Original Article

Structural Biology And Discovery Of Drugs For Rubella Virus

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Abstract

Rubella viruses are single-stranded ribonucleic acid virus with a lipid-containing membrane surrounding them. Inhalation of infected droplets after birth causes infection with the rubella virus. Rubella viruses normally cause straightforward infections in children who are infected after birth and have unspecific rashes (postnatal rubella). Adults may experience more severe rubella virus infections, which may include consequences such as joint pain and inflammation. During pregnancy foetus can also be affected by rubella virus. The Gregg syndrome, for example, is linked to severe damage to the new-born's heart, ears, and eyes. The presence of rubella-specific IgM is usually used to diagnose an acute infection with the virus. Even after the availability of the rubella vaccine in the 1970, rubella is still ubiquitous in several countries. There is no special (antiviral) treatment available. MR& MMRV vaccines can help in preventing treat the rubella virus. Gama STAN (IGIM)&Immune globulin (intramuscular) (IGIM) drugs may help to cure the rubella virus disease.

Keywords: Rubella virus, MMR vaccine, MMRV vaccine,Gama STAN, Drugs, Immune globulin

INTRODUCTION

The RV which causes rubella is comes under Matonaviridae family. It is a positive-stranded RNA virus. The RV causes rubella. It is also called as German measles or 3 measles (Lambert et al. 2015). Rubella is a contagious, acute viral infection. While RV affected children and adults usually suffer fever and rash, infection in the time of pregnancy, particularly during the first trimester, can lead to miscarriage, foetal death, stillbirth, or new borns with congenital abnormalities, sometimes known as congenital rubella syndrome (CRS). When infected persons sneeze or cough, the rubella virus spreads through the air. The only identified host is humans. Overall RV disease causes mild sickness in some of the people, with that symptoms such as low body temperature, sore throat, and rashes start on the face and spreads to another parts of the body (Lambert et al 2015, Hobman et al.2007).

HISTORY

This RV disease was first discovered in 1619 by German physician Daniel Sennert, and was as named is röteln or rubella, after the red-colored rash that accompanied the illness. In nineteenth century, rubella was separated from the more fatal contagious disease measles, or rubella. Medical studies in the twentieth century established that rubella was caused by a virus that could be transmitted through airborne droplets. Following many cases originating from a pandemic disease in Australia in 1940, extensive research into congenital rubella syndrome began. According to WHO African and South-East Asian areas have the highest CRS incidence due to inadequate immunisation coverage (Hobman et al. 2007).

OUT BREAKS

Between 1964 and 1965, an approximated 12.5 million persons in the United States contracted rubella, 11,000 childbearing women miscarried their infants, 2,100 infants were dead, and 20,000 children were born suffering from congenital Rubella syndrome (CRS). In 2004, Rubella was declared eradicated in the United States. Rubella eradication is characterized by the absence of ongoing transmission of active infections inside a particular geographic area for at least 12 months (Hobman et al. 2007).

ORIGIN AND DISTRIBUTION

The rubella name comes from the Latin word rubella which means "little red." It was only until 1814 that it was documented to cause a disease with the nickname "German measles (Bennett et al 2020). Rubella virus belongs to Kingdom – Orthornavirae, Phylum – Ktrinoviricota, Class – Flasuviricetes, Order – Hepelivirales, Family – Matonaviridae , Genus – Rubivirus , Species – Rubivirus rubella

China is the world's leading country in terms of rubella cases. China had 2,202 rubella cases as of 2020, which is 21.60 % of all rubella cases worldwide (Zheng et al. 2003).

STRUCTURE OF RUBELLA VIRUS

The structure of RV is spherical (figure 1) and positive-sense. It has a single-stranded RNA having spike-like, hemagglutinin-containing surface projections that measures 40 to 80 nanometres in diameter. A lipoprotein membrane surrounds a electron-dense 30 to 35 nm core. RV has positive-sense RNA virus having a genome of 9.6 kb. The particle diameter of the virions range from 600nm to 800nm , with the majority of the circular virions diameter in the range of around 700nm (Dorsett et al.1985). The capsid protein (31 kDa) as well as the glycoprotein's E1 (58 kDa) and E2 (42–47 kDa) are the three structural proteins found in RV. The nucleocapsid is formed when the C protein binding with the RNA genome & produces a lipid membrane around which E1 and E2 are organised. The virus was encodes with the two non - structural proteins, p90 and p150, which are crucial in virus replication (Hobman et al. 2007).

