EXTRACELLULAR MATRIX REMODELING IN THE CARDIOVASCULAR SYSTEM

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Group Members

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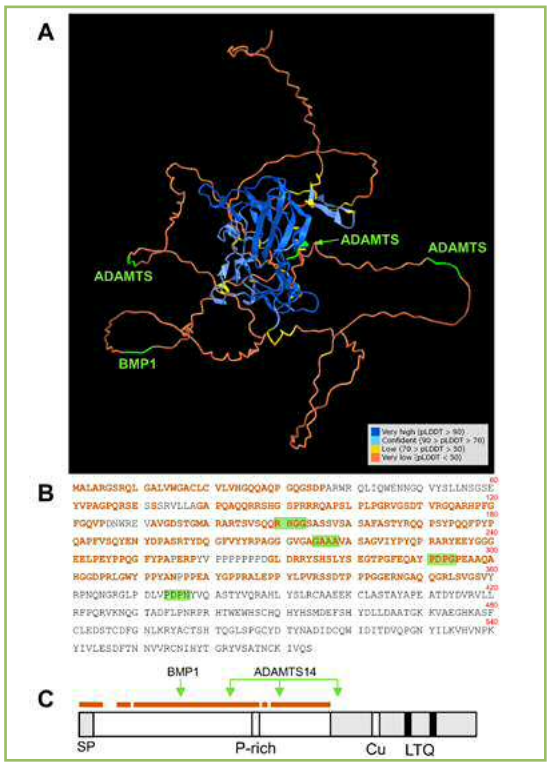
Summary

The extracellular matrix (ECM) constitutes an intricate molecular network that surrounds and integrates cells and tissues in multicellular organisms. Traditionally considered a static mass, today it is widely recognized as a highly dynamic biomaterial that confers mechanical strength to tissues, provides attachment and movement points to cells, and is also essential for the intercellular communication. Therefore, proper synthesis and assembly of the components of the ECM is essential for cell and tissue homeostasis, and defects or alterations in these processes are associated with the development of several human disorders, particularly in the cardiovascular system. The biosynthesis of collagen, the main component of the ECM, is a complex and highly regulated process involving numerous steps, including chain association and folding, extracellular secretion, proteolytic processing and cross-linking. A set of prolyl- and lysyl-hydroxylases, glycosidases, isomerases and lysyl oxidases catalyze an extensive series of post-translational modifications, most of which are unique to collagen protein. In the last few years our group has investigated different aspects of this biosynthetic pathway. To this respect, we have focused our work in the study of the biology of lysyl oxidases (LOX), the enzymes responsible for the collagen cross-linking, an essential post-translational modification that largely determines the biomechanical properties of the collagen. The LOX family of matrix-remodeling enzymes is composed by 5 members, a canonical LOX and four LOX-like isoforms from 1 to 4 (LOXL1, LOXL2, LOXL3 and LOXL4). The activity of the canonical LOX and the isoform LOXL1 are regulated by proteolysis and in the laboratory we have analyzed the molecular determinants of this proteolytic regulation. Our results have shown the existence of a complex pattern for the proteolysis of these LOX members, with multiple proteases contributing to the extracellular processing of these enzymes. Additionally, we have studied the regulation by hypoxia of several collagen remodeling enzymes, including lysyl- and prolyl-hydroxylases and analyzed the contribution of this hypoxic regulation to the development of fibrosis in several pathological contexts.



Location of BMP1 and ADAMTS14 cleavage sites within the tridimensional structure of LOXL1 protein. A) AlphaFold prediction model for LOXL1 protein showing the degree of confidence (predicted local distance difference test, pLDDT) with a color code as indicated. N-terminal region up to position 360 mostly displays an unstructured folding (pLDDT<50, brown), a predictor of disordered region. This unstructured segment is highlighted within the LOXL1 protein sequence (B, C). The position of the BMP1 and ADAMTS14 cleavage sites is indicated in green. Note that these processing sites are within the disordered region (BMP1 at 151-152, ADAMTS14 at 216-217 and 292-293), or solvent-exposed within the structure C-terminal domain (ADAMTS14 at 375-376).

List of publications

Artículos

» Rodriguez-Pascual, F., Rosell-Garcia, T. (2022) The challenge of determining lysyl oxidase activity: Old methods and novel approaches. Anal Biochem. 639:114508. doi: 10.1016/j.ab.2021.114508.

» Rosell-García, T., Rivas-Muñoz, S., Colige, A., Rodriguez-Pascual, F. (2022) Cleavage of LOXL1 by BMP1 and ADAMTS14 Proteases Suggests a Role for Proteolytic Processing in the Regulation of LOXL1 Function. Int J Mol Sci. 23(6):3285. doi: 10.3390/ijms23063285.

