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A review: role of reproductive genes in embryonic development and increasing litter size

Edlyn E. Pooten[1*], Claro N. Mingala[2]

[1]*Department of Biological Science, Central Luzon State University, Science City of Munoz, Nueva Ecija 3120, Philippines*

[2]*Philippine Carabao Center-Gene Pool, Science City of Munoz, Nueva Ecija 3120, Philippines*

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Abstract

Through the years, researchers relied simply on selective breeding to obtain and improve the desirable traits of the preferred animal. Recently, the livestock industry has gone far due to advancement in genetics which has resulted in advanced and revolutionized technologies that have made genome editing efficient, precise, rapid and economical. Candidate reproductive genes were evaluated for their functions in the different stages of the reproductive process. It was shown that the reproductive genome controls all phases of embryonic development as well as an increase in litter size. Litter size is a complex physiological trait in productive species and is affected by several component traits that are controlled by genes. A substantial increase in litter size has economic implications for swine production.

* **Corresponding Author:** Edlyn E. Pooten ✉ edlynepooten@gmail.com

Introduction

Over the past years, understanding the functions of different reproductive genes, improve the biological challenges in herd reproductive performance (Kaczmarek *et al.*, 2019). Many advances and revolutionized technologies have been developed for efficient and precise modification of the genome (Yang, 2018). Despite these enhanced processes, the incidence of pregnancy failure remains high (Haouzi *et al.*, 2009). Pregnancy loss also affects livestock breeding and has economic implications for the livestock industry (Fazeli, 2008). The high rate of pregnancy failure has been attributed mainly to asynchronous embryo development in the maternal tract and inappropriate communication between the mother and the developing embryo(s) (Simon *et al.*, 1998).

Litter size is a complex physiological trait in prolific species being affected by several component traits representing sequential events such as ovulation, fertilization, embryo development and fetal survival (Argente, 2016). One-third to one–half of viable embryo loss during peri-implantation (Ford *et al.*, 2002). Pre-implantation embryo losses are mainly associated with embryonic viability (Argente *et al.*, 2008) including chromosomal abnormalities (Pope *et al.*, 1990) and the uterine environment particularly in relation to the suitability of oviductal secretions (Bazer *et al.*, 1991). The oviduct must provide an adequate milieu for sperm capacitation, gamete fertilization and the first embryo cleavages until the embryo enters the uterus (Bhatt *et al.*, 2004).

The response of the endometrium towards the embryos at a very early stage is poorly understood. Several genes and proteins have already been described to be activated in the endometrium when the embryo arrives in the maternal tract (Wolf *et al.*, 2010; Klein *et al.*, 2011). Lee *et al.*, 2002, reported that transcriptional changes in the oviduct in response to the embryo can be regarded as maternal tract responses to the local signals received from the embryo during pregnancy. Many genes are altered in the uterine horn in response to the embryo (Almiñana *et al.*, 2012). This implied that the presence of the embryo in the maternal tract was regulated by different reproductive-related gene responses and potentially reduced the local activity. All the changes in the embryo are regulated by different lipid and hormonal substances (Ziecik *et al.*, 2018). Moreover, regulation of the expression of many proteins is necessary for the development of the embryo, endometrial remodeling, and embryo-maternal communication.

Substantial gains in the efficiency of pig production systems can be expected from genetically improving reproductive traits (Tess *et al.,* 1983; de Vries, 1989). Incremental costs related to the production of additional pigs are minimal so that substantial gains can be achieved by improving the number of piglets weaned per breeding animal per unit of time. There is some evidence that genetic improvement of numerical productivity can be enhanced by genetically acting on its component traits, i.e. age at sexual maturity, fertility, prolificacy and piglet viability, or their underlying physiological processes.

Currently, litter size varies from approximately 2 to 20 pigs per litter, with means of 9 to 11, depending on the breed. Phenotypic standard deviations are between 2.5 and 3 pigs, and heritability is 10 to 15% (Johnson *et al.*, 1999). Therefore, sufficient genetic variability exists to increase litter size. However, litter size is sex-limited and selection response could be enhanced by direct selection in both sexes for genes affecting its expression. This review presents the role of various maternal reproductive genes during different stages of porcine development and the associated increase in litter size.

