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Rafts in Our Cells: A New Role for Lipids in the Molecular Organization of Life

Por: Atomium Culture | 29 de agosto de 2013

By Rodrigo de Almeida, University of Lisbon

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Why does the membrane of each living cell contain hundreds of different kind of lipids? Why do cell membranes in different organisms differ in the kind and proportion of lipids? And, more importantly, how does that composition change in those suffering from ailments that increasingly characterize the modern society: cancer, Alzheimer’s disease and Parkinson’s disease, for example?

Questions such as these have puzzled scientists for decades, but answers to some of the questions are coming in now — and they all have converged on the role of lipids in the organization of the cell membrane.
Only in the past two decades were lipids given a prominent role among biomolecules. Most textbooks describe lipids as nutrients used for storing energy and as structural components of cell membranes — both somewhat passive roles. However, lipids moved to the top when scientists realized that lipid composition of the cell membrane is altered in those suffering from cancer, Alzheimer’s disease and Parkinson’s disease. A direct consequence of this understanding is the development of lipid therapies, that is, treatments based on managing the level of lipids in the cell membrane.

Researchers now realize that lipids are not merely a structural element of the cell membrane but are crucial to the cell’s behaviour: what we had assumed to be mere bricks in a wall were in fact sophisticated checkpoints regulating who can enter or leave the cell at any given time. It has therefore become important to know the different kinds of lipids that are involved, the changes in their levels and details of how they are organized in cell membranes. Lipids form distinct regions in the cell membrane, referred to as lipid domains (the ‘checkpoints’ mentioned above), each with its special composition and properties.

Lipid rafts are one such domain, which are rich in cholesterol and in sphingolipids, a special group of lipids named after the Sphinx, because their structure and function had remained mysterious for several decades.

Molecular interactions that occur within the cell membrane are subtle, transient and dispersed, and highly dependent on the concentration and location of molecules that participate in the interaction. The interactions pose a challenge to those who study them and have therefore attracted a fast-growing scientific community.

Of the several strategies deployed by different scientists all over the world to study molecular interactions within cell membranes, I chose membrane model systems. As the name suggests, the strategy is to build simple artificial membranes in the laboratory by mixing a few kinds, or ‘species’, of lipids. At the Molecular and Neural Biophysics Group, Centre for Chemistry and Biochemistry, Lisbon University <http://bmn.cqb.fc.ul.pt>, we prepare such artificial membranes and insert into them different membrane probes, which are molecules that are fluorescent and therefore easy to track. The fluorescence can be detected by different techniques and described by several parameters, all part of the umbrella term fluorescence spectroscopy. By combining the results of fluorescence spectroscopy with physical and chemical laws, we predict the conditions that lead to the formation of different types of lipid domains. By using appropriate membrane models, it is possible to study the composition and properties of these domains.

We then tag membranes of living cells as well as the artificial membranes with the same fluorescent probe; by comparing the behaviour of the probe in both types of membranes, we have identified major lipid domains of the cell membranes, major components of the domains and their properties, and the changes associated with different environmental conditions or diseases.

Recently, applying these methods in collaboration with the Biochemistry of Oxidants and Antioxidants Group at the Centre for Chemistry and Biochemistry, we found a new type of lipid rafts in cell membranes of the common yeast, better known to scientists as Saccharomyces cerevisiae (Aresta-Branco F, Cordeiro A M, Marinho H S, Cyrne L,
Antunes F, de Almeida R F M. 2011. The Journal of Biological Chemistry 286: 5043 – 5054). Yeasts, used for centuries in making bread and brewing beer, are also used by scientists to understand the behaviour of human cells because yeast cells are easy to manipulate in the laboratory. Moreover, although yeast cells are not as complex as human cells, both yeasts and Homo sapiens are eukaryotes and therefore related organisms. Typical lipid rafts in yeast contain sphingolipids and ergosterol (which is analogous to cholesterol). However, we found new rafts that contain only sphingolipids. The biophysical properties of these new lipid rafts are different from those of the typical lipid rafts, and interactions between molecules that make up the new rafts are stronger. We are pursuing our research on these new types of lipid rafts in yeasts and in other organisms to further elucidate the role of lipids in membrane organization and thus to better understand life itself.

