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Unlocking the ability to manipulate the properties of membranes by means of light

ICFO researchers demonstrate a new ability of the fluorescence probe Flipper to alter lipid composition, order and tension of cell membranes, unlocking the possibility to tune the biological function of membrane proteins by means of light.

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In recent years, many researchers have gradually become aware of the importance of the mechanical tension of cell membranes in regulating how proteins work. Initially, however, a technique that could locally measure the tension of the membrane was missing. Scientists had no means of discovering the mechanism underlying this phenomenon and, thus, researchers from all over the globe were eager for a solution to break through the barriers in the study of membrane protein function.

Then, in 2018, researchers from Switzerland synthesized a powerful fluorescent probe called Flipper, designed to sense and report on membrane tension. It seemed to be everything the scientific community had been looking for, so everyone rushed to use it. But the initial euphoria did not last for long. Shortly after Flipper's introduction, various research groups noticed some negative effects: after applying Flipper for some minutes, cells started to die, bringing experiments to an abrupt end. It turned out that the probe was toxic to the cells.

Now, ICFO researchers **Dr. Joaquim Torra** and **Dr. Felix Campelo**, led by **ICREA Prof. Maria F. Garcia-Parajo**, have turned this apparent weakness into a strength. The team has demonstrated a **new ability of Flipper** (previously used exclusively to measure the tension of membranes) **to alter lipid composition, order and tension of the membrane**. The team further shows that, by using blue light, one can guide proteins to specific regions of the membrane. At the same time, they elucidated the mechanisms by which Flipper induces all these changes. The reported discovery has recently been published in the Journal of the American Chemical Society.

These findings are major results in the field because the composition and arrangement of lipids in cell membranes dramatically influence the function of proteins that are embedded on specific regions of those membranes. Thus, by using light to manipulate the properties of membranes, **the team has opened the door to the possibility of tuning the biological function of membrane proteins in the near future, a long-standing goal for many researchers in the**

world.

Predicting Flipper's new ability

The ICFO team was one of those groups that noticed the negative effects of Flipper in terms of toxicity while studying cell membrane tension. This effect particularly attracted the attention of Dr. Joaquim Torra, first author of the article, when he observed it during previous experiments. But, instead of trying to get rid of it, he embraced the hurdle.

His chemical background enabled him to hypothesize that the phototoxicity of Flipper arose from the formation of reactive oxygen species, which are very toxic to cells. He then came up with an idea that would change the course of his following research projects: these species reacted in a very specific way, modifying the surrounding unsaturated lipids in a process called hydroperoxidation. He guessed (correctly, as it turned out) that these hydroperoxide lipids could increase membrane tension, trigger the separation of lipids into different regions within the membrane and drive membrane protein sorting.

Putting theory into practice: manipulation of membrane properties achieved

After Torra's initial idea, the team set to work toward this ambitious goal. In the end, they showed that, upon controlled blue irradiation (the standard wavelength used to excite Flipper), the probe could, indeed, simultaneously induce and visualize changes in the tension, lipid composition and protein order of model and biological membranes.

The specific location of proteins on the membrane plays an important role in regulating their interactions with other molecular components and what functions they carry out (for instance, sending signals to the cell, so that in turn the cell can perform a specific action). The implications of this achievement are, therefore, highly significant.

ICREA Prof. Maria F. Garcia-Parajo illustrates the concept with a down-to-earth example: ¡¿? A person can be in different environments. For instance, you could be in your home sitting in a sofa and surrounded by your family, or at work surrounded by your colleagues and in front f a computer. Depending on the environment you are, you will perform a different function Now imagine that I can change your environment, magically transforming family i to colleagues and the sofa into a computer room. Then, you would ?feel' the change of he environment and automatically change your function. This is exactly what happens in biology! The surrounding (the lipid composition, order and tension of the membrane) affe ts and defines the biological function of the proteins therei

?½. The team has found in Flipper a means to achieve exactly that, making it a **powerful tool to visualize and dynamically manipulate membrane heterogeneity -and therefore properties- with high precision in space and time**. As a consequence, this technique offers the potential to study the interplay between membrane biophysical properties and cell functions.?

Future perspectives: bringing Flipper to living cells

i¿½We are very excited about these results and the prospects for the future. So far, we ha e understood the mode of action of Flipper on model membranes and membranes extract d from living cells. Now the obvious next step is to move to living cellsi¿½, shares Garcia-Par jo. The team is actively working on this right now, but first they need to overcome Flipp r's inherent toxicity to cells, the main obstacle preventing further progress in this direct on. In the future, provided that Flipper works in the context of living cells, it could be possibl to use the probe to reverse mechanical dysfunctionalities of membranes, helping to treat t ose diseases associated with dysregulated mechanical properties. i¿½For instance, c rtain proteins, called integrins, are involved in the adhesion and migration of cells. It was shown that the mechanical properties of the membrane increase integrin nanoclustering an that this, in turn, can boost the migration of cancer cells, which contributes to their meta tatic characteri¿½, explains Garcia-Parajo. Given their successful results, she for sees an optimistic scenario: i¿½If by controlling the composition of the membrane, using our reported technique, we disturb the clustering of integrins, then we could affect the migrating properties of cells and even possibly stop metastasis. This is a dream that co ld become reality o

Reference:

Joaquim Torra, Felix Campelo, and Maria F. Garcia-Parajo. Journal of the American Chemical Society 2024 146 (34), 24114-24124. DOI: 10.1021/jacs.4c08580
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