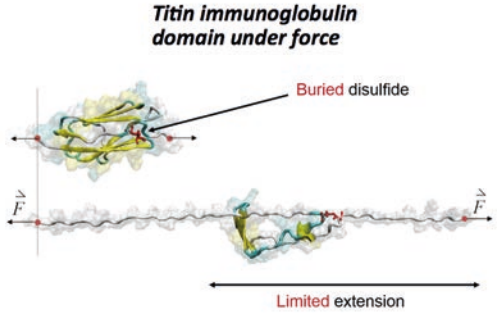
3 Scientific Highlights: by publication date

1. Nature Communications Scientists identify a key mechanism regulating a protein required for muscle and heart function

Scientists at the CNIC and Columbia University in New York have discovered an important mechanism in the regulation of a protein that plays an essential role in the function of skeletal muscle and the heart. The study, published in Nature Communications and coordinated by CNIC researcher Jorge Alegre-Cebollada, describes a new mechanism in the regulation of the elasticity of the giant protein titin. Titin, explained Alegre-Cebollada, is a key protein in the functioning of striated muscles throughout the body, particularly in the heart: "the proof of this is that mutations in the titin gene are a common cause of diseases affecting the muscles of the body and the heart."

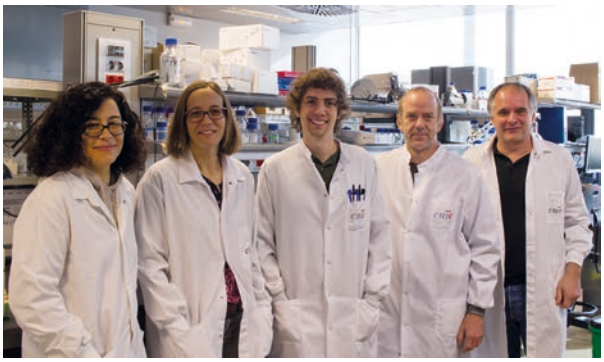
Giganti D, Yan K, Badilla CL, Fernandez JM, Alegre-Cebollada J. Disulfide isomerization reactions in titin immunoglobulin domains enable a mode of protein elasticity. Nat Commun. 2018;9(1):185. doi: 10.1038/s41467-017-02528-7



2. Journal of Experimental Medicine CNIC scientists produce an atlas of genes mutated by an immune-system protein and linked to lymphoma

Researchers at the CNIC have identified the largest collection to date of genes mutated by AID, a key protein in the immune response. The study reveals a new link between the mutagenic activity of AID and the generation of lymphomas. The information obtained, published in the Journal of Experimental Medicine, will increase understanding of the molecular mechanisms that control the activity of this enzyme and its possible contribution to the development of cancer. The research team led by Almudena Ramiro has compiled an atlas of the mutations that accumulate in the DNA of B lymphocytes during the immune response.

Álvarez-Prado ÁF, Pérez-Durán P, Pérez-García A, Benguria A, Torroja C, de Yébenes VG, Ramiro AR. A broad atlas of somatic hypermutation allows prediction of activation-induced deaminase targets. J Exp Med. 2018;215(3):761-71. doi: 10.1084/jem.20171738



3. Journal of the American College of Cardiology An enzyme variant reduces cardiac hypertrophy and improves heart function

Scientists at the CNIC have identified a variant of the enzyme calcineurin, called CnAβ1, whose action reduces cardiac hypertrophy and improves heart function. The results of the study, published in the Journal of the American College of Cardiology (JACC), are the first to identify the beneficial effects of a CnAβ1-induced metabolic pathway in the hypertrophic heart, and may open the path to new treatment strategies. The findings also show how alternative forms of the same protein, produced from the same gene, can have opposite effects on a biological or pathological process.

The study was led by CNIC scientist Enrique Lara, with group members Laura Padrón, María Villalba, and Jesús Gómez Salinero as joint first authors. The research was carried out through collaboration with Jose Antonio Enríquez and Jesús Vázquez at the CNIC and Pablo García-Pavía of Puerta de Hierro University Hospital in Majadahonda, Madrid.

