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PhD THESIS DEFENSE: Integrin dynamics and mechanobiology in leukocytes - A multiscale tracking study

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11:00

Auditorium

This thesis explores the molecular mechanisms underpinning leukocyte adhesion and migration, with a primary focus on the mechanobiology of integrin Lymphocyte function-associated antigen 1 (LFA-1). Integrins are key mediators of cell adhesion, which are pivotal in immune response and facilitate leukocyte adhesion, migration, and extravasation at infection sites. This thesis begins by summarizing the structural characteristics of integrins, their mechanobiology and the physiological processes involved in LFA-1 activation, emphasizing the roles of chemokines, adaptor proteins, and tensile forces in modulating integrin function.

The experimental research employs advanced single-particle tracking (SPT) using a home-built live-cell microscope with single molecule sensitivity. This multiline-illumination dual-view microscope, combined with a custom-built flow system, enables the investigation of LFA-1 activation at the level of individual molecules under shear flow. We use specific surface functionalization to provide the appropriate stimuli and interaction partners for leukocyte adhesion and migration.

The study highlights the characteristics of LFA-1 mobility and engagement, showing how it is regulated by various stimuli, including physiological chemokines like CXCL12 and divalent cations such as Mn2+. The critical role of adaptor proteins, particularly talin, in mediating the integrin-actin cytoskeleton linkage essential for leukocyte motility, is also examined. The findings underscore the importance of integrin ligation and cytoskeletal association in integrin activation for effective leukocyte migration, highlighting the need for precise spatiotemporal control of integrin engagement for leukocyte motility.

We further dissect the impact of external tensile forces, such as shear flow, on integrin activation. We demonstrate that these forces significantly increase integrin activation, consequently reinforcing cell adhesion and migration under varying flow conditions. The study also reveals the complex interplay between biochemical stimuli and mechanical forces in modulating integrin activation and consequently leukocyte behavior. In this context, we additionally we bring attention to the relevance of adaptor proteins like talin.

Finally, we shift focus to the spatiotemporal relationship between the C-X-C chemokine receptor type 4 (CXCR4) and LFA-1. The focus lies on the functionally relevant CXCR4 nanoclustering and its vicinity to LFA-1 activation. We uncover unexpected behaviors in functional CXCR4 nanoclustering and investigate its spatial relation to integrin activation. The study extends to both healthy CXCR4 and a pathologically altered form, a R334X mutation found in patients with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome.

The thesis concludes by synthesizing these findings, emphasizing the critical role of mechanobiology in leukocyte migration and the complex regulatory mechanisms governing integrin activation. By providing a detailed framework for understanding integrin dynamics, the research points towards its potential implications for pathophysiological alterations of the blood flow and the potential for further studies using advanced biophysical techniques to unravel the intricate molecular interplays at work. Future perspectives include investigating the interplay of the regulatory network for integrin activation, the impact of integrin ligand organization, and the effect of mechanical forces on the relevant players. The insights gained from this work could pave the way for novel therapeutic strategies that target the mechanobiological aspects of immune cell motility, offering new avenues for the treatment of inflammatory diseases and immune-related disorders where aberrant cell adhesion and migration plays a critical role.

Tuesday October 22, 11:00h. ICFO Auditorium

Thesis Director: Prof. Dr. Maria Garcia-Parajo

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