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Beyond just counting…..Part 1 – how the COVID-19 virus differ from a bacterium?

Replication of virions and bacteria differ in a way, that makes it more difficult to treat and develop a vaccine for a disease caused by a virus.

Experiencing the SARS-CoV-2 (COVID-19) pandemic we are staring at the cumulative added numbers of new infections, numbers of patients seriously ill admitted to the hospital, and numbers of death, patients succumbed because ***of and with*** the virus disease. Used to be told to live in a 'global village', millions suddenly are ordered to refrain even from leaving their homes let alone their city, province or country of residence. Utterly frustrated by now, people are asking when will they be allowed to go back to their normal life. A clear-cut answer to this sensible question is not yet forthcoming. Instead, a multitude of not very encouraging news is floating through the various media with sentences such as 'your life will be no longer than it was before' and that adds to the frustration of the 'quarantined' masses. How could such a situation evolve? Hadn't we made to believe that plaque, known as Black Death, nowadays never ever will have such a devastating effect like in the 14th century, where it killed about 20 to 40% of the European population (1)? Is modern public health not based on the achievements at the 19th century, with such ingenious people like John Snow and his investigation about the cholera outbreak at the Golden Square district in London? Why there is no vaccine yet against COVID-19? We know about vaccination since Jenner used the 8 years old James Philipps in 1775 to test the method against smallpox (2)? And why there is no efficient antibiotic therapy available, although the German Eberhard Domagk, with the first 'sulpha' drug, 'Prontosil', and the Scottish Alexander Fleming came up with penicillin being at the forefront of the developments of antibiotics, starting around the end of the Second World War (2)? Hadn't we been too sure that we can cope with infectious diseases easily?

<u>What makes a virus different from a bacterium?</u>

The historian William H. McNeill (1) mentioned, that 1976 it was widely believed that 'infectious diseases had lost their power to affect human life seriously because of advancements in scientific medicine, newly discovered antibiotics, prophylactic and public health' measures. Actually, quite recently 'AIDS', named as such in 1981 to 82, 'Severe Acute Respiratory Syndrome (SARS)' in 2002 to 2003 and the 'Middle East Respiratory Syndrome (MERS)' in 2011, told us otherwise. The so-called 'Spanish flu' 1918 to 1919, at the end of the first World War, with an estimated death of 50 Million around the world might have been a warning as well.

All those more recent catastrophes were caused by a virus and not by a bacterium. Formerly, major global epidemics were due to bacteria such as Vibrio cholera or Yersinia Pestis, also called Pasteurella pestis (the bacillus was discovered 1894 independently from a Japanese and a French bacteriologist), and in the more recent past could be avoided. Why then viruses turned out to be more capable than bacteria to cause serious epidemics nowadays? One of the reasons is that antibiotics used to treat infections with bacteria aim at particular steps of the metabolism of the bacteria used for the replication of the germ. In the development of antibiotics, it is important that the host is not damaged while interfering with the metabolism of the microbes. A virus is much more difficult to attack because it uses the metabolism of the cells of the host for replication. Attacking metabolic steps of the virus might easily being harmful to the host as well. This distinct difference between both infective agents makes it difficult to cope with virus infection through therapeutics such as antibiotics.

The present pandemic caused by a very 'novel coronavirus', for which a vaccine still have to be developed, it is necessary to look for and try an efficient treatment, and follow up clinical features of the disease and epidemic behavior of the virus has to be observed, recorded and interpreted. In the meantime, the number of infected persons cumulates, including those with serious clinical developments and successive death in the thousands and more, within a short time, and overwhelming the capabilities for care and treatment of the health delivery system of even high-income countries. To fully understand the emerging problems and to judge possible solutions it is necessary to know about the mechanism of the transmission of the infective agent, about the replication of the virus, about promising therapeutic schemes and ways to develop a vaccine.

The coronavirus

The type of Coronavirus behind the present pandemic belongs to a superfamily of Coronaviridae. Those virions are known to cause the flu, common cold, and viral encephalitis. This type of virus with 'RNA-encoded genomes' is classified into three different families and subdivided into three different lineages. They are of interest to virologists since 1960 and are known to affect animals and humans through 'zoonotic' transmission. The culprit of the pandemic on hand was named by the experts as SARS-CoV-2, because of its similarity of the SARS virus responsible for the epidemic 2002 to 2004. The general and media prefer to call it COVID-19, because of its original first occurrence in China at the end of last year.