Maternal genome during early embryogenesis

The maternal genome controls virtually all aspects of early embryo development. As development proceeds, two processes subsequently lead to the maternal-to-zygotic transition (MZT) during which developmental control is transferred to the zygotic genome: first, a subset of the maternal mRNAs is degraded; second, the embryonic genome is transcriptionally activated.

These maternal gene products such as mRNA and proteins play an important role in the regulation of the first cleavages until the embryonic genome is activated (Schultz, 2002). Zygotic genome activation (ZGA) is a critical event determining the transition from maternal to embryonic control of development. Disruption of these critical events by specific chemicals or environmental factors results in irreversible arrest of embryo development (Latham *et al.*, 1999). ZGA has been shown to be a species-specific phenomenon occurring at the 4-cell stage in pigs. Genome-wide gene activation in the zygote (ZGA) is crucial for preimplantation embryonic development. Multiple maternal genes were identified on the regulation of ZGA, which are shown in Fig. 1. Ablation of the gene encoding for these proteins results in embryonic arrest at cleavage-stage development (Argente, 2016).

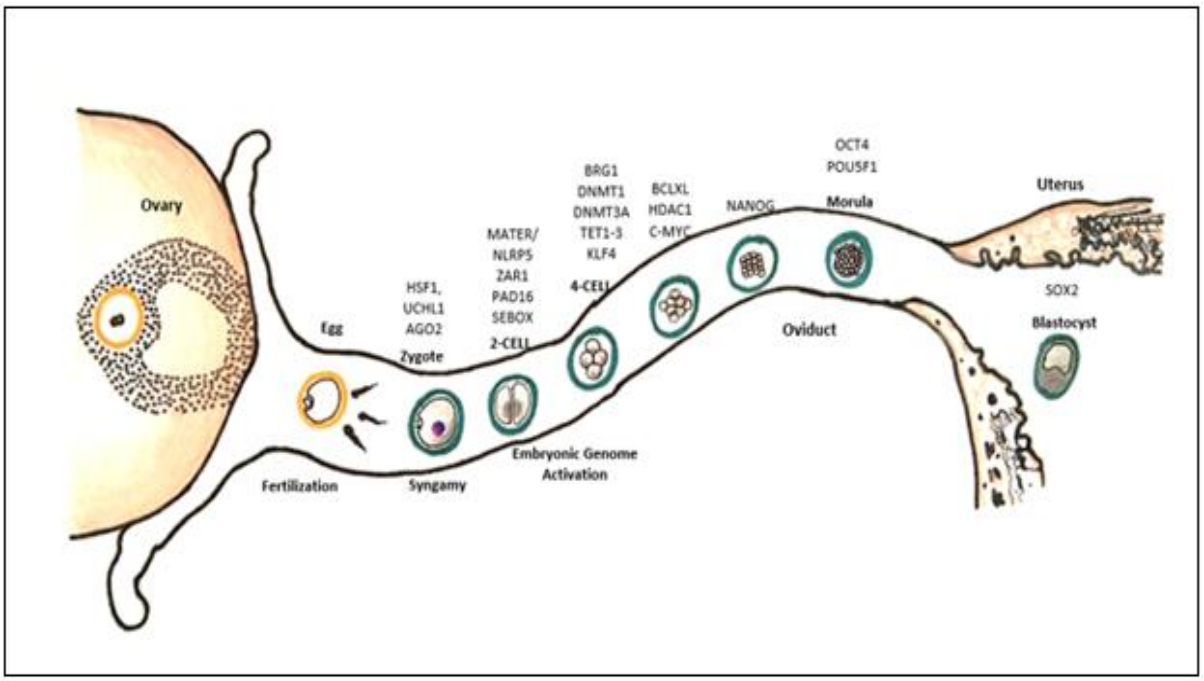

Fig. 1. Early embryogenesis regulated by maternal genes.

