IBiS researchers describe the mechanism behind blood oxygen level sensing

- The work carried out at the IBiS, with international cooperation, has been co-directed by Dr José López Barneo, head of the "Cellular Neurobiology and Biophysics" group and member of CIBERNED, and Dr Patricia Ortega Sáenz, co-first author together with Dr Daniel Cabello Rivera. The main authors of the work are IBiS researches and members of the Medical Physiology and Biophysics Department of the Seville Faculty of Medicine.
- The study published in the journal *Proceedings of the National Academy of Sciences (PNAS)* demonstrates the importance of the mitochondria for living beings' survival in situations involving a reduction of oxygen content in the blood.

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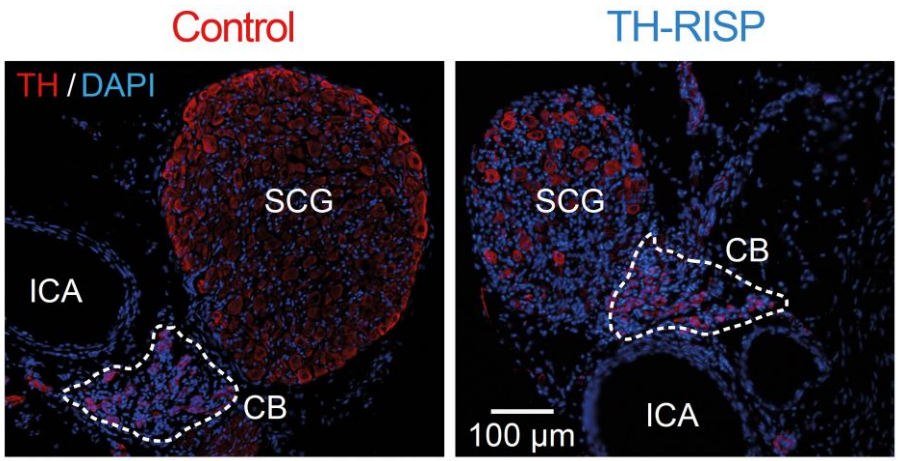
This research has been carried out by the IBiS "Cellular Neurobiology and Biophysics" group, led by Dr José López Barneo, and focuses on the basic mechanisms behind cellular oxygen sensing. As well as presenting in high-altitude areas, hypoxia (oxygen deficit) is a critical factor linked to various cardio-respiratory pathologies of high morbidity and mortality in humans. The carotid body, a highly irrigated structure located in the carotid bifurcation is considered the prototypical organ in acute oxygen sensing. Its activation during hypoxia causes hyperventilation and other cardiovascular reflexes, responses that are essential for the body's adaption to a reduction in oxygen and which minimise its harmful effects. Despite its biomedical relevance, the molecular basis of acute hypoxia sensing has remained elusive for decades.

In previous works, the group led by Dr José López Barneo has demonstrated that the chemoreceptor cells of the carotid body (glomus cells) contain specialised mitochondria that generate signals during hypoxia (including reactive oxygen species or ROS) that regulate cellular excitability. This specific sensitivity of glomus-cell mitochondria to hypoxia comes as a result of its specialised metabolism and depends on transcription factors, enzymes and specific components from the mitochondrial electron-transport chain. The study now published in the *Proceedings of the National Academy of Sciences (PNAS)* journal completes the characterisation of the molecular mechanisms of acute oxygen sensing by the carotid body, a process with potential pathophysiological relevance in maladaptive responses to hypoxia.

For this, the researchers have used a genetically modified mouse model, in which the electron-transport chain is interrupted by the carotid body. More specifically, the studies are based on a knockout mouse model for mitochondrial complex III of the respiratory chain in glomus cells, which results in the functional disconnection of mitochondrial complexes I and IV. The chemoreceptor cells of the carotid body survive mitochondrial complex III disfunction, but show selective abolition of the cellular response to hypoxia, while maintaining responses to other stimuli such as hypoglycaemia. As a consequence, the mice present a strong inhibition of the hypoxic ventilatory response, with insufficient ventilatory frequency to cope with the oxygen deficit. This maladaptation is demonstrated when the mitochondrial-complex-III-deficient mice are maintained in hypoxia for several days, as the animals show symptoms of impaired acclimatisation (excessive increase of haematocrit and cardiac hypertrophy, among others). The results obtained indicate that, for suitable acute hypoxia sensing in the cells of the carotid body, a functional electron-transport chain is required, in which the integrated action of its components makes possible the oxygen regulation of respiration.



Given the importance of the carotid body in the regulation of respiration, the researchers highlight the mitochondrial electron-transport chain as a potential therapeutic target for the pharmacological treatment of respiratory depression or pathologies involving the over-activation of the carotid body.

Alongside IBiS researchers, Dr Paul T. Schumacker, from Northwestern University, Chicago (United States) has also participated in this work.

Article reference

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About IBiS

The Institute of Biomedicine of Seville (**IBiS**) is a multidisciplinary centre whose objective is to carry out fundamental research on the causes and mechanisms of the pathologies most prevalent within the population and to develop new diagnostic and treatment methods for said pathologies.

IBiS is made up of 42 consolidated groups and 42 associated groups led by researchers from the University of Seville, the Spanish National Research Council (CSIC) and the Virgen del Rocío, Virgen Macarena and Virgen de Valme University Hospitals, organised around five thematic areas: Infectious Diseases and the Immune System; Neurosciences; Onco-Haematology and Genetics; Cardiovascular Pathology; Respiratory/Other Systemic Pathologies; and Hepatic, Digestive and Inflammatory Diseases.

IBiS is institutionally dependent on the Department of Health and Consumer Affairs of the Andalusian Government; the Andalusian Health Service (SAS); the Department of Universities, Research and Innovation; the University of Seville and the Spanish National Research Council (CSIC).

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