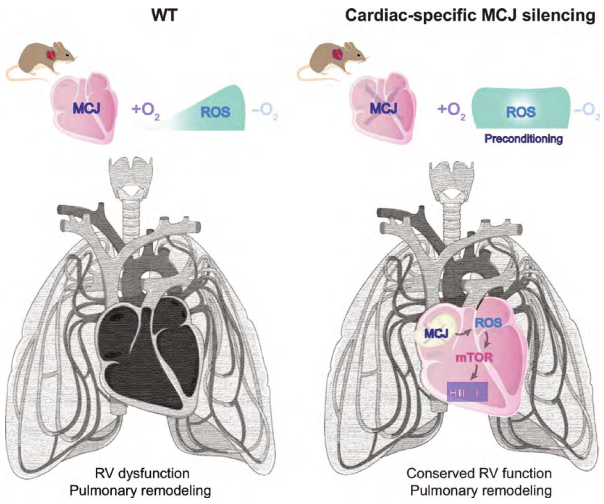
3 SCIENTIFIC HIGHLIGHTS BY PUBLICATION DATE

SCIENCE ADVANCES

FIRST THERAPEUTIC TARGET FOR PRESERVING HEART FUNCTION IN PATIENTS WITH PULMONARY HYPERTENSION

A CNIC team led by Dr. Guadalupe Sabio discovered a possible therapeutic target for pulmonary hypertension. The study, published in *Science Advances*, identified the first therapeutic target that can be modulated to preserve cardiac function in pulmonary hypertension, providing hope in the fight against this rare but fatal disease for which there is currently no cure.

The study was supported by grants from the Ministerio de Ciencia e Innovación (RED2022-134397-T, MINECO-PID2019-104399RB-I00, PGC2018-097019-B-I00), IMPACT-2021 PROJECT (PMP21/00057), Fundación Jesús Serra, the EFSD/Lilly European Diabetes Research Programme, Fundación BBVA, the Comunidad Autónoma de Madrid, and the Asociación Española Contra el Cáncer (AECC).



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CIRCULATION RESEARCH

APOE GENETIC VARIANTS LINKED TO ALZHEIMER DISEASE ARE ALSO ASSOCIATED WITH THE DEVELOPMENT OF SUBCLINICAL ATHEROSCLEROSIS

CNIC scientists found that one of the most potent genetic risk factors for Alzheimer's disease, apolipoprotein E4 (APOE4), is also associated with an increased risk of developing subclinical atherosclerosis in middle age. The study also demonstrated protection against subclinical atherosclerosis in people carrying the APOE2 variant, which protects against Alzheimer's disease.

The study received funding from the European Regional Development Fund (ERDF) and the European Social Fund (ESF).

The PESA study is funded jointly by the CNIC and Santander Bank. Additional financial support came from the ISCIII (PI15/02019, PI17/00590 & PI20/00819) and the BrightFocus Foundation. The present study involved the participation of investigators from the Spanish research networks for cardiovascular biomedicine (CIBERCV) and rare diseases (CIBERRER).

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NATURE CARDIOVASCULAR RESEARCH

NEW APPROACH TO THE DESIGN OF THERAPIES THAT ENHANCE THE EFFECT OF CHOLESTEROL-LOWERING DRUGS

A research team from the CNIC, in collaboration with Aarhus University in Denmark, uncovered a crucial mechanism that leads to the regression, or shrinkage, of atherosclerotic plaques. This discovery, published in ***Nature Cardiovascular Research***, highlights smooth muscle cell-derived cells in the arterial wall as a promising target for future therapies aimed at reducing plaque growth in advanced atherosclerosis.

The research was funded by the European Research Council (ERC 866240, JFB), the Ministerio de Ciencia e Innovación (PID2019-108568RB-I00, JFB), and the Novo Nordisk Foundation (NNF17OC0030688, JFB).

