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Chapter 4

Major Components in Limiting Litter Size

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Abstract

The litter size is an important trait in prolific species such as rabbits and pigs. However, selection on litter size has had limited success in these species because of its low heritability and sex-limited expression. The litter size is a complex physiological trait in prolific species, affected by several components that are expressed sequentially, for example, ovulation, fertilization, embryo development, and fetal survival. The selection for ovulation rate or/and prenatal survival has been proposed to improve litter size indirectly. However, these alternative methods have not reached the expected response rate. Implantation is also a critical point in successful gestation, one-third to one-half of prenatal mortality occurring during peri-implantation. The uterus must provide an adequate microenviroment for the growth and development of embryo and for receptivity to implantation. There are multitudes of cellular events involved in crosstalk between embryo and maternal uterus during peri-implantation. A better understanding of molecular mechanisms affecting the implantation process could help to propose new strategies for litter size improvement in prolific species.

Keywords: Ovulation rate, embryonic survival, litter size, candidate gene, quantitative trait loci (QTL)

1. Introduction

Litter size is a complex physiological trait in prolific species, being affected by several component traits representing sequential events, e.g., ovulation, fertilization, embryo development, and fetal survival. Fertilization rate is usually high, exceeding 90 to 95% in rabbit [1], pigs [2], and mice [3]. Therefore, prenatal survival is considered a limiting factor of litter size. Uterine capacity is an important component in prenatal survival [4; for a review address to 5]. Whenever the ovulation is not a limiting factor, this trait depicts the ability of the uterus to support embryo development through gestation [6]. Approximately 30 to 40% of ova shed do not result in fetuses at term in prolific species such as rabbits, pigs, and mice (see review [7])

due to potentially viable embryos exceeds uterine capacity. One-third to one-half of these losses occurs during peri-implantation in rabbits [8], pigs [9], and mice [10]. Preimplantation embryo losses are mainly associated with embryonic viability [4], including chromosomal abnormalities [11] and oviductal or uterine environment, particularly in relation with the suitability of oviductal or uterine secretions [12]. The oviduct must provide an adequate milieu for sperm capacitation, gamete fertilization, and the first embryo cleavages until the embryo enters the uterus [13]. Many proteins that may contribute to these functions have been identified in the oviduct, including the insulin-like growth factor 1 (IGF1) [14], oviductin (OVGP1, known also as MUC9) [15], tissue inhibitor of metalloproteinase (TIMP1) [16], plasminogen activator inhibitor 1 (PAI1) [17], uteroglobin [18], and leptin [19]. A progesterone-primed uterus coordinates the embryo survival and receptivity. The asynchrony between embryo development and uterine environment increases the number of dead embryos in the peri-implantation gestational stage [20, 21].

In rabbits, the period between pregnancy days 8 to 17 is critical for fetal survival, corresponding to the stage when the hemochorial placenta of rabbit is established and the control of the fetal nutrition is transferred to the placenta [22]. A secondary critical period for fetal survival occurs between pregnancy days 17 and 24, accompanying the uterine enlargement, the increased tension exerted on the spherical conceptus, and the reduction of blood flowing through the maternal vessels of the uterus [23]. In this moment, the placenta should compensate these limiting factors and increase its surface area for fetomaternal exchanges [24] and stimulate the development of an adequate vascular network [25, 26]. In pigs, the distribution of mortality after implantation is slightly different throughout pregnancy [9], the first peak occurring between days 30 and 40 of gestation (10-15%) while the second peak is observed in the last two weeks of gestation (5-10%). Despite the existing species differences, it is now accepted that each embryo requires a minimum space in uterus to attach, survive, and develop. Thus, a decrease in the availability of uterine space increases prenatal mortality in pluriparous species, such as rabbits [4] or pigs [27], despite that the factors involved in the process may differ among species. In pigs, the area of attachment between the placenta and endometrium is a limiting factor of uterine capacity, due to its noninvasive placentation [9]. Thus, it was proposed that uterine capacity in pigs could be defined more correctly as the total amount of placental mass or surface area that a dam can support to term [28]. Earlier studies in pigs indicate that the limiting influence of the uterine capacity is generally exerted after the day 30 of gestation and that the effects of moderate crowding of embryos before day 30 could be compensated by increased placental efficiency later in gestation (see review [29]).

