Non Viral Vector Vaccines

Presentation

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Protective efficacy of in vitro synthesized, mRNA vaccines against influenza A virus infection

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Although Influenza vaccines were established already many decades ago, seasonal Influenza is still causing many cases of human infection that usually are self-limited but can result in hospitalization or mortality, mostly after secondary bacterial infections. Moreover, pandemic outbreaks of newly emerging influenza virus strains demonstrate the limited means in prophylaxis.

Messenger RNA based vaccination is a novel and promising vaccination approach. In recent years RNActive® technology was developed providing effective two-component mRNA-based vaccines with self adjuvanting activity in the field of cancer vaccination. Therefore, we extrapolated our knowledge to investigate the use of this mRNA-based technology to generate prophylactic vaccines protecting against infectious diseases, using influenza virus infection as a model.

Experiments in mice showed that an mRNA vaccine coding for the influenza hemagglutinin (HA) elicited protective efficacy against lethal challenge infections. Protective efficacy of homologious hemagglutinin-based mRNA vaccines was demonstrated for several human strains of influenza (H1N1, H3N2) and for highly pathogenic H5N1 virus. Serum transfers from mRNA vaccinated mice to non-immunized animals showed that this protective mechanism is based on neutralizing antibodies. Moreover, when mRNA coding for the conserved nucleoprotein of the influenza virus was used for vaccination, protection was achieved not only against the homologous strain, but also against lethal challenge infection with a heterologous H5N1 virus mediated by cross-reacting T cells as shown by *in vivo* depletion of T cells. These results demonstrate the potential of an innovative mRNA technology to provide vaccines for seasonal influenza and possibly other indications in the area of infectious diseases.

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Interaction of MERS-CoV with Antigen Presenting Cells

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Nearly 10 years after the Severe Acute Respiratory Syndrome (SARS) pandemic, Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged during fall 2012 as a causative agent of a severe respiratory disease with a mortality rate of 42% among 178 confirmed human cases. Due to the significant pandemic threat and mortality, we aimed to analyze aspects of MERS-CoV pathogenesis, especially its interaction with antigen-presenting cells (APCs).

When we inoculated MERS-CoV into 3 different mouse strains by different routes (i.v., i.p. or i.n.), no significant signs of pathogenicity were observed and no replicating virus could be re-isolated 4 dpi from lung, liver, brain, or spleen. However, considerable numbers of viral genomes were detected, especially in spleens of type I interferon-receptor deficient ($IFNAR^{-/-}$) mice. This may indicate the importance of type I interferon (IFN) and an innate immune activation during MERS-CoV infection. To determine innate immune activation, we analyzed secretion of type I and type III IFNs by APCs, i.e. B cells, macrophages, myeloid dendritic cells (mDCs), or plasmacytoid DCs (pDCs) of murine or human origin, after inoculation with MERS-CoV. Infection of APCs was characterized by RT-PCR to detect viral replication intermediates. Productivity of APC infection was determined by titrating newly produced virus 1 to 3 days after infection. Neither significant infection nor replication of MERS-CoV was detected in any APC population. However, production of high amounts of type I and III IFNs was induced exclusively in human pDCs, which was significantly higher than IFN induction by SARS-CoV, the latter inducing high immune activation in patients. First results reveal endosomal uptake and functionality of Toll-like receptor (TLR)7 and TLR9 being critical for sensing of MERS-CoV by pDCs.

Our results reveal human pDCs as the APC population primarily responding upon MERS-CoV infection and suggest that the high immune activation during MERS-CoV infection might be due to pDCs´ massive IFN production upon contact.