سمینار هفتگی ماده چگال نرم

The effect of Plasma radicals on Cystine transportation by xC^- antiporter

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Abstract

We performed computer simulations to investigate the effect of oxidation on the extracellular cystine (CYC) uptake by the xC^- antiporter. The latter is important for killing of cancer cells. Specifically, applying molecular dynamics (MD) simulations we studied the transport of CYC across xCT, i.e., the light subunit of the xC^- antiporter. We studied the permeation of CYC across three model systems, i.e., outward facing (OF), occluded (OCC) and inward facing (IF) configurations of xCT. We also investigated the effect of mutation of Cys327 to Ala within xCT, which was also studied experimentally in literature. We considered the outward facing (OF) configuration of xCT, and to study the effect of oxidation, we again modified the Cys327 residue, to cysteic acid (CYO327). Finally, we investigated the effect of lipid oxidation as a result of CAP interaction, on the funnel radii of the protein channel for the OF, OCC and IF state of the xCT subunit and stability of the xCT structure. Our computational results showed that oxidation of Cys327 results in a free energy barrier for CYC translocation, thereby blocking the access of CYC to the substrate binding site of the OF system. The formation of the energy barrier was found to be due to the conformational changes in the channel. The obtained free energy barrier for CYC translocation was found to be 33.9 $kJmol^{-1}$, indicating that oxidation of Cys327, by e.g., cold atmospheric plasma, is more effective in inhibiting the xC^- antiporter than in the mutation of this amino acid to Ala (yielding a barrier of 32.4 $kJmol^{-1}$). Moreover, the results of lipid oxidation showed that, by increasing the percentage of POPC oxidation, the protein channel of the xCT subunit will be more compact. Furthermore, due to the oxidation of the membrane, the stability of the xCT structure, especially in the OCC and IF configuration, decreased. The inhibition of the xC^- antiporter may lead to Cys starvation in some cancer cells, eventually resulting in cancer cell death.

زمان: شنبه ۹۹/۳/۱۰ ساعت ۱۵:۳۰

مکان(کلاس مجازی آقای دکتر اجتهادی) :

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