Mortality Rate and Survival of Pigs Classified by Immune Response Phenotype Using the High Immune Response (HIR™) Technology

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Summary

Managing disease in pork populations is one of the most costly and difficult challenges for pork producers. The High Immune Response (HIR™) Technology developed at the University of was first successfully tested in pigs and allows for the identification of animals with more robust and balanced immune responses (IR). It's now used commercially to identify dairy cattle with increased capacity for antibody and cell mediated-IR (AMIR, CMIR), and subsequently increased disease resistance (Thompson-Crispi et al., 2013). Previously, when Yorkshire pigs were selectively bred for IR it was found that high (H) IR pigs had improved responses to vaccination and pathogen challenge compared to the control line and low (L) responders. Although previous research in pigs clearly demonstrated favourable responses to breeding pigs for HIR, this method has not been tested in commercial herds. The study discussed here focuses on the differences observed in mortality rate and length of survival of IR phenotyped Yorkshire x Landrace F1 barrows (n=1005), provided by seven different Canadian swine companies comprising PigGen Canada. It was hypothesized that high IR piglets would die less frequently and be more likely to reach slaughter than piglets classified as average (A) and L when exposed to disease. It was found that pigs with H capacity for IR died less frequently than those with an A or L capacity ($p=0.015$). The same was true when considering length of survival and ability to successfully reach market weight. Specifically, none of the pigs classified as H, for both AMIR and CMIR (H-H), died. Moreover, it was found that piglets classified as poor responders tended to die faster than piglets of A or mixed response phenotypes. The majority of pigs classified as H performed better than those of poor, A, and mixed response ($p=0.015$). Therefore, IR phenotyping of pigs clearly identifies animals with the potential to withstand pathogen-challenge by making strong and appropriate IRs. These animals may also display production related advantages, as observed in previous experiments. Therefore, the implementation and integration of the HIR™ technology into commercial pig breeding programs is expected to yield both health and production benefits.

Keywords: pigs, immune response phenotype, mortality, survivorship, disease challenge

Background and Rationale

Societal concern regarding food safety and animal health are increasing. Therefore an effective, economical alternative to current swine management practices is essential to the industry's continued success. Breeding animals for immune response (IR) traits is a potential alternative. Breeding programs which select for general IR capacity have been demonstrated to improve broad-based disease resistance (Wilkie and Mallard, 1999, Thompson-Crispi et al., 2013).

The High Immune Response technology (HIR™), developed and patented at the University of Guelph (Wagter and Mallard, 2007), was first successfully tested in pigs, and recently globally implemented in the dairy industry by the Semex Alliance Inc. under the trade-name, *Immunity*+™ (Larmer and Mallard, 2016). The HIR™ technology allows for the identification of animals with both high (H) antibody-mediated (AMIR) and cell-mediated (CMIR) immune responses, thus encompassing both major components of the adaptive IR.

Earlier studies of pigs using the HIR method demonstrated extensive individual variation in IR traits with heritability estimates in the range of 25%, similar to that of cattle, making genetic selection for IR possible (Mallard et al., 1992, Mallard et al., 1998, Wilkie and Mallard, 1999). When Yorkshire pigs were selectively bred using this method it was found that H-IR pigs had improved AMIR to vaccination and pathogen challenge compared to the control line and low (L) responders (Mallard et al., 1998). Noteworthy is the fact that H responders were generally more robust pigs with increased average daily gain, reaching 100kg 10-12 days before L responders (Mallard et al., 1998).

Although previous research in pigs demonstrated favourable responses to breeding for HIR, this method has not been tested commercially. Additionally, observations associating HIR phenotype and pig mortality have yet to be made. Mortality of pigs due to respiratory disease in the nursery and grower period is associated with decreased profitability, other factors, such as farm size and enteric disease prevalence may also play a role (Rocadembosch et al., 2016). Using the HIR™ technology to phenotype piglets prior to rearing under disease challenge, the relationship between IR phenotype and mortality was examined. It was hypothesized that pigs classified as H-IR will have decreased mortality and increased ability to survive to slaughter compared to pigs of other IR phenotypes.