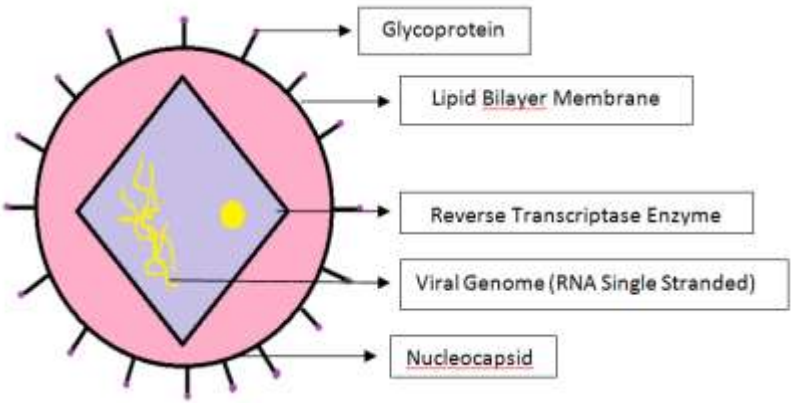

Figure :1 Structure of Rubella virus

GENOME STRUCTURE

Rubella virus has 9,762 nucleotides and a single-stranded positive-sense RNA genome . The genome encodes 2 non-structural proteins I-e - P90 and P150 and 3 structural protein out of which one is nucleocapsid and 2 envelope [E1 and E2] proteins.(Dorsett et al 1985). Based on nucleic acid sequences in the virus's E1 coding region, phylogenetic analysis showed two separate families, clades I and II. About 10 genotypes (1a, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, and 1J),have been identified as to clade I , and 3 genotypes (2A, 2B, and 2C) identified as to clade II. The genotypes 1E and 2B are widely found and are distributed in many parts of the world. Recent advances in whole-genome sequencing techniques, have resulted in 50 whole genomes sequences of rubella virus in GenBank. However there are only 13 full genomes sequences of genotype 2B isolates among these sequences (Zhu et al. 2016).

LIFE CYCLE OF RUBELLA VIRUS

1) Transmission

It is the initial phase of the life cycle. Viruses rely entirely on the host species for carrying out the transmission process. In many cases, a host organism's action directly spreads the virus to some other organism. A vector is used to transmit viruses to a new host. Viruses are transmitted from the body by cell to cell transfer to the new host. The virus must come in contact with an uninfected host cell in order to transmit successfully. Thereafter, virus enters the body and move to the particular cells that they infect (Lee et al. 2000).

2) Adsorption

The adsorption stage follows the transmission step, and involves the virus attaching to the host surface of the cell. Attachment usually takes place on the host's specific cells. Whenever viruses come across a cell with cellular membranes receptors that matching the viral attachment proteins, they attach. On the cell membrane's outer surface, there are many different types of receptors. Receptors let a cell perform a variety of tasks, including detecting substances like hormones. Viruses are unable to target a specific receptor. They are transported to the host cells at random and most of are find a cell that matches their attachment proteins by accident (Lee et al 2000, Fontana et al 2010).

3) Penetrations

This stage occurs after adsorption. The Virus that doesn't have an envelope encourages the cells to engulf them. These viruses bind to receptors cells receptor, prompting the cell to absorb the virus. Viruses are engulfed by cells whenever a bubbles of cell membrane forms around them. The bubble is then moved into the cell, engulfing the virus. The virus either merges with cell membrane or is swallowed inside as a bubble after fusion. At this stage of infection, the viruses are not active (Fontana et al 2010, Villaneva et al. 2005).

4) Uncoating

This is 4th stage of the virus life cycle. The envelope and capsid disintegrate at this point; release the viral genome into the intracellular fluid. Without this stage, viral replication is impossible. Researchers observed once the viruses is uncoated, finding the viral RNA inside the host cell is extremely challenging. As a result, scientists refer to this period as the eclipse phase, because the virus appears to be hidden within the cell. At this point, the cell can use enzymes and other substances intended to defend off viral attack and remove the virus. Such action combat viruses by digesting viral genetic material with proteins and nucleic acids (Lee et al. 2000, Fontana et al. 2010).

5) Syntheses

The following stage is one , in which the virus directs the cell to reproduce both viral genome and capsomeres. This period might be very different from one person to the next. Based on its genetic content and capsid type, every virus has a distinct production step. The viral genome acts as a template for the construction of viral components. In general, many virus begin the manufacturing stage by generating repressor proteins that regulates the functions of the host cell. At this point, some cells die prematurely, halting viral replication. Infected cells in humans normally release signalling proteins that trigger an immune response aimed at preventing virus multiplication (Fontana et al 2010, Villaneva et al. 2005).