2. Selection experiments for components of litter size

Litter size is an important economic trait in prolific species such as rabbits or pigs. However, direct selection for litter size has not presented the success expected for these species (see review [7, 30]), which may be due to the fact that it is a female sex-limited trait with low heritability. The selection response for litter size has been established around 0.1 young per generation in rabbits [31, 32] and pigs [33-36]. This response has been much lower than that

reported in mice: 0.15 to 0.20 young per generation [37-40]. Recently, in pigs, a selection experiment for litter size at day 5 after farrowing obtained a selection response around to 0.25 young per generation [41]. However, additional information on following generations will be required to confirm this trend.

The leading components of litter size are the ovulation rate and the prenatal survival; these parameters are also the limiting factors for the litter size improvement. For this reason, selection for ovulation rate and prenatal survival has been proposed as an indirect approach for increasing litter size. Selection for ovulation rate in prolific species, namely rabbits [42], pigs [43-45], and mice [40, 46], were in fact successful to improve the ovulation rate, but it was not convoyed by a corresponding increase in litter size in either pigs or rabbits, which was attributed to an increase in prenatal loss.

The selection for prenatal survival in pigs [45] and mice [40] allowed to increase litter size in both pigs and mice, but it was not more advantageous compared with the direct selection for litter size. Besides, prenatal survival might be limited by uterine capacity, defined as the maximum number of fetuses that a dam can support at birth when ovulation rate is not a limiting factor [6]. However, the ability to establish this trait is not easily performed across species, as it is dependent on the species physiology. In pigs, litter size in unilaterally ovario-hysterectomized females may be considered an indirect measure of the uterine capacity in pigs [6], since the remaining ovary nearly doubled its ovulation rate originating the fetal over-crowding in the ipsilateral uterine horn. Conversely, in unilaterally ovariectomized female rabbits and mice, which possess a duplex uterus that impedes intercornual transmigration, the number of total fetuses would represent their uterine capacity [47, 48].

Selection experiments for increased uterine capacity failed to obtain the expected success on litter size, in rabbits [8, 49], pigs [44], or mice [50]. Considering that uterine capacity in pigs would be more appropriately measured using the total amount of placental mass or the surface area that a dam can support to term as variables [28], a divergent selection experiment for placental efficiency developed in this species achieved success [51]. However, selection for increased placental efficiency will unlikely result in correlated increase in litter size [52].

A joint selection for ovulation rate and prenatal survival using an index would expectably show a greater response on litter size, since these parameters are optimally weighted [53, 54]. In pigs [55] and mice [56], the use of this joint selection successfully increased litter size, but the gain was lower than expected, probably due to a low precision of the estimated genetic correlations or the use of inappropriate economic weights [57]. Alternatively, a two-stage selection was proposed, which would be less affected by the precision of the genetic parameters; its application to rabbits [58] and pigs [59] obtained greater response on litter size than the observed in the other experiments of selection for litter size [31-36].

Selection for the environmental variability in litter size has been recently proposed as an alternative method for increased litter size. A reduction in litter size environmental variability would increase litter size heritability, and consequently its response to selection [60]. In rabbits, the environmental variance of a doe was estimated as within-doe variance of litter size.

Selection for environmental variance of litter size was successful [61], and as a consequence of reducing litter size variability the litter size was increased due to higher embryo survival [61].

3. Genetic control before implantation

The maternal genome controls virtually all aspects of early embryo development, through several maternal gene products such as mRNA and protein, which are loaded into the egg during oogenesis. 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 play an important role in the regulation of the first cleavages until embryonic genome is activated [62]. 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 [63]. ZGA has been shown to be a species-specific phenomenon, occurring at 2-cell stage in mice [64], 4-cell stage in pigs [65], and 8- to 16- cell stages in sheep, cows, or rabbits [66]. Many maternal-effect genes have been identified initially in mouse during the MZT, and several of whom have been detected posteriorly in rabbits and pigs.