Material and methods

Experimental design and protocol

Yorkshire x Landrace F1 barrow piglets (n=1005) were IR phenotyped. In brief, IR to benign test antigens (Ag), one that elicits AMIR and another that elicits CMIR, were used to determine the IR phenotype of individual piglets using an adapted standard protocol (Schmied et al., 2012). Briefly, primary immunization with type-1 and 2 Ag was made post-weaning (~25 days of age) Serum antibody activity was measured by enzyme linked immunosorbent assay and cutaneous delayed-type hypersensitivity was measured as an indicator of CMIR.

Animal usage and data collection

All pigs were obtained from seven different PigGen Canada partners. Pigs were housed and HIR tested in a disease free quarantine facility at the Centre de Développement du Porc du

Québec (CDPQ, Deschambault, Quebec). Upon completion of the HIR test, pigs were transported to an alternate CDPQ Research Station and reared to slaughter being exposed to disease by natural herd challenge (Putz et al., 2017). Disease was monitored and circulating pathogens confirmed by trained staff and the main veterinarian on the project, Dr. John Harding. Circulating pathogens included viruses and bacteria associated with respiratory disease and bacteria associated with diarrhoea (Harding, J, personal communication). Growth rates, morbidity and mortality were systematically recorded for individual IR phenotyped pigs.

Statistical Analysis

Pigs (n=1005) were ranked as H, A or L immune responders on the basis of both CMIR and AMIR. Phenotypes were determined by general linear model using SAS to calculate standardized residuals: $Y = B_i + T_j + e_{ij}$. Where Y = Immune Response Phenotype, B = Batch (i = 1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20 & 21) and T = Technician (j). Pigs with IR residual values above +1 or below −1 standard deviation from the mean were considered H or L, respectively. Average ranked pigs have values between that of H and L. All other statistical analyses were conducted using GraphPad Prism Software.

Results

Piglets classified as high immune responders had a lower mortality rate than those classified as low or average when exposed to natural disease challenge

Antibody and cell mediated immune response phenotype is associated with rate of mortality

When considering only AMIR or CMIR, piglets classified as having a L or A-AMIR died more frequently than those classified as H for AMIR (p=0.038, Figure 1A, Cochran-Armitage test for trend). The same was true for CMIR (p=0.021, Figure 1A, Cochran-Armitage).

Total immune response phenotype is associated with mortality rate

There are nine possible IR phenotypes in total to which piglets can be classified based on AMIR and CMIR, respectively (HH, HL, HA, AH, AA, AL, LA, LH, LL where the first letter represents AMIR and the second CMIR classification). Allocation of total IR phenotypes follows a normal distribution, where animals clustered toward the extreme left of the curve display poor IR and those on the extreme right display exceptional IR, with A and mixed responder phenotypes falling in the middle. The results for total IR were similar as described above. Piglets identified as poor responders were more likely to die than those classified as A or H (p=0.015, Figure 1B, Cochran-Armitage).

Piglets classified as high immune responders displayed superior survivorship in comparison to low and average responders when exposed to disease

Antibody-mediated immune response phenotype is related to piglet survivorship during disease challenge

Although 1005 piglets were HIR phenotyped, complete survival data was only available for a sub-set of animals (n=861). Of these animals, those classified as L-AMIR died more rapidly

and therefore were less likely to reach market weight than those of A and H-IR phenotypes (p=0.040, Figure 2A, Log-rank test for trend). However, the same was not true when CMIR was examined (p=0.257, Figure 2B, Log-rank).