6) Assembly

The maturation phase of a virus is sometimes referred to as viral assembly. Inside the infected cell, the viral pieces come together to generate new viruses. The cell mechanism for creating nucleic acid is used to make multiple copy of new genomes. The genome copies are subsequently combined with capsomeres by binding to viral proteins. Capsomere proteins that have been duplicated self-assemble all around genome or nucleocapsid. The host cell also produces other proteins, which self-assemble into the capsid . Many mature viruses have flaws in them, such as partial genomes and aberrant capsid. Hence when compared to the number of normal viruses that will progress to the final step of the process, the number is tiny (Villaneva et al. 2005, Fu et al. 2011).

7) Releasing

The final step of viral infection is the release phase. This stage, such as the synthesis stage, differs widely across different virus infections. Some viruses are released from cells by lysis, which causes them to degrade and die. Specific viral proteins have the ability to cause the cell to lyse. Other viruses can stay in the cell for a long time before they reach the releasing phase. Delay in infections can cause cells to proliferate fast and develop a tumour in some situations. Some tumours have the potential to become cancerous (Fu et al. 2011).

CAUSES OF SPREAD

The virus is spread by the air and replicate in the nasopharynx & lymph nodes after being inhaled. When an infected individual coughs or sneezes, the virus might spread. Immediate interaction with an affected people's respiratory secretions, such as mucus, can potentially cause spread of disease. It can also be spread through the bloodstream from childbearing women to their unborn offspring (Mawson et al.2019, Frey et al.1997).

SYMPTOMS

Rubella in children is usually moderate. The initial symptom of infection is usually a pinkish or red-spotted rash. It starts on the face and then spreads throughout the body. The rashes shown lasts around three days. That's why rubella is also known as the three-day measles. (Frey et al. 1997 , Dontigny et al. 2008). Some other common symptoms are

- A moderate fever (between 99 and 100-degrees Fahrenheit)
- Swollen and rosy colour eyes (conjunctivitis)
- Headache
- Swollen glands behind the ear as well as on the neck
- Stuffy and runny nose
- Cough
- Joint pain (more common in young women)

TREATMENT

There is no cure for rubella or a means to make the condition go away faster. Minor symptoms are treated with bed rest & fever-reducing medications such acetaminophen. MMR or MMRV vaccines may protect against rubella infection after receiving 2 doses of vaccination. Vaccination after exposure will not protect one from becoming infected (Frey et al .1997 ,Dontigny et al .2008).

DIAGNOSIS

Isolation and Identification of Virus

For the viral isolation, a patient's nasopharyngeal and conjunctival swabs, blood tests, respiratory secretions, and urine are collected at the time of the feverish episodes. For isolation attempts, monkey or human kidney cell or a lymphoblastoid cell line (B95-a) are ideal. Fluorescent antibody labelling is used to identify measles antigen in inoculation cultures, which allow the virus to develop slowly (Banatavala et al.1967 ,Revello et al .1997)

Serology

A fourfold increase in antibody titre between acute and convalescent process sera (where the 2ndserum sample is collected at least ten days after 1st, acute sample) or the demonstration of rubella specific IgM antibody in a single serum specimen drawn between one and two weeks after the onset of irritation are required for serologic confirmation of measles infection. Antibody levels of IgM peak after seven to ten days and then rapidly drop, becoming undetectable after six to eight weeks (Banatavala et al .1967).

RT – PCR (Reverse Transcription-Polymerase Chain Reaction)

The important role of RT-PCR in rubella. The RV control is genetic characterization of wild rubella and RV, as well as detection of genomic variation over time and in different parts of the world. Because RT-PCR can identify inactive virus particles, the time it takes to detect the virus after the rash appears is generally some days to weeks

longer than it takes to isolate the virus. However, RT-PCR has a variety of technical limitations with sensitivity and repeatability that might inaccurate results the test (Robinson et al. 2006).

PREVENTION

Rubella is preventable with a vaccine that is both safe and effective. All children should receive the rubella vaccine. It is usually administered to children between the ages of 12 and 15, however, sometimes it is given earlier during epidemic. Child between the age of four and six receive a booster immunisation. MMR (measles, mumps, and rubella) is a three-in-one vaccine that prevent against measles, mumps, and rubella. A blood test is frequently done on women of reproductive age to assess if they are immune to rubella. If they are not immune, women should wait 28 days after receiving the vaccine before becoming pregnant. People who should not have been immunised include pregnant women and those who are allergic to the vaccine (Dontigny et al. 2008 , Robinson et al. 2006).

