Efficient Incorporation of Matrix Protein M2 into Influenza Virus-like Particles (VLPs) to Improve Future Vaccine Production and Immunogenicity

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Influenza virus remains a heavy economic burden and poses pandemic threats to public health worldwide, causing 250,000-300,000 deaths annually and 3-5 million cases of severe illness. In the past 15 years in the United States, the efficacy of seasonal influenza vaccines has been less than 50% in all but four years, and even as low as 19% during the 2014-2015 season. One of the primary causes falls on the traditional egg-based vaccine production platform with a timeline of six to nine months during which virus undergoes mutations. Moreover, the need for hundreds of millions of chicken eggs to produce the vaccines makes the traditional production method unequipped to handle pandemics, as was the case with 2009-2010 H1N1 “swine flu” outbreak in North America. Virus-like particles (VLP) have been demonstrated to be a safe and highly immunogenic alternative which can be produced in less than three months and at a larger scale. The highly conserved influenza matrix protein M2 provides broad protection across multiple influenza strains. However, the inclusion of M2 into VLP has been left unrealized due to its ion channel toxicity, resulting in decreased protein production. While the M2 viral inhibitor amantadine has been proved to relieve this toxicity and restore protein expression, its effects on VLP production are unknown. In this study, we demonstrated that addition of 10?M amantadine into cultures of Sf9 cells infected with recombinant baculoviruses resulted in a 5-fold increase in HA, 10-fold increase in M1, and a 6-fold increase in M2 expressions on VLPs, as well as more than doubled VLP yield after 72 hours post infection. Higher VLP yield together with the efficient incorporation of influenza proteins showed promise for future “universal” vaccine production.

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