To understand the 'life' cycle of a coronavirus not only the molecular state of the cell membrane and the cell nucleus must be considered but also the cytoskeleton of the cell (3). For those of us having passed through high school decades ago, the eukaryote cell is remembered as one our organism consists out of and includes among others a nucleus, mitochondria as well as the endoplasmic reticulum and a wall wrapped around this while some sort of gel, named cytoplasm, is filling the inner part of it. The importance of the cytoskeleton is now emphasized in that it

contains ‘filamentous polymers’ and ‘regulatory proteins’. It keeps the cell in shape, is able to form vacuoles, helps in cell mobility and has a role in the immune response to germs, and seems to be involved in epigenetic functions as well. ‘Motor proteins’, linked to the ATP of the cellular respiration, transport molecules, and organelles around the cell. For a comprehensive understanding of the replication of the virus, the role of the cytoskeleton should be kept in mind.

Cell attachment of the virus and clinical significance

After the first stage of infection the virus ‘rearrange’ the cytoskeletal to ‘promote its invasion’ (4), but before it must attach to the cell surface through the ‘Spike (S) protein’ (5). The spike receptor-binding domain (RBD) of the virus use the angiotensin-converting enzyme 2 (ACE2) as cell receptor for ‘endocytosis’ into the pneumocyte, such as the alveolar type 2 cell (6). The receptor ACE2 is not only ‘expressed’ by the epithelial cells of the lung, but also of the kidney, intestine and blood vessels (7).

The way the virion is attached to and enters the cell is of clinical relevance. While the majority of infections go along with no or only mild symptoms, those people with comorbidities, especially the elderly are at high risk to fall seriously ill and even succumb to the diseases. Also, young and middle-aged individuals are not spared from such a fate (8). ACE2 is presently in the focus as far as the attachment to the cell surface is concerned. Other ways of attachment exist of course. So, for instance, the coronavirus NL63 (HCoV-NL63), besides using ACE2, also uses heparin sulfates for attachment. The adhesion to heparin sulfates increased virus density on the cell surface (9). It remains to be seen how this result, obtained by investigating NL63, has some relevance for SARS-CoV-2 and the clinical aspects of the infection as well.

The viral load of COVID-19 hast its peak within the first week of the onset of infection and the viral shedding of the severe ill cases are significantly higher compared to those with mild symptoms of the infection. The findings are not only of interest for estimating the severity of the infection and to come up with a prognosis, but also illustrates the danger for hospital staff to get infected. Virus shedding also has to be considered in the context of the overall transmission of the virions.

Also related to ACE2 it was recently hypothesized, that a genetic variation of the receptor, might make it easier for the virus to enter the cell. The possibility of such a mechanism could explain why some young individuals, not considered to be very much at risk, anyway can seriously fall ill.

In general, ACE2 receptors might be protective against a lethal infection because of its anti-inflammatory and antioxidant properties detected in case of coronavirus infections with the influence A H5N1 (10). COVID-2 infected patients, suffering from diabetes, belong to a high-risk group, probably because ACE2 expression is reduced in diabetes mellitus. In such a situation, the

anti-inflammatory effect of ACE2 might be weaken. A short publication from India pointed out that the frequent use of angiotensin-receptor blockers prescribed to patients with diabetes and hypertension may aggravate a COVID-2 infection (11). It is argued that downregulating of ACE2 results in viral replication with a subsequent increase of ‘aldosterone and renal potassium wasting’.

Replication and ‘egress’

Attachment to the cell is followed by the entrance of the germ into the cell, a course of action called ‘endocytosis’ and the formation in the ‘early endosome’. This is facilitated through a chain reaction facilitated by the clathrinid protein resulting in a ‘caveolae-dependent invagination’ also described as pinocytosis (9, 12). Further on the endosome is transported to the cell with the help of cytoskeleton components such as motor proteins and microtubules to the perinuclear region. The virus RNA then escapes the vesicle and virion capsule, enters the nucleus and through reverse transcription, complementary DNA (cDNA) is generated. The DNA replicon, after transcribed back into RNA, exits the nucleus. Through complex mechanisms (13-15) by using the cytoskeleton’s structures, including as an important component the microtubules, replicated virions make their ‘egress’ (16).

Conclusion

This summary describes how the virus makes its way through the cell for replication. The information has been compiled by referring to research results investigating various different coronavirus infections especially based on the investigation of the outbreaks of SARS and MERS. Those viruses are thought to be similar to the SARS-CoV-2 virus. Anyhow the present pandemic will keep researchers busy for the next decades. It is hoped, however, that it won’t take that long to collect the information needed to find ways and means to treat the infection. Ultimately, metabolic steps in the reduplication of the virus must be identified, which can be blocked but are not lethal for the host cell es well. Information about COVID-19 treatment attempts will be briefly described together with the manifold attempts to develop a vaccine, and that will be given in a successive contribution.

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