At short notice - how viruses may play havoc with the immune system

Three examples are given including COVID-19, Zika, and Dengue viruses, and the poliovirus

Seeping through the international literature week by week results in quite a number of topics of interest for public health. This is true, especially at a time of a pandemic virus infection, while great attention is focused on vaccination and consequently the immune system. Here three examples, for three different viruses are given in short, mentioning how complex the immune system reacts while challenged by virus infections, and the implication for vaccination.

A case of Covid-19 reinfection

The hope to fight against COVID-19 is based on a vaccine making us immune against the COVID-19 virus infection. However, how the human immune system reacts towards this virus infection still is not well understood. A precondition for a vaccine is, that it is possible to stimulate our immune system to fight against the invading virus. Likewise, it should be expected, that once a patient has overcome and survived the infection, she or he should be protected against reinfection. The immune system will not allow invading the human cell again.

However, reports about re-infections appeared. End of August this year, a case study reviled the possibility of re-infection without a doubt (1). A man from Hong Kong got a mild infection in March this year. He traveled to Europe and was tested positive again in August, after 142 days from the first infection. The second episode was asymptomatic. The second positive test was not caused by 'persistent viral shedding', but genome analysis and laboratory results, 'including RT-PCR CT values and serum SARS-CoV-2 IgG proofed the occurrence of a re-infection. This was no good news for the optimists expecting a safe and protective vaccine soon.

An example of how tricky viruses play around with the immune system

Remember the news about the Zika virus (ZIKV) in the years 2015 to 2016? At that time, ZIKV spread through Central and South America and the Caribbean. Reading the media were frightening, with reports about birth defects to newborns of infected mothers and the effect of the infection on peripheral nerves. The latter symptom is known to the experts with the mysterious name of 'Guillain-Barre syndrome'.

Fortunately, most of the infections with the ZIKV are not serious. The virus is transmitted mainly through the mosquito Aedes aegypti and belongs to the family of Flaviviridae. To this single-stranded RNA genera also the dengue hemorrhagic fever virus belongs (DENV).

The DENV is well known in Thailand. In Central- and South America DENV also was around at the time ZIKV was a hot topic there. While investigating the spread of dengue hemorrhagic fever through a cohort at Nicaragua it appeared, that ZIKV infection increases the risk for dengue

fever (2, 3). Fortunately, presently Thailand seems not to be affected by ZIKV but still is very much aware of DENV. Just in case, what was found in Nicaragua might be of interest for Thailand as well.

DENV comes along with four serotypes. As probably even most of the village health volunteers know, the first attack of the virus is causing not much harm to the victim. But, the second infection, with a different serotype, might be quite serious. The kind of reactions of the immune system triggering such an after-effect is quite complex. The first infection generates cross-reactive neutralizing antibodies. It seems that over time these antibodies turn to be 'sub neutralized'. The following infection results in an antibody-dependent enhancement, binding to the virus but unfortunately, not neutralizing but promoting the virus to enter the cell.

A similar mechanism seems to work when ZIKV infects after a foregoing DENV infection. In vitro experiments with sera from those with a previous DENV infection enhanced the response to the ZIKV (4). So, the other way round works as well: ZIKV versus DENV increases the severity of the infection. This has important implications for vaccination. One might expect, that through a cross-protective mechanism after the first infection with one serotype results in a low risk when the second serotype attacks. The contrary is the case for DENV and a similar reaction works when DENV and ZIKV spread to one and the same population as observed in the case of the cohort studied in Nicaragua. ZIKV increased the risk of infection with dengue hemorrhagic fever (2). The development of a vaccine against one of the two viruses in question should consider the possible cross-reaction against the other virus in areas, where both viruses are causing a thread for the population.

Vaccination against a vaccine

The virologist Vincent Racaniello, from Columbia University was quoted to have said, that it is actually crazy to vaccinate against a vaccine in most parts of the world. The vaccine in question is given to protect against polio infection. To elucidate the riddle it is necessary to distinguish a 'wild' poliovirus from a 'vaccine-derived' poliovirus (VDPV).

The poliovirus is a single-stranded RNA virus belonging to the Enterovirus C species of the family Picornaviridae, and causes poliomyelitis, a severe disease among children under 5 years. The disease is highly contagious, involves the central nervous system, and leads to muscle weakness and paralysis. There are three serotypes of the virus causing the disease. At the end of the 1980th, a global polio eradication program was started. All in all, the project turned out to be a real success (5). Very recently it was announced that the wild poliovirus has been 'wiped out' of Africa (see Science, Vol 369 Issue 6506 page 886).

The achievement is due to the Sabin oral poliovirus vaccine (OVP). This allowed immunizing children orally with only two drops of the vaccine. Door-to-door campaigns were most efficient in the eradication efforts. Two countries, Pakistan and Afghanistan, remain to have the wild poliovirus still spreading around. OVP is a live vaccine with attenuated strains of the three serotypes. The Salk inactivated polio vaccine (IPV), administered by injection, is used in more

affluent countries from the west. The orally administered vaccine works in that the virus replicates in the gut and induces immunity in preventing the occurrence of the disease and the transmission to another person.

However, while triggering immunity within the gut, the attenuated strains might become infective again through mutations (6). In areas with less rigorous vaccination campaigns and long intervals between vaccination attempts, the muted virus becomes infective again and will be transmitted. The result is 'circulating vaccine-derived polioviruses (cVDPV)' (7-9). The main offender of such a mishap was serotype 2, and the Sabin OPV was withdrawn and 2016 a Sabin OVP2 with the serotype 1 and 3 was used. Still, cVDPV continued to emerge (10-13). The last wild serotype 2 was detected in 1999 in India but poliovirus type 2 occurs, obviously going back to the originally used OVP vaccine.

Using advanced new techniques new oral polio vaccines are developed (14), and more countries resort to IVP. However, experts believe that to work against poliomyelitis, especially in Pakistan and Afghanistan, an oral vaccine would be more feasible and cost-effective. Total eradication of the wild virus and the cVDPV therefore will take more time.

Literature

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