Genome-wide gene activation in the zygote (ZGA) is regarded as crucial for preimplantation embryonic development. Multiple maternal factors were identified on the regulation of ZGA, which are listed in Table 1. Ablation of the gene encoding for these proteins results in embryonic arrest at cleavage-stage development.

These factors play critical roles in the regulation of embryo preimplantation development. For example, DICER1 enzyme is required for completion of oocyte mitotic maturation, and oocytes are arrested in metaphase of meiosis II when DICER1 gene is deleted [67, 68]. HSF1 protein is required for oocyte maturation. Embryos produced in knockout females for this gene are unable to proceed into the 2-cell stage after fertilization, possibly due to mitochondrial damage and altered redox homeostasis [69, 70]. UCHL1 is an import factor in blocking polyspermy [71, 72]. AGO2 is involved in the destruction of maternally inherited transcripts and activation of zygotic gene expression; knockout female for this factor is infertile because embryos fail to undergo the first cleavage [73, 74]. Moreover, embryos from MATER, ZAR1, PADI6, and SEBOX knockout females do not develop beyond the 2-cell stage embryo [75-82], and embryos lacking SMARCA4, DNMT1, DNMT3A, TET, and KLF4 are unable to reach the 8-cell stage [83-91]. BCLXL, HDAC1, and C-MYC exhibit maximum expression in 8-cell rabbit embryos coinciding with start of ZGA [90]. Hence the peak expression of transcripts at ZGA might be a requirement for embryo development. OCT4, NANOG, and SOX2 were co-expressed in epiblasts, and the combinatorial expression of these three genes is critical for the embryo development [92, 93].

Symbol gene	Name	Effect	References in	
			Mice*	Rabbits and pigs
DICER1	Endoribonuclease Dicer or helicase with RNase motif	Metaphase II	[67]	[68]
HSF1	Heat shock factor 1	Zygote	[69]	[70]
UCHL1	Ubiquitin carboxyl-terminal hydrolase L1	Zygote	[71]	[72]
AGO2	Argonaute 2	Zygote	[73]	[75]
MATER or *NLRP5*	Maternal antigen that embryos require	2-cell stage	[75]	[76]
ZAR1	Zygote arrest 1	2-cell stage	[77]	[78]
PADI6	Peptidylarginine deiminase type 6	2-cell stage	[79]	[80]
SEBOX	Skin-embryo-brain-oocyte homeobox	2-cell stage	[81]	[82]
BRG1 or *SMARCA4*	Brahma-related gene 1	4-cell stage	[83]	[84]
DNMT1	DNA cytosine methyltransferase 1	4-cell stage	[85]	[86]
DNMT3A	DNA cytosine methyltransferase 3 alpha	4-cell stage	[87]	[86]
TET1, *2* and *3*	Ten-eleven translocation (Tet) dioxygenases	4-cell stage		[88]
KLF4	Kruppel-like factor 4	4-cell stage		[89, 90]
BCLXL	B-cell lymphoma-extra large	8-cell stage		[89]
HDAC1	Histone deacetylase 1	8-cell stage		[89]
C-MYC	Avian myelocytomatosis viral oncogene homolog	8-cell stage		[90]
NANOG	The homeoprotein Nanog	16-cell stage	[91]	[84, 89, 93]
OCT4 or *POU5F1*	Octamer-binding protein 4	Morula	[92]	[89, 90, 93]
SOX2	SRY-box containing gene 2	Blastocyst		[84, 89, 93]

* Using gene-knockout mouse models.

Table 1. Maternal genes acting on early fetal embryogenesis.

