A new IBiS study sheds light on the relationship between the peripheral inflammatory response and Parkinson's disease

- **The research reveals relevant aspects in the development of what is known as the peripheral immune inflammatory response and points to the importance of genetic variants in the development of the disease.**
- **Although it is known that inflammation may be a crucial factor in the appearance and development of this disease, genetic factors, and their involvement in other physiological processes such as this, still represent an unexplored map.**
- **With this research, they get a little closer to new therapeutic pathways, as well as helping to understand how the neurodegeneration process affects patients with Parkinson's.**

Sevilla, March 22nd, 2023

Researchers from the Institut of Biomedicine of Sevilla (IBiS) have demonstrated the existence of an important relationship between the inflammatory response, Parkinson's disease and its genetic characteristics. The peripheral inflammatory immune response is different depending on the presence of variants in genes associated with the disease, which implies that there are different pathophysiological mechanisms and, therefore, different potential ways of treatment and action against the disease. For researchers, the results highlight the need to subclassify patients in research based on their genetics.

“Many” Parkinson's diseases

The origin of Parkinson's disease lies in neurodegeneration, that is, in the chronic and progressive deterioration of the nervous system. Parkinson's, however, has various variants that actually make this disease to be many. The classic motor symptoms of are due to degeneration of dopaminergic neurons in the substantia nigra of the midbrain. However, the combination of mechanisms responsible for neuronal death is likely to be variable and different in each patient with the disease. Therefore, considering Parkinson's disease as a single entity may be a limitation to advance our knowledge of the disease.

“Parkinson's is the second most prevalent neurodegenerative disease today, after Alzheimer's, and belongs to the so-called Movement Disorders. This disease has a great personal and socioeconomic impact worldwide, which makes it necessary to persevere in the study of its causes in order to identify disease-modifying treatments. It is well known that the clinical characteristics and their evolution are highly variable between patients", explains ***Laura Muñoz Delgado***, a specialist in the ***Movement Disordes Unit***, of ***IBiS***, “which is probably also translating different underlying causal mechanisms”.

The probable existence of various diseases depending on the mechanisms that lead to neuronal death, as indicated by the specialist, can lead to completely different needs and approaches when dealing with the pathology. “The identification of associated genes represents an excellent opportunity to investigate the cellular mechanisms in which they are involved”, she continues. “Two well-established genes associated with Parkinson's disease are LRRK2, the most common cause of familial Parkinson's disease, and GBA, which is the major genetic risk factor for Parkinson's disease”.

Currently, the causes are not fully known, but the evidence points to the fact that inflammation, related with both, the central and the peripheral blood, is a key element in the initiation and progression of neurodegeneration. “The research group led by ***Dr. Pablo Mir*** previously demonstrated the existence of peripheral inflammation and immune dysregulation in patients with Parkinson's disease”. The investigators previously described that the neutrophil-to-lymphocyte ratio is higher in patients with Parkinson's disease compared to healthy individuals. This ratio is a well-established biomarker of the presence of inflammation in the body. As detailed by ***Dr. Muñoz Delgado***, the increase in the ratio reflects greater systemic inflammation and deregulation between two types of cells of our immune system, neutrophils, and lymphocytes. In other words, the number of neutrophils, a type of white blood cell, is in an abnormal ratio to lymphocytes, another type of essential immune cell. In the current study, the group has verified that this, and the associated inflammatory response, is directly related to the genetic characteristics of the patients.

More or less inflammation: the relationship with the genetic background

“In this study”, explains ***Dr. Laura Muñoz Delgado*** about the research published in the prestigious journal npj Parkinson's disease, “we have shown that this peripheral inflammatory response differs in patients with Parkinson's disease according to their genetic characteristics. In the study we observed that patients with

sporadic Parkinson's disease, without identified genetic variants, and those with mutations in the GBA gene have a higher neutrophil-lymphocyte ratio and a lower number of lymphocytes in peripheral blood". This, in the words of the doctor, supports the presence of greater peripheral inflammation in these patients.

"This ratio is a well-established marker of inflammation, reflecting dysregulation between two cell populations: neutrophils represent chronic inflammation, while lymphocytes show the regulatory pathway. The decrease in the number of lymphocytes in the blood in patients with Parkinson's disease is a constant finding in many published works. This suggests that it could be due to a deregulation in their subpopulations [the number of cells of this specific type] with an increase in proinflammatory lymphocytes and a decrease in anti-inflammatories" he explains.

