Artykuł przeglądowy *Review*

Genetics of swine osteochondrosis

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Summary

Osteochondrosis (OC) is a developmental bone disease of serious clinical consequences that occurs in various anatomical locations. This disease is frequently seen in pigs, horses, poultry, and dogs, and has also been described in humans. Osteochondrosis, often referred to as leg weakness, is a common problem in pig herds. It causes economic losses and is considered as an animal welfare issue in pig production. Most traits related to animal health and welfare are complex, difficult to define, and often characterized by low heritability. Osteochondrosis is a multifactorial disease, and its etiopathogenesis can be traced to a combination of genetic, environmental and mechanical factors, as well as stress. Environmental factors thought to be important in the modulation of gene expression include nutrition, disease, and physical weight-bearing conditions. Feeding and management conditions (floor type, humidity, etc.) have influence on the development of osteochondrosis in pigs susceptible to this disease. The genetic background of osteochondrosis, which resembles tissue alterations related to aging and degeneration, has also been examined and identified. The heritability of leg weakness in pigs of different breeds ranges from 0.2 to 0.6. As the defect is hereditary, it should be controlled in the course of selection. It is well known that there are two approaches for genetic evaluation of complex and quantitative traits: genome-wide scanning and candidate gene approaches. Recent studies of the pig genome, presented in numerous scientific publications, point to the possibility of identifying the chromosome regions that carry the genes connected with osteochondrosis – the so-called QTL (Quantitative Trait Loci). The presence of QTL with an impact on osteochondrosis was established on chromosomes 5, 13, and 15. Other QTL studies identified eleven QTL affecting leg weakness on eight autosomal chromosomes. Some authors suggest that three QTL associated with osteochondrosis may be located on SSC2, SSC6, SSC10. Candidate genes are generally defined as those that have an important, direct or indirect, effect on the trait of interest. By focusing on candidate genes that play roles in the biology of bone and cartilage development it may be possible to understand the biological background of traits related to leg weakness. Studies of candidate genes for OC have focused on cytokines, growth factors, genes that encode components of bone matrix, and genes that encode receptors for calciotrophic hormones, yielding more than 200 potential candidates. Some of them are presented in this paper. In recent years, genomic selection based on candidate genes, as well as on SNP markers and SNP microarrays, has become a promising tool for the breeding of osteochodrosis-free pigs.

Keywords: osteochondrosis, genetic base, pig

Osteochondrosis (OC) is a developmental bone disease of serious clinical consequences that occurs in various anatomical locations. This disease is frequently seen in pigs, poultry, horses (33), and dogs, and has also been described in humans (37). More precisely, OC is a non-infectious, degenerative condition of the articular-ephiphyseal cartilage and growth plate with secondary changes in the bone (53). This is seen in growing animals. In joints affected by OC macroscopically visible lesions are typically found, such as the local thickening of articular cartilage, irregular cartilage surfaces, fissures between cartilage and subchondral bone, osteochondrosis dissecans (OCD), and necrosis of subchondral bone (39). Osteochondrosis, often referred to as leg weakness, is a common problem in pig herds. It causes economic losses and is considered as an animal welfare issue in pig production (16, 20, 24). Some authors report that leg weakness is an important reason for involuntary culling in the pig industry (50) and involves animal welfare and ethical aspects. Various studies have shown that between 35% and 100% of pigs are eliminated from breeding because of lameness (46). In Sweden, the second most frequent reason for culling, after reproductive failure, is an inferior leg and foot status (11), which shortens the life span and worsens the reproductive performance of breeding animals (50). The etiology and the pathogenesis of OC have not yet been clarified, but the

