Rotavirus Pathogenesis

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Diseases Associated with Rotavirus Infections

- Rotaviruses are the primary cause of severe gastroenteritis in young children.
- These viruses have also been etiologically or incidentally associated with numerous other diseases.
- These include diseases such as encephalitis and meningitis, various upper and lower respiratory infections, hepatic abscess, pancreatitis, diabetes, and necrotizing enterocolitis.
Hepatitis and biliary atresia can be induced in newborn mice by certain G3 rotaviruses

- Serotype G3 simian rotaviruses RRV and SA11 and the asymptomatic human HCR3 strain spread extraintestinally and cause both hepatitis and biliary atresia (blockage of the bile ducts) after oral inoculation of newborn mice.

- These properties appear to be restricted to a very limited number of rotavirus strains, i.e., murine and bovine rotaviruses evaluated do not have these properties.
Question: Are some G3 rotaviruses overly permissive?

- Very recently it was reported that murine rotaviruses can also spread from the intestine. However, they do not cause hepatitis or biliary atresia in orally inoculated mice.

- Intraperitoneal (i.p.) inoculation of newborn mice with RRV also consistently induces biliary atresia while i.p. inoculation with murine rotavirus does not.

- This is probably due to the ability of RRV to infect cholangiocytes that line the bile ducts.

- It seems likely, therefore, that the abilities of a limited number of G3 strains to cause diseases such as biliary atresia is not due merely to their extraintestinal spread but to their unique aptitude to infect and replicate in extraintestinal tissues.
Rotavirus and intussusception (IS)

- Vaccination of young children with Rotashield, which has the G3 RRV strain as one of its components, is associated with the induction of IS in ca. 1/12,000 vaccinees.

- This rare association caused removal of the vaccine from the market in the USA, the only place where the vaccine had been licensed.

- IS is not seasonally associated with natural rotavirus infection. However, an association has been suggested between IS and infection with natural G3 strains in Japan.

- It is possible, therefore, that IS can be induced by a limited number of G3 strains due to, or in concert with, the greater tropism of these viruses for extraintestinal tissues as suggested by the studies in mice.
**Host specificity of rotavirus**

- Rotaviruses are a major pathogen in the young of many animal species.

- Although they are generally species-specific, cross-species infections and illnesses are not uncommon.

- For example, the HCR3 strain that produces biliary atresia and hepatitis in newborn mice is probably either a canine or feline rotavirus that infected humans.

- This virus, however, was isolated from an asymptomatic child and may not cause disease in humans. This is typical of animal strains that have infected humans but is not always the case.

- In addition, coinfection of a human or animal with rotaviruses from both species leads to the formation of reassortant rotaviruses and these new strains can be as pathogenic in humans as their human parents.

- More often, these animal/human reassortants are attenuated for humans. Such strains have been developed as vaccine candidates (Rotashield, RotaTeq).
Why are rotaviruses host range-restricted?

- One reason for restriction is the inability of rotavirus to attach and enter cells of heterologous species.

- Recent studies have identified several rotavirus receptors, primarily integrins. However, most animal rotaviruses appear to attach first to sialic acid before making secondary contacts with integrin molecules.

- Human rotaviruses typically do not bind to sialic acid, thus suggesting one major difference between human and animal rotavirus receptors.
Host range restriction can also occur within the infected cell during viral replication

- Using reassortants made between RRV and a murine rotavirus, Greenberg and colleagues reported that the gene segment most associated with host range restriction appeared to be that encoding the non-structural protein NSP1.

- If this protein is a determinant of host restriction, its effects must come into play during virus replication.

- NSP1 is, however, clearly not the only determinant of host restriction because when this gene from a bovine strain that caused abortive infections in piglets was substituted into a virulent porcine strain, the reassortant was still virulent.
Rotavirus diarrhea is highly related to age

- In animal species, including non-human primates, severe rotavirus diarrhea occurs only during the days or weeks after birth.

- One possible reason is that rotavirus receptors on intestinal cells decrease with age.