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CIRCULATION RESEARCH

NEW MECHANISM DISCOVERED FOR THE LIFE-THREATENING ARRHYTHMIAS IN ANDERSEN-TAWIL SYNDROME

A team at the CNIC led by Dr. José Jalife made a significant breakthrough in understanding the genetic basis of cardiac arrhythmias, particularly those related to Andersen-Tawil syndrome (ATS). The research, published in ***Circulation Research***, reveals how a specific genetic mutation (C122Y) in the Kir2.1 potassium channel not only disrupts the function of Kir2.1 itself but also impairs the main cardiac sodium channel, NaV1.5. This discovery establishes a direct link between the mutation and the life-threatening arrhythmias characteristic of ATS1.

The study was funded by the National Heart, Lung, and Blood Institute of the NIH (USA); Fundación "la Caixa"; Fundació La Marató de TV3; CIBERCV; the European Union Horizon 2020 Programme; and Program S2022/BMD7229 (Comunidad de Madrid). Imaging studies were performed at the TRIMA@CNIC node of the Distributed Biomedical Imaging Network (ICTS ReDIB).

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JACC: CARDIOONCOLOGY

CNIC SCIENTISTS IDENTIFY THERAPEUTIC TARGETS FOR THE PREVENTION OF HEART INJURY LINKED TO CANCER TREATMENT

CNIC scientists identified the mechanisms through which anthracyclines, a widely used class of anticancer drugs, damage the hearts of patients receiving this treatment. The study, published in ***JACC: CardioOncology***, also identified possible treatments for this complication, which affects an estimated one third of cancer survivors.

The study received support from the European Commission (ERC-CoG 819775 and H2020-HEALTH 945118), the Ministerio de Ciencia, Innovación y Universidades (PID2022-140176OB-I00), and the Comunidad Autónoma de Madrid through the Madrid Network for Nanomedicine in Molecular Imaging (P2022/BMD-7403 RENIM-CM).

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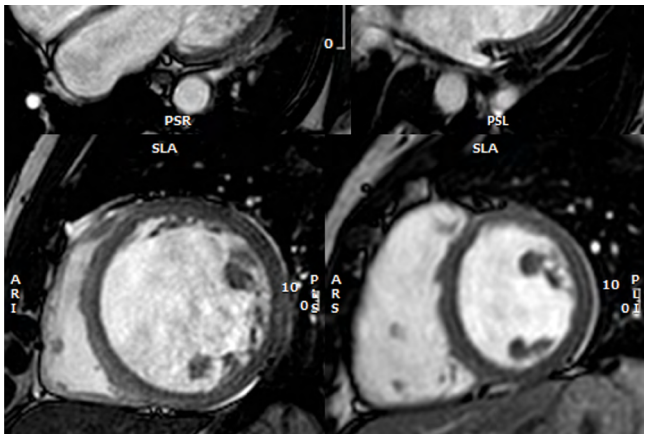
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

A NEW SPANISH STUDY PROVIDES THE FIRST STRATIFICATION OF THE RISK OF DILATED CARDIOMYOPATHY AMONG SYMPTOM-FREE GENETIC CARRIERS

Dilated cardiomyopathy is the leading cause of heart failure in young people and a major reason for heart transplants. This condition causes the heart to enlarge and lose its ability to effectively pump blood, putting patients at high risk of arrhythmias and sudden death. In 30%–40% of cases, the disease is linked to genetic mutations, and identifying these mutations allows doctors to screen family members for the altered gene.

The study was supported by the Sociedad Española de Cardiología (a Hereditary Cardiac Disease grant awarded in 2022) and the Instituto de Salud Carlos III through projects PI18/0004 and PI20/0320 (cofunded by the ERDF and the ESF).



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PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA

CNIC SCIENTISTS IDENTIFY THE KEY CELL TYPE FOR STRATEGIES TO PREVENT ATHEROSCLEROSIS IN PROGERIA SYNDROME

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare genetic disease that causes accelerated aging, severe atherosclerosis, and premature death at an average age of 15 years. Despite the absence of typical cardiovascular risk factors, the leading cause of death in HGPS is premature atherosclerosis. The disease is caused by a mutation in the LMNA gene that leads to the production of progerin, a harmful version of the lamin A protein. The study demonstrated that premature atherosclerosis in a mouse model of HGPS is prevented by elimating progerin expression in arterial smooth muscle cells.

