Few articles about the evaluation of EGF in models of Chronic Renal Failure are reported in the world.[30-33] Since there are no EGF evaluation studies in models of Chronic Renal Failure in advanced stages in Cuba, we determined to work on a model developed in the laboratory by ablation technique of 5/6 renal mass. The tissue adhesive (Tisaucryl) was used.[34] It is a national product used as sealant of the cut surface, with results expressed by the variables of renal function as a model of 3-4 degree of insufficiency.

OBJECTIVE

This research is aimed at evaluating the reno-protective and reno-restorative effect of the Recombinant Human Epidermal Growth Factor (hEGF) in a biomodel of Chronic Renal Failure in rats.

MATERIAL AND METHODS

A longitudinal prospective experimental study was conducted in 120 non-isogenic young male and femaleadultWistar rats, of 11 weeks, with a weight range between 200 and 250 grams, and a variation smaller than 15 grams in each group. The animals came from the National Center for Laboratory Animals Production (CENPALAB).

The ethical norms for the handling of laboratory animals were fulfilled during the experimental test. These norms were established by the national pre-project for the protection of animals.

These animals were distributed in 3 work series (A, B and C), each one with 40 animals, formed by 2 groups: a control group and an experimental one of 20 animals, with a 1: 1 sex ratio.

A Series was composed of all the animals of the Control group in the evaluation. It included a negative control group or a 56-day control C-(C56) that underwent laparotomy by

midabdominal incision, whose renal vasculonervous packages were dissected. There was also and a positive control group or Tisuacryl of 56 days C + (T56), to which a biomodel of Chronic Renal Insufficiency with 5/6 ablation of the renal mass was applied, using the national product Tisuacryl tissue adhesive as sealant of the cut surfaces.

B Series was formed by the groups selected for the evaluation of the reno-protective effect of EGF with a Single Dose of Saline Solution (SS-SD) control group and a Single Dose of EGF (EGF- SD) group, to which a single dose before provoking kidney damage by biomodel of Chronic Renal Insufficiency were given.

C series: The C Series was formed by the groups selected for the evaluation of the reno-restorative effect of EGF with a group Multiple Dose of Saline Solution SS-MD and a group Multiple Doses of EGF (EGF-MD), which were caused kidney damage and lately, 3 weekly doses were subsequently administered for 8 weeks.

The Saline Solution groups were administered isotonic Saline Solution (0.9% Sodium Chloride), in the same volume as the one calculated for the administration of EGF. The EGF groups were administered this product at a dose of 100 µg / kg of weight diluted in 1 mL of physiological saline solution in each of the applied doses.

All the animals underwent an evolution of 56 days of experimental period and, at the end of the experimental test, blood sample was taken by cardiac puncture.

The determined variables were creatinine, urea and uric acid in plasma. The respective tests of HELFA DIAGNÓSTICOS ® Quimefa Epb. "Carlos J. Finlay", Cuba wereused for the determination of these substances in serum and plasma by enzymatic method.[35]

The statistical processing of the results was carried out in a database made in the GraphPad Prism 5, a program developed by GraphPad Software for Winodws.

The variables were determined by means of the mean, standard deviation, standard error, coefficient of variation and confidence interval for 95%, expressed in their lower and upper limits.

The Kolmogorov-Smirnov test was used for the testing of normality, whereas Bartlett's test was used as the variance homogeneity test. When the normal behavior and homogeneity of variances were demonstrated, the parametric test single classification analysis of variance (ANOVA) was applied (one way); Tukey´s HSD multiple comparison test was carried out, and the significant results were considered for a $p < 0.05$.

