Gnotobiotic pig models: Illuminating the enigma of human norovirus infection and immunity

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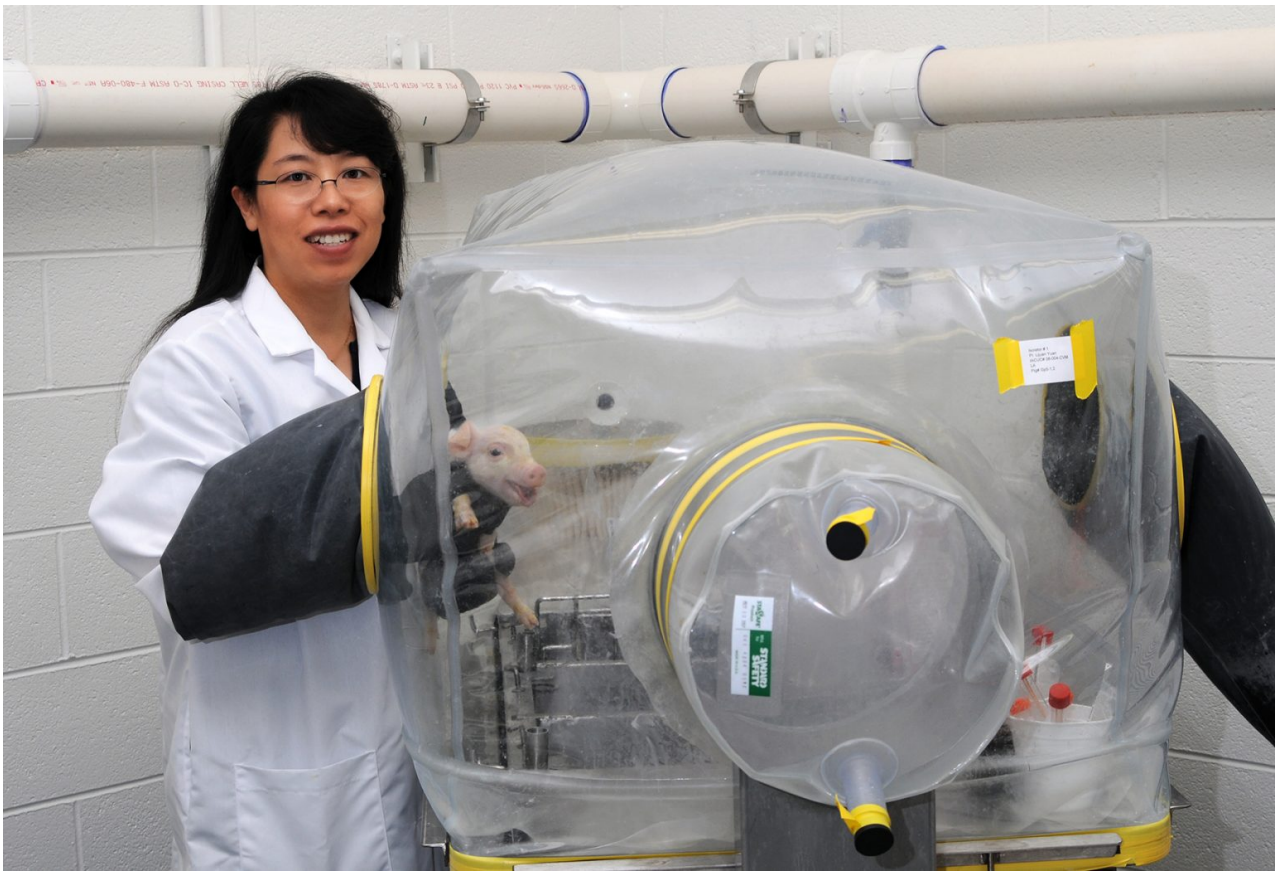

Lijuan Yuan

Dr Lijuan Yuan and her team have studied human noroviruses (HuNoV) in gnotobiotic pigs for over 15 years. Here, she explains how such research is advancing our understanding of HuNoV pathogenesis, infectivity, and immunity

The intricate interplay between pathogens and their hosts has been a focal point of infectious disease research, especially for elusive viruses like human noroviruses (HuNoV).
With their capacity to cause acute gastroenteritis and notorious ability to evade traditional cell culture methods, the study of HuNoV has been particularly challenging.

However, gnotobiotic pig models have emerged as a potent tool in unveiling the complex dynamics of HuNoV pathogenesis, infectivity, and immunity. This review delves into the application of gnotobiotic pig models in deciphering the enigmatic world of HuNoV, shedding light on their elusive interactions with the host.

