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Analysis of interactions between cytosol-penetrating antibody and cell membranes through MD simulation

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Antibodies are essential for targeting extracellular and membrane-bound antigens, but they have the limitation of being unable to penetrate the cell membrane to access intracellular targets. This limitation is particularly important in diseases where the target molecule is located within the cytosol or organelles, such as cancer or viral infections. This study introduces a new antibody derived from human IgG designed to improve its interaction with and ability to cross cell membranes. The antibody, called 2C11, is modified with arginine (Arg), tryptophan (Trp), and glutamic acid (Glu) to improve its ability to cross cell membranes at acidic pH levels. The corresponding 2C11-E lacks the Glu modification; at pH 7.4, 2C11 is unable to cross the cell membrane, but at pH 5.5, due to protonation of the Glu patch (E patch), it crosses the cell membrane, which is expected to facilitate endosomal escape and improve therapeutic efficacy. We evaluated the ability of the CH3 domain of the wild-type (WT), 2C11, and 2C11-E antibodies to interact with the POPC 80%, POPS 20% membrane at pH 7.4 and pH 5.5 through molecular dynamics (MD) simulations. The results showed that the protonated E patch of 2C11 significantly enhanced membrane interaction, contributing to membrane insertion. This study provides valuable insights into how antibodies engineered through MD simulations can interact with and penetrate cell membranes under neutral and acidic conditions. Understanding these interactions is essential for designing next-generation antibody therapies that target proteins in the cytosol.