4. Genetic control during implantation

Implantation requires a complex interaction among the developing embryo, decidualizing endometrium and developing maternal immune tolerance. For the successful implantation, it is of upmost importance the synchronization between the acquisition of implantation competency by the blastocyst and a receptive state in the uterine endometrium, for which the concurrence of the ovarian steroid hormones dynamics is crucial. The ovarian hormones determine a complex interplay of locally produced molecules in the endometrium, including

cytokines, growth factors, homeobox transcription factors, lipid mediators, and morphogen genes that are involved in the complex process of implantation. The crosstalk between the blastocyst and the uterus is limited in most mammal species for a brief period, named as *window of implantation*. During this short period, in response to a viable embryo, the endometrium responds through species-specific transformation of the superficial tissue architecture, a process known as decidualization, allowing the organ to accommodate embryonic growth and placentation. The decidua will function like a barrier, protecting the embryo against the maternal immune system [see review 94].

Steroid hormones

The progesterone receptor (PR) was identified as one of the molecules that genetic polymorphisms were associated with the risk of implantation failure. The PR is encoded by *PGR* gene, and has two isoforms, PRA and PRB, both of them are expressed in the uterus [94]. Studies in mice showed that a deletion on PRA provokes severe abnormalities in ovarian and uterine function and impairs implantation [94]. A study in rabbits reported that favorable allele of PRG had an additive effect of 0.25 for implanted embryos and kits for litter size [95].

Estrogen receptor (ER) was also implied in uterine receptivity for embryo implantation. ER presents two isoforms, known as ERα (encoded by *ESR1* gene) and ERβ (encoded by *ESR2* gene). In mice, knocking out the ERα gene leads to unsuccessful implantation [94]. In pigs, favorable allele of ESR shows an additive effect between 0.45 and 0.75 piglets for litter size [96, 97]. In another hand, it has been shown that the ERBB receptor feedback inhibitor 1 (*ERRFI1*) gene is involved with successful implantation, which was associated with its suppression of *ESR1* activity in the uterine epithelium, a crucial event for embryo implantation. Despite that the ovaries of ERRFI1 knockout female mice show a normal morphology and steroidogenesis function, its uterine horns do not develop an implantation site [98]. The steroid receptor coactivators (SRC1 and SRC2) present distinct physiological functions in the female reproductive system. For example, female mice lacking either *SCR1* or *SCR2* show progesterone resistance and compromised decidualization, whereas deletion of both *SCR1* and *SCR2* genes provoke infertility in female due to a complete blockage of decidualization [99], suggesting that one of the steroid receptor coactivators may, at least in part, compensate the absence of the other. Also the blockage of the repressor of estrogen receptor activity (REA), a significant modulator of estrogen responsiveness, was reported to induce implantation failures [100].

Moreover, prostaglandins (PGs) play an important role in various reproductive processes, including ovulation and implantation [101]. Cyclo-oxygenases (COX-1 and COX-2) are crucial enzymes in the synthesis of various PGs. Females lacking COX-1 and COX-2 are infertile, due to abnormalities in ovulation, fertilization, implantation, and decidualization [102]. A study in pigs showed that favorable allele of COX-2 had an additive effect of 0.3 piglets for litter size [103].

Cytokines

During the embryo implantation, the endometrium undergoes a dramatic transformation into a specialized transitory tissue known as the decidua in species with invasive hemochorial placenta, such as rodents and lagomorphs. In other species with no invasive placenta as pigs, the changes in endometrium ought to allow the trophoblast and its supporting layer of

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extraembryonic mesoderm to contact successfully with the uterine epithelium. The placenta surrounding the developing embryo facilitates the nutrient transfer and limits trophoblast invasion. The endometrium is recognized as an important site of production of cytokines and their receptors, which are also potential regulators of the phenotype and activation status of the uterine-resident leukocytes. Leukocytes infiltrated in the endometrium are required for the immunotolerance pathways that allow the maternal organism to accommodate the conceptus during implantation and placental development. Several cytokines, such as the macrophage colony-stimulating factor 1 (CSF1, also known as M-CSF), granulocyte colony-stimulating factor (CSF3, also known as G-CSF), and granulocyte-macrophage colony-stimulating factor (CSF2, also known as GM-CSF), are implicated in the recruitment and phenotypic regulation of the abundant populations of endometrial macrophages, granulocytes, and dendritic cells. These cytokines appear to be related to the successful embryo implantation and placental growth [104]. Also leukemia inhibitory factor (LIF), interleukin-6 (IL-6) and interleukin-11 (IL-11), and its receptor (IL-11Ra) have unquestionable roles in the implantation process [105-107]. Studies in pig have reported an association between certain polymorphisms in LIF gene with the number of piglets [108-111].

