COST Action F1401 PiGutNet

Open document on the characterization of the influence of host genetics on the pig gut microbiome, including genome-wide association studies (GWAS)

The gut microbiota composition can be influenced by a great number of factors, from environmental events like nutrition to host physiological factors like age, sex or health status. While it is globally acknowledged that the impact of nutrition can induce major changes in composition, there is growing evidence that the host genetic variation is having also a significant influence. The evaluation of the host genetics effects remains nevertheless challenging, as it implies evaluating a considerable number of individuals (at least a few hundred) for their microbiota composition, and the performance of inferences based on the family structure of this population and/or the use of genome-wide SNP genotypes. At the beginning of the PiGutNet COST action this type of datasets was still very uncommon for human or model species, and obviously also pigs. Interestingly, during the action major advances have been performed in the field; we have summarized them in the following lines.

In a pioneering work in humans by using 416 twin pairs, it was shown that monozygotic twins share a slightly greater similarity in gut microbiota than dizygotic twins (Goodrich *et al.* 2014), which confirmed that the microbiota composition is partially controlled by the host genetics. Alike, in mice Benson *et al.* (2010) demonstrated the polygenic determinism of gut microbiota by using 645 individuals. In addition, they reported the identification of several genome regions (*i.e.* quantitative trait loci) associated to the genetic control of gut microbiota composition (Benson *et al.* 2010). The human twins study was later extended with the triple of individuals, which allowed to confirm the heritability results, to replicate one of the mice QTL signal and the identification of additional ones by using a candidate gene approach (Goodrich *et al.* 2016). Several other papers performing genome-wide association studies (GWAS) appeared in the same year and confirmed a consistent genetic determinism of gut microbiota composition in humans (Bonder *et al.* 2016; Turpin *et al.2016 ;* Wang *et al.2016*).

The performance of similar studies in pigs is limited by the big number of animals that are needed for the performance of genetic studies for the heritability and GWAS analyses. Nevertheless, a few studies have been performed in parallel to human and mice analyses. Indeed, heritability studies have demonstrated

that the genetic determinism observed in humans and mice exist also in pigs (Camarinha-Silva *et al.* 2017; Estellé et al. 2014), which implies that it is possible to implement genetic selection programs to partially direct the gut microbiota composition of the following generations. As in humans and mice, the exploration of the possible genomic regions potentially implicated in this genetic determinism have also provided significant results and the identification of a few GWAS signals in the porcine genome (Chen *et al.* 2018, Estellé *et al.* 2017).

Overall, the results in humans, model species and in pigs themselves confirm the existence of a consistent host genetic determinism of gut microbiota composition. Nevertheless, once this fact has been established numerous questions remain open. In our view, one of the most prominent for the pig production field will be the study of the triple interaction between diets, host genetics and gut microbiota composition: which host genetics and which gut microbiota composition is more suitable for the digestion of a particular diet? In fact, in the light of the results of Zeevi *et al.* (2014), who proved the influence of gut microbiota on postprandial glycemic status, it is foreseen that these interactions will prove to be very complex and that will imply the generation of even bigger cohorts of individuals. Given that the pig research community is well structured and is used to perform well balanced nutritional studies in a controlled environment, if we manage to replicate these designs in big cohorts suitable for genetic analyses the pig will be a particularly well suited species for answering this type of questions.

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