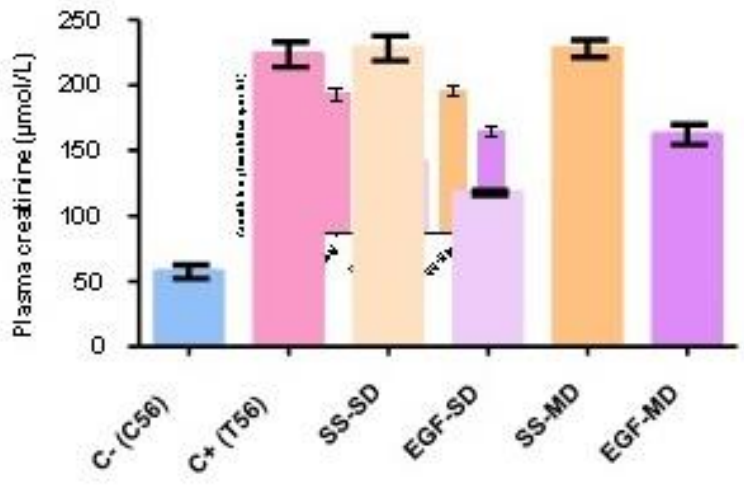
RESULTADOS

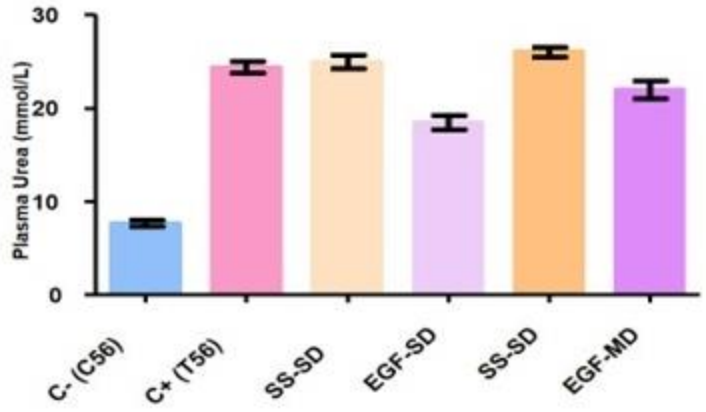
The results of the concentrations of the variables determined in plasma, creatinine, urea and uric acid were expressed in the working groups, with their mean plus minus standard error. The p value for each variable was expressed when performing the single classification analysis of variance (ANOVA). The differences among the groups were very significant ($p<0.05$) in all cases. (Table).

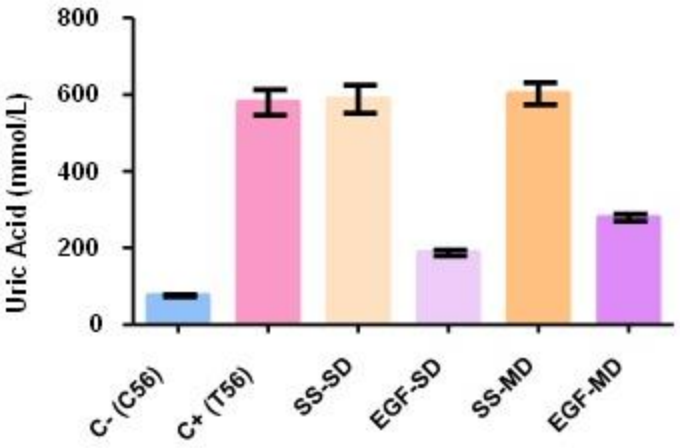
Table. Variables of plasma concentrations in the different work groups

Groups	Plasma creatinine (µmol/L)	Plasma Urea (mmol/L)	Uric Acid (mmol/L)
C- (C56)	57,28 ± 5,292	7,665 ± 0,3191	75,45 ± 2,675
C+ (T56)	223,5 ± 9,566	24,40 ± 0,5708	580,3 ± 33,49
SS-SD	228,1 ± 9,577	24,93 ± 0,7154	588,5 ± 36,38
EGF- SD	117,6 ± 1,700	18,47 ± 0,7624	187,3 ± 7,902
SS-MD	227,8 ± 6,685	26,02 ± 0,5238	603,0 ± 28,17
EGF-MD	162,1 ± 7,547	21,97 ± 0,9134	279,6 ± 9,037
P	< 0.01	< 0.01	< 0.01

The results of the concentrations of creatinine, urea and uric acid in plasma were represented in the different work groups, with a similar behavior in the three variables. The values increased significantly when comparing the negative control group with the rest of the groups. There were no significant differences when comparing the positive control group with the groups of saline solution (SS-SD and SS-MD), results expected for being groups to which the solvent of the product was administered. There were significant differences when comparing the positive control with the EGF-SD and EGF-MD groups, which showed a decrease in the variables, thus evidencing the reno-protective and reno-reparative effect of EGF. (Figure).