disease is attributed to several factors associated with changes in cartilaginous structures. One of the most important of these is an abnormal vascularization or a focal failure of blood supply to the growing cartilage, leading to a focal disturbance of endochondral ossification (52). Articular cartilage does not contain blood vessels, but prior to the formation of a secondary ossification centre, temporary vessel-containing structures, 'cartilage canals', which are involved in the nourishment of the cartilage for an appropriate ossification process, are found within the growing cartilage (4). The presence of necrotic areas with degenerating vessels in OC cartilage canals suggests that any defect in cartilage canals at focal sites might lead to the disruption of blood supply to the growing cartilage, which contributes to OC development (30). Osteochondrosis is multifactorial disease, and its etiopathogenesis can be traced to a combination of genetic factors, growth rate, lean meat percentage, and mechanical stress. This degenerative disease is a major problem in modern intensive rearing of pigs, in which the effects of breeding, nutritional, and environmental factors tend to produce the largest weight gain, as well as some muscle hypertrophy. These diseases can thus be classified as lifestyle diseases, resulting from overexploitation (27). The prevalence of osteochondrosis in purebred Duroc sires and Landrace × Yorkshire sows have been reported in Denmark (21). It was found that pathological abnormalities on the joint surface of the medial humeral condylus occurred in 38.0% of 9,360 pigs, and 11.7% suffered from osteochondritis dissecans. This result was similar to those obtained in earlier studies on Danish Landrace boars (22) and Norwegian Landrace × Yorkshire crossbred pigs (53). In addition, many researchers have found a difference in the frequency of osteochondrosis between sexes, in which castrated males show a higher OC frequency than female pigs (24, 53). The differences in growth patterns between pigs with and without OC have also been investigated. Piglets with severe OC at slaughter, grew faster after 28 days of age and were significantly heavier after 70 days of age than pigs without OC at slaughter. These results suggest that OC might be related to high growth rates during a specific time period (15).

Environmental factors predisposing to OC

Researchers have explored genetic and environmental factors with a potential impact on the incidence and progression of OC disorders in swine. Environmental factors thought to be important in the modulation of gene expression include nutrition, disease, and physical weight-bearing conditions. Feeding and management conditions (floor type, humidity, etc.) have influence on the development of osteochondrosis in pigs susceptible to this disease (26). In fattening pigs, the prevalence of OC was 41%. The prevalence was the highest for individuals kept on a concrete, partially slatted floor with *ad libitum* feeding (58%), and the lowest for individuals kept on a deep litter floor with restricted feeding (34%). These results demonstrate that the prevalence of OC can be reduced by applying deep litter floors and restricted feeding. Dietary interventions that potentially affect OC lesions include dietary fatty acid sources (omega-3 vs omega-6 fatty acids) and glucosamine (6). The use of alternate sources of dietary fatty acids to reduce lameness disorders has received attention in humans and animals. Fatty acids are precursors for prostaglandins, and may show anti-inflammatory properties in tissues. In a comprehensive review of fatty acids and arthritis, Darlington and Stone (7) concluded that sufficient evidence existed to claim that dietary fatty acids relieve OC symptoms. However, no sufficient evidence was found to support a role of fatty acids in the prevention of this disorder. The primary benefit of elevated n-3 fatty acids was a reduction in inflammatory responses. As such, n-3 fatty acids have little potential for beneficial roles in earlier stages of OC lesions. Work with neonatal pigs offers some evidence for an improvement in bone mass in pigs fed a formula with n-3 fatty acids compared with a formula based on n-6 fatty acids (3). Although a trauma affects the incidence and extent of OC lesions, evidence to support or reject the impact of a particular type of housing is not available. The historical occurrence of OC across various housing types and conditions excludes housing as a primary cause. Certainly, traumas associated with slippery conditions on frozen dirt lots or wet concrete surfaces can exacerbate OC lesions. The stocking rate also affected morbidity and mortality in grower/finisher pigs (9). As the stocking rate increased from 22 to 27 and then to 32 pigs per pen (0.78, 0.64 and 0.54 m^2 per pig), the morbidity and mortality increased from 8.5% to 10.2% and 12.7%, respectively. No evidence exists to suggest that the induction of OC disorders is primarily a result of responses to pathogenic organism(s). However, secondary consequences of certain diseases will exacerbate pre-existing conditions. These secondary consequences may be as simple as traumatic injuries, often experienced by animals weakened by disease, or as complex as alterations in cytokine signals, which stimulate aberrant responses in cartilage and bone tissues. The effect of intensive vaccination on the modification of cellular signals in bone and cartilage tissues is not known (6).