Dicer 1 regulates metaphase II and has the ability to digest dsRNA into uniformly sized small RNAs ~22 nucleotides in length (Bernstein *et al.*, 2001). Dicer 1 is responsible for pre miRNA recognition and miRNA production (Lee *et al.*, 2014d). The miRNA is a class of small single-stranded ribonucleic acids that regulate gene expression port-transcriptionally and involved in embryonic development (Stowe *et al.*, 2012). Also, DICER 1 performs in nuclear localization, formation of heterochromatin involved in DNA double-stranded break. Moreover, it plays a pivotal role in the initiation of RNA silencing by recognizing double-stranded RNAs (dsRNAs) and cleaving them into small RNAs using its RNase III-like double-stranded RNA-specific nuclease activities (Andika, 2019). Furthermore, DICER1 is an enzyme required for the completion of oocyte mitotic maturation. The oocytes are arrested in the metaphase of meiosis II when Dicer 1 gene is deleted (Stowe *et al.*, 2012).

During zygote development, there are three genes involved: HSF1, UCHL1 and AGO2. Heat Shock Factor 1 (HSF1) is a maternal factor essential for the reproductive success of pre-implantation embryos (Christians, 2000) and involved in zygotic genome activation (ZGA) specifically at the late one-celled stage (Metchat *et al.*, 2009) and two-celled stage (Christian *et al.*, 1997). The zygotic genome undergoes massive chromatin remodeling. The majority of transcription occurs in the male pronucleus which displays higher levels of hyperacetylated histones and DNA demethylation (Xing *et al.*, 2005). Heat shock factors trigger the expression of gene encoding and protein functions as

molecular chaperons, perform crucial roles during development, protect and prevent the formation of damaged gametes and secure future reproductive success (Abane and Mezger, 2010). In addition, HSF1 protein is required for oocyte maturation. Embryos produced in knockout females for this gene are unable to proceed into 2–cell stage after fertilization, possibly due to mitochondrial damage and alter redox homeostasis (Le Masson *et al.*, 2011). The ubiquitin C-terminal hydrolase (UCHs) participate in gametogenesis (Kwon *et al.*, 2005; Susor *et al.*, 2007; Gu *et al.*, 2009) and components of the ubiquitin system are involved in early steps of mammalian fertilization, including sperm capacitation (Kong *et al.*, 2009), acrosomal exocytosis (Chakravarty *et al.*, 2008) and zona pellucida (ZP) penetration (Sakai *et al.*, 2004; Sutovsky, 2004). A recent study of porcine fertilization revealed that sperm-acrosomal UCHL3 can participate in sperm-zona pellocida (ZP) interactions and inhibition of polyspermy (Yi *et al.*, 2007) UCHL1 is one of the most abundant proteins in mammalian oocytes (Ellederova *et al.*, 2004). UCHL1 accumulates in the oocyte cortex, where it may also inhibit polyspermy defense (Yi *et al.*, 2007b; Mtango *et al.*, 2012). UCHL1 and UCHL3, two members of the ubiquitin C-terminal hydrolase (UCH) family of deubiquitinating enzymes (DUBs), responsible for hydrolyzing carboxyl-terminal esters and amides of ubiquitin (Fang *et al.*, 2010) and regulating different cellular processes. Before fertilization UCHL1 is associated with the oocyte cortex and meiotic spindle in UCHL3. Mtago *et al.*,(2012) reported that UCHL3 into mature metaphase II oocytes blocked fertilization by reducing sperm penetration of the zona pellucida and incorporation into the ooplasm while the UCHL1 at the onset of oocyte maturation (germinal vesicle stage) reduced the fertilizing ability of the oocytes. Argonaute 2 (AGO2) /RNA –induced silencing complex, providing the mRNA "slicer" activity in gene silencing. AGO2 is required for the successful development of early embryos and involved in the maternal to zygotic transition. AGO2 is expressed in oocytes and throughout pre-implantation development. The depletion of Ago2 mRNA leads to the developmental arrest at the two-cell stage at the time of the maternal to zygotic transition. GFP-tagged AGO2 localizes with the decapping enzyme, Dcpla, to cytoplasmic P. bodies supporting that Ago2/RISC could be involved in maternal mRNA degradation. Ago2 downregulation prevents the onsets of expression of the number of zygotic transcripts, mRNAs for these genes accumulate in the two-cell stage (Lykke-Andersen *et al.*, 2008).