When comparing the EGF-SD and EGF-MD groups, the variables behaved differently. The values of creatinine and urea in plasma were lower with the single dose scheme, differences that were significant, and allowed to affirm that the reno-protective effect was greater than the reno-restorative effect of EGF for the treatments used. These differences were not significant for the uric acid variable because the decrease shown by both groups was similar, which allowed affirming that both effects were analogous for this variable. (Figure).

It is noted that in Tukey's test for multiple comparison for the variable on plasma urea levels, the differences between the EGF-MD and the positive control groups (T56) were not significant, demonstrating that the decrease in these values did not differ from the positive control group and confirming that the reno-restorative effect is not substantial for this variable.

DISCUSSION

In the literature that refers to the models of kidney damage, the 5/6 nephrectomy is, undoubtedly, the most widespread and accepted.36-38 It is characterized by slow glomerulosclerosis, vascular sclerosis, tubulo-interstitial fibrosis and inflammation of the kidney; features that resemble the human disease. The methods of obtaining this technique in animal models make their results and analogies vary with the disease in humans.[39]

The pathophysiology of renal fibrosis has not been fully elucidated yet, but we can say that it is characterized by glomerulosclerosis and / or tubulo-interstitial fibrosis; which is believed to be due to the proliferation of renal cells together with defective restoration and interstitial fibroblasts activation and the extracellular matrix (ECM).[40]

The study of the reno-protective action of EGF has been studied in depth, especially in models of acute tubular necrosis by chemical compounds, aminoglycosides or mercurial substances, and in different models of ischemia reperfusion.[26,41-43] The effects of the attenuation of cell damage and cell resistance to acute renal injury on patients have been corroborated, mainly for the division of indigenous cells.[43] The critical role of the EGF receptor in epidermal cells in the restoration of acute kidney damage and the management of electrolytes has been expressed.[32]

In Cuba, this reno-protective effect of EGF was evaluated in the work of Sánchez I,[29] who, before causing acute damage with the use of Kanamycin, he administered a single dose of the product at 100µg and concluded that EGF prevented kidney damage in the rats.[30] It is important to highlight that this was a work in a model of acute toxic nephropathy using an aminoglycoside. This work was developed in a chronic model by surgical ablation technique of 5/6 renal mass, with a 3-4 degree of insufficiency,[34] as compared to the current classification, as a result of a drop in glomerular filtration rate. The reno-protective evaluation was performed by single dose and equal concentration of the product.

The evaluation of the trophic-restorative effect in the kidney or the reno-restorative effect of the EGF has been less studied. There are discrepancies among the works found in the literature.[3,4,6,41,42] To achieve a reno-restoration there should be an structural and functional reconstruction of the tubular epithelium, although it is known that growth factors are important in the restoration of kidney tubules.26 In Cuba, the work of Taboada D was developed.[28] He studied the effect of EGF in an ablation model of 5/6 of the renal mass using the gelaspon as a sealant of the cut surface, in initial stages of Chronic Renal Insufficiency. The author stated these stages because the creatinine concentrations in the model showed a slight increase within normal limits with slight significance and the variables effective renal plasma flow and glomerular filtration rate did not show statistical significance. Besides, the author concluded on the effect of EGF that this did not show significant changes with the treatment scheme used. This would be recognized as the first evaluation work on the trophic restorative effect of EGF in Cuba, but would fail to demonstrate the beneficial effects of the product.

In contrast, in this study as in the Taboada study, the ablation model was studied by 5/6 of the

renal mass and with the same dose of the product, after renal damage, but with a treatment scheme of 3 doses tests per week that extended to 8 weeks, which could explain the beneficial results found.

The EGF evaluations in chronic damage models are much less frequent in the literature[44,45], with discrepancies in their effectiveness.

