Peripheral nerve injuries are common and lead to loss of functions such as sensation or mobility of the extremities, as well as pain. These injuries may cause permanent disabilities, negatively impacting quality of life. Peripheral nerve surgery has evolved significantly in recent decades. Nowadays a wide spectrum of reconstructive techniques is available: nerve grafts, nerve transfers, tendon transfers, functional free muscle transfer, in addition to the combination with myoelectric orthesis and prostheses. However, there are still several factors that limit reconstructive options: muscle degeneration after a nerve injury, axonal regeneration speed or sequelae and limitation of using donor's nerves are three challenges to be investigated in the future of this field. To face these challenges at the biological level and combine them with current surgical strategies, we believe that collaboration between basic and clinical research is essential.

MODULACIÓN TERAPÉUTICA DE LA PRODUCCIÓN ENDÓGENA DE KLOTHO PARA RETRASAR EL ENVEJECIMIENTO BIOLÓGICO DE LA ENFERMEDAD RENAL

THERAPEUTIC MODULATION OF ENDOGENOUS KIDNEY KLOTHO EXPRESSION TO DELAY BIOLOGICAL AGING IN CHRONIC KIDNEY DISEASE

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Resumen: La enfermedad renal crónica es la causa de muerte que más rápidamente está aumentando a nivel mundial y se convertirá en la quinta causa de muerte en 2040. Además, la enfermedad renal crónica es el factor de riesgo más prevalente y que más aumenta el riesgo de Covid-19 letal. El fenotipo de la enfermedad renal crónica se ha asimilado al de un envejecimiento biológico acelerado. La mejor comprensión de los mecanismos que median el envejecimiento acelerado puede ayudar a diseñar nuevos tratamientos que aumenten la supervivencia de los enfermos renales.

Klotho es una proteína originada en los túbulos renales que tiene propiedades antienvejecimiento, antiinflamatorias y antifibróticas. En la evolución de la enfermedad renal crónica, la producción de Klotho es la primera función renal que se pierde, antes de que disminuya el filtrado glomerular. Puesto que cuando se pierde la producción de Klotho, la estructura tubular es esencialmente normal, hay que postular que hay mediadores que disminuyen la producción de Klotho en células tubulares que todavía tendrían la capacidad de expresar Klotho. En los últimos años nuestro laboratorio ha investigado los mediadores que regulan la producción de Klotho durante el daño renal. Tanto la albuminuria, que suele ser el marcador más temprano de enfermedad renal crónica, como la inflamación local disminuyen la producción de Klotho por células tubulares renales. En concreto, citoquinas como TNF o TWEAK disminuyen la producción tubular de Klotho de una forma dependiente de NFκB y de mecanismos epigenéticos como la acetilación de histonas. Además, diversas proteínas reguladoras de NFκB modulan el impacto de este factor de transcripción sobre la producción renal de Klotho. Así por ejemplo Bcl3 aumenta la producción tubular de Klotho. Con vistas a una traslación clínica, hemos comprobado que el inhibidor inespecífico de la fosfodiesterasa, Pentoxifilina, conserva la producción de Klotho en células tubulares expuestas a albuminuria. Estos datos pueden ayudar a diseñar tratamientos para la enfermedad renal y para el envejecimiento biológico basados en el aumento de producción de Klotho endógeno.

PAPEL NEFROPROTECTOR DE CD74 EN LA ENFERMEDAD RENAL CRÓNICA

PROTECTIVE ROLE OF CD74 IN THE PATHOGENESIS OF CHRONIC KIDNEY DISEASE

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Introduction: Chronic kidney disease is one of the fastest growing causes of death worldwide, pointing to the need to develop novel therapeutic approaches. CD74 (invariant MHC class II) is a non-polymorphic type II transmembrane glycoprotein that regulates protein trafficking and is a receptor of macrophage migration factor and D-dopachrome tautomerase. CD74 has been implicated in inflammatory conditions. However, the role of CD74 in kidney has not yet been characterized. We explored the expression and function for CD74 in chronic kidney disease.

Methods: The function of CD74 was explored in unilateral ureteral obstruction and adenine-induced chronic kidney disease in wild-type and CD74-deficint mice. Western blotting, immunohistochemistry and qRT-PCR were used to study the distribution and expression of fibrosis markers in kidney tissue.

Results: CD74 expression was low in healthy murine and human kidney tubular epithelium and

its expression increased in human and murine kidney fibrosis. Genetic CD74 deficiency resulted in upregulation in RNA and protein levels of fibrosis markers α-SMA, collagen, fibronectin, and downregulation of the nephroprotective gene Klotho, and in more a severe chronic kidney disease than inwild type mice.

Conclusion: Our study provides evidence that CD74 has a nephroprotective role in kidney fibrosis in chromic kidney disease.

GDF15 PRESERVES KLOTHO EXPRESSION IN ACUTE KIDNEY INJURY AND KIDNEY FIBROSIS

GDF15 MANTIENE LA EXPRESIÓN DE KLOTHO EN LA INSUFICIENCIA RENAL AGUDA Y LA FIBROSIS RENAL

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Growth differentiation factor-15 (GDF15) is a member of the GDF subfamily with potential nephroprotective functions. We have now explored the role of GDF15 in the regulation of the expression of the nephroprotective factor Klotho in acute kidney injury (AKI) and kidney fibrosis in mice. GDF15 was the most upregulated GDF family gene in experimental nephrotoxic AKI and in kidney fibrosis transcriptomics. The function of GDF15 was explored in nephrotoxic AKI in genetically modified mice and following the exogenous administration of recombinant GDF15. *Gdf15*-deficient mice developed more severe AKI induced by either folic acid or cisplatin while GDF15 overexpressing mice were protected and recombinant human GDF15 administration protected from folate-induced AKI. Kidney expression of Klotho was more severely depressed in *Gdf15* deficient mice and was preserved by GDF15 overexpression or rhGDF15 treatment. Kidney fibrosis induced by unilateral ureteral obstruction was also more severe in *Gdf15*-deficient mice while constitutive *GDF15* overexpression decreased kidney injury and preserved Klotho expression. In tubular cells cultured in an inflammatory milieu, GDF15 preserved Klotho expression.

In conclusion, a spontaneous increased kidney expression of endogenous GDF15 is not enough to prevent kidney injury, but further increments in GDF15 are nephroprotective and preserve the kidney expression of the nephroprotective factor Klotho in acute and chronic settings.