HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 12, 3110–3112
http://dx.doi.org/10.1080/21645515.2016.1210745

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COMMENTARY

Mumps virus pathogenesis: Insights and knowledge gaps

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ABSTRACT
The recent mumps outbreaks among MMR vaccinated persons have raised questions about the biological mechanisms related to mumps symptoms and complications in the background of waning immunity. Contrary to other paramyxoviruses, the understanding of mumps virus pathogenesis is limited, and further in-depth clinical studies are required to provide answers to important research questions.

ARTICLE HISTORY
Received 21 June 2016
Accepted 4 July 2016

KEYWORDS
MMR vaccination; mucosal immunity; Mumps virus; orchitis; parotitis; symptoms; T cell immunity; viruria

In the pre-vaccination era, mumps was an endemic childhood disease with epidemic peaks every 2–5 y and the majority of cases among those aged 5–9 y.[1] Classic mumps is characterized by parotitis and is usually a mild disease, although in the pre-vaccination era up to 15% of the mumps patients developed meningitis.[2] Other complications included encephalitis, orchitis, oophoritis, mastitis, pancreatitis and deafness. Myocarditis and nephritis have been rarely reported as complications associated with mumps.[3] Introduction of the measles, mumps and rubella (MMR) vaccination has greatly reduced the morbidity rates as well as the number of hospitalizations due to mumps.[4,5] However, during the last decade various mumps outbreaks occurred among MMR vaccinated populations worldwide. The majority of mumps patients in these outbreaks were adolescents and some outbreaks were specifically associated with educational settings or student events.[6-9]

The understanding of mumps virus pathogenesis and the immune responses required for protection against mumps virus infection is limited, whereas this knowledge is important for the development of new mumps vaccine strategies and outbreak control measures. Therefore, the recent outbreaks create the opportunity to gain more insights into mumps virus pathogenesis in humans, especially in relation to the vaccine-acquired immune response, as MMR vaccination does not provide lifelong sterile immunity in a significant proportion of individuals. One reason for the limited knowledge about mumps virus pathogenesis is the lack of relevant animal models. Mice and ferrets do not develop clinical symptoms and are considered poor candidates for pathogenesis studies.[10] Much of our current understanding of mumps virus pathogenesis is based on hamster and monkey models, but the unnatural routes of inoculation and the inability to distinguish attenuated mumps virus strains from wild-type strains makes the relevance of these findings questionable.[11,12] One study with marmosets shows that intravenous inoculation with a clinical mumps virus isolate induces meningitis, whereas another study in which rhesus macaques were infected via the natural route with a clinical mumps virus isolate shows that these animals develop parotitis but no fever or neurological symptoms.[10,12] Although these findings suggest that monkeys might be a candidate model for mumps virus pathogenesis studies, the costs and ethical considerations limit the applicability of this model for mumps.

Mumps virus is transmitted via direct contact or by airborne droplets and the incubation period varies between 2 and 4 weeks.[13,14] The virus has been isolated from saliva from 7 d before until 8 d after onset of symptoms, which shows that the virus can be transmitted before disease onset.[15] Mumps virus binds to sialic acid to enter the polarized epithelial cells in the upper respiratory tract from both sides.[16] Apical entry facilitates transmission of virus to neighboring cells, whereas infection from the basolateral side is probably important for secondary infection via the bloodstream.[16] Mumps virus is predominantly released from the apical side of epithelial cells, which enables virus replication in the glandular eptihelium and mumps virus shedding in saliva.[16] Mumps virus infected cells might escape host immunosurveillance via degradation of STAT1 and STAT3 by the mumps virus V protein. In this way, IFN and IL-6 signaling are blocked and the virus can evade both innate and adaptive antiviral responses.[18-22] Furthermore, blockage of the IFN pathway enhances mumps virus replication, as IFN inhibitors promote mumps virus replication *in vitro*.[23] However, the effect of the V protein on the magnitude of the IFN and IL-6 response is unclear, because IFN and IL-6 levels appear to be elevated in mumps patients, especially in patients with meningitis and/or encephalitis.[24]