Piglets classified as high-antibody high-cell mediated immune responders have exceptional survivability compared to other immune response phenotypes

Of the 861 piglets phenotyped with available survivorship data, none of the pigs classified as HH-IR's died before slaughter. Piglets classified as poor responders (LL, LA, AL) tended to die faster and more frequently than piglets of A or mixed response (AA, HL, LH). The majority of pigs classified as good responders (AH, HA) survived longer than those of poor, A and mixed response (p=0.015, Figure 3, Log-rank test), reaching market weight more often.

Concluding statements

HIR phenotyping of pigs clearly identifies animals with the potential to withstand pathogen-challenge by making strong and appropriate IRs. These animals may also display production related advantages, as observed in previous experiments. Therefore, the use of HIR™ technology in commercial pig breeding programs is expected to yield both health and production benefits placing Canadian swine producers at the forefront of sustainable and profitable pork.

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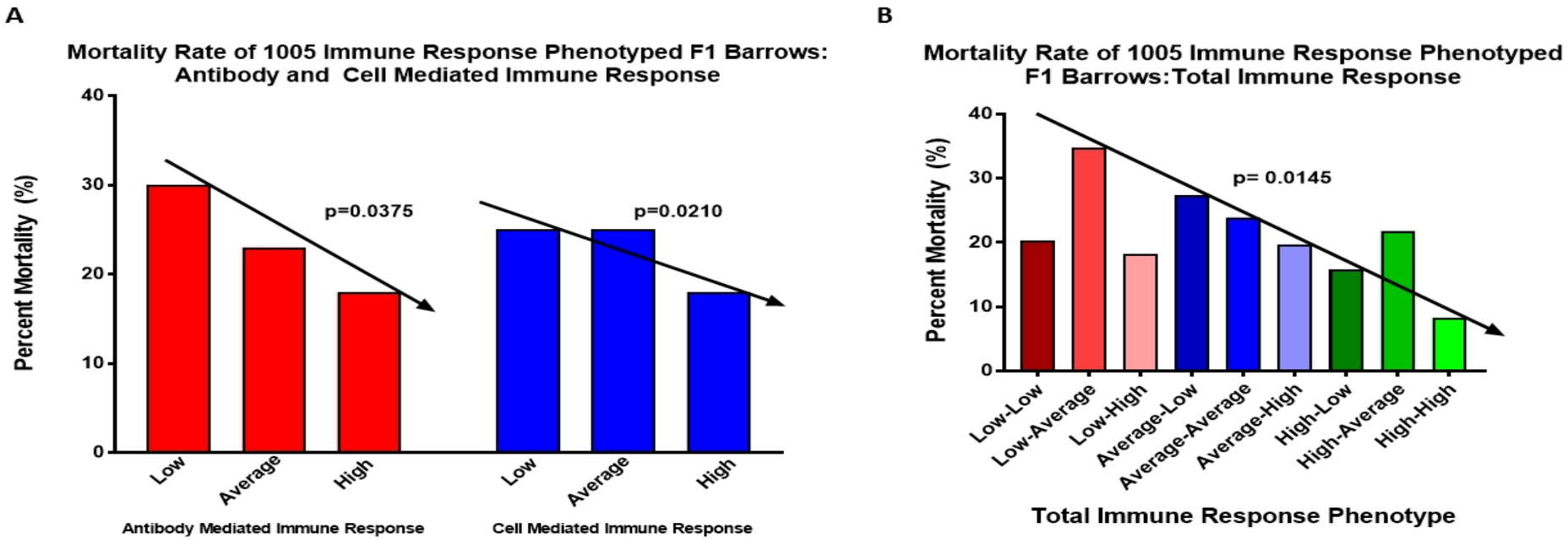