Heritability of OC

The genetic background of osteochondrosis, which resembles tissue alterations related to aging and degeneration, has been examined and identified. As we mentioned before, OC is a multifactorial disorder, a quantitatively inherited trait resulting from a combination of small variations in different genes, as well as environmental factors (18). OC lesions have a genetic basis and are inheritable by progeny generations with

polygenic heritability. The heritability of leg weakness in pigs of different breeds has been estimated to range from 0.2 to 0.6. It has been reported that Landrace pigs are more susceptible to osteochondrosis than Yorkshire, Hampshire or Duroc pigs (26). The heritability estimates for OC in different breeds are 0.08 to 0.39 (20), 0.1 to 0.5 (34, 45), and 0.06 to 0.42 (23). Moreover, OC is also reported to have negative effects on important performance traits, such as sow longevity, growth and feed conversion, and meat quality traits (24, 43-45). The disease occurs in high frequency in growing pigs in all commercial breeds, but its causes remain unclear. Many studies of associations between the growth rate and osteochondrosis have been conducted, the results usually showing weak and inconsistent correlations (1, 17, 34, 35, 45, 49). As the defect is hereditary, it should be controlled in the course of selection. The studies of osteochondrosis are successfully carried out in Sweden, Denmark, Finland, Germany, the Netherlands, the United States, and other countries. Pigs raised in a fattening test station in Sweden are checked for osteochondrosis after slaughter, and evaluated on a 0-5 point scale. Front and hind legs are checked. If elbow and knee joint lesions have been found in the progeny, their parents can further be used for breeding provided that their performance is very high and no significant gait distortions are visible. In Sweden, an osteochondrosis check is one of the obligatory criteria for the BLUP evaluation of breeding pigs. In Denmark and Finland, at test stations, osteochondrosis is measured in live pigs by a radiograph on a 1-5 points scale. If osteochondrotic joint lesions are found, the progeny is not used for breeding. In the Netherlands and the United States, the leg weakness syndrome in pigs is evaluated on a 1-9 point scale by the so-called mixed threshold model (26).

Radiography is a useful tool for diagnosing osteochondrosis in pigs. Few reports are available on radiological diagnosis and description of osteochondrotic lesions in pigs (10). Previous genetic analyses of osteochondrosis, involving radiological diagnoses of purebred Landrace and Yorkshire boars, demonstrated a heritability of 0.08 to 0.39 (20, 21). Another method to quantify the level and risk of osteochondrosis is to use computed tomography (CT). This method is applied by Norsvin Company in a project conducted to promote a better understanding of traits related to the robustness of pigs and to develop a more robust animal that would be competitive in current and future swine markets.

Searching for chromosomal regions (QTL) for OC

Traits associated with leg weakness are partly influenced by the genetic background of the animal, but the genetic basis of these traits is not yet fully understood. Studies in humans have also shown that variation in OC can be explained by genetic factors (29). In the last decade there has been huge progress in the understanding of the processes occurring in animal organisms at the molecular level. This area has provided new, previously unknown tools by which it became possible to understand many fundamental life processes e.g. the genetic background of a disease at the molecular level. Recent studies of the pig genome, presented in numerous scientific publications, point to the possibility of identifying chromosome regions that carry genes connected with osteochondrosis – QTL (quantitative trait loci). The identification and use of quantitative trait loci for OC may help in breeding for disease resistance, but would need costly resource populations and QTL mapping experiments, for example using cross breeds between exotic and commercial pig breeds (23). A well known QTL database called PigQTLdb has been developed and has become a valuable tool for pig research (41). Up to date, over 5,986 QTL for 581 different traits are reported. Andersson-Eklund et al (1) found QTL with an impact on osteochondrosis on chromosomes 5, 13 and 15 with the wild boar alleles reducing the level of osteochondrosis. The authors observed fewer incidents of osteochondrosis in the humerus than in the femur in a Wild Boar × Large White population. According to the research by Lee et al (32), none of the osteochondrosis effects reached the chromosomal significance level, but this may have been due to a relatively low occurrence (18% of the total) and the moderate number of animals studied. The frequency of osteochondrosis effects was similar to its level in the humeral condyles in Yorkshire pigs reported by Jorgensen and Andersen (20). The authors found that the occurrence of OC lesions in the front legs, and particularly in the humeral condyles, was much smaller than at sites in the back legs, especially in the femoral condyles. A similar study has recently been conducted by Laenoi et al. (29) on the Duroc × Pietrain population. It has been reported that the pure Duroc breed shows the highest incidence of OC compared to other European pig breeds (Pietrain, Landrace and Yorkshire). The results by Laenoi suggest that the unfavorable QTL allele for OC originates from both Duroc and Pietrain breeds. QTL studies have identified eleven QTL affecting leg weakness on eight autosomal chromosomes. All QTL reached the 5% chromosome-wide significance level. Three QTL were associated with osteochondrosis on the humerus: on SSC2, SSC6, SSC10. In addition, data show that the frequency of OC is as high as 31.05%, which is in agreement with 30.0% as previously reported (24).