DRUGS DISCOVERY

Vaccination

Rubella is preventable with MMR immunisation. Measles, mumps, and rubella all are protected by this vaccine. The doctor advises children receive two doses of MMR vaccine, the first at between twelve to fifteen months of age and the second at four to six years of age. The MMR vaccine is a very effective and safe vaccine. The MMR vaccine is estimated to be approximately 97 percent effective in preventing rubella with just one dose. MMRV vaccination, which prevents against measles, mumps, rubella, and varicella, is also available for children (chickenpox). The posterior triceps portion of the upper arm is the recommended injection location for adults (Dold et al .1968 , Meyer et al. 1966).

MMR Vaccine

The MMR vaccine prevents against measles, mumps, and rubella. MMR vaccine is given subcutaneously in a dose of 0.5 mL. If a 2nd dose is required, the period between the first & second doses should be at least four weeks (28 days). For most adults, 1 dose of MMR vaccine or other probable evidence of protection is adequate (Dold et al 1968 , Meyer et al 1966 , Lievano et al 2012).

MMRV Vaccine

MMRV vaccinations are available from a number of firms. Merck markets ProQuad, which was approved by the (FDA) in 2005 for use in children aged 12 months to 12 years in the United States. The live, attenuated measles, mumps, and rubella viruses are present in both vaccines. MMRV also contains live varicella-zoster virus that has been attenuated. The live MMR vaccination and MMRV vaccine must be reconstituted and administered according to the manufacturer's instructions (Dold et al.1968 , Meyer et al 1966 , Lievano et al. 2012).

Drugs

Meruvax is a Measles, Mumps, and Rubella medication that is available on prescription. Meruvax can be taken alone or in combination with other drugs. Meruvax belongs to the Vaccines, Live, and Viral class of medicines. Rubella itself has no specific drug that can be used to cure rubella or make it go away faster (Dold et al. 1968).

Procedure of drugs administration include:

- A steroid that can be taken orally, nasally, inhaled, or injected,
- Azathioprine (Imuran), efalizumab (Raptiva), etanercept (Enbrel), leflunomide (Arava), and other drugs for psoriasis, rheumatoid arthritis, and other autoimmune illnesses can be consumed as pills.
- Basiliximab (Simulect), cyclosporine (Sandimmune, Neoral, and Gengraf), muromonab-CD3 (Orthoclone), mycophenolate mofetil (CellCept), sirolimus (Rapamune), or tacrolimus are immunosuppressive medications that can also be used.

Other medicines may have an impact on this vaccination. Taking a new drug without first consulting the physician is not recommended.

Gama STAN (IGIM) and **Immune globulin (intramuscular) (IGIM) Drugs**

Immune globulin is a sterile human plasma-based solution. Antibodies in it protect from various. After exposure to measles, chickenpox (varicella), or rubella, immunoglobulin intramuscular (IGIM, for injection into a muscle) is being used to prevent infection. IGIM cannot be used in place of routine polio, varicella, mumps, or rubella vaccine. Gama STAN has the potential to cause blood clots, therefore, who have had blood clots, cardiac difficulties, or blood circulation problems must not avoid it. Long-term bedrest, the use of contraceptive pills or hormone replacement treatment, or the uses of a central intravenous (IV) catheter all increase the risk of blood clots. While utilizing immune globulin for up to six months after the last dosage, getting a "live" vaccine is not recommended. The vaccine may not work as well as it should and may not provide complete protection against disease if above mentioned precautions are taken (Dold et al 1968, Mclean et al 2013).

CONCLUSION

Rubella viruses are single-stranded ribonucleic acid virus with a lipid-containing membrane surrounding them. Although symptoms are mild it can cause problematic symptoms in children and adults. To prevent fatal outcomes proper vaccination and discovery of new drugs is necessary.