Figure 1. Mortality rate of piglets classified as high, average or low immune responders. A) Percent mortality of piglets classified as high (H), average (A) and low (L) antibody-mediated immune responders (IR, red bars). Antibody-mediated IR category is significantly associated with mortality rate, where L IRs have a higher mortality rate than IRs categorized as A or H (p=0.0375, Cochran-Armitage test for trend). B) Percent mortality of piglets classified as H, A and L cell-mediated IRs (blue bars). Cell-mediated IR category is significantly associated with mortality rate, where L and A IRs have a higher mortality rate than IRs categorized as H (p=0.0210, Cochran-Armitage test for trend). C) Percent mortality of piglets classified for total IR category. Antibody-mediated IR category is defined before cell-mediated IR category. Total IR category is significantly associated with mortality rate, where poor IRs (L-L, L-A, A-L) had a higher mortality rate than animals with an average/mixed IR (L-H, A-A, H-L) and good /exceptional IR (A-H, H-A, H-H, p=0.0145, Cochran-Armitage test for trend).

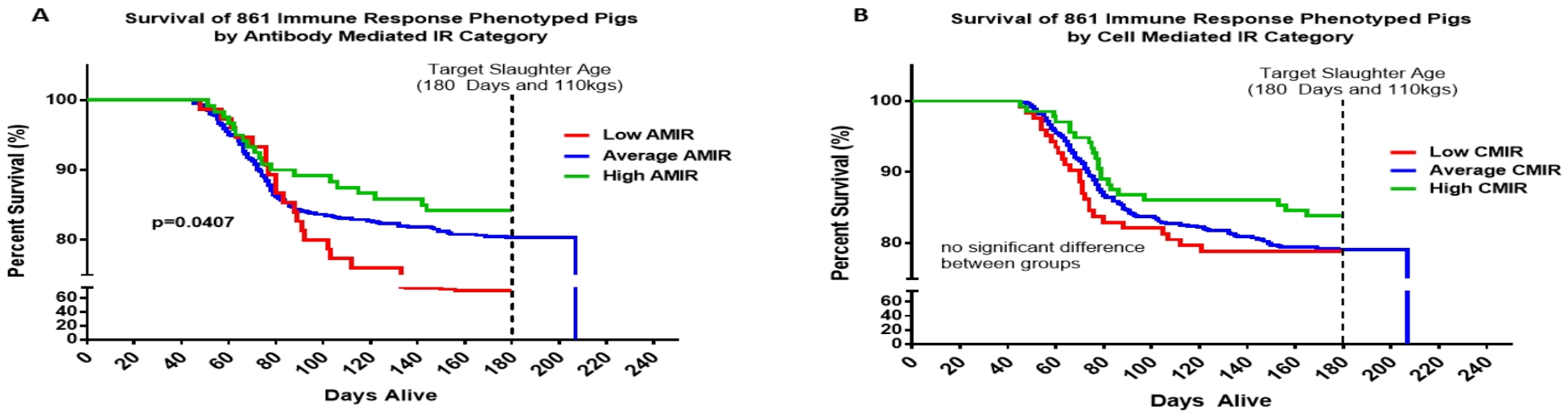

Figure 2: Survival curves for a sub-set of immune response phenotyped piglets. A) Survival of piglets categorized as low (red line), average (blue line) and high (green line) antibody-mediated immune responders (AMIR). Low AMIR pigs died faster and more frequently than pigs classified as average and high (p=0.0407, Log-rank test for trend). B) Survival of piglets categorized as low (red line), average (blue line) and high (green line) cell-mediated immune responders (CMIR). There was no difference in length or frequency of survival when comparing low, average and high CMIR piglets (p=0.2571, Log-rank test for trend).

