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A Review on Lipid Bilayer for Bio Molecular Caging

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Abstract: ***A lipid bilayer is a biological membrane consisting of two layers of lipid molecules. Each lipid molecule, or phospholipid, contains a hydrophilic head and a hydrophobic tail. Here the review is on synthesis of lipid and caging of biomolecules by lipid. There have been lot of work done on lipid, among the lipid there are 3 classes phospholipid, cholesterol and glycosides.***

Keywords: Lipid, biomolecules, caging, phospholipid

1. Introduction

Caged compounds are light - sensitive probes that functionally encapsulate biomolecules in an inactive form. Irradiation liberates the trapped molecule, permitting targeted perturbation of a biological process. Uncaging technology and fluorescence microscopy are 'optically orthogonal': the former allows control, and the latter, observation of cellular function. Used in conjunction with other technologies (for example, patch clamp and/or genetics), the light beam becomes a uniquely powerful tool to stimulate a selected biological target in space or time [1].

The idea behind the caging technique is that a molecule of interest can be rendered biologically inert (or caged) by chemical modification with a photo removable protecting group (Fig.1). The biologically active molecule that can bind to its cellular receptor, switching on (or off) the targeted process. Virtually every kind of signaling molecule or second messenger, of every size from protons to proteins has been caged [2].

A single component of cellular chemistry can control the function of a cell, and such cellular regulation can be temporally or spatially defined, intracellular or extracellular, and amplitude - or frequency - modulated [3]. Photo manipulation of cellular chemistry using caged compounds provides a uniquely powerful means to interact with such cellular dynamics, as it can touch upon any one of the above dimensions. Thus, since light passes through cell membranes, uncaging can rapidly release a biomolecule in an intracellular compartment [1]. Furthermore, uniform illumination results in release throughout the cytosol, or the release can be localized by focusing the uncaging beam on one part of a cell. Likewise, extracellular uncaging of neurotransmitters and hormones is tunable, allowing stimulation of many neurons simultaneously or of single synapses by global or focused illumination, respectively. Light cannot only be directed, but also modulated in time and amplitude. Thus, uncaging can also be used to produce rapid, repetitive release of biomolecules or finely graded changes in the magnitude of stimulation.

Examples of important caged biomolecules or second messengers are calcium [4 - 7], neurotransmitters [8 - 11], inositols [12 - 13], nucleotides [14 - 15], peptides [16 - 17], enzymes [18 - 20], mRNA [21] and DNA [22]. Apart from Ca^{2+}, all these molecules are caged by covalent modification of one part of their structure with a photo removable chromophore.

Caged compounds are made using synthetic organic chemistry. Syntheses are usually multistep, but some caged compounds are made with one - step 'direct' caging (Fig.1). Multistep syntheses are usually required because most natural products have many functional groups of equivalent reactivity.

The caging chromophore prevents receptor binding until it is cleaved by light. Second messengers can be caged by both strategies, but the illustration shows only two examples for simplicity [1].

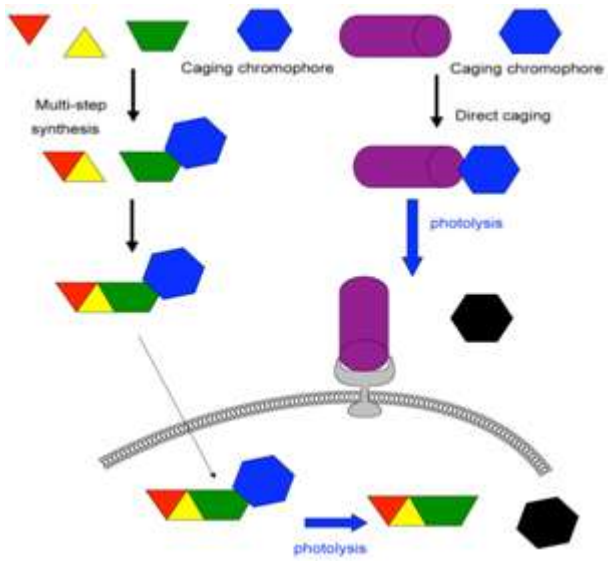

Figure 1: General strategies caged by either multistep or direct caging

Such research are based on structure and activity of lipid bilayer within a membrane - protein transporter [23], Biological Interactions of Supported Lipid Bilayers (SLB) [24], research of phospholipid and their use in drug delivery [25], synthesis and biosynthetic trafficking of membrane lipids [26], Organelle - Specific Uncaging of Lipid Messengers [27].

The tail regions, being repelled by water and slightly attracted to each other, congregate together. This exposes the

head regions to the outside, creating a barrier between two bodies of water. A lipid bilayer is the foundational part of all cellular membranes, typically completed with species - specific integral proteins and other functional aspects. A lipid bilayer functions through the actions of polarity.

