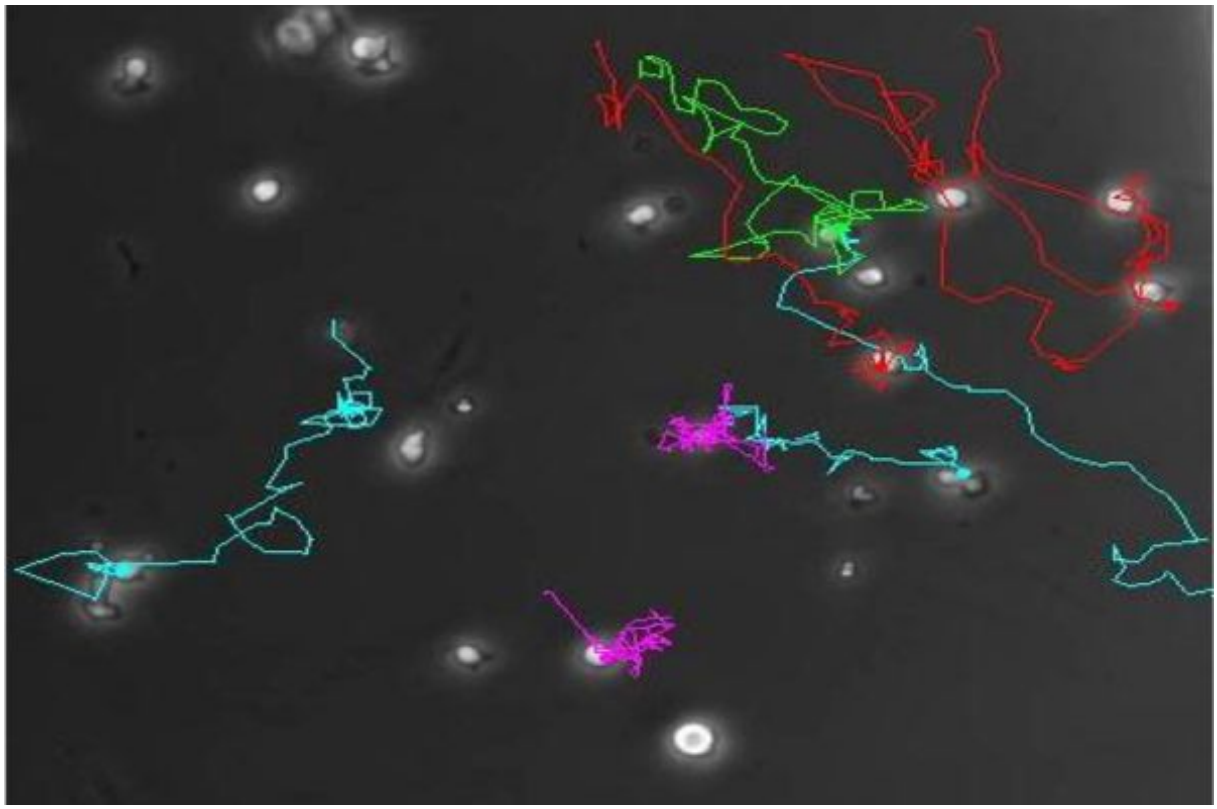

Single-molecule imaging to study the molecular mechanisms of a rare immunodeficiency disorder

Advanced imaging-based approaches are incorporating new concepts into our knowledge of biological processes. Using single-molecule imaging, researchers analyse the molecular mechanisms behind the malfunction of the receptor CXCR4, involved in the WHIM syndrome.

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Cell migration is involved in the major developmental stages of all complex organisms and is essential for many physiological and pathological processes. It occurs during vital processes, such as tissue renewal and repair and plays a key role in mediating immune responses during infections. Being a complex gear, it requires the coordinated intervention of a wide variety of signalling proteins and receptors, that activate pathways inside the cells in response to external stimuli.

One of the parts that participate in the correct deployment of cell migration is the actin

cytoskeleton. The cellular cytoskeleton is a network of protein filaments inside the cells, constantly remodelling itself in response to the changing cellular microenvironment. Failures in the actin cytoskeleton remodelling or signalling pathways can cause losses in cell movement or cell migration, which can result in several immune system problems.

WHIM syndrome, a rare disorder

The WHIM syndrome is a rare primary immunodeficiency disorder, characterized by irregularities in the cell development or the cell maturation process of the immune system. The syndrome is linked to specific mutations in the chemokine receptor CXCR4, a special type of protein involved in cell migration. Chemokine receptors respond to chemoattracting gradients to guide cell migration.

Patients with WHIM syndrome are more susceptible to potentially life-threatening bacterial or viral infections, such as the human papillomavirus, which can cause skin and genital warts and potentially lead to cancer.

Analyzing the dynamics of individual CXCR4 receptors

Researchers already know that in WHIM patients, the receptor CXCR4 has an excessive activity due to a failure to down-regulate. However, it is still unclear if this excess affects B cells, the ones in charge of producing antibodies, and if it can lead patients to be more susceptible to the papillomavirus.

Now, ICFO researchers **Nicolas Mateos** and ICREA researcher **Prof. Maria Garcia-Parajo** from the Single Molecule Biophotonics group provide insights into how these mutations influence immune cell trafficking. The findings have been published in a study in PNAS, in collaboration with researchers from the National Center for Biotechnology, the Andalusian Molecular Biology and Regenerative Medicine Centre, the Hospital Universitario de la Princesa, the 12 de Octubre Health Research Institute, the Weill Cornell Medicine and ETH Zürich.

The altered function of CXCR4 impairs cell migration

Correct functioning of the receptor CXCR4 requires its nanoclustering on the cell membrane, which is enhanced upon the binding of chemokines. Researchers discovered that this process of nanoclustering does not happen in the appropriate way when CXCR4 is altered. The team studied the molecular mechanisms directing the CXCR4 function using quantitative single-molecule imaging and detailed data algorithm analysis. By using single molecules to track the spatial receptor dynamics, researchers saw that CXCR4 receptors carrying specific mutations associated with the WHIM syndrome failed to cluster after being stimulated by chemokines.

This failure to cluster -or group-, after stimulation, caused an abnormal activation of a protein known as ?-arrestin1. As a result, the actin cytoskeleton remodelling is impaired, and the lateral mobility and spatial organization are altered. These defects, associated with the

mutant expression, explain the severe immunological symptoms associated with WHIM syndrome.
The findings add more information about the molecular mechanisms of the CXCR4 receptor, pointing out the links between the spatiotemporal organization of CXCR4 and the symptoms of WHIM syndrome. Moreover, the study also highlights the importance of new imaging-based techniques, allowing to unveil more details about several biological processes.