Shining a light on the hidden viral infection that causes birth defects

Researchers at the University of California are paving the way in discovering potential targets to help us fight the devastating impacts of infection with the birth defect virus, human cytomegalovirus (CMV). Dr Lenore Pereira is leading the current research into this common, yet relatively unfamiliar, virus.

What inspired you to focus your research on human cytomegalovirus (CMV)? When I began studying CMV, little was known about the protein composition of virions, the breadth of target cells for human infection and the mechanisms of infection and transmission during pregnancy leading to birth defects in the foetus.

What have been the biggest challenges you have faced conducting this research? The extreme species specificity of human CMV requires that only human cells be used for infection, making it difficult to model congenital disease except for experiments using cells from the human placenta and explants of the early gestation, developing placenta.

Why do you think there is so little awareness of CMV in comparison to other viruses? The public is most aware of viruses featured in newspapers, i.e., epidemics (Ebola and Zika viruses), annual seasonal outbreaks (influenza virus), local outbreaks that occur in unvaccinated children (measles, mumps), and sexually transmitted viruses and those spread by drug use (human immunodeficiency and hepatitis C viruses). In contrast, CMV causes a relatively benign infection, without a rash and with a usually mild fever. Nor does infection cause complications in healthy children and adults. Hopefully, this lack of awareness will soon change. The internet has created a new venue for families whose children were born with congenital CMV to communicate with one another at the national and international level to raise awareness about testing newborns and alerting pregnant women about birth defects from first-time congenital infection.

What will be the next steps for the development of therapeutics based on your findings? Our work, and that of other groups, has focused on understanding the role of maternal immunity that can reduce infection in the developing human placenta, especially in the first trimester when the foetus is most severely affected. We found that potent neutralising antibodies, to specific CMV proteins in the virion envelope, effectively block infection of cytrophoblasts (target cells in the placental). Hopefully, in the near future, novel vaccines and antiviral products based on monoclonal antibodies to these proteins can be developed to prevent or reduce CMV infection in early pregnancy.

How do you see your research progressing in future? In recent studies of placentas from mothers who deliver congenitally infected babies with intrauterine growth restriction, we found persistent CMV infection in epithelial cells of the amniotic sac (foetal membranes). We also discovered persistent infection in membranes of babies born with symptomatic and asymptomatic infection. We plan to dissect the molecular processes that lead to persistent infection in these special cells and identify the route of virus spread in late gestation. This could be different from early gestation and explain why infection in the third trimester is usually benign. In addition, we recently reported that the Zika virus infects the human placenta and proposed two routes of virus transmission from mother to baby. We hope to decipher the mechanisms that target Zika infection to specific cell types.

Why is there still no treatment or vaccine for congenital CMV infection? At the University of California in San Francisco, Dr Lenore Pereira leads a research team that endeavours to understand how a common virus can cause intrauterine infection in some women that spreads to the developing placenta and foetus and causes congenital birth defects worldwide.

Human cytomegalovirus (CMV), a member of the Herpesviridae family, is highly specific and infects only humans. In pregnancy, it specifically infects placental cells and impairs their differentiation that is essential for foetal development. It has been known for over 50 years that CMV infection during pregnancy can result in damage to the foetus. However, there are still no treatments available for infection during gestation. Currently, there is also no vaccine to prevent infection, and although several possible candidates have now been identified, they are still under investigation or in early clinical trials for organ transplant recipients, where CMV infection can involve severe complications.

**THE MAJOR VIRAL CAUSE OF BIRTH DEFECTS AND HEARING LOSS**

Between 0.2% and 3.0% of all newborns in the US are infected with CMV and 5 to 10% of those may have poor clinical outcomes or hearing loss. A child is born affected by congenital CMV every hour; outnumbering disabilities caused by other conditions routinely screened for in the US. Birth defects that result from CMV infection also exceed those caused by other more widely known conditions, such as Down’s syndrome and fotal alcohol syndrome. Despite the severity of congenital disease and the cost of resultant healthcare estimated to be nearing 2 billion dollars in the US, CMV has been neglected with regards to medical research. This can be partly attributed to the complexity of the viral infection and the high degree of variation in clinical outcomes. The molecular and cellular basis for its impacts and the role of the placenta have until recently been poorly understood. **Q&A**
Dr Pereira has been at the forefront of work to understand the biology of infection during pregnancy and her ground-breaking research in the human placenta has led to several promising avenues for the development of novel therapeutics and vaccines.

The most severe outcomes of infection occur when a woman contracts the virus for the first time during early pregnancy. This is known as primary maternal infection and poses the highest risk of birth defects for the foetus. These are unpredictable and range from severe motor and neurological disabilities such as microcephaly and cerebral palsy, to levels of vision impairment and hearing loss. Out of primary maternal infections, the majority of cases resulting in disability occur when a mother is infected during her first trimester of gestation. However, infection can occur at any stage of pregnancy and even late infections can sometimes cause birth defects. Some infants also die soon after birth or their life expectancy is greatly reduced due to complications of congenital disease.

**INVESTIGATING THE INFECTION**

Dr Pereira and her team’s investigation has been focused on the affects of the virus on placental development and function, as this is the major route of transmission to the foetus. They also suspected that placental infection and subsequent injury could be a cause of intrauterine growth restriction (IUGR). Dr Pereira’s team analysed biopsy samples for pathology, patterns of viral proteins in infected cells, and the presence of viral DNA. They found not only evidence of infection but also evidence of active viral replication and increased expression of viral proteins.

The virus is a major cause of permanent disabilities in children with a child born affected by congenital CMV every hour. In addition to these findings, their research has shown that the virus suppresses the production of proteins that block self-production of antiviral proteins made by host cells and activates pathways that increase the production of proteins that block self-destruction of infected cells in the amniotic sac allowing the virus to continue with a persistent infection. Targeting interventions to the signalling pathways that contribute to CMV persistence, and enhancing those with the capacity to suppress it, could also lead to novel treatments.

**NEW HOPE IN FIGHTING CMV**

Excitingly, the team’s most recent project has unveiled another promising line of enquiry for developing interventions to fight against congenital CMV infection. Their recent study has shown that the virus suppresses the production of antiviral proteins made by host cells and activates pathways that increase the production of proteins that block self-destruction of infected cells in the amniotic sac allowing the virus to continue with a persistent infection. Targeting interventions to the signalling pathways that contribute to CMV persistence, and enhancing those with the capacity to suppress it, could also lead to novel treatments.

As a result of the studies on infection of the human placenta led by Dr Pereira, researchers are now equipped with a deeper understanding of how CMV can lead to IUGR and several promising strategies to improve the outcome of cases of primary congenital infection. Further work into developing antibody-based therapeutics based on their findings could yield interventions to reduce the number of babies affected by severe congenital disease. Finally, by tailoring the design of new vaccines to protect the foetus from infection, the future looks brighter for pregnant women and the health of their babies.