Rodrigo de Almeida
University of Lisbon
www.atomiumculture.eu

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di DE ALMEIDA (University of Lisbon) – giovedì 29 agosto 2013 - 15:24

Example of a lipid raft organisation scheme.

DE ALMEIDA (University of Lisbon):

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Cardiovascular problems are among the more important causes of death in many European countries. One therapeutic strategy for a person that has a cardiac disease or has had a brain stroke is the delivery of small amounts of nitric oxide (NO) to the affected area. This causes dilation of arteries and other blood vessels and prevents blood aggregation by aiding in the removal of blood clots or other restrictions from the affected area, thereby normalizing blood supply.

NO is also used in the prevention of thrombus (blood clot) formation, nerve signal enhancement, wound repair and is the biological signalling agent responsible for the effects of Viagra. In fact, use of NO is an expansive field for drug developers, because of its multipurpose effects. However, like many other therapeutic substances, in high concentrations NO is poisonous and its handling and administration to patients must be done with extreme care. Some medicines that deliver NO are already available, but many are limited by the fact that, following delivery, they become distributed throughout the body, which may result in undesirable side effects and impair the selective delivery of NO. These limitations stress the need for the development of materials that can deliver NO in biologically relevant amounts to the targeted part of the body.

**NO Release by Porous Materials**

Some solid materials with tiny pores have the ability to store small gaseous molecules in those pores. In the faculties of science at the universities of Lisbon and Aveiro, Portugal, work is being done on the synthesis and applications of porous materials such as zeolites, clays and titanosilicates. The studies are aimed at determining if such materials can be loaded with gaseous NO and, more importantly, if the NO can be released slowly to the surrounding medium. Initially, the research measured the capacity of various materials to store NO. Intriguingly, it was found that the best capacity to store and release NO was not among materials with larger pores (higher porosity). Instead, material with the smallest pores presented the best results, due to the materials very slow release of NO.
Combining data obtained from adsorption, spectroscopic and computer simulation techniques it was possible to identify the characteristics of the porous materials that were responsible for the observed NO adsorption/desorption kinetics. For example, it was determined that the presence of unsaturated titanium atoms—with their ability to form additional chemical bonds—in the material’s framework plays an important role on the binding of NO inside the material’s small pores. On that basis, a novel approach to the designs of NO storage and releasing agents, based on very stable zeolite-type silicates that possess a framework of unsaturated transition-metal centres, has been proposed. Research based on that proposal has produced a titanosilicate (ETS-4) that displays excellent NO adsorption capacity and slow NO release kinetics. Not all of the molecular-level details are yet fully understood, but this type of porous materials has potential as an alternative approach to delivering NO to a specific location.

Possible Applications
Materials such as ETS-4, which can store and subsequently release NO, have the potential to be used in future treatment applications that can deliver NO to specific parts of the body, thereby avoiding the side effects associated with systemic administration (for example, oral-based or respiratory-based treatments) to a patient. Regardless, such materials could find more immediate application if used to treat skin ulcers or other wounds that are failing to heal. In addition, transdermal patches could be used to deliver NO to the blood stream. Similar patches are commercially available, but they are not made from porous solids. The immobile and insoluble nature of porous solids also favours their placement in or on affected tissue areas, thus enabling a controlled and continuous NO release while, at the same time, limiting the production of side effects.

Such treatment approaches may require the localised application of small implants. Preclinical development of nanometre-sized porous materials for use as implants requires a multidisciplinary research work ranging from materials’ science to biochemistry and medicine. Research regarding the long-term stability of such products, the toxicology of the materials and the NO amount that can be released under “real” application conditions needs to undertaken before moving forward to clinical trials involving patients. Nonetheless, nanoporous materials will certainly find their way into future treatments that can deliver NO to targeted tissues or areas.

Moisés Luzia Pinto
University of Lisbon
www.atomiumculture.eu