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SIRT1 AS A KEY FACTOR FOR HISTONE CODE ESTABLISHMENT IN EARLY EMBRYO, FROM A PERSPECTIVE OF ASSISTED REPRODUCTION

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ABSTRACT

Both the paternal and the maternal pronuclear chromatin undergo the erasure and re-establishment of epigenetic marks during mammalian zygotic development. These epigenetic changes regulate the totipotency, self-renewal and eventually cell differentiation within the preimplantation embryo. The demethylation of DNA and establishment of adequate post-translational histone modifications, called histone code within the zygote, are required for successful development and reflects the male or female origin of chromatin.
Further epigenetic changes are necessary for developmentally regulated transcription and determination of embryonic cell lineage as the embryo blastomeres become transcriptionally active during major zygotic genome activation (MZGA). In addition to DNA methylation, histone code modifications and their regulation are intensively studied. Sirtuin SIRT1, a member of the $NADP^+$-dependent histone deacetylase family, modifies histones via direct deacetylation as well as indirectly through non-histone substrate regulation. Positive effects of SIRT1 activation on cell viability and embryonic development have been described, and correct histone code modulation is the proposed mode of SIRT1 action. Understanding SIRT1-dependent signalling will provide new tools for assisted reproductive technology in animals and therapy in humans, wherein the inadequate epigenetic modification is a possible explanation for the failure of embryo development *in vitro*.

Key words: zygote; embryonic development; DNA methylation; histone code; deacetylase; sirtuin; SIRT1

INTRODUCTION

The oocyte, a terminally differentiated haploid female germ cell, becomes a totipotent zygote after fusion with a spermatozoon during the precisely orchestrated process of fertilisation. Thereafter, second oocyte meiosis is complete, second polar body is extruded, and the paternal (male) and maternal (female) pronucleus formation takes place. At the onset of pronuclear development, male chromatin tightly packed within the sperm head undergoes rapid decondensation, protamine-histone exchange and male pronucleus formation. The zygote containing female and male pronuclei enters first mitosis, termed embryo cleavage, and produces two nearly identical diploid blastomeres. Subsequent cell cycles follow and further milestones of pre-embryo

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development are reached, such as the major zygotic genome activation (MZGA), formation of morula and blastocyst differentiation and hatching. Chromatin consisting of DNA and histones is dynamically regulated during this period (Yanagimachi, 1988).

Nucleosome, the functional unit of eukaryotic chromatin, consists of ~ 147 base pairs (bp) of DNA wrapped around a histone core formed by an octamer of four different core histone variants (H2A, H2B, H3 and H4), and strung together by linker histone H1. The DNA within this complex is modified by the ligation of methyl groups onto developmentally pre-programmed CpG sites, termed DNA methylation. Together with post-translational modifications of core histones, such epigenetic modifications play a key role in both gametogenesis and early embryonic development (reviewed by Shi and Wu, 2009).

A number of core histone splicing variants are known in somatic cells as well as in gametes, zygotes and embryos. In addition to alternative splicing, histones‘ post-translational modifications, e.g. methylation and acetylation, affect the structure and function of chromatin (reviewed by Yuan and Zhu, 2013). Adequate epigenetic changes determine the transcriptional activity/chromatin status of a zygote; they are essential for gene imprinting and transition of the totipotent zygote to the differentiated embryo expressing its own genome during MZGA (Patrat *et al.*, 2009; Dahl *et al.*, 2010; Latham and Schultz, 2001). Various upstream factors regulate epigenetic changes, resulting in embryonic chromatin remodelling observed during development. Correct epigenetic changes affecting zygotic pronuclei determine both the zygote quality and the subsequent embryo development. In their sum, these epigenetic changes endow the nearly transcriptionally silent embryonic genome with only minor gene expression activity. As such, maternal storage and inheritance of mRNAs and proteins plays a key role in the regulation of early epigenetic changes that essentially rely on the existing, oocyte-stored pool of RNAs and proteins. Epigenetic changes are subsequently required for modulation of transcriptional activity through genome reprogramming, setting the stage for ensuing cellular differentiation (Latham *et al*., 1991; Latham and Sapienza, 1998; Segev *et al.*, 2001; Yan, 2014; Uysal *et al*., 2015).

In vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), common methods utilised in assisted reproductive therapy (ART), allow for the continuous observation of early embryonic development including pronuclear biogenesis and subsequent embryo cleavage all the way up to, and including blastocyst formation. On the other hand, IVF- and ICSI-derived embryos show lower efficiency in development success, lowering the success rate of human ART *in vitro* embryo production, as well as in livestock and rodents. Differences in epigenetic modifications are likely contributors to such developmental failures (Peat and Reik, 2012; Farifteh *et al.*, 2014; Matoba *et al.*, 2014; Mao *et al.*, 2015). Therefore, the study of the epigenetic mechanism offers possibilities to improve ART and *in vitro* embryo production.

Epigenetic regulation through DNA methylation

Epigenetic changes of the embryo start immediately after fertilisation when the pronuclear development takes place. These changes include DNA methylation based on 5‘-methylcytosine (5mC) appearance, associated with gene imprinting and DNA stabilisation (Wigler, 1981; Stein *et al*., 1982). In addition to DNA methylation, post-translational modifications of histones, generally called histone code, occur and predetermine transcriptional activity and chromatin stability (Dimitrov *et al*., 1993; Aoki *et al*., 1997).

The DNA methyl transferases (DNMTs) are responsible for 5‘-methylcytosine formation, thus determining gene expression, gene imprinting and predisposition to DNA strand breakage. The DNMT1 protein binds to a hemi-methylated double-stranded DNA during replication (Bestor, 2000; Giraldo *et al*., 2013) and is responsible for the maintenance of methylation patterns (Hirasawa *et al*., 2008). Enzyme DNMT3 is able to *de novo* methylate existing double-stranded DNA (Okano *et al.*, 1999). Both DNMT1 and DNMT3 are involved in gene imprinting during gametogenesis and embryonic cell differentiation, as well as in the maintenance of specific methylation patterns during preimplantation development (Kato *et al*., 2007; Hirasawa *et al*., 2008; Smallwood *et al.*, 2011).

Before MZGA, the ooplasm-stored proteins and proteins translated from maternally inherited mRNAs after fertilization control epigenetic modifications, assuring that the embryonic DNA undergoes demethylation for the maintenance of totipotency. Such pre-MZGA modifications prepare the embryo for *de novo* DNA methylation and cell differentiation via heterochromatin formation, gene silencing and X-chromosome inactivation (Mayer *et al*., 2000; Dahl *et al*., 2011). Therefore, DNA demethylation of a highly methylated zygotic pronucleus is a key event immediately after fertilisation (Mayer *et al*., 2000; Dean and Ferguson-Smith, 2001; Reik *et al*., 2001). Asymmetric parent-of-origin dynamics of chromatin and DNA demethylation patterning of maternal and paternal pronuclei have previously been described (Guo *et al*., 2014). Demethylation of DNA in the paternal pronucleus occurs earlier than in the maternal pronucleus. Whereas the paternal pronucleus is demethylated within four hours after fertilisation, the maternal DNA

methylation persists until blastocyst stage (Mayer *et al*., 2000; Dean and Ferguson-Smith, 2001; Reik and Walter, 2001; Guo *et al.*, 2014). The major wave of genome-wide demethylation occurs at the 2-cell stage of the human embryo development (Guo *et al*., 2014). Rapid paternal DNA demethylation appears to be an active TET3 dioxygenase-dependent process, resulting in the creation of oxidised 5mC forms, already detectable prior to first round of zygotic DNA replication (Mayer *et al*., 2000; Dean and Ferguson-Smith, 2001; Gu *et al*., 2011; Wossidlo *et al*., 2011). Contrary to the general assumption of passive maternal DNA demethylation over consecutive embryo cleavages until late morula stage, recent studies have identified a basal level of active demethylation process in the maternal DNA through detection of oxidised 5mC forms in both parental pronuclei (Guo *et al*., 2014; Shen *et al*., 2014).

Altogether, correct zygotic DNA demethylation is essential for embryonic cell totipotency and re-methylation of DNA during subsequent embryonic cell differentiation. Besides DNA methylation, adequate post-translational modifications of histones determine zygotic genome stability, inheritance/maintenance of parent-specific gene expression and proper formation of the zygotic pronuclei and blastomere nuclei.

