Peptide translocation through the plasma membrane of human cells: a process mediated by oxidative stress

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Cell-penetrating peptides (CPPs) are promising tools to deliver proteins and nucleic acids into live cells. However, the fundamental mechanisms by which CPPs translocate across cellular membrane remains uncharacterized. This in turn impedes their therapeutic applications and usage for cell biology studies. Here we report that the cell penetration activity of CPPs is dependent on the oxidative state of the membrane. We found that hypoxic culture and supplement of antioxidants abolish the cell delivery efficiency of peptides. Mild oxidation of live cells by oxidants significantly promotes the translocation of CPPs. We also revealed that the native anionic oxidized lipids mediate the efficient and direct transport of the peptide across the plasma membrane of human cells. Our results support a model that CPPs permeate through the lipid bilayer via forming inverted micelles with anionic lipids, which is present as a result of oxidative damage. Our data point to a highly complex and underappreciated interplay between CPPs and oxidized membrane species. This novel mechanism also provides a fundamental basis for rationale design of highly efficient cell-permeable compounds and robust drug delivery strategies.