The study was funded by the Ministerio de Ciencia, Innovación y Universidades and the Agencia Estatal de Investigación (MICIU/AEI/10.13039/501100011033 and ERDF/EU (grants PID2022-141211OB-I00 and PID2022-137111OA-I00); the Comunidad Autónoma de Madrid (grants 2017-T1/BMD-5247 and 2021-5A/BMD-20944) cofinanced with European structural and investment funds; RYC2021-033805-I (MICIU/AEI/10.13039/501100011033 and European Union NextGenerationEU/PRTR); the Ministerio de Educación, Cultura y Deporte; Fundación "la Caixa"; and the Wellcome Trust.

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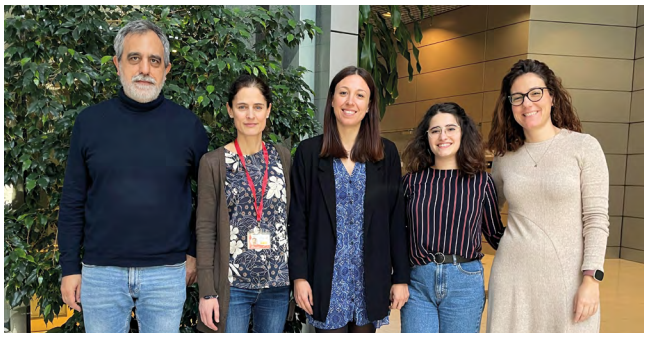
DEVELOPMENT CELL

A CNIC STUDY REVEALS THE KEY ROLE OF MITOCHONDRIAL PROTEINS IN CARDIAC REGENERATION

A study by the CNIC and the University of Bern revealed new insights into the role of mitochondria in heart regeneration. Published in ***Development Cell***, the research, led by Dr. José Antonio Enríquez and Dr. Nadia Mercader, identifies the cox7a protein family as crucial for the assembly of complex IV (CIV) in the mitochondrial respiratory chain, which is essential for cellular energy production.

The study was supported by the European Union Horizon 2020 programme (grants 874764 and 819717), the Human Frontier Science Program (grant RGP0016/2018), and the Swiss National Science Foundation (grant 320030E-164245).



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NUCLEIC ACIDS RESEARCH

A CNIC TEAM HAS CREATED AN INNOVATIVE TOOL FOR THE RELIABLE AND EFFICIENT STUDY OF GENE FUNCTION

A team from the CNIC, led by Rui Benedito, developed a new genetic tool called iSuRe-HadCre, which improves the precision and reliability of genetic alterations in tissues or individual cells. Published in ***Nucleic Acids Research***, this technology overcomes the limitations of the Cre-Lox system, which has been traditionally used for gene function analysis.

The study was funded by the Ministerio de Ciencia e Innovación, Fundación "la Caixa", the European Research Council, the Leducq Foundation, the Knut and Alice Wallenberg Foundation, and the Göran Gustafsson Foundation.

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

THE SOONER THE BETTER: TEACHING HEALTHY HABITS IN ELEMENTARY SCHOOL REDUCES ABDOMINAL FAT

A study led by the CNIC and the SHE Foundation, with support from Fundación "la Caixa", highlights the effectiveness of teaching healthy

habits in elementary schools as a way to prevent accumulation of abdominal fat. Published in ***The Journal of the American College of Cardiology***, the study is among the largest health promotion studies conducted in schools, with an extensive follow-up of participants.

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JOURNAL OF CLINICAL INVESTIGATION

A NEW STUDY REVEALS A KEY MECHANISM DRIVING ATHEROSCLEROSIS IN HUTCHINSON-GILFORD PROGERIA SYNDROME

A team of researchers from the CNIC, CIB-CSIC, and ICMM-CSIC has made a significant breakthrough in understanding the mechanisms underlying atherosclerosis in Hutchinson-Gilford Progeria Syndrome (HGPS), a rare genetic disorder that accelerates aging. The study, published in ***The Journal of Clinical Investigation***, identifies abnormal activation of the YAP/TAZ pathway in endothelial cells as a key driver of atherosclerosis in HGPS patients.