Growth factors

The epidermal growth factor (EGF), heparin-binding epidermal growth factor-like growth factor (HB-EGF), the vascular endothelial growth factors (VEGFs), the IGF-I and IGF-II as well as the IGF-binding protein-1 (IGFBP-1) are important factors for implantation. It was shown that EGF plays a critical role in trophoblast invasion, differentiation, and proliferation. EGF deficiency during pregnancy causes intrauterine growth retardation or abortion [112], while the deletion of epidermal growth factor receptor (*EGFR* or *ERB1)* gene causes failure in the embryo development and the placenta formation [113]. Likewise, other factors involved in the implantation process, such as HB-EGF, are expressed in endometrial stromal and epithelial cells. It has been demonstrated that HB-EGF regulates endometrial cell proliferation, glandular epithelial secretion, and decidual transformation [113]. Gene knockout studies reveal that deletion of *HBEGF* reduces litter size [114].

VEGF is an endothelial-cell specific mitogen *in vitro*, and it is the main factor responsible for de novo blood vessel formation (vasculogenesis) and angiogenesis in vivo [115]. Proper level of VEGF expression is required for implantation [116]. Many critical cell responses, including mitogenesis, proliferation, growth, differentiation, and angiogenesis, are mediated by IGF-I and IGF-II [117]. Both IGF-I and IGF-II are necessary to maintain normal embryonic growth rates [117]. In addition, higher expression of *IGF1* mRNA has been observed during the peri-implantation period in mouse uterus [118]. Also in rabbit, it has been observed that IGF-II receptor plays an important role in embryo development and its implantation [119].

Transcription factors

Homeobox genes are transcriptional regulators evolutionarily conserved that control embryonic morphogenesis and differentiation [120]. *Homeobox A* (*HOXA10* and *HOXA11*) and *H6 homeobox 3* (*HMX3*) genes are expressed in uterine stromal cells during the receptivity period, and upregulated upon decidualization in response to steroid hormone stimulus. Ablation of *HOXA10*, *HOXA11*, or *HMX3* genes leads to implantation defects [121-123]. *MSX1* (also known as *HOX7.1*) and *MSX2* also belong to *homeobox* genes, and deletion of both genes results in

female infertility due to altered uterine polarity and integrity of the surface epithelium [124]. The Kruppel-like transcription factors (*KLFs*) are implicated in diverse cellular processes, including proliferation, differentiation, and apoptosis. The Kruppel-like factor 5 (*KLF5*), one of these transcription factors, is essential for the establishment of uterine receptivity [125], and its depletion induces implantation failure [126]. *KLF9* is another KLF that plays an important role in blastocyst attachment; its loss reduces female fertility due to defective implantation [127]. The transcription factor named heart and neural crest derivatives-expressed transcript 2 (*HAND2*) and its protein are present in endometrial stromal cells adjacent to the surface epithelium in the uterus prior to the onset of implantation [128], suggesting that they may play a key role in uterine receptivity in mice [129]. Forkhead box protein A2 (FOXA2) is only expressed in the glandular epithelium of the uterus, and FOXA2 deficiency affect the endometrial gland formation and decidualization [130]. Deletion of chicken ovalbumin upstream promoter transcription factor II (*COUP-TFII*), which is mainly expressed in uterine stromal cells, originates implantation failure due to disrupted uterine receptivity associated with high estrogen activity [131].

