News from our members: Photosensitizer degradation is critical to destroy biological membranes

by [Maria Celia Wider]
Edited by [Pilar Acedo]

Study challenges PDT paradigms

In an article published in the Journal of the American Chemical Society (JACS), research led by Professor Mauricio S. Baptista (Department of Chemistry, University of São Paulo) showed that photosensitizer (PS) degradation caused by contact-dependent reactions is a necessary step to induce irreversible damage to biological membranes. Therefore, in medical applications of photodynamic therapy, contact-dependent reactions can damage biological targets much more accurately than those in which diffusive species, such as singlet oxygen and other reactive oxygen species, are formed. The results can impact the design of more efficient PSs.

"For decades, researchers have focused on the same mechanism of action of PDT, which is singlet oxygen generation. It is a paradigm. We now propose that contact-dependent reactions must be considered for the development of more efficient PSs. Hundreds of types of molecules have been tested and function well as photosensitizers. We propose to investigate other important factors for the efficiency of these molecules besides the generation of excited state oxidizing species. Our work also breaks another paradigm in this area, according to which PS photobleaching causes loss of efficiency because they no longer generate singlet oxygen. Our results show that PSs photobleaching induces membrane leakage, - and for that, the PSs have to be attached to the membrane", Prof Baptista said.

One great advantage of PDT in the treatment of tumors is to preserve the original tissue. But, according to Prof. Baptista, one of the technical problems is to deliver light efficiently at the required depth. Therefore, the importance of developing PSs that work with less light.

As antimicrobial therapy, the perspectives of PDT are also interesting. "I think using PDT as an antimicrobial strategy will make a difference considering the emergence of superbugs resistant to antibiotics because nothing resists to this kind of damage", the researcher said.

Photobleaching

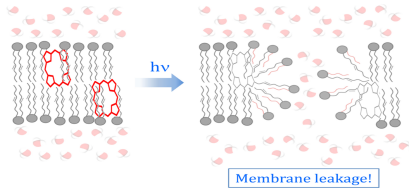
Several processes that require light absorption and the subsequent photoinduced action of PSs, such as photosynthesis, for example, cause PS photobleaching or photodegradation. Photobleaching causes loss of light absorption capacity, i.e. PSs no longer function. In medical applications, photostability is considered an essential feature for photosensitizers. However, according to the researchers, recent evidence points to the key role of contact-dependent reactions, which often cause PSs photobleaching. It calls into question the paradigm of photostability versus photosensitizer efficiency in medical applications.

In this study, the researchers produced a series of magnesium-porphyrazine complexes (MgPzs) capable of generating the same amount of singlet oxygen but with different redox properties. Porphyrazines are pigments analogous to porphyrins, but with greater redox activity. The research group also investigated the photobleaching mechanism of these complexes in solution and found that it was independent of singlet oxygen, occurring mainly via electron abstraction of surrounding electron-rich molecules (solvents or lipids). In the process, the complexes are reduced to a radical intermediate.

Photoinduced cell death by a PS is often associated with membrane damage. To correlate photobleaching with membrane permeabilization, the researchers compared two photosensitizers (CF_3Pz and FPz) with similar photophysical properties but with distinct photobleaching efficiencies. They used two membrane models, liposomes, which are small spherical phospholipid vesicles, and giant unilamellar vesicles (GUV), which can be observed under a microscope. They found that the higher the rate of PS photobleaching the faster the leakage induced in the membranes. The photobleaching occurs through an electron abstraction from the lipid double bond, which causes irreversible membrane damage.

"This work is a continuation of an earlier study also published in the JACS in which we compared two compounds, one bonded to the membrane and one not bonded, and we saw that the bonded compound caused more membrane damage, through the generation of aldehydes, and that it was degraded. Now we have made a system in which both compounds are bonded to the membrane and the only parameter that matters is their redox property. One of them is a more active oxidant and it is the one that undergoes the greatest photodegradation and induces a stronger membrane permeabilization", explains Prof Baptista.

This study was conducted as a postdoctoral project by Thiago T. Tasso, currently a Professor at the University of Federal de Minas Gerais, first author and corresponding co-author of the article, with the collaboration of researchers from the Federal University do ABC and the Chemistry Department at the University of São Paulo (USP).



Hydrophobic photosensitizers (in red) adsorb on biological membranes. After light absorption, the excited state of the photosensitizer is formed near the main oxidation target (double lipid bonds). Membrane leakage implies a direct reaction of the photosensitizer with the pairs, which necessarily leads to the photosensitizer photobleaching. Image: Thiago T. Tasso

Resources and more information:

The article "*Photobleaching Efficiency Parallels the Enhancement of Membrane Damage for Porphyrazine Photosensitizers*", by Thiago T. Tasso, Jan C. Schlothauer, Helena C. Junqueira, Tiago A. Matias, Koiti Araki, Erica Liandra-Salvador, Felipe CT Antonio, Paula Homem-de-Mello and Mauricio S. Baptista, can be accessed at https://pubs.acs.org/doi/10.1021/jacs.9b05991