Progress Toward Rubella Elimination and CRS Prevention in Europe

8-10 February 2010 Rome

Background Information

Rubella Virus

Joseph P. Icenogle
Rubella Laboratory Team Lead
MMRH Laboratory Branch

1: National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA
2: J. Craig Venter Institute, 9704 Medical Center Drive, Rockville, MD 20850, USA
Outline

1. A brief history of rubella virus, before the development of vaccines
2. Structure of the virus, partly by analogy to related viruses
3. Description of the genome of rubella virus
4. Variability in the genome of circulating rubella viruses
5. Some properties of specific viral proteins
6. The life cycle of rubella virus in tissue culture; details matter
7. Emphasis on a couple of important virus-host cell interactions
Brief, Selected History of Rubella and Congenital Rubella Syndrome, Before Vaccines were Developed.

18th Century----Description of disease by German authors

1881-----------Recognition of rubella as a disease independent from measles and scarlet fever by an International Congress of Medicine in London

1881 to 1941---Little or no recognition of rubella as anything other than a mild childhood rash illness. Significant influence of prevalent opinion that birth defects were all of genetic origin.

1941-1950s----Lack of Clarity on the importance of Congenital Rubella Syndrome


Very clever assays developed to detect the rubella viruses which is difficult to detect because some wild type viruses have non-distinct cytopathic effect.

1962-1965--------Devastating worldwide rubella epidemic. United States history of rubella control and elimination can be viewed as starting with this epidemic.
Rubella Cases in Selected areas (sentinel cities) of the US 1928-1969

Epidemics every 6-9 years
Rubella virus in Vero cells: Electron Microscopy

- replication complexes (RC) in membranous spherules inside cytopathic vacuoles (CPV)
- mature virions in TGN and extracellular spaces
- no virions in cytoplasm

Data from Rubella Laboratory Team, MMRHLB, CDC
Structure of Alphaviruses Determined Using Cryo-EM

A. Sinbis virus as determined by cryo-EM
B. Alphavirus nucleocapsid as determined by cryo-EM
Lipid Membrane (bilayer)

Dimers of E1 and E2, 3 dimers arranged in one spike

Capsid protein

RNA

Similar but not Identical Proteins exist for SINV and Rubella Virus
Genome Replication of Rubella Virus

http://www.ncbi.nlm.nih.gov/books/NBK7633/
Antigenicities of Rubella Glycoproteins

- E1 alone is sufficient enough to elicit neutralizing anti-rubella virus antibodies (Perrenoud et al., 2004);
- E1 and E2 play a major role in the long-lasting protective immunity to rubella virus. (Nates et al., 1989);
- Antibodies to E1 were present up to 3 years following immunization. Antibodies to E2 and C protein of the M33 virus often gradually disappeared (Cusi et al., 1989);
- E2 is less immunogenic (lack of reactivity in human sera) (Trudel et al., 1985);
- An E2 monoclonal antibody failed to recognize BRDII E2 (a clade 2 virus) by western blot (Zheng et al., 2004).
Capsid Protein is associated with the membrane

Fields Virology, 5th edition
Rubella virus is the only member in the Rubiviruses genus in Togaviruses Family

Single-stranded positive strand RNA viruses.
Togaviridae
(2 Genera - 348 complete genomes)

Genus: Alphavirus (18 Species - 302 complete genomes)
- Aura virus (2 strains - 2 complete genomes)
- Barmah Forest virus (5 strains - 6 complete genomes)
- Chikungunya virus (153 strains - 152 complete genomes)
- Cloning vector pBR-XJ160 (1 strains - 1 complete genomes)
- Eastern equine encephalitis virus (21 strains - 16 complete genomes)
- Fort Morgan virus (1 strain - 2 complete genomes)
- Getah virus (6 strains - 7 complete genomes)
- Highlands J virus (3 strains - 4 complete genomes)
- Mayaro virus (3 strains - 3 complete genomes)
- Middelburg virus (1 strain - 1 complete genome)
- Norwegian salmonid alphavirus (4 strains - 0 complete genomes)
- O'nyong-nyong virus (4 strains - 4 complete genomes)
- Ross River virus (15 strains - 16 complete genomes)
- Salmon pancreas disease virus (4 strains - 4 complete genomes)
- Semliki forest virus (16 strains - 14 complete genomes)
- Sindbis virus (13 strains - 12 complete genomes)
- Venezuelan equine encephalitis virus (42 strains - 44 complete genomes)
- Western equine encephalomyelitis virus (13 strains - 14 complete genomes)

Genus: Rubivirus (1 Species - 46 complete genomes)
- Rubella virus (44 strains - 46 complete genomes)

http://www.viprbrc.org/brc/home.do?decorator=toga
SEQUENCE WINDOW OF RUBELLA VIRAL RNA
FOR MOLECULAR EPIDEMIOLOGY

Positive strand RNA---9762 nucleotides

Nonstructural Proteins

Structural Proteins

SEQUENCE REGION (739 NT)

SEQUENCE
REGION (739 NT)
PDF file of 233 curated rubella sequences, 739 nucleotides, MEGA Maximum Likelihood
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Alphavirus Life Cycle
Protein synthesis and RNA replication in infected cells (MOI=5)

Kinetics of genomic RNA replication by qRT-PCR

Kinetics of viral protein synthesis by Western Blot

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Kinetics of rubella virion secretion

Data from Rubella Laboratory Team, MMRHLB, CDC
Comparison of plaque assay and colorimetric-based virus quantification method

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Data from Rubella Laboratory Team, MMRHLB, CDC
Rubella postnatal

- Replication in mucosal epithelium
  - Lymph nodes (nasopharynx)
  - Primary viremia (lymphatic)
  - Unknown target organs
  - Secondary viremia (blood)

- Skin, joint tissue, other?
  - Persistent infection of placenta
  - Persistent infection of joint tissue
  - Infection cleared

Abs, CTLs

Rubella in utero

- Persistent infection of fetus
  - Systemic infection, multiple organ damage
  - Postnatal persistent infection
  - Congenital rubella syndrome (CRS)
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Acknowledgements

CDC
Min-Hsin Chen
Ludmila Perelygina
Emily Abernathy
Lijuan Hao
Adaeze Ogee-Nwankwo
Qi Zheng

J. Craig Venter Institute
Jayati Bera
Susmita Shrivastava
Ewen Kirkness

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.