Morphogen genes, lipid mediatiors, integrins, mucins, and others molecules

Proteins belonging to the transforming growth factor beta superfamily (TGF-β), Wingless (WNT), Hedgehog, and Notch have been identified as morphogens. Morphogens act directly on angiogenesis, cell growth, pattern formation, embryo development, metabolic regulation, cell migration, and tissue repair, while also presenting neurotropic effects. Five TGF-βs have been identified, of which TGF-β1, β2, β3 are abundant in mammals. However, only TFG-β1 appears to limit the number of implanted embryos [132]. Activins are also members of the TGF-β superfamily that participate in the regulation of several biological processes, including cell differentiation and proliferation, apoptosis, and the immune response [133]. Activin A plays an important role in the implantation of embryos in rabbits and mice, promoting decidualization and preventing the activation of T cells [134]. Among all bone morphogenetic proteins expressed in the uterus, only BMP2 shows intense expression in the stromal cells surrounding the implanted embryo under response to progesterone [135]. *In vitro* studies in undifferentiated stromal cells demonstrated that silencing the expression of BMP2 efficiently blocks the decidualization [136]. Deletion of *NODAL* gene was accompanied by severe malformation of the maternal decidua basalis during placentation and increasing fetal losses before birth [137]. Several components of WNTs signaling pathway are spatiotemporally regulated in the peri-implantation uterus and are crucial to implantation. The absence of WNT4, WNT5a, and WNT7a in the uterus induces defective embryo implantation and subsequent decidualization failure [138-140], while deletion of *WNT7b* gene provokes fetal losses during mid-gestation, due to failure of chorioallantoic fusion [141]. Indian hedgehog (IHH) is a member of the Hedgehog family. It has been reported that conditional deletion IHH protein in the uterus results in implantation failure [142]. Activation of smoothened (SOM), another member of the Hedgehog family, provokes hypertrophy in uterus along and consequently failure to decidual response [143]. The *NOTCH1* is responsible for cell survival, cell-to-cell communication, differentiation, and all fundamental processes for successful decidualization [144].

The blastocyst has a significant number of cannabinoid receptors (CB1) that are activated by the anandamide (AEA) produced in the uterus. It has been found that the levels of AEA are

lower in the receptive uterus and at implantation sites than in the non-receptive uterus or at inter-implantation sites. These findings suggest the need for low AEA levels to activate uterine receptivity [145].

The integrin family of cell adhesion molecules is a major class of receptors for the extracellular matrix. They have many functions in cellular processes including differentiation, apoptosis, and attachment [146]. Previous studies have demonstrated that integrins exhibit distinctive expression patterns in different phases of uterine receptivity. Both α4β1 and αvβ3 integrins are present in uterus at the time of implantation, and intrauterine inhibition of these two molecules results in defective implantation [147, 148].

Symbol gene	Name	Effects	References
Morphogens			
TFG-β1	Transforming growth factor beta 1	Failures in immunotolerance during embryo implantation	[132, 133]
INHBA	Activin A	Limiting decidualization, and no preventing activation of T cells	[134]
BMP2	Bone morphogenetic protein 2	Block the decidual reaction	[135, 136]
NODAL	NODAL	Abnormal decidua basalis at midgestation and aberrant placental development	[137]
WNT4, *WNT5A*, *WNT7A* and *WNT7B*	Wingless-related MMTV integration site 4, 5a, 7a, 7b.	Implantation and decidualization failures	[138-141]
IHH	Indian hedgehog	Implantation failure	[142]
SMO	Smoothened	Uterine hypertrophy with the reduction in the number of uterine glands and impaired decidualization	[143]
NOTCH1	Notch1	Failure in decidualization	[144]
Lipid mediators			
AEA	Anandamide	Uterine receptivity	[145]
Integrins			
ITGA4/ITGB1	α4β1 integrin	Implantation and decidualization failures	[146, 147]
ITGAV/ITGB3	αvβ3 integrin	Implantation and decidualization failures	[146, 148]
Mucins			
MUC1	Mucin 1	Embryo attachment failure	[149, 151]
OVGP1 or *MUC9*	Oviductal glycoprotein 1	Fertilization and implantation failures	[152]
Other molecules			
CTNNB1	β-catenin	Defects in embryonic ectoderm cell layer	[153-154]
CX43 or *CJA1*	Connexin 43	Comprised decidualization; neovascularization defects	[155]

Table 2. Genes considered as critical to implantation.