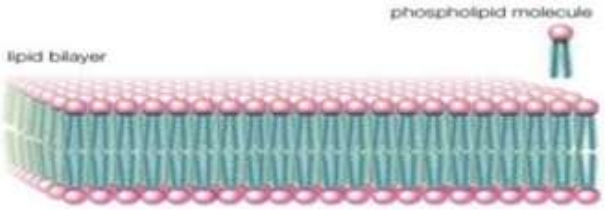

Figure 2: Biological membrane consisting of two layers of lipid molecules

The inside of the lipid bilayer is non - polar, while the heads are polar molecules and create hydrogen bonds with other polar molecules. This also means that polar molecules like water and ions cannot easily cross through the nonpolar tail region of the lipid bilayer. The cellular membranes of most organisms are created with lipid bilayer, as well as the nuclear membrane and various organelle membranes. The various functions of these membranes are then specified with a variety of proteins which allow or disallow certain substances to cross the membrane. In doing so, cells and individual organelles can create an ideal environment for biochemical reactions to occur, allowing them to stay in homeostasis [28].

There are different lipids that give different signals to different part of body.

There are several, typically redundant, mechanisms to transport lipids from their site of synthesis to other cellular membranes. Biosynthetic lipid transport helps to ensure that each cellular compartment will have its characteristic lipid composition that supports the functions of the associated proteins. [26]

In phospholipids, the sn - 1 and sn - 2 position of the glycerol backbone are esterified with fatty acids of varying length and degree of saturation. The remaining sn - 3 position is esterified with phosphoric acid, which, in turn, is esterified with an alcohol [30]. Depending on the structure of the alcohol, different types of phospholipids are formed, for example, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI), or phosphatidylserine (PS) [31]. The specific an dnon - random distribution of substituents over the positions sn - 1, sn - 2, and sn - 3 of the glycerol introduces chirality [25]. Depending on the structure of the polar head group and pH of the surrounding medium, PE and PC are zwitterionic and have a neutral charge at pH 7, whereas PG, PI, and PS are negatively charged at this pH value.

2. Bilayer Lipid as Carrier

Lipid messengers exert their function on short timescales at distinct subcellular locations, yet most experimental approaches for perturbing their levels trigger cell - wide concentration changes. Reports on a coumarin - based photocaging group that can be modified with organelle targeting moieties by click chemistry is found and thus enables photorelease of lipid messengers in distinct organelles. It has been reported that caged arachidonic acid and sphingosine derivatives can be selectively delivered to mitochondria, the ER, lysosomes, and the plasma membrane. By comparing the cellular calcium transients induced by localized uncaging of arachidonic acid and sphingosine, it shows that the precise intracellular localization of the released second messenger is crucial for the signaling outcome. Ultimately, this new class of caged compounds will greatly facilitate the study of cellular processes on the organelle level. [27]

Photochemical release of lipid messengers from inactive (caged) precursors offers a much broader substrate scope, but spatial control of the induced concentration bursts by optical means remains highly challenging [32 - 34].

Ideally, caged compounds should be prelocalized to their target organelles prior to photorelease by dedicated chemical groups to ensure spatially controlled uncaging [35]. This strategy has been realized in a limited number of examples [36 - 39]. However, its applicability is compromised by the fact that caged compound sets have to be generated by total synthesis for each messenger and the respective subcellular localizations. Addressing this issue, the development of caged compounds for organelle specific photo release by synthesizing a coumarin - based caging group ("click cage") that can be attached to bioactive molecules and subsequently modified by click chemistry with established organelle - targeting moieties [40].

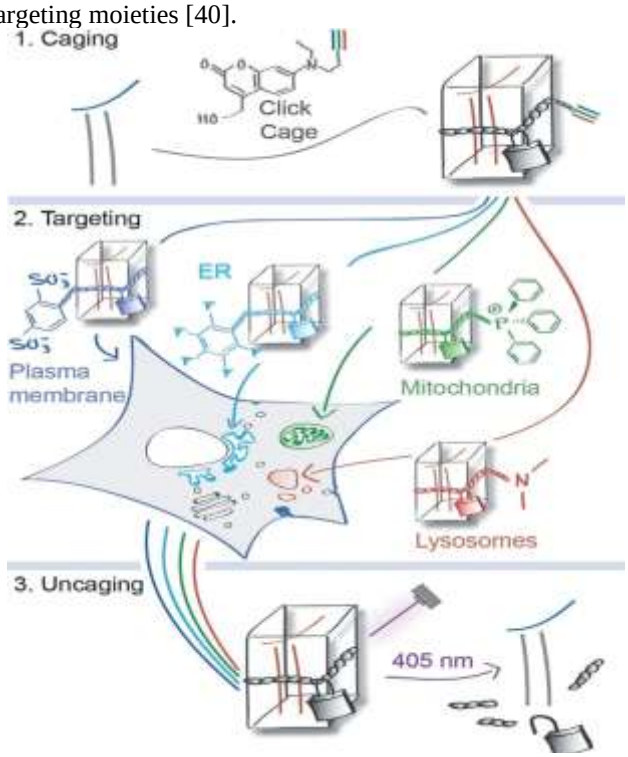

Figure 3: Schematic representation of organelle - specific uncaging. Lipid messengers are equipped with an alkyne - containing photocaging group and functionalized with targeting groups that localize them to specific compartments in living cells, where the active compounds can subsequently be photo released (uncaged) without initially affecting the messenger levels in neighboring compartments.