Padrón-Barthe L, Villalba-Orero M, Gómez-Salinero JM, Acín-Pérez R, Cogliati S, López-Olañeta M, Ortiz-Sánchez P, Bonzón-Kulichenko E, Vázquez J, García-Pavía P, Rosenthal N, Enríquez JA, Lara-Pezzi E. Activation of Serine One-Carbon Metabolism by Calcineurin Abeta1 Reduces Myocardial Hypertrophy and Improves Ventricular Function. J Am Coll Cardiol. 2018;71(6):654-67. doi: 10.1016/j.jacc.2017.11.067

4. Nature Communications CNIC scientists describe a mechanism of heart regeneration in the zebrafish

Some animals, including the zebrafish, have a high capacity to regenerate tissues, allowing them to recovery fully after cardiac injury. During this process, the heart muscle cells divide to replace the damaged tissue. However, there has been uncertainty about whether all cells contribute equally to the reconstruction of the heart wall. Now, a team of scientists led by Nadia Mercader at the CNIC and the University of Bern (Switzerland), working with collaborators at the University of Zurich (Switzerland), have discovered a high level of plasticity among the cells of the zebrafish heart muscle. The study is published in Nature Communications.

After a heart attack, the human heart loses millions of cardiomyocytes, the cells that form the muscle wall. In contrast, other animal species have a high regenerative capacity, enabling them to replace the injured myocardium with new cardiomyocytes. One such species is the zebrafish (Danio rerio). According to first author Héctor Sánchez-Iranzo, the zebrafish "is a widely used model system in cardiovascular research into the mechanisms controlling regeneration, and an inspiration for attempts to develop future regenerative therapies."

Sánchez-Iranzo H, Galardi-Castilla M, Minguillón C, Sanz-Morejón A, González-Rosa JM, Felker A, Ernst A, Guzmán-Martínez G, Mosimann C, Mercader N. Tbx5a lineage tracing shows cardiomyocyte plasticity during zebrafish heart regeneration. Nat Commun. 2018;9(1):428. doi: 10.1038/s41467-017-02650-6

5. Nature Communications Blocking a protein could improve the effectiveness of intravascular cellular 'policing'

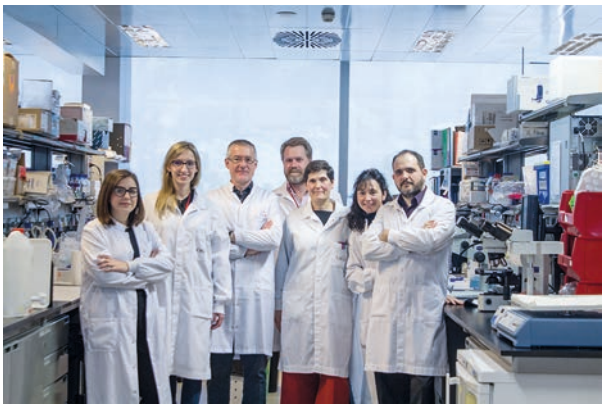
Researchers at the CNIC, led by Alicia G. Arroyo, have identified a function of a protease that could be targeted for the treatment of some infections and even tumor metastasis. The study shows that blockade of the protease MT4-MMP increases the surveillance activity of a type of white blood cell in the circulation, the blood-patrolling monocytes. These cells act like 'police patrols' to detect foreign or undesired material in the blood. The findings, indicated Alicia G Arroyo, "have possible clinical implications and could contribute to strategies to eliminate foreign or undesired materials from the blood, such as infectious agents or tumor cells." The study thus "suggests new strategies to combat infection or prevent metastasis, which are currently being evaluated for patent protection."

Clemente C, Rius C, Alonso-Herranz L, Martín-Alonso M, Pollán Á, Camafeita E, Martínez F, Mota RA, Núñez V, Rodríguez C, Seiki M, Martínez-González J, Andrés V, Ricote M, Arroyo AG. MT4-MMP deficiency increases patrolling monocyte recruitment to early lesions and accelerates atherosclerosis. Nat Commun. 2018;9(1):910. doi: 10.1038/s41467-018-03351-4

6. Circulation Scientists discover the cause of accelerated atherosclerosis and premature death in progeria

Scientists at the CNIC and the CIBER de Enfermedades Cardiovasculares (CIBERCV), led by Vicente Andrés, have generated the first genetically modified mice with accelerated atherosclerosis induced by the protein progerin, which causes the development of HGPS. The research team found that the main cause of accelerated atherosclerosis and premature death in these mice was alterations in the smooth muscle cells lining the blood vessels. The results of the study, published in Circulation, identify vascular smooth muscle cells as a possible therapeutic target for combatting the premature atherosclerosis in progeria. The study was conducted in collaboration with Carlos López-Otín of the University of Oviedo and Jacob Bentzon at the CNIC.