Numerous studies demonstrate the growth factors actions, and especially the activation of EGF and its receptor in the initiation and progression of chronic kidney diseases such as diabetic nephropathy, polycystic kidney disease and obstructive nephropathy, by dysregulation through the promotion of renal cell proliferation, fibrosis and inflammation.[31] These studies involve the activation of fibroblasts of the renal interstitium, tubular and glomerular atrophy, achievement and overproduction of inflammatory factors and / or the production of vascular injury.[26,43 46]

We also found works where there were no differences in renal function for week 6 between rats treated with EGF or placebo, with regard to urea, inulin, proteinuria and renal morphometry.[32,40] However, it showed significant differences in attenuation to the rise in systolic blood pressure, the clearance of free water and the total excretion of sodium and potassium solutes. Daily doses of 19.1 µg were used for 3 or 6 weeks of treatment in these studies, a different scheme in terms of much lower doses and less prolonged than those used in this study.[32,40,4]

In addition, we collected some works where the restorative effect of EGF was demonstrated, which propose a regulation by the production of exosomes and their regulation by the EGF receptor.[26,32]

The reno-protective effect is demonstrated in this work. It is the first study of the reno-restorative effect of the EFG Cuban recombinant human in a model of Chronic Renal Insufficiency degree 3-4, by surgical ablation technique of 5/6 renal mass, with the use of the Tisuacryl as sealant of the cut surfaces in rats.

The reno-protective effect is greater than the reno-restorative one but there is no total protection or repair of the renal cells, which is evidenced by the decrease in the index variables of kidney damage. In addition, since EGF is a mitogenic and motogenic stimulator, special care must be taken during parenteral administration and especially in the future extrapolation of the results in humans.

CONCLUSIONS

Recombinant Human Epidermal Growth Factor (hEGF)showed a reno-protective and reno-restorative effect in a biomodel of Chronic Renal Insufficiency in rats, by decreasing the hematological variables of kidney damage, creatinine, urea and plasma uric acid.

REFERENCES

1. Martínez-Castelao A, Górriz JL, Bover J, Segura-de la Morena J, Cebollada J, Escalada J, et al. Documento de consenso para la detección y manejo de la enfermedad renal crónica. Aten

Primaria [Internet]. 2014[Cited: 2017 Apr 15]; 46(9):501-519.

2. Ávila-Zaldívar MN, Conchillos-Olivares G, Rojas-
Báez IC, Ordóñez-Cruz AE, Ramírez-Flores HJ. Enfermedad renal crónica: causa y prevalencia en la población del Hospital General La Perla. Med Interna México [Internet]. 2013[Cited: 2017 Apr 15];473-478.

3. Abdel-Azeem AS, Hegazy AM, Zeidan HM, Ibrahim KS, El-Sayed EM. Potential Renoprotective Effects of Rosemary and Thyme Against Gentamicin Toxicity in Rats. J Diet Suppl [Internet]. 2017[Cited: 2017 Jul 4];14(4):380-94.

4. Liu P, Feng Y, Dong D, Liu X, Chen Y, Wang Y, et al. Enhanced renoprotective effect of IGF-1 modified human umbilical cord-derived mesenchymal stem cells on gentamicin-induced acute kidney injury. Sci Rep[Internet]. 2016 [Cited: 2017 Feb 2];6:20287.

5. Kujal P, Čertíková Chábová V, Škaroupková P, Husková Z, Vernerová Z, Kramer HJ, et al. Inhibition of soluble epoxide hydrolase is renoprotective in 5/6 nephrectomized Ren-2 transgenic hypertensive rats. Clin Exp Pharmacol Physiol[Internet]. 2014[Cited: 2017 Mar 4];41(3):227-37.

6. Matsuo T, Miyata Y, Sagara Y, Higami Y, Tobu S, Matsuo M, et al. Renoprotective effects of telmisartan after unilateral renal ablation in rats. Int J Nephrol Renov Dis[Internet]. 2013 [Cited: 2017 Oct 10];6:207-14.

7. Song J, Li S, Meng L, Qu L, Li X. [Renoprotective effects of Astragalus and Angelica mixture in rats with 5/6 nephrectomy]. Beijing Da Xue Xue Bao[Internet]. 2009 [Cited: 2017 Apr 18];41(2):196-202.

