February 13, 2019

Health & Physiology

Gene edited “superpigs” resist devastating disease

by Christine Burkard[1] | Assistant Professor

[1]: The Roslin Institute, University of Edinburgh, Edinburgh, UK

This Break was edited by Dr. Carlos Rivera-Rivera, *Managing Editor* - TheScienceBreaker

ABSTRACT

Genome editors are simple tools that allow scientists to make very precise changes to the genome of any organism. Here we present the use of these "gene scissors" to make pigs resistant to a devastating viral disease by removing a small portion of their genome and disrupting the key-lock interaction of the virus with its host.

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Genome editors are simple tools that allow scientists to make very precise changes to the genome of any organism by cutting the genome at a very precise location. If you imagine the genome as a single, continuous string of information containing the instructions to build an organism, genome editors are “gene scissors” that can cut and modify that information. This opens new avenues for investigating basic principles of biology but also to introduce novel traits to domesticated animal and plants. Here we present the use of “gene scissors”, in order to make pigs resistant to a devastating disease.

Porcine reproductive and respiratory syndrome (PRRS), is arguably the most costly pig disease worldwide, and is present in almost every pig-producing country. The disease causes respiratory distress, fever and reduced appetite in pigs of all ages and often results in death of suckling piglets. In pregnant sows it leads to the death of unborn fetuses or to complete abortions. The disease is caused by the PRRS virus (PRRSV) and, to date, vaccination strategies have been ineffective in preventing the spread. PRRSV is a master at incapacitating the pig’s defenses (their immune system), leaving the door wide open for other infections by bacteria or other pathogens. This results in more severe disease due to the additional infections whilst the pigs defenses are incapacitated. As a consequence this also increases the need to use antibiotics in pig breeding to fend off these other infections.

No pigs have been found in commercial breeding stocks that are naturally resistant to PRRSV infection. However, when investigating the interaction between PRRSV and pig cells in the lab, scientists found that there is a key-lock mechanism required for the virus to gain access. The lock, a protein called CD163, looks a bit like a string of nine beads on the surface of immune cells, the target for PRRSV infection. The virus only binds to bead number 5, and whilst all the other eight beads are involved in important biological functions in protecting pigs from disease, bead 5 is not known to be involved in any. A very small segment of the pig genome (450 letters from the 2,700,000,000 letter genomic code) was found to be the genetic blueprint of CD163 bead 5. Using gene scissors that targeted this small segment we were able to remove it from the pig genome!

So, exactly how does one "edit" a pig's genome? Using a microscope, we insert a very fine needle into a fertilised pig egg, delivering the gene scissor reagents. Before the injection, the fertilised pig egg had all the necessary instructions to produce a full pig, including the segment for bead 5 which we want to remove. Once the reagents for our gene scissors are injected, they target and cut out the instructions to produce bead 5, and after all that is done, both the removed segment and the injected reagents are broken down by the cell within a few hours. The fertilised eggs are then transferred into a surrogate sow and almost 4 months later, new, "edited" piglets are born naturally.

After confirming that the piglets indeed lacked the bead 5 segment, a small herd of these animals was produced by natural breeding. Cells from the animals were collected and exposed to PRRSV in the lab. By using cells rather than exposing pigs to the virus, multiple variants of PRRSV can be tested. The cells from pigs having a CD163 gene copy lacking bead 5 from both mother and father were found to be completely resistant to infection with all tested variants of PRRSV. Having demonstrated that there was a good chance that the edited pigs would be resistant to infection by this devastating virus, a cohort of eight pigs (four edited and four unedited controls) were exposed to the virus by spraying virus into their nostrils, the natural route of infection. The animals were all housed together and whilst unedited pigs contracted the disease, pigs lacking bead 5 were completely resistant to infection. At the same time the edited version of CD163 protein (which lacked bead 5) was found to perform its natural functions, and the animals were healthy and bred normally under standard farm conditions.

The creation of pigs lacking bead 5 holds tremendous opportunities for the pork industry worldwide to improve both animal welfare and productivity. PRRSV-resistant animals are not only free of disease but they also don't spread the virus, which means they can help protect other animals, opening avenues for eradicating PRRS. PRRSV-resistant animals could also reduce the prevalence of bacterial infections (secondary infections are a big problem during PRRSV infection), reducing antibiotic use in pig production. At the same time these edited pigs don't contain anything else but pig so there is no fear of novel allergens or other compounds that could be harmful to the consumer. This shows that targeted genetic changes can be an alternative path to tackle animal disease and improve overall health and welfare in animals, as well as reducing the need for antibiotic and other drug inventions.