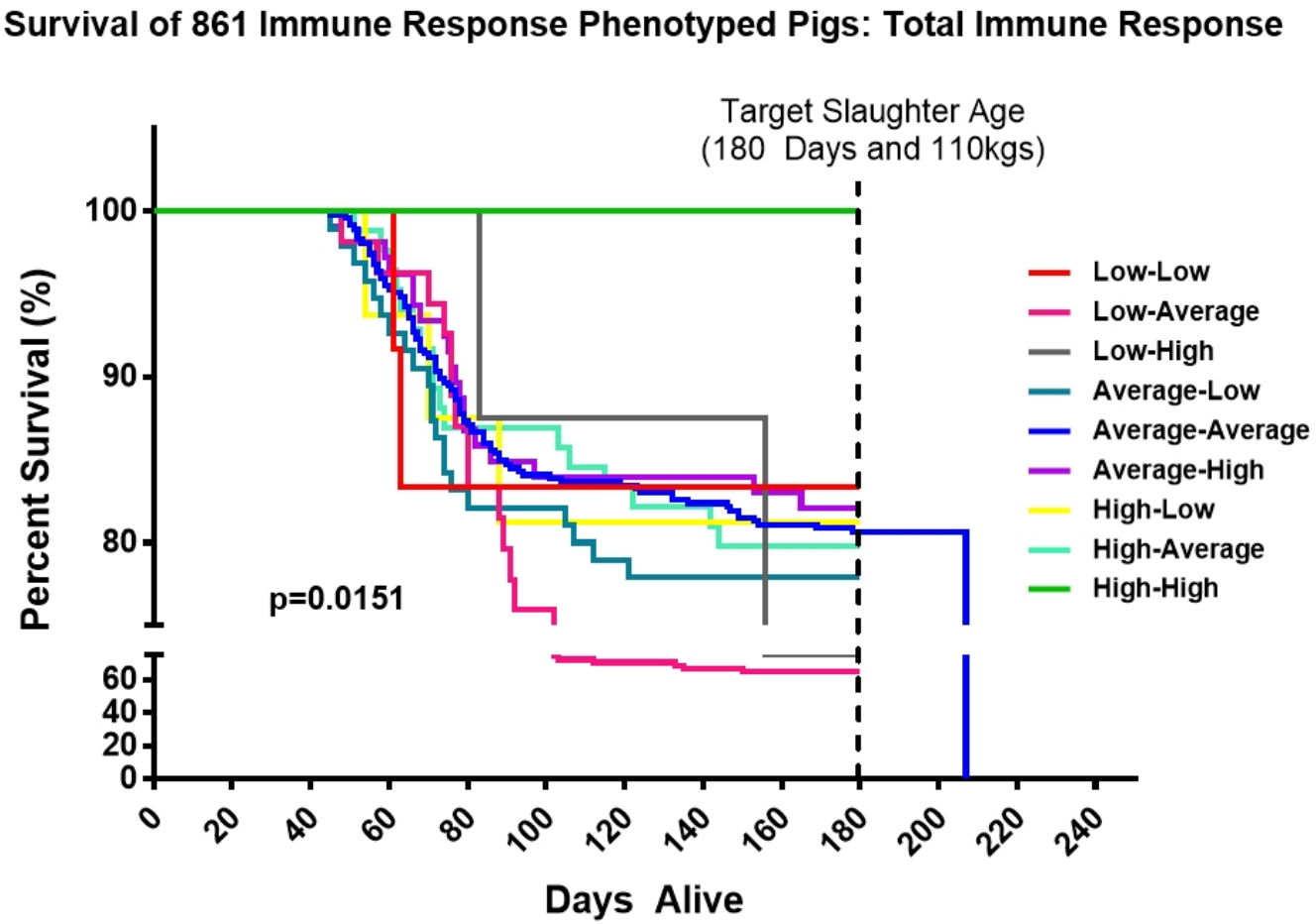

Figure 3. Survival curves for a sub-set of immune response phenotyped piglets based on total immune response phenotype. Antibody-mediated immune response (IR) category is defined before cell-mediated IR category. None of the pigs classified as High (H)-H immune responders died before slaughter. Piglets classified as poor responders (Low (L)-L, L-Average (A), A-L) had a tendency to die faster and more frequently than piglets of A or mixed response (A-A, H-L, L-H). The majority of pigs classified as good responders (A-H, H-A) survived longer and died less frequently than those of poor, A and mixed response (p=0.0151, Figure 3, Log-rank test).