Viremia results in dissemination of the virus to other organs, including the kidneys and testes. Analysis of large diagnostic datasets including saliva and urine specimens from twice MMR vaccinated mumps patients shows that high salivary viral loads at day of onset of disease is positively associated with mumps

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virus shedding in urine and with the occurrence of bilateral parotitis and orchitis.[30,31] The dissemination of mumps virus needs further study, as the virus has only been sporadically detected in blood during infection.[11,27,32] It has been suggested that mumps virus targets T cells, because the virus has a high affinity for T cells and efficiently replicates in these cells.[17] Migrating mumps virus-infected T cells could facilitate spread from the respiratory tract to other sites of the body and might therefore play an important role in disease pathogenesis.[17]

The mechanism behind the development of mumps parotitis and orchitis is unknown. It has been hypothesized that these complications result from lymphocytic infiltration and destruction of periductal cells that lead to blockage of the ducts in the salivary glands and the semeniferous tubules of the testes, respectively.[25] Furthermore, the degree and duration of parotitis may be related to the amount of virus replication in the parotid gland and the development of a vigorous immune response, as was shown after experimental infection of rhesus macaques.[10] Replicating mumps virus has been isolated from the testis and semen, which indicates that orchitis is the result of direct invasion of the testicular cells.[27,28] Mumps virus shedding in urine is caused by dissemination of mumps virus to the kidneys and is associated with abnormal renal function.[11,29] The hypothesis that orchitis is caused by an immune mediated reaction is strengthened by the relatively rapid development of orchitis after MMR vaccination as was reported for 2 persons who had been exposed to mumps in the past.[26]

Arguing against immune-mediated pathogenesis is the clear protection provided through vaccination. First, we observed that 66% of the mumps virus infections among MMR vaccinated persons were asymptomatic,[33] compared with 30–40% of the mumps virus infections among unvaccinated persons in previous studies, thus showing a clear protective effect.[2,34] Second, MMR vaccination reduces the development of bilateral parotitis and orchitis and shedding of mumps virus in urine.[30] Thus, once the virus has entered the body via the upper respiratory tract, vaccine-induced adaptive immune responses seem to prevent mumps virus spread, although it is not clear which immune responses are essential for protection against systemic mumps virus infection. There is no clear cutoff for pre-outbreak serum antibody titers between infected and non-infected persons and various mumps outbreaks among MMR vaccinated persons occurred in high exposure settings, suggesting that serum antibodies are insufficient to prevent infection.[33] Neutralization of the virus in the upper respiratory tract by mucosal antibodies might limit mumps virus spread, as it was shown for measles virus that IgA can effectively inhibit virus replication by intracellular neutralization of polarized epithelial cells.[38] Alternatively, T cell immunity seems to play a major role in control and clearance of other paramyxoviruses, like RSV and measles virus infections, and may therefore also be involved in the resolution of mumps virus infection.[35,36] Especially tissue-resident memory T cells located in mucosal tissues may help to prevent viral entry.[37]

In summary, clinical and laboratory data obtained from recent mumps outbreak investigations have improved our understanding of mumps virus pathogenesis and the role of immunological factors, but important gaps in knowledge remain. Prospective studies are needed with adequate biological sampling to address the outstanding questions regarding pathogenesis and immune response. Especially studies with repeated sampling of diverse clinical specimens, including whole blood, are of interest. These studies will enable the analysis of the presence and function of cells that are either targeted for infection as well as cells that operate as immune effectors in the clearance of mumps virus infection. Assuming that the resurgence of mumps will not stop unless additional preventive measures will be taken, this is an important and feasible first step to improve our understanding about mumps virus pathogenesis. Secondly, clinical trials in mumps outbreak settings and intervention studies using the mumps vaccine could learn us more about the development of complications such as orchitis, the correlation with MMR vaccine-acquired immune responses, and the role of asymptomatically infected persons in mumps virus transmission.

Disclosure of potential conflict of interest

No potential conflicts of interest were disclosed.

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