Mucins also participate in the decidualization process. For example, mucin (MUC1) has been identified as an effective barrier that prevents embryo attachment to the uterine epithelium. Uterine MUC1 expression declines to undetectable levels prior to blastocyst attachment, reinforcing the impression that loss of MUC1 contributes to the establishment of a receptive uterus [149-151]. Other oviductal glycoprotein, as OVGP1 or MUC9, seems to affect the differentiation of endometrial and fetal cells by paracrine pathway, inhibiting the implantation and fetal development [152]. The active beta-catenin (CTNNB1) is only detected in morula and early blastocyst stages, its signal disappearing as soon as the blastocyst hatches from the zona pellucida [153]. Furthermore, deletion of *CTNNB1* gene provokes severe gastrulation defects that results in embryonic lethality [154]. Connexin 43 (CX43, also known as GJA1) is a major gap junction protein that is markedly expressed in the uterine stromal cells surrounding the implanted embryo during early pregnancy. Deletion of *CX43* gene leads to aberrant differentiation of uterine stromal cells, preventing the secretion of angiogenic factors, such as the VEGF. As consequence, the development of new blood vessels within the uterine stromal compartment suffers a striking impairment, resulting in the arrest of embryo growth and early pregnancy loss [155]. All these critical genes on successful implantation are listed on Table 2.

5. Approaches for identifying genes in pigs and rabbits

In pigs and rabbits, genetic markers associated with reproductive traits have been identified through two complementary approaches. The first approach has been performed through unbiased genome scans with anonymous DNA markers, such as microsatellites and more recently with thousands of single nucleotide polymorphisms (SNPs), which have been used to identify quantitative trait loci (QTL) with effects on reproductive traits. Genome-wide scanning usually proceeds without any presuppositions regarding the importance of specific functional features of the investigated traits. Until now, a total of 28 suggestive QTL have been reported on pig chromosomes (SSC) 2, 6, 7, 8, 11, 12, 14, 15, 16, 17, and 18 for litter size [156-165], on SSC 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 14, 15, 16, 17, and 18 for ovulation rate [165-171], and on SSC8 for the uterine capacity and prenatal loss [159, 166, 168].

In the second approach, the physiological role of candidate gene is known, and the gene is scanned for polymorphisms and associations to variations within the trait. Numerous genes have been evaluated as candidate genes affecting litter size in pigs, such as the estrogen receptor (*ESR*) [95-97], retinol binding protein 4 (*RBP4*) [172], gonadotrophin-releasing hormone receptor (*GNRHR*) [173], osteopontin (*OPN*) [174], folate-binding protein (*FBP*) [175], mitogen-activated protein kinase 3 (*MAP3K3*) [176], vascular endothelial growth factor receptor (*KDR*) [176], ERBB2 interacting protein (*ERBB2IP)* [176], and peroxisome proliferator-activated receptor delta (*PPARD*) [176]. Another candidate genes have been found for progesterone receptor (*PRG*), *TIMP1*, oviductal glycoprotein 1 (*OVPG1*), hydroxysteroid-17-beta- dehydrogenase 4 (*HSD17B4*), endoplasmic oxidoreductin-1-like protein (*ERO1L*), and octamer-binding transcription factor 4 (*OCT4*) in rabbits [177-181]. However, associations of these genes with litter size are always population specific, and the causative mutations underlying litter size remain unexplored.

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DNA microarray is a new powerful tool for studying the molecular basis of interactions on a scale that is impossible using conventional analysis, making possible to examine the expression of thousands of genes simultaneously. In order to expand the understanding of the biological processes involved in the success of female reproduction, several studies in gene expression were developed in pigs targeting to identify the changes in ovaries [182, 183] and the endometrium at implantation [184-191]. For example, after selecting for 11 generations using an index of ovulation rate and embryonic survival, followed by 7 generations of selection for litter size, a total of 71 differentially expressed genes were identified in ovarian tissues of the selected and control lines at days 2–6 of the follicular stage of the estrous cycle [182]. Many of these genes had not been previously associated with reproduction. From these genes, 59 were homologous to genes of known function, 5 had no known matches in GenBank, and 7 were homologous to sequences of unknown function. Among the differentially expressed genes identified were those associated with the transport of cholesterol in ovarian follicles and the synthesis of steroids, such as collagen type I receptor (*CD36L1*, also known as scavenger receptor class B type I). The experiment also showed the importance of studying the expression of all these genes at different times of estrous cycle. For instance, genes of steroidogenic acute regulatory protein (*STAR*), 3-β-hydroxysteroid dehydrogenase (*3βHSD*), were overexpressed in higher producing pig ovaries at day 2 of analysis, while were underexpressed at day 3. In contrast, plasminogen activator inhibitor 1 (*PAI1*) and cytochrome P450 17-α-hydroxylase (*CYP17*) were overexpressed at day 3.