8. Kohzuki M, Yasujima M, Kanazawa M, Yoshida K, Sato T, Abe K. Do kinins mediate cardioprotective and renoprotective effects of cilazapril in spontaneously hypertensive rats with renal ablation? Clin Exp Pharmacol Physiol Suppl[Internet]. 1995[Cited: 2016 Dec 15];22(1):S357-9.

9. Sociedad Española de Nefrología. Acción estratégica de la Sociedad española de Nefrología frente a la Enfermedad Renal Crónica. [Internet]. [Cited 2017 Apr 20]. Available from: http://www.revistanefrologia.com/es-publicacion-suplementosextra-imprimir-articulo-accion-estrategica-de-la-sociedad-espaola-de-nefrologa-frente-a-X0211699506019142

10. Bohlouli B, Jackson TJ, Tonelli M, Hemmelgarn B, Klarenbach S. Adverse Outcomes Associated with Preventable Complications in Hospitalized Patients with CKD. Clin J Am Soc Nephrol CJASN[Internet]. 2017 [Cited: 2017 May 8];12(5):799-806.

11. Quiroz Y, Ferrebuz A, Vaziri ND, Rodríguez-Iturbe B. Effect of chronic antioxidant therapy with superoxide dismutase-mimetic drug, tempol, on progression of renal disease in rats with renal mass reduction. Nephron Exp Nephrol[Internet]. 2009[Cited: 2017 Sept 15];112(1):e31-42.

12. Berlanga-Acosta J, Fernández-Montequín J, Valdés-Pérez C, Savigne-Gutiérrez W, Mendoza-Marí Y, García-Ojalvo A, et al. Diabetic Foot Ulcers and Epidermal Growth Factor: Revisiting the Local Delivery Route for a Successful Outcome. BioMed Res Int[Internet]. 2017[Cited: 2017 Aug 21];1-10.

13. Hardwicke J, Schmaljohann D, Boyce D, Thomas D. Epidermal Growth Factor Therapy and Wound Healing - Past, Present and Future Perspectives. Surg Edinb Univ Press[Internet].