Epigenetic regulation by histone code

Histone variants (H1, H2A, H2B, H3, H4), their splicing forms (*e.g*. H2A.Z, MacroH2A, H2A-Bbd and H2A.X for H2A), and post-translational modifications, such as acetylation, methylation, phosphorylation, ubiquitination and sumoylation together termed histone code, are responsible for structural and functional modifications of the nucleosome (Kamakaka and Biggins, 2005). Zygote formation represents a dynamic phase of early development encompassing rapid protamine-histone exchange and immediate pronucleus biogenesis including histone code modification. Histone modifications in the zygote are associated with specific nucleosomal features. Whereas histone acetylation and methylation on lysine residues are markers of transcriptional activity, phosphorylation (*e.g*. that of H2A.X, abbreviated as γH2A.X) or ubiquitination (*e.g*. that of H2A.Z) determine histone recycling and DNA breaks (Chen *et al*., 1998; Kuo and Yang, 2008).

Among aforementioned histones, splicing variants and post-translational modifications histone H3 are well known. Histone H3 variants in differentiated somatic cells and embryonic stem cells comprise H3.1, H3.2 and H3.3 (Yuan and Zhu, 2013; Zhou and Dean, 2015). Pronuclear asymmetry is manifested at the onset of development wherein H3.1 and H3.2 variants are absent from the paternal pronucleus of early mouse zygotes, and H3.3 is the predominant H3 variant within paternal chromatin (van der Heijden *et al*., 2005; Torres – Padilla *et al*., 2006).

Histone H3 acetylation is denoted as a marker of transcriptional activity (Hebbes *et al.*, 1988, 1994), facilitating the binding of transcription factors to chromatin (Lee *et al*., 1993; Vettese – Dadey *et al*., 1996). However, H3 acetylation is also frequently associated with DNA damage (Khobta *et al*., 2010). Lysine residues K9 and K14 are critical sites for the acetylation of histone H3 (Bjerling *et al.*, 2002). Despite the transcriptional silence inherent to meiosis, the histone acetylation pattern plays a role in oocyte maturation (Kim *et al*., 2003; Endo *et al*., 2005). In the embryo, histone acetylation predicates the oncoming major wave of transcription at MZGA (Adenot *et al.*, 1997).

Histone methylation is considered as an opposite to histone acetylation. Histone methylation is crucial for genome stabilisation, epigenetic inheritance and cellular memory maintenance (Grunstein, 1997; Zhang and Reinberg, 2001; Grewal and Jia, 2007; Muramatsu *et al*., 2013). In the zygote, while the maternal pronucleus is typically di- and tri-methylated (me2/3) on lysine residues K4, K9, and K27 of histone H3, the paternal pronucleus displays lesser histone methylation (Figure 1). Paternal pronucleus is restricted to monomethylation of H3 on K4, K9 and K27, which, however, is also present in the maternal pronucleus (Lepikhov and Walter, 2004; Santos *et al*., 2005; van der Heijden *et al*., 2005). In addition to the pronucleus, H3K9me2/3 is fundamental for epigenetic changes resulting in DNA stabilisation, gene silencing, heterochromatin establishment and X-chromosome inactivation during inner cell mass (ICM) formation (Bannister and Miska, 2000; Rea *et al*., 2000; Cao *et al*., 2002; Plath *et al*., 2004). Although the above-mentioned patterns of histone methylation are associated with gene silencing, the methylation of H3K4 coincides with active transcription sites (Heintzman *et al*., 2007; Eissenberg and Shilatifard, 2010) and appears essential for genome reprogramming, increasing around the time of MZGA in the mouse (Shao *et al*., 2014).

Regulation of the histone code

Histone acetylation is specifically catalysed by histone acetyltransferases (HATs) capable of removing the acetyl group (Brownell and Allis, 1996). Alternatively, non-HATs enzymes with histone acetyltransferase activity, such as transcription initiation factors TFIID and ELP3, are subunits of elongator/RNA polymerase II (Mizzen *et al*., 1996; Wittschieben *et al*., 1999). Among them, HAT1 is responsible for acetylation of newly synthesised histones including H3, as well as the maintenance of acetylation during mammalian embryo development

(Nagarajan *et al*., 2013). On the other hand, histone deacetylases (HDACs), discussed in more detail below, are responsible for acetyl group removal and thus enact under-acetylation of their substrate histones (Tauton *et al*., 1996; Dangond *et al*., 2001). Early embryonic development is regulated by HDACs through deacetylation of both histones and non-histone substrates including α-tubulin, especially until fertilisation when HDACs activity is naturally reduced (Matsubara *et al*., 2013). Interestingly, overall inhibition of HDACs improves the quality of somatic cell nuclear transfer (SCNT)-derived embryos by an increase of histone acetylation and down-regulation of DNMT1 (Hou *et al*., 2014; Mao *et al*., 2015).