In a different study, 189 genes were found to be differentially expressed in the ovaries of pregnant pigs with high and low prolificacy, of which 72 were overexpressed in the high prolificacy group, while 133 of them were overexpressed in the low prolificacy group [183]. These genes appear to cluster in three main biological processes: the first group would be related to the immune system response activation against external stimulus, the second group included integrated genes that regulate maternal homeostasis by complement and coagulation cascades, and the third was involved in lipid and fatty acid enzymes of metabolic processes of the steroidogenesis pathway. Among validated genes, 2-5-oligoadenylate synthetase 1 (*OAS1*) was found overexpressed in high prolificacy females, while a family with sequence similarity with 46 member C (*FAM46C*), secreted phosphoprotein 1 (*SPP1*), thiosulfate sulfurtransferase (*TST*), and vitronectin (*VTN*), were reported overexpressed in low prolificacy females.

Recent microarray analysis revealed more than 2000 differentially expressed genes in endometrium between pregnant and cyclic pigs at the time of implantation, i.e., on days 12 [186], 13 [191], 14 [187], 15 [188], 16 [192], 18 [191], or 24 [191] of gestation. Most genes were involved in cell motility as well as apoptosis, transporter activity, calcium ion binding, lipid metabolic processes, hormone activity, vascular development and proteolysis, immune response. The identified and validated genes that are upregulated included ADAM metallopeptidase with thrombospondin type 1 motif 20 (A*DAMTS20*), mucin 4 (*MUC4*), leukemia inhibitory factor receptor alpha (*LIFR*), interleukin 6 receptor (*IL6R*), interferon regulatory factor 1 (*IRF1*), immunoresponsive 1 homolog (IRG1), secreted phosphoprotein 1 (*SPP1*), osterocrin (*OSTN*), nuclear receptor interacting protein 1 (*NRIP1*), proteolipid protein 1 (*PLP1*), signal transducer

and activator of transcription 1 (*STAT1*), serpin peptidase inhibitor, clade B (ovalbumin), member 7 (*SERPINB7*), s100 calcium binding protein A 9 (*S100A9*), Erb-B2 receptor tyrosine kinase 3 (*ERBB3*), and fibroblast growth factor 9 (*FGF9*). Contrasting, mucin 5AC, oligomeric mucus/gel-forming (*MUC5AC*), interleukin 11 receptor alpha (*IL11RA*), interleukin 24 (*IL24*), brain and acute leukemia cytoplasmic (*BAALC)*, defensin beta 1 (*PBD-2*), defensin beta 1 (*PBD-2*), cadherin 17 li (*CDH17*), FXYD domain containing ion transport regulator 4 (*FXYD4*), G protein-coupled receptor 83 (*CPR83*), and fibroblast growth factor receptor 3 (*FGFR3*) are downregulated [182-187, 191]. Litter size is controlled by a large number of genes.

Improvement in litter size has become one main objective of selection in pig and rabbit breeding programs. However, litter size is a complex trait, because it is controlled by numerous genes in complicated physiological networks such as those affecting ovulation rate, embryo survival, and uterine capacity. The genomic approaches, both QTL mapping and candidate gene analysis, have helped increase understanding in genetic control of litter size. Moreover newly developed tools based on DNA microarray techniques appear to be useful for in-depth understanding of the genetics of litter size in pigs and rabbits. A better understanding of genetic mechanisms controlling litter size could help to design more efficient selection strategies in improvement of this trait.

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