2008 [Cited: 2017 Jun 15];6(3):172-7.
14. López Mola E. Heberprot-P®: una idea convertida en producto. Biotecnol Apl[Internet]. 2012 [Cited: 2017 Oct 12];29(4):358-61.
15. Berlanga J, Fernández JI, López E, López PA, del Río A, Valenzuela C, et al. Heberprot-P: a novel product for treating advanced diabetic foot ulcer. MEDICC [Internet]. 2013[Cited: 2017 Jan 25];15(1):11-5.
16. Berlanga-Acosta J, Gavilondo-Cowley J, López-Saura P, González-López T, Castro-Santana MD, López-Mola E, et al. Epidermal growth factor in clinical practice - a review of its biological actions, clinical indications and safety implications. Int Wound J[Internet]. 2009 [Cited: 2017 Oct 28];6(5):331-46.
17. Ertugrul BM, Buke C, Ersoy OS, Ay B, Demirez DS, Savk O. Intralesional epidermal growth factor for diabetic foot wounds: the first cases in Turkey. Diabet Foot Ankle[Internet]. 2015 [Cited: 2017 Aug 11];6:28419-28419.
18. Escobar-Pérez X, Lahera-Sánchez T, Blanco-Santana D, Calvo-Pérez A, Álvarez-Goyanes RI, de Armas-Fernández MC, et al. Implementación de la técnica de micromatrices de tejidos para la investigación oncológica en Cuba. (Spanish). Implement Tissue Microarrays Tech Cancer Res Cuba Engl[Internet]. 2015[Cited: 2017 Jan 15];24(1):45-51.
19. González G, Lage A, Crombet T, Rodríguez G, García B, Cuevas A, et al. CIMAvax-EGF: A novel therapeutic vaccine for advanced lung cancer. Biotecnol Apl[Internet]. 2009 [Cited: 2017 Oct 15];26(4):345-8.
20. Raíces M. II International congress addressed to the integral care of diabetic foot ulcer patient with the use of Heberprot-P 2012: healthy doorways wide-open to the 2014 edition. II Ed Congr Int Sobre Aten Integral Al Paciente Con Úlceras Pie Diabét Con El Uso Hebeprot-P 2012 Puertas Sanas Abiertas Ed 2014. 2013 [Cited: 2017 Jan 25];30(1):63-4.
21. Santiago T, Clay MR, Azzato E, Newman S, Fernández-Pineda I, Nichols KE, et al. Clear cell sarcoma of kidney involving a horseshoe kidney and harboring EGFR internal tandem duplication. Pediatr Blood Cancer[Internet]. 2017 [Cited: 2017 Oct 4];64(11).
22. Traxl A, Komposch K, Glitzner E, Wanek T, Mairinger S, Langer O, et al. Hepatocyte-Specific Deletion of EGFR in Mice Reduces Hepatic Abcg2 Transport Activity Measured by [(11)C]erlotinib and Positron Emission Tomography. Drug Metab Dispos Biol Fate Chem[Internet]. 2017 [Cited: 2017 Oct 10];45(10):1093-100.
23. Xu MJ, Johnson DE, Grandis JR. EGFR-targeted therapies in the post-genomic era. Cancer Metastasis[Internet]. 2017 [Cited: 2017 Sept 2].
24. Blute ML Jr, Kucherov V, Rushmer TJ, Damodaran S, Shi F, Abel EJ, et al. Reduced estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m2) at first transurethral resection of bladder tumour is a significant predictor of subsequent recurrence and progression. BJU Int[Internet]. 2017 [Cited: 2017 Sept 10];120(3):387-93.
25. Chen R, Jin G, McIntyre TM. The soluble protease ADAMDEC1 released from activated platelets hydrolyzes platelet membrane pro-epidermal growth factor (EGF) to active high-molecular-weight EGF. J Biol Chem[Internet]. 2017 [Cited: 2017 Jun 16];292(24):10112-22.
26. Zhou X, Zhang W, Yao Q, Zhang H, Dong G, Zhang M, et al. Exosome production and its regulation of EGFR during wound healing in renal tubular cells. Am J Physiol Renal Physiol[Internet].

2017 [Cited: 2017 Jun 1];312(6):F963-70.
27. Caballero M, Calunga J, Barber E, Cruz E, López-Saura P, Boix E. Epidermal Growth Factor-mediated Prevention of Renal Ischemia/Reperfusion Injury. Biotecnol Apl[Internet]. 2000[Cited: 2017 Sept 15];17:161-5.
28. Bencomo DT, Brito S del R, González TM. Efecto del Factor de crecimiento epidérmico humano recombinante en estadios iniciales de insuficiencia renal crónica experimental. Resumen. Rev Haban Cienc Méd [Internet]. 2005;4(5). [Cited: 2017 Sept 30]. Available from: http://www.revhabanera.sld.cu/index.php/rhab/article/view/841
29. Sánchez Pérez I, Navarro Fernández R. Efecto protector del factor de crecimiento epidérmico ante la nefritis tóxica causada por kanamicina. Rev Cuba Investig Bioméd[Internet]. 2007 [Cited: 2017 Jun 17];26(2):0-0.
30. Chang J-W, Tsai H-L, Chen C-W, Yang H-W, Yang A-H, Yang L-Y, et al. Conditioned mesenchymal stem cells attenuate progression of chronic kidney disease through inhibition of epithelial-to-mesenchymal transition and immune modulation. J Cell Mol Med[Internet]. 2012 [Cited: 2016 Dec 15];16(12):2935-49.
31. Cozzolino M, Lu Y, Sato T, Yang J, Suárez IG, Brancaccio D, et al. A critical role for enhanced TGF-alpha and EGFR expression in the initiation of parathyroid hyperplasia in experimental kidney disease. Am J Physiol Renal Physiol[Internet]. 2005[Cited: 2017 Sept 15];289(5):F1096-102.
32. Harskamp LR, Gansevoort RT, van Goor H, Meijer E. The epidermal growth factor receptor pathway in chronic kidney diseases. Nat Rev Nephrol [Internet]. 2016 [Cited: 2017 Aug 10];12(8):496-506.
33. Ju W, Nair V, Smith S, Zhu L, Shedden K, Song PXK, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Sci Transl Med[Internet]. 2015[Cited: 2016 Dec 2];7(316):316ra193-316ra193.
34. Carlos Rafael Núñez Cairo. Biomodelo de insuficiencia renal crónica con el uso del tisuacryl en ratas. Rev Haban Cienc Méd[Internet]. 2012[Cited: 2017 Sept 15];11:593-604.
35. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and moleculas diagnostics. Fourth Edition. WB Saunders Co: Philadelphia; 2006[Cited: 2017 Mar 15]; 419-422 p.
36. Fedorova LV, Tamirisa A, Kennedy DJ, Haller ST, Budnyy G, Shapiro JI, et al. Mitochondrial impairment in the five-sixth nephrectomy model of chronic renal failure: proteomic approach. BMC Nephrol[Internet]. 2013 [Cited: 2017 Oct 4];14:209-209.
37. Fujihara CK, Kowala MC, Breyer MD, Sena CR, Rodrigues MV, Arias SCA, et al. A Novel Aldosterone Antagonist Limits Renal Injury in 5/6 Nephrectomy. Sci Rep[Internet]. 2017 [Cited: 2017 Ago 11];7(1):7899-7899.
38. Sedláková L, Čertíková Chábová V, Doleželová Š, Škaroupková P, Kopkan L, Husková Z, et al. Renin-angiotensin system blockade alone or combined with ETA receptor blockade: effects on the course of chronic kidney disease in 5/6 nephrectomized Ren-2 transgenic hypertensive rats. Clin Exp Hypertens N Y N 1993. 2017[Cited: 2017 Apr 16];39(2):183-95.
39. Liu N, He S, Tolbert E, Gong R, Bayliss G, Zhuang S. Suramin alleviates glomerular injury and inflammation in the remnant kidney. Plos