Hamczyk MR, Villa-Bellosta R, Gonzalo P, Andrés-Manzano MJ, Nogales P, Bentzon JF, López-Otín C, Andrés V. Vascular Smooth Muscle-Specific Progerin Expression Accelerates Atherosclerosis and Death in a Mouse Model of Hutchinson-Gilford Progeria Syndrome. Circulation. 2018;138(3):166-82. doi: 10.1161/CIRCULATIONAHA.117.030856



7. Science Translational Medicine
CNIC scientists identify a promising target for the treatment of heart failure

Researchers at the CNIC led by José Antonio Enríquez have described a new therapeutic target for the prevention of heart failure, one of the leading causes of death and disability in the world. The new target, a mitochondrial protease called OMA1, is activated when the heart is under stress. Inhibition of OMA1 protects cardiomyocytes (the muscle cells of the heart), preventing their death and stemming the deterioration in heart function. The study is published in Science Translational Medicine.

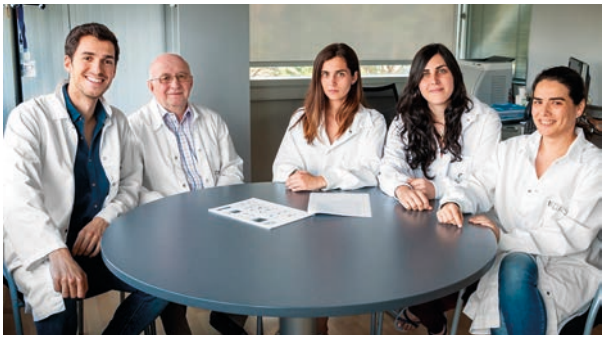
Acin-Perez R, Lechuga-Vieco AV, Del Mar Muñoz M, Nieto-Arellano R, Torroja C, Sánchez-Cabo F, Jiménez C, González-Guerra A, Carrascoso I, Benincá C, Quiros PM, López-Otín C, Castellano JM, Ruíz-Cabello J, Jiménez-Borreguero LJ, Enríquez JA. Ablation of the stress protease OMA1 protects against heart failure in mice. Sci Transl Med. 2018;10(434):eaan4935. doi: 10.1126/scitranslmed.aan4935

8. Nature Communications
Mitochondrial DNA in exosomes is the alarm that initiates the antiviral response

Researchers at the CNIC have provided valuable information about the defense mechanisms of the immune system during the early stages of the response to pathogens such as viruses and bacteria. The research findings, published in Nature Communications, contribute to the understanding of the cellular processes initiated at early stages and explain how the distinct cell populations of the immune system communicate to mount an effective response against pathogens.

The CNIC researchers have shown that mitochondrial DNA contained in nanovesicles triggers a state of alertness in recipient cells that activates an antiviral genetic program. These nanovesicles, known as exosomes, are produced by T lymphocytes and taken up by dendritic cells via intercellular contacts.

Torralba D, Baixauli F, Villarroya-Beltri C, Fernández-Delgado I, Latorre-Pellicer A, Acín-Pérez R, Martín-Cófreces NB, Jaso-Tamame ÁL, Iborra S, Jorge I, González-Aseguinolaza G, Garaude J, Vicente-Manzanares M, Enríquez JA, Mittelbrunn M, Sánchez-Madrid F. Priming of dendritic cells by DNA-containing extracellular vesicles from activated T cells through antigen-driven contacts. Nat Commun. 2018;9(1):2658. doi: 10.1038/s41467-018-05077-9



9. PLoS Biology
P38 alpha: the switch controlling obesity and diabetes

One of the research lines targeting the worldwide obesity epidemic is the manipulation of brown fat, a 'good' type of fat tissue that burns lipids to maintain an appropriate body temperature. Researchers at the CNIC have now uncovered the mechanism by which brown fat cells are activated to generate heat and eliminate excess fat. The results, published in PLoS Biology, have potential clinical implications for the treatment of obesity and related diseases like diabetes.

