An Innovative Oral Targeted Mini Gene-Vaccine Platform that Fights Influenza

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Perspective

Each year, seasonal influenza claims the lives of between 250,000 and 500,000 people. The recent appearance of a new influenza A (H1N1) virus, which is causing a global pandemic, has increased this hazard. More than 5–15% of the world's population is affected by influenza virus infections every year, which causes enormous human misery and financial burden. All ages are affected by influenza infection, although the elderly and young children are more at risk, and higher fatality and morbidity rates are frequently seen in these populations. The influenza genome Eight single-stranded, negative sense RNAs make up a virus sections that code for one or more proteins. Hemagglutinin (HA) and neuraminidase (NA), the virus' surface proteins, can be divided into 16 HA subtypes (H1-H16) and 9 NA subtypes (N1–N9). The crucial component, known as HA, is what causes the viral fusion with the endosomal membranes by binding to its receptor produced on the cells. A heterotrimer comprised the polymerase subunits PB2, PB1, and PA and the nucleoprotein is responsible for the replication and transcription of viral RNAs (NP). The Nuclear Export Protein (NEP) and the M1 matrix protein then move the produced Viral Ribonucleoprotein (vRNP) complexes from the nucleus to the cytoplasm, where they are organised into virions at the plasma membrane. By cleaving the sialic acids from cellular and viral HA and NA subunits, the NA starts the viral release from infected cells. Although there are already antiviral medications and influenza vaccinations available, their effectiveness is limited. Additionally, the world community is ill-prepared for the development of pandemic influenza strains. It may take three to six months to produce a vaccine against a recently discovered strain, giving the virus plenty of time to proliferate and significantly tax global health care systems. The majority of influenza vaccination campaigns focus on at-risk groups like the elderly. The elderly, however, only seem to respond weakly to these vaccines in terms of their immune systems. Furthermore, viral antigenic drift that causes a mismatch between the vaccination and the virus in circulation may be of concern as it can result in an ineffective vaccine response. According to studies, the functional quality and breadth of the immune response as well as the time needed for vaccine delivery restrict the efficiency of the influenza vaccination. Therefore, there is a pressing need for better vaccines. With the intention of using these peptides to target antigens specifically to DCs, we developed 12-mer peptides derived from a phage display peptide library that specifically bind to professional antigen presenting dendritic cells (DCs). This allowed us to explore new directions for the effective targeted vaccine strategy known as mini gene-platform against microbial challenge (i.e.*Influenza A*). This type of DC-peptide targeting technique boosts the bioavailability and immunological effectiveness of given immunogenic T cell epitopes by having commensal gut bacteria like Lactobacillus acidophilus or Lactobacillus gasseri express peptides. This method has been employed by us in the past to produce strong immune responses against B. anthracis and breast cancer challenge. We used this DC-peptide approach to deliver highly immunogenic influenza A(*H1N1* and *H3N2*) sequences composed of HA, NA, PA, NS2, PB1, PB2, HP, and NP subunits to intestinal DCs in order to stimulate potent T cell immune responses against influenza infection. This furthered the potential of such a targeted mini-vaccine. The main goal was to create a DC-based small gene-vaccine method that was expressed and administered mucosally by L. gasseri, a healthy member of the normal gut microbiota and a powerful adjuvant that causes DC activation and robust Th1 polarisation. This beneficial mucosal influenza targeted micro gene vaccine is anticipated to be well-tolerated by recipients and is so conveniently distributed to a sizable susceptible populace. In order to stimulate powerful immune responses against viral challenge, the idea behind such a small gene-vaccine platform was to combine the benefits of the orally supplied probiotic bacterium with precise targeting of the influenza immunogenic*CD4+* and*CD8+ T* cell epitopes to DCs. As a result, we looked into how this special targeted micro gene platform expressed by L. gasseri, which is widely thought to be safe for oral ingestion, would be delivered by oral means. Furthermore, high concentrations of viable L. gasseri expressing the targeted mini genes of HA/NA/PA/HP/NP/NS/PB fused to our special DC-peptide can be produced effectively in a fermenter, concentrated, lyophilized to a powder, and stored for lengthy periods of time without suffering significant viability losses. The overall objective of our research was to develop a platform for vaccination against influenza A strains, whereupon two novel approaches were combined: (1) increasing vaccine potency by specifically targeting the chosen T cell epitopes of different influenza subunits to intestinal DCs; and (2) expressing such a chosen mini gene platform in a probiotic strain that serves as both a potent adjuvant and an efficient oral delivery vehicle. To effectively stimulate both humoral and cellular immune responses against the viral challenge, we next postulated that targeting highly immunogenic epitopes from the HA, NA, PA, HP, NP, NS, and PB proteins of*H1N1/H3N2* will be effective. The oral inoculation of L. gasseri expressing the DC-peptide fusion protein was used to test this idea. The codon sequences of the mini gene-flu vaccine platform, which contains a range of CD4+ and CD8+ T cell epitopes, including HA/NA/PA/HP/ NP/NS/PB, of*H1N1* and*H3N2* Influenza A strains, were initially optimised in order to create this oral targeted vaccine. After then, the micro geneDC peptide fusion was cloned in a heterogonous vector appropriate for*L. gasseri* expression. Then, groups of mice (n=5) received four weeks of vaccination in a row, two weeks of rest, and two weeks of booster vaccination with*L. gasseri* carrying an empty vector, L. gasseri expressing mini Gene-Flu vaccine fused to a control peptide (FluVac-Ctrl), or L. gasseri expressing mini Gene-Flu vaccine fused to DC-binding peptide (FluVac-DC). Mice were slaughtered, and lymphocytes were extracted from the spleen, draining Mesenteric Lymph Nodes (MLNs), and lungs one week following the last vaccination booster. To find CD8+ T cells that are specific to NP and PA, single cell suspensions were created and lymphocytes were treated with the PA and NP tetramers that are already on the market. Then, using flow cytometry, cells were labelled to detect the surface expression of *CD3, CD8,* and*CD44 (BD Canto II*). According to our findings, as compared to mice treated with FluVac-Ctrl and empty vector, our FluVac-DC vaccine elicits a higher percentage of live NP and PA specific *CD3+CD8+* T cells in the MLNs and spleens. In order to ascertain if live, NP and PA specific *CD3+CD8+* T cells produce pro-inflammatory cytokines (such as IFN, TNF, and Granzyme B), lymphocytes from the spleen and MLNs were restimulated with NP and