The study was funded by grants from the Ministerio de Ciencia, Innovación y Universidades and the Agencia Estatal de Investigación (MICIU/AEI/10.13039/501100011033); FEDER/EU funds and the NextGenerationEU/PRTR (PID2022-141211OB-I00, PID2022-137111OA-I00, RYC2021-033805-I); and the Comunidad Autónoma de Madrid (grants 2017-T1/BMD-5247, 2021-5A/BMD-20944), with cofunding from the European Structural and Investment Fund.

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EUROPACE

A NEW IMAGE PROCESSING STRATEGY FOR CARDIAC MAGNETIC RESONANCE IMAGING IDENTIFIES CULPRIT AREAS UNDERLYING COMPLEX TACHYCARDIAS

A multicenter study published in ***Europace*** and led by investigators at Hospital Clínico San Carlos and the CNIC validated a new method that uses magnetic resonance imaging (MRI) to guide ablation procedures in patients with post-infarction ventricular tachycardias. The strategy precisely identifies the regions responsible for these arrhythmias in tissue affected by scarring after a myocardial infarction, thereby eliminating biases from manual parameter selection and allowing safer and more efficient planning.

The research was supported by the Ministerio de Ciencia e Innovación (MCIN/PID2019-109329RB-I00) and the Pro-CNIC Foundation, with additional support from the Sección de Arritmias de la Sociedad Española de Cardiología, the Fundación Interhospitalaria para la Investigación Cardiovascular, and the Eugenio Rodríguez Pascual Foundation.

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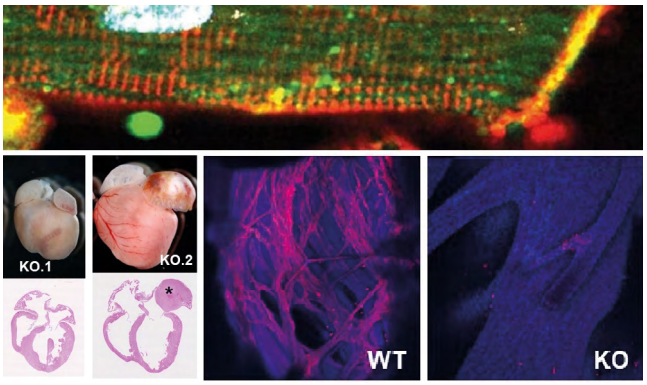
NATURE COMMUNICATIONS

KEY MECHANISM DISCOVERED IN THE DEVELOPMENT AND FUNCTIONING OF THE CARDIAC CONDUCTION SYSTEM

A study published in ***Nature Communications*** by a team of researchers from the Rare Diseases Research Institute of the Instituto de Salud Carlos III (ISCIII), CIBER, the CNIC, Universitat Pompeu Fabra (UPF), and the Severo Ochoa Molecular Biology Center (CBM, CSIC-UAM) identified the protein Dhx36 as an essential regulator of heart development and function, particularly in the cardiac conduction system.

The study, led by scientists Pablo Gómez del Arco (ISCIII), Pura Muñoz-Cánoves (UPF and Altos Labs), and Juan Miguel Redondo (CBM, CSIC-UAM), demonstrates that Dhx36 modulates gene networks controlling cardiomyocyte differentiation by resolving G-quadruplex structures in the promoters of key genes in the cardiac conduction system. This function is critical for the formation of specialized cells that make up the conduction system, which transmits and regulates the heart's electrical impulses.



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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PROGRESSION OF SUBCLINICAL ATHEROSCLEROSIS PREDICTS ALL-CAUSE MORTALITY RISK

A study led by Dr. Valentín Fuster at Mount Sinai Fuster Heart Hospital and the CNIC demonstrates that atherosclerosis burden and progression in asymptomatic individuals are independently associated with all-cause mortality. Published in ***The Journal of the American College of Cardiology***, the study highlights the value of quantifying carotid and coronary atherosclerosis using advanced imaging technology to predict overall mortality.