Candidate genes for leg-weakness-related traits

Most traits related to animal health and welfare are complex, difficult to define, and often characterized by low heritability. The application of conventional genetics in combination with molecular genetic approaches is therefore of worldwide interest. It is well known that there are two approaches for genetic evaluation of complex and quantitative traits: genome-

-wide scanning and candidate gene approaches (55). Candidate genes are generally defined as those that have an important, direct or indirect, effect on the trait of interest. The candidate gene approach has been applied for identifying many genetic diseases in both humans and animals. However, the identification of candidate genes involved in leg-weakness-related traits remains challenging. By focusing on candidate genes that play roles in the biology of bone and cartilage development it may be possible to better understand the biological background of traits related to leg weakness. Studies of candidate genes for OC have focused on cytokines, growth factors that regulate bone turnover, genes that encode components of bone matrix, and genes that encode receptors for calciotrophic hormones, yielding more than 200 potential candidates. However, as mentioned previously, body weight, growth rate, and mechanical stress are also regarded as the main contributing factors. Therefore, genes involved in animal growth, including bone and cartilage as well as molecular networks underlying articular cartilage development, should also be considered. Transforming growth factor beta 1 (TGFβ1) is a multifunctional peptide dimmer from a family of important regulators of chondrocytes and other cells that controls growth, differentiation, and other functions (2). It has been reported that in normal pig epiphyses, TGFβ1 is present in the chondrocytes of the epiphyseal hyaline cartilage. This growth factor was found to be deficient in chondrocytes at sites of osteochondrosis (48). However, in a horse with OC lesions, the expression of TGFβ1 in the affected tissues was higher (but not significantly) (42). This growth factor is therefore thought to be involved in a cascade of events associated with the chondrocyte function during endochondral ossification. Taken together, these data suggest that TGFβ1 may play a role in the development of OC, and that this gene is a candidate for further functional and association studies in relation to the incidence of leg weakness or OC in pigs. Other genes, collagen type II alpha 1 (COL2A1) and collagen type X alpha 1 (COL10A1) are involve in animal growth. Articular cartilage consists of an extensively cross-linked collagen network. Different types of collagen molecules are expressed in articular cartilage. In young cartilage, the main type is a copolymer of collagens type II, IX and X (12). Once the chondrocyte cells have initiated hypertrophy, collagen type X is synthesized and is the only known hypertrophic chondrocyte-specific molecular marker (54). Possible involvement of collagens type II and X in the development of OC has been reported. Increases in type II collagen cleavage by collagenases in OC lesions have been observed in osteoarthritis (31). Moreover, studies in pig have shown that collagen type II was reduced and collagen type X increased in and near OC lesions (19). Therefore, COL2A1 and COL10A1 may be good candidate genes for osteochondrosis. On the other hand, metalloproteinase 3 (MMP3) and metalloproteinase 9 (MMP9) proteins of the matrix metalloproteinase family are involved in the breakdown of the extracellular matrix in normal physiological processes and disease condition (25). MMPs are involved in cartilage collagen breakdown. The progression of OC with the degradation of cartilage matrix components is generally agreed to be due to the over-synthesis and activation of extracellular proteases. Several studies in humans have measured MMPs in synovial fluid or articular cartilage and reported varied expression of those enzymes in different stages of cartilage disease (5, 8, 25, 51). In a paper by Rai (38), a significant correlation was found between SNP of MMP3 (g.158 C > T) and OC at the head of the femur ($P < 0.05$) and bone mineral density ($P < 0.05$) in the Duroc × Petrain population. However, the molecular mechanisms underlying cartilage destruction are still poorly understood. Two master transcription factors, sex-determining region Y-box9 (SOX9) and runt-related transcription factor 2 (RUNX2), are involved in skeletal development. SOX9 is expressed in all chondrocytes and is essential for the expression of proteoglycan aggrecan, which is secreted by chondrocytes to form the characteristic glycosaminoglycan-rich extracellular matrix of cartilage (47). RUNX2 plays important roles in many steps of skeletal development. RUNX2 determines the lineage of osteoblasts from multipotent mesenchymal cells, enhances osteoblast differentiation at an early stage, and inhibits osteoblast differentiation at a late stage (13, 28). Both transcription factors were found to be involved in the development of osteochondrosis. RUNX2 down-regulation resulted in a reduced MMP-13 expression in osteoarthritic chondrocytes. Inhibition of SOX9 increased the expression of RUNX2 and MMP-13 mRNA in normal chondrocytes (36). Relative expression of both transcription factors might be important in the regulation of other genes that play roles in cellular changes occurring in ostechondrosis development. In the paper by Rai (38), TGFβ1 and RUNX2 genes showed a higher expression in cartilage affected by OC ($P < 0.05$) compared to healthy cartilage. There were no significant differences in the mRNA expression of MMP3, SOX9, MMP9, and COL10A1 genes. However, the expression of MMP3 in OC cartilage tended to be lower, whereas SOX9 tended to be up-regulated in OC lesions. Among the genes examined, the transcription factor SOX9 gene was most expressed where MMP9 was least expressed in articular cartilage compared with the other genes.