One[Internet]. 2012[Cited: 2017 Sept 15];7(4):e36194-e36194.
40. Liu F, Zhuang S. Role of Receptor Tyrosine Kinase Signaling in Renal Fibrosis. Int J Mol Sci[Internet]. 2016 [Cited: 2017 Sept 15]Jun 20;17(5).
41. Blunt LW Jr, Matsumura J, Carter MF, González CM, Smith ND. Repair of superior mesenteric artery ligation during left nephrectomy with a native renal vein patch. Urology[Internet]. 2004[Cited: 2017 Aug 18];64(2):377-8.
42. Rodríguez Salgueiro S, González Núñez L, García Del Barco Herrera D, Santos Febles E, Maza Ares D, Millares López R, et al. Role of epidermal growth factor and growth hormone-releasing peptide-6 in acceleration of renal tissue repair after kanamycin overdosing in rats. Iran J Kidney Dis[Internet]. 2014 [Cited: 2017 Sept 8];8(5):382-8.
43. Yen T-H, Alison MR, Goodlad RA, Otto WR, Jeffery R, Cook HT, et al. Epidermal growth factor attenuates tubular necrosis following mercuric chloride damage by regeneration of indigenous, not bone marrow-derived cells. J Cell Mol Med[Internet]. 2015[Cited: 2017 Feb 12];19(2):463-73.
44. Hotchkiss H, Chu TT, Hancock WW, Schröppel B, Kretzler M, Schmid H, et al. Differential expression of profibrotic and growth factors in chronic allograft nephropathy. Transplantation [Internet]. 2006 [Cited: 2017 Feb 15];81(3):342-9.
45. Viau A, El Karoui K, Laouari D, Burtin M, Nguyen C, Mori K, et al. Lipocalin 2 is essential for chronic kidney disease progression in mice and humans. J Clin Invest[Internet]. 2010 [Cited: 2017 Sept 18];120(11):4065-76.
46. Tang J, Liu N, Zhuang S. Role of epidermal growth factor receptor in acute and chronic kidney injury. Kidney Int[Internet]. 2013 [Cited: 2017 May 8];83(5):804-10.

Carlos Rafael Núñez Cairo. Universidad de Ciencias Médicas de La Habana. La Habana, Cuba.
E-mail: crn@infomed.sld.cu