Matesanz N, Nikolic I, Leiva M, Pulgarín-Alfaro M, Santamans AM, Bernardo E, Mora A, Herrera-Melle L, Rodríguez E, Beiroa D, Caballero A, Martín-García E, Acín-Pérez R, Hernández-Cosido L, Leiva-Vega L, Torres JL, Centeno F, Nebreda AR, Enríquez JA, Nogueiras R, Marcos M, Sabio G. p38α blocks brown adipose tissue thermogenesis through p38δ inhibition. PLoS Biol. 2018 Jul 6;16(7):e2004455. doi: 10.1371/journal.pbio.2004455.

10. Journal of Experimental Medicine The dual and unknown function of the immune system

The cells of the immune system sustain life by infiltrating infected and damaged tissue and eliminating pathogenic microorganisms and cell debris. However, immune action produces a collateral damage of its own that can lead to autoimmune disease or contribute to the injury associated with myocardial infarction or stroke. Now, a new study led by CNIC researcher Andrés Hidalgo and published in the Journal of Experimental Medicine shows that in addition to its defense function and the associated damage to affected tissues, the immune system also plays an important role in the day-to-day function of healthy organs. The research results show that the immune cells called neutrophils help to maintain the normal function of healthy tissues.

Casanova-Acebes M, Nicolás-Ávila JA, Li JL, García-Silva S, Balachander A, Rubio-Ponce A, Weiss LA, Adrover JM, Burrows K, A-González N, Ballesteros I, Devi S, Quintana JA, Crainiciuc G, Leiva M, Gunzer M, Weber C, Nagasawa T, Soehnlein O, Merad M, Mortha A, Ng LG, Peinado H, Hidalgo A.Neutrophils instruct homeostatic and pathological states in naive tissues. J Exp Med. 2018;215(11):2778-95. doi: 10.1084/jem.20181468 10.1084/jem.20171738

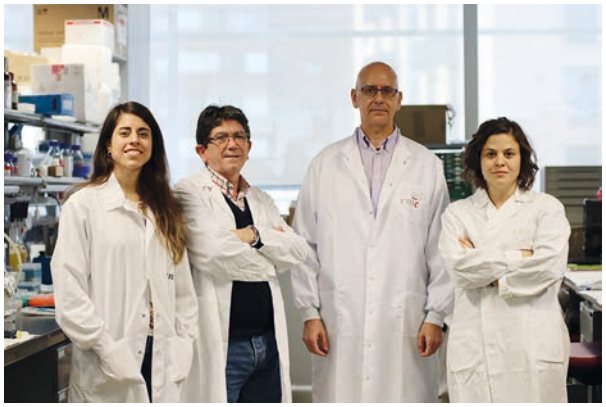
11. Science A new mechanism in the control of inflammation

In response to infection or tissue injury, our bodies react by activating the inflammatory immune response, which attacks the infection and repairs the damaged tissue. However, excess inflammation can sometimes have the opposite effect, increasing injury in a process known as immunopathology. Now, researchers at the CNIC have discovered a new inflammation control mechanism that shows how the damage caused by the immune response can be controlled. The study is published in Science.

Del Fresno C, Saz-Leal P, Enamorado M, Wculek SK, Martínez-Cano S, Blanco-Menéndez N, Schulz O, Gallizioli M, Miró-Mur F, Cano E, Planas A, Sancho D. DNGR-1 in dendritic cells limits tissue damage by dampening neutrophil recruitment. Science. 2018;362(6412):351-6. doi: 10.1126/science.aan8423

12. Nature Communications
Blocking hypertension with antihypertensive drugs prevents the development of a lethal disease

Researchers at the CNIC and the Consejo Superior de Investigaciones Científicas (CSIC) have discovered that effective control of high blood pressure with antihypertensive drugs prevents the development of aortic intramural hematoma (IMH), a serious and potentially lethal disease. The research has also identified specific proteins implicated in the disease, and the authors have generated a preclinical model be for the study of intramural hematoma that will be useful for evaluating possible pharmacological treatments. The study, published in Nature Communications, was co-directed by Miguel Campanero of the Instituto de Investigaciones Biomédicas Alberto Sols (CSIC), and CNIC group leader Juan Miguel Redondo.



Villahoz S, Yunes-Leites PS, Méndez-Barbero N, Urso K, Bonzon-Kulichenko E, Ortega S, Nistal JF, Vazquez J, Offermanns S, Redondo JM, Campanero MR. Conditional deletion of Rcan1 predisposes to hypertension-mediated intramural hematoma and subsequent aneurysm and aortic rupture. Nat Commun. 2018;9 (1):4795. doi: 10.1038/s41467-018-07071-7