"On the other hand," the specialist points out, "it should be noted that patients carrying severe variants in the GBA gene tend to have a more aggressive course in terms of dementia. Interestingly, the development of dementia in Parkinson's disease has also been linked to increased peripheral inflammation". This relationship emphasizes the importance of the inflammatory response in some of the most aggressive manifestations of Parkinson's, which could put the spotlight on new ways of studying the pathology.

The most relevant finding, however, is that patients with mutations in the LRRK2 gene did not show differences in either the neutrophil-lymphocyte ratio or the lymphocyte count compared to healthy individuals. "This may indicate that the inflammatory pathogenic mechanisms could be different in these patients", clarifies ***Muñoz Delgado***. "This result is very much in line with other recent publications that suggest that the inflammation associated with mutations in the LRRK2 gene would be associated with circulating inflammatory mediators instead of a deregulation of lymphocytes", which implies a different pathophysiological mechanism and, therefore, Therefore, it suggests other avenues of investigation.

"We believe", emphasizes the researcher, "in light of the study results, that there is a need to subclassify patients in research based on their genetic characteristics, since they involve different cellular pathways that could facilitate understanding of the pathophysiology of the disease and apply personalized medicine".

In search of new therapeutic targets

The Institute of Biomedicine of Seville (**IBiS**) works to promote biomedical research from a multidisciplinary point of view, based on fundamental research at the molecular or cellular level, with the aim of immediately transferring knowledge to clinical reality, empowering the research of clinical and epidemiological quality at the same time. The ***Movement Disorders Unit***, of the Neurology and Neurophysiology Department, is currently working on projects that study the mechanisms underlying the peripheral inflammatory response, as well as its relationship with the clinical, genetic and neuroimaging characteristics of Parkinson's disease.

The research projects developed within ***Dr. Pablo Mir's group*** will allow a better understanding of the causes involved in the pathology, seeking potential implications in the development of future individualized

therapeutic targets. Although it is a complex path, and a major scientific challenge, research such as the one reviewed help to clarify the correct direction in which research efforts must be directed, laying the foundations for future new treatment possibilities for the disease.

Reference:

Peripheral inflammatory immune response differs among sporadic and familial Parkinson's disease | npj Parkinson's Disease (nature.com)

Fig:

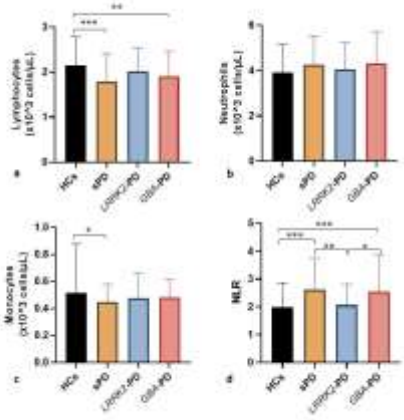

Fig 1.- HCs, healthy controls; sPD, sporadic Parkinson's disease; NLR, neutrophil-lymphocyte ratio; sPD, sporadic Parkinson's disease

Fig 2.- IBiS Researchers - Laura Muñoz Delgado, Pilar Gómez Garre, Pablo Mir Rivera

About IBiS

The Institute of Biomedicine of Seville (**IBiS**) is a multidisciplinary center focused on (1) carrying out fundamental research on the causes and mechanisms of the most prevalent pathologies in the population and (2) the development of new methods to diagnose and to treat diseases.

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

IBiS depends institutionally on the Department (Consejería) of Health and Consumption of the Junta de Andalucía; the Andalusian Health Service (SAS); the Department (Consejería) of University, Research and Innovation; the University of Seville and the Spanish National Research Council (CSIC). It is managed by the Public Foundation for the Management of Health Research in Seville (FISEVI).

More information:

Angeles Escudero
Unidad de comunicación| UCC+i
InstitutodeBiomedicinadeSevilla - **IBiS**
Campus Hospital Universitario Virgen del Rocío
Avda. Manuel Siurot s/n
41013 Sevilla
Tel 682730351
Email: comunicacion-ibis@us.es