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The importance of the contact-dependent reactions for the efficiency of PDT photosensitizers

Photosensitized oxidations, which are reactions triggered by the interaction of light with photosensitizer (PS) molecules, are being used in medical technologies, such as photodynamic therapy (PDT), in order to trigger oxidation of biomolecules and consequently to eliminate cancer cells or pathogens. Damage in cytoplasmic or organelle membranes is key to modulate the mechanism as well as the overall efficiency of regulated cell death.[1] There are two major mechanisms of photosensitized oxidations, called type I and type II, representing respectively, the direct oxidation of biological targets (direct-contact reactions) and the oxidations mediated by diffusing species, such as singlet oxygen. In the direct-contact reactions the damage is performed precisely in the place where the excited species is generated and for type II processes, singlet oxygen or other diffusing species can carry oxidation potentials hundreds of nanometers or of micrometers away from the point of light absorption. Nevertheless, the detailed molecular steps leading to biological injury remains largely uncharacterized and it is not clear how precise can be the spatial damage induced by the photosensitized oxidation reactions. In the direct-contact reactions the damage is performed precisely in the place where the excited species is generated and for type II processes, singlet oxygen or other diffusing species can carry oxidation potentials hundreds of nanometers or of micrometers away from the point of light absorption. In this presentation I will discuss the data and the consequences of recent publications of the group related with direct-contact reactions.[1-3] For a PS to fully compromise membrane function, it needs to engage in electron transfer reactions either with the lipid double bond or with the lipid hydroperoxide, forming peroxyl and alkoxyl radicals within the membranes that suffer Beta-scission and generate lipid-truncated aldehydes, which cause membrane leakage.[2] Therefore, relevant damage that definitively changes the outcome of cells occur precisely in the PS locus, and therefore, justifies the search for molecular-specific oxidation-induced photodamage. Since the efficiency of membrane leakage correlates with an electron transfer reaction that usually causes PS photobleaching, PS regeneration should be exploited as an effective tool to developed improved PDT photosensitizers.[3]

(1) WK Martins et al. Autophagy 2019, 15, 259; (2) I Bacellar, et al. J Am Chem Soc 2018, 140, 9606; (3) TT Tasso et al. J Am Chem Soc 2019, 141, 15547.