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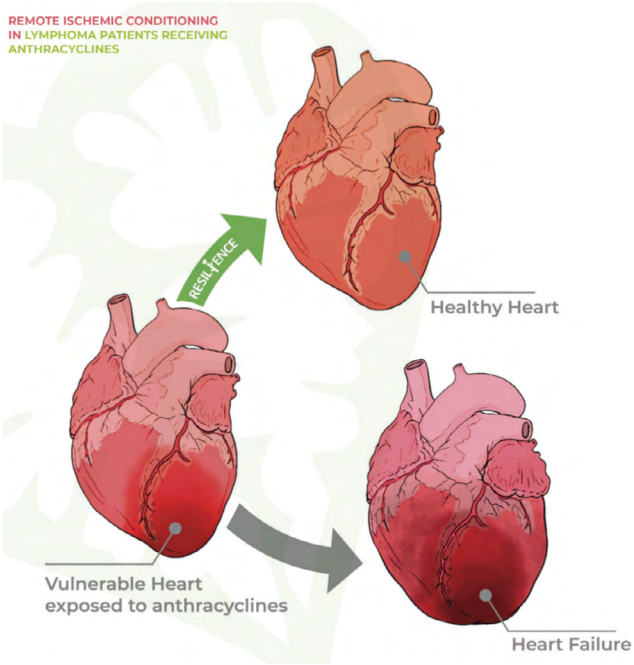
EUROPEAN JOURNAL OF HEART FAILURE

THE RESILIENCE TRIAL: PREVENTING HEART INJURY CAUSED BY ANTICANCER DRUGS

The RESILIENCE clinical trial investigates the safety and effectiveness of remote ischemic conditioning in preventing cardiac injury caused by anthracycline chemotherapy in lymphoma patients. This innovative multinational double-blind project, funded by the European Union, aims to reduce the incidence of chronic heart failure in cancer survivors and improve their quality of life.

Coordinated by the CNIC and supported by the European Society of Cardiology and Philips Healthcare, among other partners, RESILIENCE aims to validate innovative methods to protect patients at high risk of cancer therapy-related cardiac dysfunction, offering new therapeutic perspectives for a significant medical challenge.

The RESILIENCE trial is funded by the European Commission (H2020-HEALTH, grant number 945118).



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JACC: CLINICAL ELECTROPHYSIOLOGY

GENETICS COULD EXPLAIN A LARGE NUMBER OF YOUNG ADULTS WITH PACEMAKERS WITHOUT AN IDENTIFIED CAUSE

A study led by CNIC cardiologists Juan Pablo Ochoa and Pablo García-Pavía, published in ***JACC Clinical Electrophysiology***, revealed that rare genetic variants increase the risk of cardiac conduction disorders in young adults requiring a pacemaker. According to the study, 15% of patients have a direct genetic mutation, while an additional 30% show relevant genetic alterations. This highlights the importance of genetics in the diagnosis and management of these disorders.

Ochoa JP, Espinosa MÁ, Gayan-Ordas J, Fernández-Valledor A, Gallego-Delgado M, Tirón C, Lozano-Ibáñez A, García-Pinilla JM, Rodríguez-Palomares JF, Larrañaga-Moreira JM, Llamas-Gómez H, Ripoll-Vera T, Braza-Boïls A, Vilches S, Méndez I, Bascompte-Claret R, García-Álvarez A, Villacorta E, Fernández-Lozano I, Lara-Pezzi E, García-Pavía P. Rare Genetic Variants in Young Adults Requiring Pacemaker Implantation. JACC Clin Electrophysiol. 2024 Oct;10(10):2250-2260. doi: 10.1016/j.jacep.2024.05.008. Epub 2024 Jul 10. PMID: 39001760.