The 2-cell stage is controlled by MATER or NLRP5, ZAR1, PAD16 and SEBOX genes. Maternal Antigen that Embryos Require (MATER) is also known as NLRP5, NLR pyrin domain containing 5. MATER/NLRP 5 is an oocyte–selective factor that affects development beyond 2 cell-stage of preimplantation development in mice, 16-cell stage in bovine embryos (Penneetier *et al.*, 2006), the 8 cell stage in a non-human primate (McDaniel *et al.*, 2009) and germinal vesicle in human (Tong *et al.*, 2002). MATER/NLRP5 gene has the earliest effects on embryogenesis (Tong *et al.*, 2000). The MATER transcripts accumulate during oogenesis and are translated into protein during meiotic maturation and ovulation. The transcripts are degraded, but the cytoplasmic protein persists until the early blastocysts stage, suggesting a physiological role beyond the first embryonic cleavage. Li *et al.*, 2008 presented that MATER is a cytoplasmic protein present in the ovaries specifically in the subcortex of oocytes of central follicles. The maternal factors present in oocytes perform a critical role beyond events (Dean, 2002) which shown a block in embryonic development (Tong *et al.*, 2000). Zygote arrest 1 (ZAR1) is an oocyte-specific maternal effect gene. A single copy gene, positioned on chromosome 8 in the pig. ZAR 1 is one of transcriptional regulation acting during the oocyte to embryo transition of gene expression (Wu *et al.*, 2003). Peptidylarginine deiminase 6 (PAD16), a novel maternal-effect gene, localizes in oocyte and early embryo- restricted protein (Wright *et al.*, 2003). PAD16, is essential for the formation of a novel oocyte-restricted fibrous structure, the cytoplasmic lattices (CPLs) (Kan *et al.*, 2008). Pad16 is mainly expressed in the ovary and plays an important role in oocyte growth, fertilization

and early embryo development. Overexpression of Sp1 significantly increased the promoter activity and promoted PAD16 gene expression while inhibition of SP1 expression with specific siRNA significantly reduced the promoter activity and suppressed the PAD16 expression. Moreover, inhibition of Sp1 binding by mithramycin reduced the transcriptional activity of PAD16. Sp1 is essential for the transcriptional regulation of PAD16 (Xia *et al*., 2015). Skin–embryo brain oocyte homeobox (SEBOX), is homeobox genes that direct the formation of many-body structures during early embryonic development and shared a highly conserved DNA-binding domain that recognizes and binds to specific DNA sequences in the regulatory sequences of genes. (Zheng *et al*., 2013). SEBOX, a paired-like homeobox gene, was found to be essential for early oogenesis (Kim *et al*., 2008) by regulating during gene cell development. SEBOX is an essential maternal transcription factor that regulates both the degradation of mRNAs coding and activation of maternal factors during embryonic genome activation. These genes may have a specific role within the embryo as activators for transcription of genes essential for subsequent development and clarify the basic mechanisms controlling cell proliferation and differentiation during the early embryo development (Zhang *et al.* 2015). However, lacking BRG1 or SMARCA4, DNMT1 AND 3A, TET 1-3 and KLF4 genes are unable to reach the 8-cell stage while BCLXL, HDAC1 and CMYC exhibit maximum expression in 8-cell embryos coinciding with the start of zygotic genome activation. OCT4, NANOG and SOX2 were co-expressed in epiblast and these three genes are critical for embryo development (du Puy *et al*., 2011).

