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Highlight

A novel pig model capturing clinical symptoms of harlequin ichthyosis

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The application of proper animal models is essential for developing effective treatments in biomedicine. Due to practicality, rodent models have been dominantly used as a model to identify potential treatments for patients. However, differences in physiology and anatomy between rodents and humans have been an obstacle when translating the data generated from rodents to clinics. Large animal models such as pigs can recapitulate symptoms of human diseases, making pigs an ideal model for preclinical assessment of new treatments (Prather et al., 2013). For instance, symptoms of primary immunodeficiency are more accurately represented in pigs compared to mice (Suzuki et al., 2012), demonstrating their suitability as an animal model in biomedicine. Unfortunately, the number of available pig models is low, in part, because of challenges in establishing pig models through current genetic engineering technology.

Harlequin ichthyosis (HI) is an autosomal recessive disease that leads to severe skin disorders. This rare genetic disease affects 1 out of 300000 new born babies (Ahmed and O'Toole, 2014), and although treatable, mortality from the disease is significant (>20%). Mutations on the ATP-binding cassette A12 (*ABCA12*) gene are known to be responsible for the disease. Mouse models lacking functional *ABCA12* have been reported and present a similar phenotype as HI patients. However, application of the models is limited because the animals do not respond to the typical treatments, retinoid or retinoid-like agents, used in clinics to treat HI, indicating differences in physiology between the animal models and HI patients.

Wang et al. (2019) reports a novel pig model that displays clinical characteristics of HI (Figure 1). These pigs were previously generated using ethylnitrosourea-induced mutagenesis using Bama miniature pigs (Hai et al., 2017). A mutation was introduced to an intron of *ABCA12* and disrupted splicing of the gene, resulting in inactivation of the gene. Similar to HI patients, the *ABCA12* mutant pigs manifested severe skin disorders and failed to thrive even under intense care. Authors extended their study to investigate if the pig model would respond to the most common clinical treatment of HI, retinoid. Remarkably, in utero and neonatal feeding of acitretin, a synthetic retinoid, could prolong the lifespan of the *ABCA12* mutant pigs, indicating that the model could mirror clinical progression and treatment of HI.

Another significant finding of the present study is that authors demonstrated the pig model can be used to investigate the mechanistic action of retinoid in alleviating symptoms of HI. Although retinoid is widely used to as a remedy for HI patients, the mechanistic action of the retinoid is still elusive. In this study, authors introduced a potential mechanistic action of retinoid in rescuing *ABCA12* mutant pigs from the severe skin disorder. Elucidating how retinoid prevents progression of HI can have a dramatic impact on developing more efficient therapies towards curing HI.

As mentioned above, large animal models such as pigs highly resemble human anatomy and physiology. However, application of pig models in biomedicine requires a significant investment because of longer gestation period and days to reach puberty, compared to rodent models. This study performed multiple rounds of breeding to establish pig models representing symptoms of HI, which would have taken years in propagating and characterizing the model. Nevertheless, as presented by results in the study, the quality of information that can be obtained from pig models validates the need to apply these animal models in biomedicine.

The recent development of genome editing technologies increases the value of animal models capturing genetically inherited diseases. Genome editing technologies have been successfully applied to reverse the trajectory of genetically inherited diseases in animal models (Villiger et al., 2018). This *in vivo* genome editing technology can be used to cure diseases caused by genetic defects, and its safety should be validated prior to

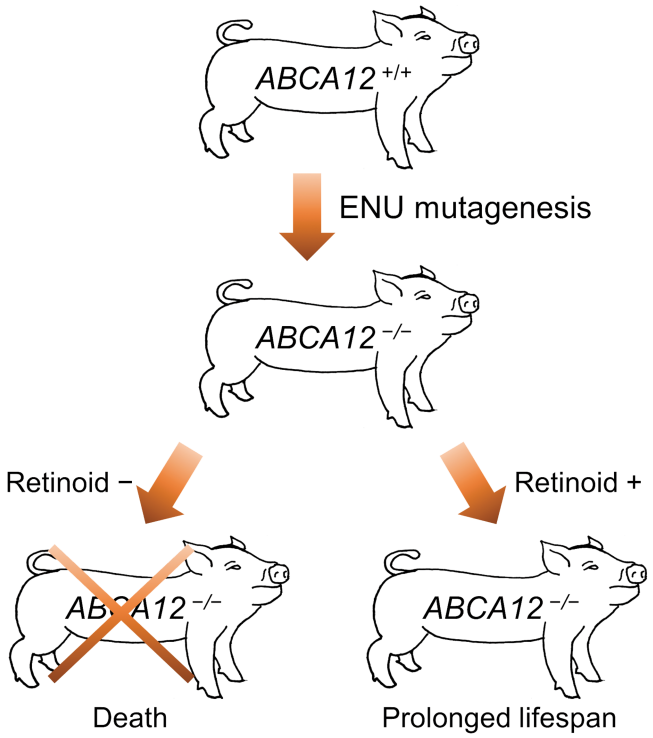

Figure 1 Establishing a pig model representing HI.

clinical application. For instance, the efficacy and safety of *in vivo* genome editing technology to cure HI can be optimized using the HI model pigs presented in this study, then safely applied to patients suffering from the disease. Genome editing technology can provide a permanent cure, but safety of the approach should be examined using a relevant animal model to minimize risk associated with the technology.

In summary, Wang et al. (2019) reports a valuable pig model that can present typical symptoms of HI patients. Clinical symptoms of HI were observed from the model pigs, and current clinical treatment effectively extended lifespan of the model pigs. It is envisioned that the model pigs will offer new mechanistic insights to the progression of HI and be used to develop more effective treatment options for the HI disease.

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