NATURE MEDICINE AND EUROPEAN HEART JOURNAL

CNIC SCIENTISTS DISCOVER A NEW CARDIOVASCULAR RISK FACTOR AND IDENTIFY A DRUG ABLE TO REDUCE ITS EFFECTS

A study by researchers at the CNIC, published in ***Nature Medicine***, establishes clonal hematopoiesis—caused by acquired mutations in blood stem cells—as a direct risk factor for atherosclerosis, a condition underlying most cardiovascular diseases. Previously, it was unclear whether clonal hematopoiesis was a cause or consequence of cardiovascular disease. A second CNIC study, published in the ***European Heart Journal***, suggests that colchicine, an ancient anti-inflammatory medication, could be used to mitigate the effects of TET2-related clonal hematopoiesis.

These findings, presented at the European Society of Cardiology meeting, pave the way for personalized treatments targeting this newly confirmed risk factor for cardiovascular disease.

The PESA study is funded jointly by the CNIC and Santander Bank. The two studies were additionally funded by the Ministerio de Ciencia, Innovación y Universidades (PLEC2021-008194), CIBERCV, Fundación "la Caixa" (LCF/PR/HR17/52150007; LCF/PR/HR22/52420011), and Fundació La Marató de TV3 (202314-31).

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CIRCULATION

A NEW MECHANISM OF EARLY-ONSET ATHEROSCLEROSIS IN A PREMATURE AGING SYNDROME

A CNIC study, led by Drs. Vicente Andrés and Magda Hamczyk and published in ***Circulation***, identifies endothelial-to-mesenchymal transition (EndMT) as a key mechanism in premature atherosclerosis and a potential therapeutic target. EndMT involves pathological changes in endothelial cells, such as increased immune cell recruitment and LDL permeability, which accelerate the formation of atherosclerotic plaques.

The study focuses on progeria, a genetic disease that causes early-onset atherosclerosis and premature death. Researchers found that the TGFβ1-SMAD3 pathway, central to EndMT, is hyperactivated in mouse models of progeria, while its inhibition with the drug SIS3 improves vascular symptoms.

The study was funded by the Ministerio de Ciencia, Innovación y Universidades and the Agencia Estatal de Investigación (MICIU/AEI/10.13039/501100011033) and the ERDF/EU (PID2022-141211OB-I00).

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CELL

SCIENTISTS AT THE CNIC DISCOVER AN UNEXPECTED INVOLVEMENT OF SODIUM TRANSPORT IN MITOCHONDRIAL ENERGY GENERATION

The GENOXPHOS group from the CNIC and CIBERFES, led by Dr. José Antonio Enríquez, has uncovered an essential role of sodium in cellular energy production. The study, published in ***Cell***, reveals that mitochondrial complex I not only transports protons, as proposed by the chemiosmotic theory of 1961, but also exchanges sodium ions, creating a gradient critical for efficient production of ATP, the primary carrier of cellular energy. This discovery sheds light on the molecular mechanism behind Leber's Hereditary Optic Neuropathy (LHON), a neurodegenerative disease caused by mitochondrial DNA defects. Dysfunction in sodium-proton transport by complex I leads to cell death, triggering this pathology.

The study was supported by the Ministerio de Ciencia e Innovación (MCIN/RTI2018-099357-B-I00), CIBERFES (CB16/10/00282), the Human Frontier Science Program (grant RGP0016/2018), and Leducq Transatlantic Networks (17CVD04).

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SCIENCE ADVANCES

A NEW CNIC STUDY REVEALS HOW CELLS RESPOND TO MECHANICAL SIGNALS FROM THEIR ENVIRONMENT

A study conducted at the CNIC, led by Dr. Jorge Alegre-Cebollada, has revealed the fundamental role of tissue viscoelasticity—a largely unexplored property—in cellular function. The extracellular matrix (ECM), a network of proteins that supports and connects cells, influences processes such as cell migration, proliferation, and differentiation through its mechanical properties, including stiffness and viscoelasticity.