» García-Izquierdo, E., Mingo-Santos, S., Olivo-Rodríguez, C., Moñivas-Palomero, V., Rivas-Lasarte, M., Martín-López, C.E., Rosado-García, S., Sánchez-López, A.J., Redondo, J.M., Rodríguez-Pascual, F., Segovia-Cubero, J., Forteza-Gil, A. (2022) Exploring the potential relationship between collagen cross-linking and impaired myocardial relaxation in Marfan syndrome: An observational study using serum biomarkers. Int J Cardiol. 352:125-130. doi: 10.1016/j.ijcard.2022.01.050.

Capítulos de libros

» Rosell-García, T, Rodriguez-Pascual, F. (2021) Techniques to Assess Collagen Synthesis, Deposition, and Cross-Linking In Vitro. Methods Mol Biol. 2299:115-122. doi: 10.1007/978-1-0716-1382-5_8.

» Rodríguez-Pascual, F. (2021) The Evolutionary Origin of Elastin: Is Fibrillin the Lost Ancestor? In book: Extracellular Matrix: Developments and Therapeutics. doi: 10.5772/intechopen.95411.

Participation in projects

» RTI2018-095631-B-I00. "Activación proteolítica de lisil oxidasas. Aplicaciones biotecnológicas y contribución al remodelado de la matriz extracelular en el desarrollo de enfermedades humanas". Proyectos I+D+i "Retos Investigación" del Programa Estatal de I+D+i orientada a los retos de la sociedad. Convocatoria 2018. PI: Fernando Rodríguez Pascual. 01/01/2019-30/09/2022.

Other activities

» Fernando Rodríguez Pascual. Member of the Editorial Board of the journals "Scientific Reports" (Molecular Biology Section), "Asia-Pacific Journal of Ophthalmology" (Visual Sciences Section) and the "Molecular Biology Reports" (Extracellular Matrix Biology Section).

MOLECULAR PATHOPHYSIOLOGY OF FIBROSIS

Group Members

Principal Investigator:
Santiago Lamas Peláez

Postdoctoral fellows:
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Carlos Rey Serra

Predoctoral Fellow:
Belén Sirera Conca

Technicians:
Jessica Paola Tituaña Fajardo
José Ignacio Herrero Lahuerta (until January 2022)

Undergraduate and Master Students:
Irene Ranz Fernández. 09/2020- 06/2021, final degree project (co-supervisor Verónica Miguel Herranz)
Laura Fernández Hernández. 09/2020-06/2021, final degree project (co-supervisor Verónica Miguel Herranz)
María Madejón Sánchez. (09/2022-), final degree project, (co-supervisor Carlos Rey Serra)

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Summary

Fibrosis results from an unbalanced cellular response to inflammation and wound healing leading to the activation of specific subpopulations of resident mesenchymal cells promoting their transition towards myofibroblasts. These cells synthesize extracellular matrix components, such as collagen, that ultimately replace the cellular living tissue and establish fibrosis. While major advances regarding the mechanistic knowledge on the underlying cell biology alterations in fibrosis have helped to characterize the main phases and mediators involved, this knowledge has not yielded significant progress in treatment. This is due in part to a very incomplete understanding of the cellular types involved in the fibrotic response, the metabolic features associated to each of them, their mutual influence and the changes ultimately related to the metabolic shift or reprogramming occurring in the transition from physiological to pathological conditions. Metabolic derangement is now identified as a key culprit in the pathophysiology of fibrogenesis.

During the past years we have studied the role of metabolism in the genesis of renal injury and repair focusing on: a) the importance of fatty acid oxidation and b) the crosstalk between fibrosis and circadian regulation. To this end we use animal models with specific gain-of-function for critical enzymes involved in fatty acid oxidation, such as CPT1a, as well as animals with a disruption of the circadian rhythm. These studies are complemented by cellular models and biochemical approaches directed towards the study of mitochondrial biogenesis and function. We have found that overexpression of the enzyme Cpt1a in kidney tubules promotes enhanced fatty acid oxidation, restores mitochondrial homeostasis and protects from fibrosis. By dissecting the role of specific components of the circadian clock through the employment of genetically modified mouse models, we have investigated the cross-regulation between the circadian rhythm and kidney inflammation and fibrosis, with a particular emphasis on the metabolic component. We have complemented this approach by evaluating the impact of circadian-related metabolically healthy diets, such as time restriction feeding, on kidney fibrosis and function.

List of publications

» Miguel V, Tituaña J, Herrero JI, Herrero L, Serra D, Cuevas P, Barbas C, Rodríguez-Puyol D, Márquez-Exposito L, Ruiz-Ortega M, Castillo C, Sheng X, Susztak K, Ruiz-Canela M, Salas-Salvadó J, Hu FB, Martínez Gonzalez MA, Ortega S, Ramos R and Lamas S. (2021). Renal tubule Cpt1a overexpression mitigates kidney fibrosis by restoring mitochondrial homeostasis. Journal of Clinical Investigation.140695. doi: 10.1172 /JCI140695.

