MEMBRANE FUSION AS A TARGET FOR VIRAL INACTIVATION AND VACCINE DEVELOPMENT

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Membrane fusion is an essential step in the entry of enveloped viruses into their host cell. Therefore, understanding the virus induced membrane fusion at the molecular level should provide means to develop new viral inactivating compounds. For this purpose, we evaluated the interaction of vesicular stomatitis (VSV) with lipid vesicles. Previous studies have shown that membrane fusion occurs at a very narrow pH range, between 6.2 and 5.8, suggesting that His protonation is required for this process. To investigate the role of His in VSV fusion, we chemically modified these residues using diethypyrocarbonate (DEPC). We found that pH-induced conformational changes in virus envelope glycoprotein G and membrane fusion mediated by VSV were inhibited by His modification, suggesting that His protonation drives G protein interaction with the target membrane at acidic pH. Based on these results, we decided to assess whether treatment with DEPC was able to inactivate the virus. VSV infectivity in BHK_{21} cells and pathogenicity in Balb/c mice were abolished by viral treatment with 0.5mM DEPC. In addition, DEPC treatment did not alter the conformational integrity of surface proteins of inactivated VSV as demonstrated by transmission electron microscopy and competitive ELISA. Antibodies elicited in mice by intraperitoneal immunization with DEPC-inactivated VSV mixed with adjuvants were able to recognize and neutralize the native virus and efficiently protected animals against the challenge with lethal doses of VSV. These results together suggest that viral inactivation with DEPC based on membrane fusion inhibition seems to be a suitable method for the development of vaccines.

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