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REFERENCES

1. Banatvala, J. E., Best, J. M., Kennedy, E. A., Smith, E. E., & Spence, M. E. (1967). A serological method for demonstrating recent infection by rubella virus. British medical journal, 3(5560), 285.
2. Bennett, A. J., Paskey, A. C., Ebinger, A., Pfaff, F., Priemer, G., Höper, D. & Goldberg, T. L. (2020). Relatives of rubella virus in diverse mammals. Nature, 586(7829), 424-428.
3. Dold, H. J., & Northrop, R. L. (1968). The nonspecific inhibitors of rubella-virus hemagglutination. Proceedings of the Society for Experimental Biology and Medicine, 128(2), 577-581.
4. Dontigny, L., Arsenault, M. Y., Martel, M. J., Biringer, A., Cormier, J., Delaney, M., ... & Wilson, A. K. (2008). Rubella in pregnancy. Journal of Obstetrics and Gynaecology Canada, 30(2), 152-158.
5. Dorsett, P. H., Miller, D. C., Green, K. Y., & Byrd, F. I. (1985). Structure and function of the rubella virus proteins. Clinical Infectious Diseases, 7(Supplement_1), S150-S156.
6. Fontana, J., López-Iglesias, C., Tzeng, W. P., Frey, T. K., Fernández, J. J., &Risco, C. (2010). Three-dimensional structure of Rubella virus factories. Virology, 405(2), 579-591.
7. Frey, T. K. (1997). Neurological aspects of rubella virus infection. Intervirology, 40(2-3), 167-175.
8. Fu, C. Y., & Johnson, J. E. (2011). Viral life cycles captured in three-dimensions with electron microscopy tomography. Current opinion in virology, 1(2), 125-133.
9. GREEN, R. H., BALSAMO, M. R., Giles, J. P., Krugman, S., & MIRICK, G. S. (1965). Studies of the natural history and prevention of rubella. American Journal of Diseases of Children, 110(4), 348-365.
10. Hobman TC, Chantler J. Rubella virus. In: Knipe DM, Howley PM, editors. Fields Virology. 5th Ed. Vol I. Philadelphia: Lippincott Williams & Wilkins; 2007. pp. 1069–1100.
11. Lambert, N; Strebel, P; Orenstein, W; Icenogle, J; Poland, GA (7 January 2015). "Rubella". Lancet. **385** (9984):2297–307. doi:10.1016/S0140-6736(14)60539-0. PMC 4514442. PMID 25576992.
12. Lee, J. Y., & Bowden, D. S. (2000). Rubella virus replication and links to teratogenicity. Clinical microbiology reviews, 13(4), 571-587.
13. Lievano, F., Galea, S. A., Thornton, M., Wiedmann, R. T., Manoff, S. B., Tran, T. N., ... & Plotkin, S. A. (2012). Measles, mumps, and rubella virus vaccine (M–M–R™ II): a review of 32 years of clinical and postmarketing experience. Vaccine, 30(48), 6918-6926.
14. Mawson, A. R., & Croft, A. M. (2019). Rubella virus infection, the congenital rubella syndrome, and the link to autism. International journal of environmental research and public health, 16(19), 3543.
15. McLean, H. Q., Fiebelkorn, A. P., Temte, J. L., & Wallace, G. S. (2013). Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report: Recommendations and Reports, 62(4), 1-34.

16. Meyer Jr, H. M., Parkman, P. D., &Panos, T. C. (1966). Attenuated rubella virus: Production of an experimental live-virus vaccine and clinical trial. New England Journal of Medicine, 275(11), 575-580.
17. Revello, M. G., Baldanti, F., Sarasini, A., Zavattoni, M., Torsellini, M., &Gerna, G. (1997). Prenatal diagnosis of rubella virus infection by direct detection and semiquantitation of viral RNA in clinical samples by reverse transcription-PCR. Journal of Clinical Microbiology, 35(3), 708-713.
18. Robinson, J. L., Lee, B. E., Preiksaitis, J. K., Plitt, S., & Tipples, G. A. (2006). Prevention of congenital rubella syndrome—what makes sense in 2006?. Epidemiologic reviews, 28(1), 81-87.
19. Villanueva, R. A., Rouillé, Y., &Dubuisson, J. (2005). Interactions between virus proteins and host cell membranes during the viral life cycle. International review of cytology, 245, 171-244.
20. Zheng, D. P., Frey, T. K., Icenogle, J., Katow, S., Abernathy, E. S., Song, K. J.,&Croxson, M. (2003). Global distribution of rubella virus genotypes. Emerging infectious diseases, 9(12), 1523.
21. Zhu Z, Chen MH, Abernathy E, Icenogle J, Zhou S, Wang C, Zhao C, Wang Y, Chen H, Si Y, Xu W. (2016). Analysis of complete genomes of the rubella virus genotypes 1E and 2B which circulated in China, 2000–2013. Sci Rep 6:39025. Doi: 10.1038/srep39025