Early embryos gradually develop developmental independence once EGA occurs, a developmental process by which an embryo begins to transcribe its newly formed genome. The onset of EGA varies among species, in pig 4-8 cells and 8-16 cells in cow and sheep. Proper EGA is critical for normal development (Lee *et al*., 2014d). Thus, many studies have been performed to determine the mechanism of EGA and gene expression profile changes occurring during the maternal-to-zygotic transition (Lee *et al*., 2014d). A growing list of maternal factors involved in the regulation of EGA has been identified such as BRG1, Mater (official name, Nlrp5) (Tong *et al*., 2000), Padi6, Hsf1 (Christians *et al*., 2000), Zar1 (Wu *et al*., 2003), Npm2, Ago2 (official name, Eif2c2) (Lykke-Andersen *et al*. 2008), Basonuclin, Ring1, Rnf2, and Sox2 (Pan and Schultz, 2011). Mutations of any one of the genes encoding these proteins cause developmental arrest at cleavage stages can result in pregnancy failure or decreased litter size of certain species.

The maternal-to embryonic transition consists of critical development processes including maternal RNA depletion and embryonic genome activation. The maternal proteins encoded by maternal –effect – genes have been determined, these proteins are implicated in various aspects of embryo development including maternal mRNA degradation, epigenetic reprogramming, signal transduction, protein translation and initiation of embryonic genome activation. The maternal genes control decreased oocyte quality and are also associated with ovarian aging. (Zhang *et al*., 2015). Moreover, the majority of embryo mortality occurs during early developmental stages in various species. Thirty-seven percent (37%) of embryo deaths occur during the first week after fertilization (Sartoli *et al*., 2010), Oocyte quality a critical component contributing to pregnancy success and improvement of litter size.

Reproductive genes associated to increase litter size

In pigs, the leading components of litter size are ovulation and the prenatal survival, these parameters are also the limiting factors for the litter size improvement. The selection of prenatal survival in pigs (Rosendo *et al*., 2007) allows for increased litter size in the pig. A joint selection for ovulation rate and prenatal survival using an index would expectably show a greater response on litter size (Bernett *et al*., 1989). Conceptus development requires the uterus and concomitant with a maternal recognition of pregnancy (days 10- 13 post–estrus) via embryonic signaling to maintain the corpus luteum function as

well as the onset of implantation (days 14-19). During embryonic development, genes are expressed to resemble the loss of cellular pluripotency (Waclawik 2017).

Improvement of reproductive traits in livestock species has become of increasing interest, especially in swine where the moderate increase in litter size can equal a large gain in profit. Advances in molecular techniques can now be used to increase the rate of response to selection. It has been proposed that candidate gene analyses be used to identify individual genes responsible for traits of economic importance (Rothschild and Soller, 1997).

Using the candidate gene approach numerous genes affecting litter size in pigs include estrogen receptor (*ESR*), retinol-binding protein 4 (*RBP4*) gonadotrophin-releasing hormone receptor (*GNRHR*), folate-stimulating hormone (FSH), mitogen-activated protein kinase 3 (*MAP3K3*), N-acetyltransferase 9 (NAT 9), progesterone receptor (*PRG*), and peroxisome proliferator-activated receptor delta (*PPARD*). (Argente, 2016).

Estrogen is involved in maternal recognition of pregnancy (Geisert *et al.*, 1990). It is produced by the growing conceptus and is recognized by receptors in the uterus of the sow. Also, estrogen acts to induce hypertrophy and hyperplasia of the myometrium cell. The estrogen receptor (ER) locus is associated with an increase in litter size. Rothschild *et al.*, 1996 reported that the Chinese Meishan Pig allele produced 2.3 more pigs in first parities and 1.5 more pigs averaged over all parties. In addition, ESR gene, a steroid-binding hormone receptor gene has been demonstrated to have large allelic effects ranging from 0.4 to 1.15 pigs per litter increased in pig (Rothschild *et al.*, 1996). Retinol-binding protein 4 (*RBP4*) was studied as a possible candidate gene affecting litter size because it is involved in embryonic development. Yelich *et al.* (1997) stated that most embryonic death losses occur between d 10 and 18 of gestation, concurrent with trophoblast elongation and secretion of estrogen by the conceptus. Retinol binding protein 4, a major protein produced by the conceptus, may have a role in trophoblast elongation. It also enhances gene expression of transforming growth factor β via retinoic acid receptors (Yelich *et al.*, 1997). Rothschild *et al.* (2000), using data of 2,500 litters of six commercial lines, reported an additive effect associated with *RBP4* of 0.23 pigs/litter. Follicle-stimulating hormone is a heterodimer composed of alpha and beta subunits that are coded by two distinct genes.