- Even so, older naïve animals can be readily infected with homologous rotavirus strains and shed large quantities of viral antigen in their feces.

- Therefore, age related loss of susceptibility to disease appears to be due to more than decreases in receptor numbers.
Susceptibility to severe rotavirus disease in humans is also age related

- Rotavirus infections are almost always asymptomatic in full term neonates and severe rotavirus disease in uncommon until children are about 6 months of age.

- In contrast, rotavirus infections in premature newborns often causes severe disease.

- Most maternal antibody is transferred into the unborn child during the last weeks before a normal full-term birth, suggesting that this antibody may play a role in protection during the first weeks of life.

- The age of susceptibility to severe rotavirus disease coincides with the degradation of this antibody.
Natural rotavirus infections protect children against severe rotavirus disease

- However, protection against subsequent rotavirus infection and mild illness is often only transitory.

- Protection against severe disease has been found even if the first infection occurred as a neonate.

- This protection appears to be independent of the serotype of the rotavirus that caused the initial infection.
Lack of protection in newborn animals may be due to the lack of transplacental antibody

When neutralizing antibody to a challenge rotavirus is delivered to the intestine of an animal, it can be protected against rotavirus disease

However, most animals lack significant titers of maternal transplacental antibody

This correlates with their susceptibility to rotavirus disease immediately after birth
Intestinal damage in piglets after rotavirus infection
The intestinal villi of mice are also altered by rotavirus infection

- Newborn mice develop severe diarrhea for up to two weeks of age when challenged with a murine rotavirus.

- Although the pathological changes in their intestines are not as dramatic as seen in larger animals and humans, they are still very evident.

- The most thorough study of changes in mice villi after rotavirus infection were reported by Boshuizen et al (J. Virol., Dec. 2003).
Histopathological lesions in mouse small intestine 1 day after rotavirus infection
Kinetics of rotavirus mRNA production in mice villi
Change in the speed of migration of cells from crypt to villus tip after rotavirus infection of mice.
Destruction of mature enterocytes on the tips of the intestinal villi after rotavirus infection is a possible cause for diarrhea.

- Early studies suggested that this destruction resulted in absorptive abnormalities that were associated with diarrhea.

- Since only mature enterocytes were infected with rotavirus, their destruction caused the immature, uninfected enterocytes in the villus crypts to migrate at an accelerated rate to the tips but these cells lacked full absorptive capabilities.
The NSP4 protein of rotavirus may be responsible for diarrhea?

- It was reported that the NSP4 protein of rotavirus, and even a 22-amino piece of this protein, can induce diarrhea in infant mice and rats.

- Subsequently, NSP4 was found to stimulate increased intracellular calcium concentrations that may contribute to altered ion transport and diarrhea.

- Based on these and other observations, it has been suggested that NSP4 acts as a diarrheal-inducing enterotoxin and may be a major cause of rotavirus diarrhea.

- There is, however, no evidence that NSP4 causes diarrhea in humans.

- We reported that the attenuated precursor of Rotarix (strain 89-12) had only one amino acid difference in its NSP4 protein when compared to the wild type 89-12 parent strain and this amino acid change could not account for the change in virulence.
Virulence of rotavirus has also been associated with other rotavirus proteins

- Through the use of rotavirus reassortants in piglets and mice, it has been variously concluded that VP3, VP4, VP7, NSP1 and NSP4 all play roles in rotavirus virulence.

- From these results, as well as from studies concerning other properties of rotavirus, it is likely that specific combinations of genes in the different viruses dictate which strain will induce severe diarrhea.
Rotaviruses are the major cause of severe diarrhea in young children but these viruses have also been associated with other disease symptoms.

Rotaviruses do cross species barriers and often form cross-species reassortants but heterologous rotaviruses and their reassortants are usually avirulent.

The age of susceptibility to rotavirus diarrhea is quite different between humans and animals, possibly due immunological factors and viral receptor differences.

The causes for diarrhea after rotavirus infection have been primarily associated absorptive changes due to destruction of villi cells and enterotoxin properties of NSP4.