The study was made possible thanks to funding from the Ministerio de Ciencia, Innovación y Unoversidades, the European Research Council, and the Comunidad Autónoma de Madrid through the interdisciplinary consortium Tec4Bio-CM. The study included core contributions from four Tec4Bio-CM principal investigators, at the CNIC, ICMM-CSIC, and Polytechnic University of Madrid.

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NATURE COMMUNICATIONS

CNIC SCIENTISTS DISCOVER A KEY MECHANISM IN FAT CELLS THAT PROTECTS THE BODY AGAINST ENERGETIC EXCESS

A team from the CNIC led by Professor Miguel Ángel del Pozo Barriuso has identified a key mechanism in fat cells that allows them to safely expand and store energy, preventing tissue damage. The study, published in ***Nature Communications***, could pave the way for new therapies for metabolic diseases such as obesity and lipodystrophy.

The study was funded by Ministerio de Ciencia, Innovación y Universidades and the Agencia Estatal de Investigación with cofunding from the ERDF (MICIU/AEI/SAF2017-83130-R, IGP-SO grant MINSEV1512-07-2016, BFU2016-81912-REDC, and SAF2020 [PID2020-118658RB-I00]), Fundación "la Caixa" (AtheroConvergence, HR20-00075), the Comunidad Autónoma de Madrid (Tec4Bio-CM, S2018/...), Fundació La Marató de TV3 (201936-30-31), and the AECC (PROYE20089DELP).

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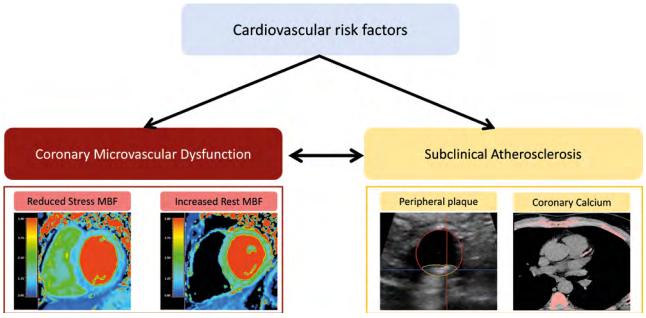
JACC: CARDIOVASCULAR IMAGING

CARDIOMETABOLIC RISK FACTORS IN APPARENTLY HEALTHY INDIVIDUALS ARE LINKED TO ALTERED CORONARY MICROCIRCULATION

A CNIC study, published in ***JACC: Cardiovascular Imaging***, examines how cardiometabolic risk factors and subclinical atherosclerosis impact coronary microvascular function in asymptomatic middle-aged individuals. Microvascular function, essential for regulating blood flow and oxygen supply to the heart, was assessed using magnetic resonance imaging in 453 participants of the PESA-CNIC-Santander study.

The PESA study is funded jointly by the CNIC and Banco Santander. Additional support was provided by the European Commission (ERC-CoG 819775 and H2020-HEALTH 945118), the Ministerio de Ciencia, Innovación y Universidades (PID2019-110369RB-I00), and the Madrid Network of Nanomedicine in Molecular Imaging- Comunidad Autónoma de Madrid (S2017/BMD-3867 RENIM-CM).



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NATURE METHODS

CNIC PRESENTS IFLPMOSAICS, AN INNOVATIVE GENETIC TOOLKIT FOR THE STUDY OF GENE FUNCTION

A team from the CNIC led by Dr. Rui Benedito has developed iFlpMosaics, an innovative set of genetic tools and mouse lines that enhances the study of gene function and its implications in health

and disease. The study, published in ***Nature Methods***, presents a groundbreaking approach that overcomes the limitations of current methods for generating genetic mosaics, enabling more precise investigation of the effects of somatic mutations on cellular biology and diseases.

This study was funded by the European Research Council through Starting Grant AngioGenesHD (638028) and Consolidator Grant AngioUnrestUHD (101001814), the Ministerio de Ciencia e Innovación (SAF2017-89299-P and PID2020-120252RB-I00), and Fundación "la Caixa" (HR19-00120 and HR22-00316 AngioHeart).

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