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pH Sensing by Lipids in Membranes: The Fundamentals of pH-driven Migration, Polarization and Deformations of Lipid Bilayer Assemblies

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Abstract

Most biological molecules contain acido-basic groups that modulate their structure and interactions. A consequence is that pH gradients, local heterogeneities and dynamic variations are used by cells and organisms to drive or regulate specific biological functions including energetic metabolism, vesicular traffic, migration and spatial patterning of tissues in development. While the direct or regulatory role of pH in protein function is well documented, the role of hydrogen and hydroxyl ions in modulating the properties of lipid assemblies such as bilayer membranes is only beginning to be understood. Here, we review approaches using artificial lipid vesicles that have been instrumental in providing an understanding of the influence of pH gradients and local variations on membrane vectorial motional processes: migration, membrane curvature effects promoting global or local deformations, crowding generation by segregative polarization processes. In the case of pH induced local deformations, an extensive theoretical framework is given and an application to a specific biological issue, namely the structure and stability of mitochondrial cristae, is described.

Keywords: lipid bilayer, giant unilamellar vesicle, membrane dynamics, local perturbation, chemical modification

1. Introduction

Throughout their life, cells are submitted to an inhomogeneous and variable environment, to which they adapt and respond. In particular, local pH inhomogeneities at the cellular scale are ubiquitous and very important, e.g. in migrating cells [1] and in mitochondria [2]. While cellular response to complex molecules are mediated by dedicated biochemical signaling pathways, e.g. in chemotaxis [3], cellular response to pH may also involve more universal physico-chemical mechanisms. Indeed, membrane lipids are directly affected by pH, due to their acido-basic properties. Such chemical modifications of lipids have generic physical effects on the cell membrane.

In order to quantitatively investigate these generic effects of pH on lipid bilayer membranes, experiments on biomimetic membranes [4] are particularly useful. A line of our work has focused on studying the various effects of pH changes on giant unilamellar vesicle (GUV). We demonstrated that a pH change can induce vesicle migration and global deformation [5], as well as polarization in vesicles involving phase-separated membrane domains [6]. Furthermore, we showed that localized pH heterogeneities can induce local dynamical membrane deformations and developed a theoretical description of this phenomenon [7–10]. We were also able to mimic the formation and behavior of healthy and diseased mitochondrial cristae using purely lipidic biomimetic membranes [7, 11, 12]. In this paper, we review this work, and we discuss its context and implications.

2. pH-induced migration, deformation and polarization processes in cells

The ability of cells to detect and react to chemical concentration gradients is instrumental for cell motility, proliferation and differentiation, and therefore essential for processes such as immunological response, development and wound healing. The mechanisms underlying cell chemotaxis toward complex organic or biosynthetic molecules have been widely documented [13]. Additionally, the role of gradients of "morphogens", i.e. secreted signaling molecules that determine the arrangement and developmental fate of cells according to their position inside a developing tissue or organism, is now recognized [14]. The role of pH gradients, which involve the ubiquitous H^+ (H_3O^+) and OH^- ions, in cell motility and deformation processes, emerged more recently. Proton gradients across membranes are well characterized as an essential intermediate electrochemical potential form for ATPase/synthase-associated bioenergetic processes in mitochondria, chloroplasts and unicellular organisms [15]. Also well-known is the role of intracellular vesicle transmembrane pH gradients as regulatory factors in endosomal, lysosomal and secretory pathways [16]. However, more recently, it has been found that pH gradients also act as chemotactic cues for microorganisms such as bacteria or