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Synergistic effect of electric field and lipid oxidation on the permeability of cell membranes

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Abstract

Background: Strong electric fields are known to affect cell membrane permeability, which can be applied for therapeutic purposes, e.g., in cancer therapy. A synergistic enhancement of this effect may be accomplished by the presence of reactive oxygen species (ROS), as generated in cold atmospheric plasmas. Little is known about the synergy between lipid oxidation by ROS and the electric field, nor on how this affects the cell membrane permeability.
Method: We here conduct molecular dynamics simulations to elucidate the dynamics of the permeation process under the influence of combined lipid peroxidation and electroporation. A phospholipid bilayer (PLB), consisting of di-oleoyl-phosphatidylcholine molecules covered with water layers, is used as a model system for the plasma membrane.
Results and conclusions: We show how oxidation of the lipids in the PLB leads to an increase of the permeability of the bilayer to ROS, although the permeation free energy barriers still remain relatively high. More importantly, oxidation of the lipids results in a drop of the electric field threshold needed for pore formation (i.e., electroporation) in the PLB. The created pores in the membrane facilitate the penetration of reactive plasma species deep into the cell interior, eventually causing oxidative damage.
General significance: This study is of particular interest for plasma medicine, as plasma generates both ROS and electric fields, but it is also of more general interest for applications where strong electric fields and ROS both come into play.

keywords: cell membrane, molecular dynamics simulation, reactive oxygen species, electric field, plasma medicine, electroporation

1. Introduction

Over the past decade, cold atmospheric plasma (CAP), i.e., an ionized gas near room temperature, has shown promising applications in cancer therapy [1-4]. There is a growing body of literature to support the claim that CAP may selectively target the destruction of cancer cells [4-6], which might give an advantage to CAP over traditional anti-cancer methods, such as chemotherapy and radiotherapy.

The possible selectivity of CAP towards cancer cells is most probably due to the noticeable rise of intracellular reactive oxygen species (ROS) occurring in cancer cells compared to normal cells upon the same CAP treatment [7-11]. However, the underlying mechanisms explaining the enhanced concentration of ROS in cancer cells still remain elusive.

Several studies in literature have tried to understand these mechanisms of plasma-based cancer treatment [6, 12, 13]. Yan *et al.* proposed a mechanism for the possible selectivity of ROS towards cancer cells, based on aquaporins (AQPs), i.e., the only verified H_2O_2 channels on the cytoplasmic membrane of cancer cells [6]. H_2O_2 is regarded as one of the main anti-cancer ROS from CAP based on *in vitro* studies [6]. They found that after the CAP treatment, CAP-generated H_2O_2 species diffuse into cancer cells significantly faster than in homologous normal cells, causing a significantly higher rise of ROS in cancer cells compared to normal cells [6]. Recently, Szili *et al.* investigated how plasma and plasma-generated ROS might interact with real cells in contrast to synthetic phospholipid (PL) vesicles [12]. The authors suggested some mechanisms for the transport of reactive plasma species into cells, i.e., by interplay of