» Rey-Serra C, Tituaña J, Lin T, Herrero JI, Miguel V, Barbas C, Meseguer A, Ramos R, Firsov D, Chaix A, Panda S, Lamas S. (2022). Cross regulation between the molecular clock and kidney inflammatory, metabolic and fibrotic responses. bioRxiv doi: 10.1101/2022.05.18.492458.

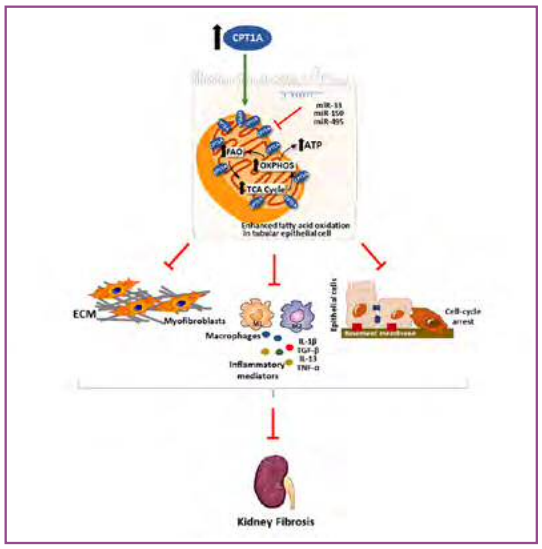
» Perramón M, Carvajal S, Reichenbach V, Fernández-Varo G, Boix L, Macías-Muñoz L, Melgar-Lesmes P, Bruix J, Melmed S, Lamas S and Jiménez W. (2022). The pituitary tumour-transforming gene 1/delta-like homologue 1 pathway plays a key role in liver fibrogenesis. Liver Int. 42(3):651-662. doi: 10.1111/liv.15165.

» Ruiz-Ortega M, Lamas S and Ortiz A. (2022). Antifibrotic agents for the management of CKD: a review. Am J Kidney Dis. 80(2):251-263. doi: 10.1053/j.ajkd.2021.11.010.

» Miguel V and Lamas S. (2021). Linking transcription to energy: the path to understand kidney injury. Kidney Int 100(6):1165-1167. doi: 10.1016/j.kint.2021.09.018.

» Miguel V, Ramos R, García-Bermejo L, Rodríguez-Puyol D and Lamas S. (2021). The program of renal fibrogenesis is controlled by microRNAs regulating oxidative metabolism. Redox Biology 40:101851 doi: 10.1016/j.redox.2020.101851.

» Márquez-Exposito L, Rodrigues-Díez RR, Rayego-Mateos S, Fierro-Fernandez M, Rodrigues-Díez R, Orejudo M, Santos-Sánchez L, Blanco EM, Laborda J, Mezzano S, Lamas S, Lavoz C and Ruiz-Ortega M. (2021). Deletion of delta-like 1 homologue accelerates renal inflammation by modulating the Th17 immune response. FASEB J. 35(1):e21213. doi: 10.1096/fj.201903131.



The enhancement of fatty acid oxidation in renal tubular epithelial cells protects against kidney fibrosis

Participation in projects

» Red de Investigación Renal (ISCiii) REDinREN. RD16/0009/0016. (2017-2021) (RETIC), PI: Santiago Lamas.

» Enfermedad Renal Crónica: nuevas estrategias para la prevención, diagnóstico y tratamiento (NOVELREN-CM). S2017/BMD-3751. (2018-2021). (Programa Biomedicina Comunidad de Madrid) PI and Coordinator: Santiago Lamas.

» Fibrosis pulmonar post CoVid19: marcadores y opción terapéutica con Metformina. CSIC-COV19-096. (2020-2021), PI: Santiago Lamas.

» Mesenchymal metabolic rewiring to cure organ fibrosis (FIBROMET). EIN2020-112282. (2020-2022), PI: Santiago Lamas.

» Combating kidney fibrosis by metabolic reprogramming (RENFIBMET). PID2019-104233RB-I00. (2020-2023), PI: Santiago Lamas.

Other activities

» Coordination of the NOVELREN-CM consortium of the Biomedicine programme from the Comunidad de Madrid for the study on chronic renal failure. 2018-2022.

» Group leader in the research network RedinRen, RETICS programme, Instituto de Salud Carlos III. 2020-2022

» Collaboration with M2R laboratories for the establishment of an experimental model of acute respiratory distress syndrome.

Awards

» 2021: Doctor Honoris Causa, Facultad de Medicina, Universidad de la República, Uruguay

» 2022: Basic Research Award, Society for Free Radical Research-Europe

Doctoral theses

» Carlos Rey Serra (2021). Impact of the circadian regulation on the metabolic basis of kidney fibrosis. Universidad Autónoma de Madrid. Director: Santiago Lamas.