The beta subunit offers specificity. The follicle-stimulating hormone was chosen as a candidate gene because it functions in the maturation of small and medium follicles into large follicles that ovulate (Mannaertz *et al.*, 1994). Follicle-stimulating hormone (FSH) stimulates granulosa cell proliferation and controls the development and maturation of oocytes. For pigs, Zhao *et al.* (1999) present that in a 229bp insertion in intron 1 of the FSHβ gene, between bases 809 and 810 can increase of 1.5 litter size (Niu *et al.*, 2019). Gonadotropin-releasing hormone (GnRH) is an essential neuropeptide in the onset and control of reproduction. Regulator of the growth, maturation, and ultimately, the ovulation of follicles.

The *Gnrhr* null pup provides a model in which both the direct and indirect effects of GnRH are blocked in their reproductive and non-reproductive functions during this period. The direct effects are blocked because the GnRH receptor is knocked out in all central and peripheral tissues and the indirect effects are blocked as the GnRHR is disrupted in the pituitary resulting in a downstream lack of sex steroids. An additional advantage of the *Gnrhr* knockout model is that sexual differentiation of the brain is permanently blocked; in the null male, this occurs at birth, whereas in the null female, brain feminization occurs at P15-P22. Both losses are due to the lack of sex steroids following the dysfunctional GnRHR. In contrast, *Gnrhr* null mice have gonadal differentiation and early stages of gonadal development as these events are activated before birth and are independent of GnRH action.

Hwang *et al.*, (2018), reported that RNA sequencing of N-acetyltransferase 9 (NAT 9) and. Mitogen-activated protein kinase 3 (*MAP3K3*) genes using single nucleotide polymorphisms (SNPs) showed that NAT9 SNP was located in chromosome 12 exon 640 mRNA (A>G) and the MAP3K# was located in chromosome 12 intron 11 (80, C>T). The GG genotype of NAT9 and CT genotype of MAP3K3 had the highest values of litter size traits. NAT9 AND MAP3K3 genes associated in the breeding program for improvement of litter size traits of Berkshire pigs. Furthermore, Progesterone receptor (PGR) paracrine signaling has been recognized to play role in embryonic implantation. Chen *et al.*, (2016), detected the PRG paracrine signaling including IHH, NR2F2, BMP2, FKBP4 and HAND2 using SNPs in Large white, Landrace and Duroc pigs. Results revealed that NR2F2 gene responsible for litter size based on its mRNA/protein expression level during embryonic implantation. The genotype CC has a higher litter size (Chen *et al.*, 2016). Wang *et al.,* (2014) presented the peroxisome proliferator-activated receptor delta (*PPARD*) gene associated with litter size.

The result showed that genotype AA, BB and AB of Large White and Landrace increased in litter size.

Conclusion

Using different approaches, candidate genes were evaluated for their functions in the different stages of the reproductive process. It was revealed that the maternal reproductive genome controls all aspects of embryonic development. There are specific genes that control the reproductive development of various livestock species from fertilization, up to implantation and determination of litter size. Increased litter size has economic implications for the swine industry. Globally, the livestock industry grows tremendously in line with the projected demand for meat products and increasing consumer pressure on livestock production. Hence, the world finds ways to create efficient and precise technologies for genome modification to increase litter size. Substantial gain in litter size can significantly increase profit in swine production ventures.

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