The gnotobiotic pig model: A biologically relevant system

Gnotobiotic (Gn) pig models, which involve raising pigs in a controlled environment devoid of conventional microbiota and then introducing defined microbial communities, provide a unique tool to study HuNoV. By mimicking the in vivo environment of HuNoV infections more accurately, these models offer a valuable platform to explore the elusive HuNoV-host interactions.

Dr Lijuan Yuan and her team at Virginia Polytechnic Institute and State University have been studying HuNoV in Gn pigs for over 15 years. They established the Gn pig model of HuNoV infection and diarrhea and studied the tropism of HuNoV infection, the functions of immune effector cells in norovirus immunity, and tested changes in infectivity, pathogenesis, and immunity in response to various factors influencing the host immune system and gut microbiota.

Pathogenesis unveiled: Deciphering viral tropism and replication site

One of the foremost challenges in studying HuNoVs is their exquisite host range, which restricts infection primarily to humans. Gn pig models, however, offer an avenue to overcome this hurdle. By introducing HuNoV into these pigs, researchers can explore viral tropism and replication sites in a system closely resembling the human gut.

Dr Yuan's team tested the influences of E. cloacae on HuNoV infectivity and whether HuNoV infects B cells in vivo. [(1)] In both control and E. cloacae colonized pigs, HuNoV infection of enterocytes was confirmed, infection of B cells was not observed in the ileum, and the entire lamina propria in sections of duodenum, jejunum, and ileum were HuNoV-negative.

The conclusions were unequivocal that E. cloacae inhibited HuNoV infectivity, and B cells were not a target cell type for HuNoV in gnotobiotic pigs, with or without E. cloacae colonization, opposite to what was reported in mice.

Immunity in focus: Unveiling complex host reactions

The elusive nature of HuNoV extends to their interaction with the host immune system, making the study of immune responses challenging. Gn pig models, designed to mimic human-like immune responses, have offered a breakthrough in understanding the interplay between HuNoV and the host immune system. Dr Yuan's team determined HuNoV infectivity in RAG2/IL2RG deficient pigs presenting SCID phenotype. [(2)]

They demonstrated that RAG2/IL2RG deficient Gn pigs supported increased and prolonged HuNoV infection. Higher virus shedding was observed during early infection, indicating SCID hosts were more susceptible to HuNoV infection at the initial stage. Furthermore, the prolonged HuNoV shedding in SCID pigs was asymptomatic and sporadic, similar to asymptomatic low virus shedding in immunosuppressed human patients, indicating the importance of lymphocytes in HuNoV clearance.

Unlike the reports of decreased murine norovirus titers in RGA1 and B cell-deficient mice, increased HuNoV titers were observed in RAG2/IL2RG deficient pigs, signifying again that B cells are not the target cell type of HuNoV.

In addition, they showed that a cholesterol-lowering drug, simvastatin, significantly increased the infectivity and diarrhea severity after HuNoV infection [(3)] and abolished the partial protection conferred by an intranasal HuNoV vaccine through impairing T cell immunity. [(4)] Using the immune-deficient pig model, they explored the balance between viral evasion mechanisms and host immune defense strategies.

Illuminating the complex interactions between human gut microbiome and HuNoV

The role of commensal microbiota and probiotics in enteric viral infections has been explored extensively, but the interaction between human gut microbiota (HGM) and HuNoV is poorly understood. Dr Yuan's lab established an HGM-transplanted pig model of HuNoV infection and disease. [(5)]

Compared to germ-free pigs, HuNoV inoculation in HGM pigs resulted in increased HuNoV shedding and a significantly longer duration of virus shedding. In addition, virus titers were significantly higher in the duodenum and distal ileum of HGM pigs on post-infection day 10. 16S rRNA gene sequencing demonstrated that HuNoV infection dramatically altered intestinal microbiota in HGM Gn pigs.

Colonization of Gn pigs with *Lactobacillus rhamnosus GG* (LGG) and Escherichia coli Nissle 1917 (EcN) prevented HuNoV fecal shedding in Gn pigs [(6)]. Dietary rice bran, in combination with LGG+EcN, exhibited dramatic anti-HuNoV effects, including reduced incidence and shorter duration of diarrhea. Such effects were associated with IFN-g+ T cell responses, increased intestinal IgA and IgG levels, and longer villus length.

Conclusion

Gn pig models have emerged as a transformative tool in advancing our understanding of HuNoV pathogenesis, infectivity, and immunity. Gn pig models provide a more representative platform for studying HuNoV by bridging the gap between traditional murine models and human systems.

From elucidating viral tropism to unraveling immune responses, the insights gained from Gn pig models hold significant promise for translational applications. As our understanding of HuNoV interactions deepens, Gn pig models could be a robust platform for testing antiviral drugs and vaccine candidates.

As the field continues to evolve, Gn pig models will undoubtedly remain a cornerstone in our pursuit of effective interventions to mitigate the impact of HuNoV infections on global health.

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