PA peptides in vitro. The CD44hi PA and NP specific CD3+CD8+ T cells from FluVac-DC vaccinated mice generated more IFN, TNF, and Granzyme B, according to the data (data not shown). The effect of the small gene vaccination platform on all CD3+CD4+CD44hiT cells was also examined. Comparatively to FluVac-Ctrl or empty vector vaccinated mice, CD4+ T cells from FluVac-DC-vaccinated mice dramatically increased the production of IFN, TNF, and Granzyme B. The effects of such a targeted micro gene-vaccination on CD4+ and CD8+ T cells in the lungs, the location of influenza infection, were examined in later studies. After injecting cells into the lungs with a PBS/Heparin solution (20U of Heparin/1 mL of sterile PBS), lymphocytes were extracted using collagenase. Mice immunised with FluVac-DC produced more NP and PA-specific CD8+ T cells overall and in the lungs. Furthermore, compared to FluVac-Ctrl or empty vector vaccinated animals, restimulated lymphocytes from the lungs of FluVac-DC vaccinated mice dramatically increased the production of IFN, TNF, and Granzyme B. Parallel to this, two weeks after the final booster shot, groups of mice given the identical doses of empty vector, FluVac-Ctrl, or FluVac-DC were exposed to the influenza A virus strain A/HKx31 (x31, H3N2=A/Hong). These experiments unequivocally demonstrate the effectiveness of oral targeted micro gene vaccination in inducing antigen-specific T cell immunity. Mice were slaughtered one week after becoming infected with x31, and the lungs were perfused and homogenised in order to measure the viral titers in this tissue using a plaque test. Our findings imply that induced antigen-specific T cells were effective in a mouse vaccine model because FluVac-DC-vaccinated animals exhibited decreased virus titers in the lungs. In conclusion, there is an urgent need for innovative vaccine approaches that focus on conserved Cytotoxic T Lymphocyte (CTL) epitope areas of viral proteins. As a result, data suggest that a number of CTL epitopes that trigger powerful antiviral CD8+ T cell immune responses may be found in viral genes. Our lab's current scientific focus is on creating innovative, multivalent, CD4+ and CD8+ T cell targeted vaccinations that can be administered orally and protect against a variety of influenza A strains. In vivo immunological protection against a variety of viral diseases, including influenza A, is provided by such a vaccine regimen. To combat influenza A, our technology for delivering an oral targeted micro gene-vaccine that can optimally activate lung T cells specific to the Flu antigen will offer a novel treatment approach in the realms of both vaccination and therapy.

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