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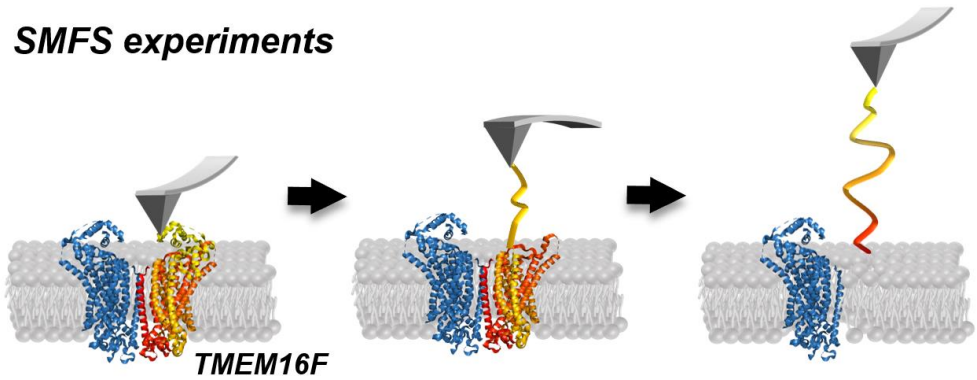
PRESS RELEASE

Through the microscope: TMEM16F protein and its molecular dance

A new SISSA study expands the understanding of TMEM16F, a membrane protein involved in various biological processes such as blood coagulation.



Trieste, 1st March 2024

TMEM16F, a membrane protein involved in several crucial biological processes, including blood coagulation and Covid-19 pathogenesis, has been the focus of an innovative study conceived and led by a team of researchers and former PhD students from SISSA in collaboration with other institutions such as the University of Zurich and the Nano Life Science Institute at the University of Kanazawa. Membrane proteins, including TMEM16F, constitute a particularly complex field of study. To fully comprehend their structure and function, it is necessary to study them in their native environment. Using cutting-edge techniques such as single-molecule force spectroscopy (SMFS) and high-speed atomic force microscopy (HS-AFM), the team has unveiled new insights into the complex structural dynamics of TMEM16F. The results of this study, published in *Nature Communications*, open new pathways in medical research and could lead to the development of targeted therapies for diseases linked to the functioning of membrane proteins.

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Membrane proteins, as suggested by their name, are proteins found in cell membranes and play a key role in regulating cell functions, from nutrient transport to immune defence. However, studying these biological structures in their native environment is a complex challenge. In 2022, a group of researchers at SISSA overcame this difficulty by introducing an innovative approach that leverages artificial intelligence and atomic force microscopy. This new method allows for the study of the properties and mechanical stability of membrane proteins in their physiological conditions without the need for isolation.

‘Vincent, Zhongjie, Arin, and I had the idea several years ago to use atomic force microscopy to study membrane proteins in their native cell membrane, a challenge that seemed almost impossible. After years of careful design and problem-solving, we successfully developed a technique (Galvanetto et al., eLife (2022)) that appeared to solve the problem. Thanks to this innovative technique, we were able to successfully study the structure of the TMEM16F protein. Our pioneering work is now yielding tangible results, and this publication in Nature Communications is an example,’ explained Nicola Galvanetto, former SISSA PhD student and current researcher at the University of Zurich. ‘The structural heterogeneity revealed by our research was not predicted by the renowned AlphaFold program. It is very likely that this heterogeneity is present, albeit in different forms, in the structure of practically all proteins. Despite the usefulness of AlphaFold, it is essential to verify its results through other techniques, such as those used in our study.’

TMEM16F plays two key roles in cells: on one hand, it acts as a calcium-activated ion channel, allowing the selective passage of ions through cell membranes when the cell detects the presence of calcium; on the other hand, it functions as a lipid scramblase, facilitating the movement of lipids between cell membranes. This dynamic movement regulates essential biological functions, including blood clotting, bone development and virus entry. To examine the behaviour of TMEM16F at the molecular level in physiological environments, the research team, mainly composed of former SISSA researchers, adopted advanced approaches such as single-molecule force spectroscopy (SMFS) and high-speed atomic force microscopy (HS-AFM) These techniques provided significant insights into the structure, dynamics and mechanical properties of the protein, challenging the previous idea that TMEM16F functions as a simple 'gate'.

The study revealed that TMEM16F exhibits a wide range of previously overlooked structural conformations. Further investigation unveiled unexpected changes in the structural organisation of TMEM16F, indicating a more dynamic and flexible functioning than previously assumed. These changes in structure are fundamental to the way TMEM16F performs its tasks, such as mixing lipids and moving ions across cell membranes and highlight the importance of the dynamic element in

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understanding biological phenomena. Indeed, as Aristotle pointed out, 'Movement is life and life is movement.' Additionally, researchers discovered that when bound to calcium, the protein undergoes significant changes in specific areas, opening a kind of 'gate' for the passage of ions and fats.

This publication deepens previous studies, emphasises the importance of probing membrane proteins in native-like environments, and broadens the understanding of the structural peculiarities of TMEM16F. Understanding these structural features could pave the way for targeted therapies and interventions to modulate TMEM16F activity in various diseases and physiological conditions.

USEFUL LINKS
Full paper: nature communications

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