

CIC biomaGUNE collaborates in the study of a key mechanism in hypoxia, published in *Nature*

The study, led by researchers from the CNIC and IIS Princesa, shows that sodium controls hypoxic signaling in the mitochondrial respiratory chain

The findings represent an important advance in the understanding of cell physiology and could be exploited in the future to treat diseases in which hypoxia plays a role

Donostia-San Sebastian (Basque Country), 29 July, 2020. A multidisciplinary study published in *Nature* in which the Laboratory of Molecular and Functional Biomarkers of CIC biomaGUNE has participated, led by Ikerbasque Professor Jesús Ruiz Cabello —specialist in the study of pulmonary vascular diseases—, have made a major advance toward deciphering the mechanism through which the production of reactive oxygen species (ROS) increases in the early phases of hypoxia (acute reduction in tissue oxygen). The finding represents an important advance in the understanding of cell physiology and could be exploited in the future to treat a variety of diseases in which hypoxia plays a role, such as stroke and heart attack.

In most eukaryotic cells, energy is generated by the consumption of oxygen in the mitochondrial oxidative phosphorylation (OXPHOS) system. The consumption of oxygen by this system generates reactive oxygen species (ROS), a group of molecules that until recently were considered to be metabolic toxins. However, it is now known that when produced in small amounts, these reactive species act as signals that trigger cell adaptations. In this way, a drop in oxygen concentration triggers the rapid generation of ROS, which initiate the adaptive response of cells to oxygen deficiency.

The 2019 Nobel Prize in Physiology or Medicine was awarded to the scientists who discovered the mechanism by which cells mount a response to sustained hypoxia. This long-term response is mediated by hypoxia-inducible factor (HIF). But the body has other, faster ways to respond to hypoxia that are independent of HIF and are mediated by ROS. The exact mechanism through which ROS production is increased in the early stages of hypoxia is still unclear, but the new study makes an important advance toward defining this process. The study has determined that sodium ions act as second messengers that regulate mitochondrial function, specifically the function of the mitochondrial electron transport chain (ETC), by inducing the controlled production of ROS. This mechanism of ROS production is fundamental to the ability of the pulmonary circulation to respond to hypoxia by redistributing blood flow to regions with less irrigation, a phenomenon known as hypoxic pulmonary vasoconstriction.

Several of the study findings provide important information about cell physiology. First, the study shows that mitochondrial sodium regulates cell membrane fluidity. This, which scientists at CIC

Further information:
Elhuyar Komunikazioa
Alaitz Imaz

688 860 706 – 943 36 30 40

biomaGUNE helped to decipher, was unknown before and could have major implications for the understanding of a multitude of cellular processes. A second important discovery is that the mitochondrial supercomplexes of the ETC play an important role in this process by adopting structural conformations that are sensitive or insensitive to sodium, thus ensuring that the action of sodium is nontoxic. Also, the entry of sodium is preceded by the solubilization of calcium deposits inside the mitochondria. These calcium structures were first described more than 50 years ago, but their function was unknown until now.

Finally, the study shows that inhibition of the mitochondrial $\text{Ca}^{2+}/\text{Na}^{+}$ exchanger NCLX is sufficient to block this pathway, preventing hypoxia adaptation. This finding indicates that NCLX could be a future therapeutic target for diseases in which hypoxia plays a role. The study results reveal that sodium controls OXPHOS function and cell signaling in hypoxia through an unexpected interaction with phospholipids, with major consequences for cell metabolism.

The study is the fruit of a partnership between the groups led by Dr Antonio Martínez, at Hospital Santa Cristina (part of the IIS Princesa), and Dr José Antonio Enríquez, at the CNIC. The study was led by Dr Pablo Hernansanz-Agustín, a postdoctoral researcher at the CNIC. In addition to the Centre for Cooperative Research on Biomaterials (CIC biomaGUNE), the study also involved contributions from scientists working at the Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), the Centro Andaluz de Biología del Desarrollo-Universidad Pablo de Olavide-CSIC (Seville), and the Spanish biomedical research networks (CIBER) in Respiratory Diseases (CIBERES), Rare Diseases (CIBERER), Frailty and Healthy Aging (CIBERFES), and Cardiovascular Disease (CIBERCV).

About CIC biomaGUNE

The Centre for Cooperative Research in Biomaterials, CIC biomaGUNE, member of the Basque Research and Technology Alliance (BRTA), conducts state-of-the-art research at the interface between Chemistry, Biology and Physics devoting particular attention to studying the properties of biological nanostructures on a molecular scale and their biomedical applications. It was recognised in 2018 as a “María de Maeztu” Unit of Excellence for meeting requirements of excellence, which are characterised by a high impact and level of competitiveness in its field of activity on the global scientific stage.

Bibliographical references

Jose Enriquez, Pablo Hernansanz-Agustín, Carmen Choya-Foces, Susana Carregal-Romero, Elena Ramos, Tamara Oliva, Tamara Villa-Piña, Laura Moreno, Alicia Izquierdo-Álvarez, Daniel Cabrera-García, Ana Cortes, Ana Lechuga-Vieco, Pooja Jadiya, Elisa Navarro, Esther Parada, Alejandra Palomino-Antolín, Daniel Tello, Rebeca Acin-Perez, Juan Carlos Rodríguez-Aguilera, Plácido Navas, Angel Cogolludo, Iván López-Montero, Alvaro Martínez-del-Pozo, Javier Egea, Manuela López, John Elrod, Jesús Ruiz-Cabello, Anna Bogdanova, Antonio Martínez-Ruiz.

Na⁺ controls hypoxic signalling by the mitochondrial respiratory chain

Nature

DOI: [10.1038/s41586-020-2551-y](https://doi.org/10.1038/s41586-020-2551-y)