SNP microarray analysis

In recent years SNPs (Single Nucleotide Polymorphism) have been preferred genetic markers for large scale genetic mapping projects and have been successfully used to identify chromosomal regions associated with complex human diseases. Since 2008, commercially available SNP microarrays (chips) for many

animal species, containing thousands of SNPs, have made it possible to perform genome-wide association analyses, QTL identification and additional QTL validation. The chip is a microscope slide on which DNA sequences are immobilized and which helps to detect variation in DNA components between different individuals. Researchers around the globe use SNP microarrays to investigate common single gene defects and mutagenic diseases, including musculoskeletal, neuromuscular, cardiovascular, and respiratory disorders. Also the Swine Genome Sequencing Consortium has developed an SNP chip for pigs. The pig SNP chip enables researchers to genotype each animal for more than 60,000 SNPs and is helpful in understanding which genes are associated with differences in production traits and genetic abnormalities. This SNP chip has helped to revolutionize genetic research and to understand the underlying differences between animals in cases of traits such as growth rate, feed efficiency, meat quality, and reproduction. The chip will also allow breeders and breeding companies to employ „genomic selection" to estimate the breeding value of each animal on the basis of these individual gene differences and not merely on their phenotypic or physical trait records. Such selection will improve accuracy, increase the efficiency of pork production, and improve pork meat products available for the consumer. Genomic selection based on candidate genes and SNPs seems to be a promising tool also for the breeding of osteochondrosis-free pigs (40).

Selection perspectives

In the last 10 years, genomic selection has developed enormously. Simulations and real-life data suggest that breeding values can be predicted with high accuracy using genetic markers alone. To achieve high accuracies, large reference populations are needed. In many livestock populations, these cannot be obtained when traits are difficult or expensive to record, or when the population size is small. In such cases the value of genomic selection becomes questionable. Recently, both these limitations have been overcome in most livestock species, following the sequencing of the genomes and the subsequent availability of high density SNP-chips (14). It is now feasible to meet the requirements for the implementation of genomic selection in breeding programs. Thus genomic selection can potentially cut the costs of producing and testing potential breeding animals considerably (15).

The leg weakness syndrome includes a number of sub-traits, of which osteochondrosis is one. In view of the unfavorable genetic correlations between osteochondrosis and growth rate, found in a number of studies, osteochondrosis must clearly be included in one way or another (directly or indirectly) in the breeding evaluation of pigs. In breeding programs, which include carcass evaluation of pigs, osteochondrosis can easily be scored at a very low extra cost. Radiological examination of live pigs would be a better alternative than post-mortem examination, but this technique requires a higher input of labour. Nevertheless, since the leg weakness syndrome involves a number of other component traits, the exterior appraisal of live pigs should also be included in the breeding evaluation.

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