Adialkylaminocoumarin scaffold as the caging group as this group can be cleaved with 405 nm laser light, which isavailable on most confocal microscopes. This relatively short wavelength offers the possibility to combine live - cell uncaging experiments with fluorescence imaging of green, red, and far - red fluorescent proteins. Furthermore, the alkyl residues of the dialkylamino group can be readily replaced with functional moieties without affecting the photocleavage reaction [41].

Arachidonic acid and sphingosine generated derivatives equipped with the new caging group as these cellular messengers have been reported to perform widely varying functions depending on their sub-cellular localization. [36 - 39]

Caged Lipids

Caged (photoactivatable) signaling lipids offer an experimental approach to exclusively perturb second messenger levels in an acute and spatially defined manner. Even though the term "cage" is antiquated and even deceptive, as it suggests the lipid is arrested in a type of molecular cage, it has remained popular. Suggestions for more appropriate terminology did not prevail. Furthermore, it might be misleading to name caged molecules "photoactivatable" since this term has been used to describe molecular probes designed for photo - induced covalent cross linking. Caged lipids are obtained by attaching a photo cleavable group to a position which is crucial for the function of the respective lipid, thereby rendering it inactive. Upon irradiation with light of suitable wavelength, the protection group is cleaved and the active lipid is liberated. Since lipids often feature charged head groups which prevent them from crossing the plasma membrane, it is frequently required to mask these charges with bioactivatable protection groups (Fig.18). The major advantage of caged, membrane - permeant lipids is the possibility to alter the concentration of a well - defined molecular species in a stepwise manner on a subcellular level at any given point in time [32].

Many biological processes are regulated by lipids in one way or another and depend on often transient changes of the signaling effectors. Caged lipids are ideally suited to dissect such processes and will likely see much wider application in the future [32].

Caged lipids have been used for a number of different purposes.

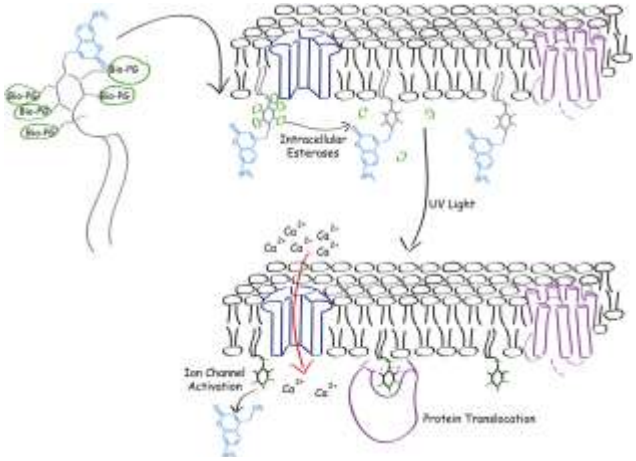

Figure 4: Application of caged lipids

A given lipid is equipped with a photo cleavable group at a position of crucial importance for its interaction partners. Charges and other polar functional groups at the lipid head group are masked with bioactivatable protection groups (Bio - PGs) and the lipid is thus rendered membrane - permeant. Bio - PGs are usually cleaved swiftly after cell entry by endogenous intracellular esterases. Subsequent photo activation yields the active compound, while the cellular signaling responses are monitored with suitable biosensors.

3. Conclusion

Biomolecular caging is a photochemical strategy for achieving spatially and temporally controlled release of bioactive compounds, with wide range of applications in cell biology, chemistry, medicine, materials, pharmacology, and physiology. The success of this strategy depends upon the availability of photo - activators suitable for applications under physiological conditions. Several photo - activators have been designed. However, most of these do not produce satisfactory result when used under physiological conditions, leaving much scope for design and development of efficient photo - activators.

Owing to the progressive development of metal–organic-frameworks (MOFs) synthetic processes and considerable potential applications in last decade, integrating biomolecules into MOFs has recently gain considerable attention. Biomolecules, including lipids, oligopeptides, nucleic acids, and proteins have been readily incorporated into MOF systems via versatile formulation methods. The formed biomolecule-MOF hybrid structures have shown promising prospects in various fields, such as antitumor treatment, gene delivery, biomolecular sensing, and nanomotor device. By optimizing biomolecule integration methods while overcoming existing challenges, biomolecule-integrated MOF platforms are very promising to generate more practical applications.

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