After the HDACs release acetyl group, methyltransferase activity increases following the exposure of binding sites for the methyl group (Dangond *et al*., 2001). A wide spectrum of enzymes with methyltransferase activity appears to be essential for the zygote and early embryo where they are responsible for histone methylation. Among histone methyltransferases, the suppressor of variegation 3-9 homologue 1 and 2 (SUV39H1, SUV39H2, also known as KMT1A, KMT1B), euchromatic histone-lysine

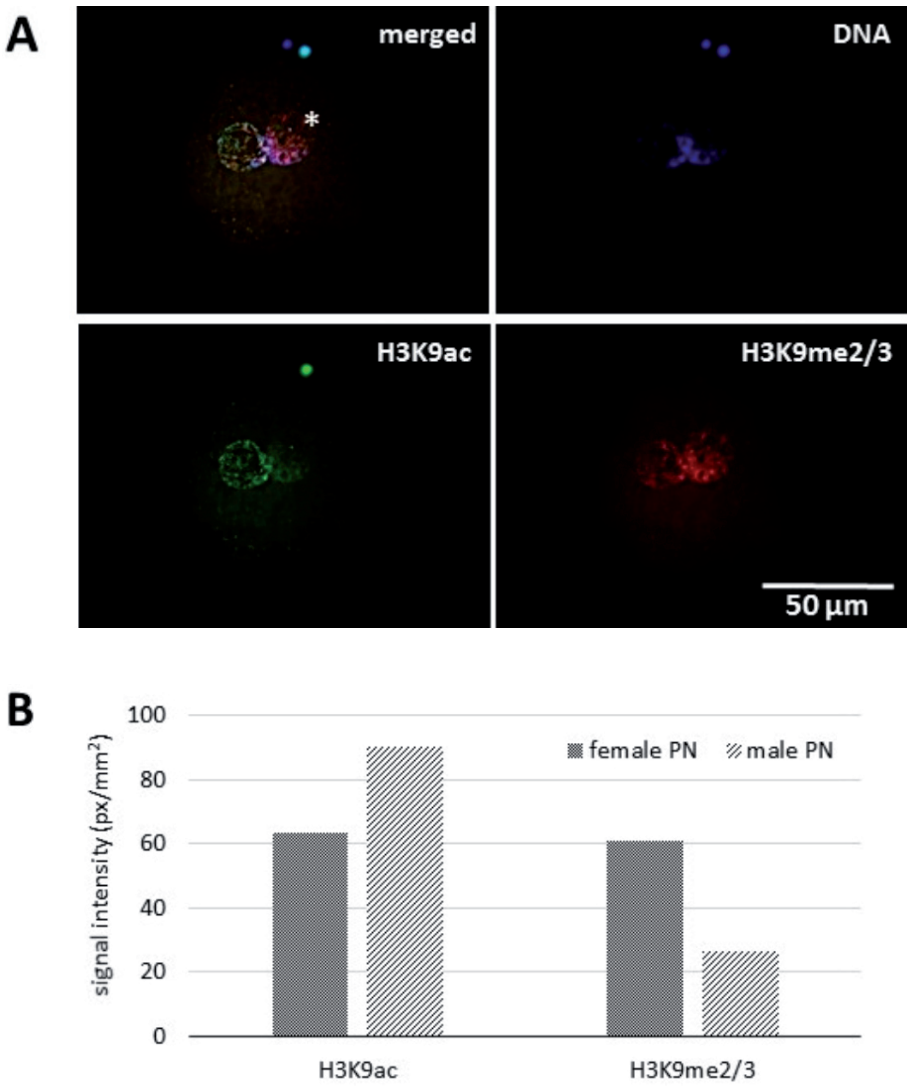

Fig. 1: Asymmetry of the histone code in the porcine zygote pronuclei. Different intensities of acetylated (green) and methylated (red) histone H3 labeling, representing paternal and maternal female pronucleus (PN), respectively, is present (A). The paternal pronucleus was identified by the presence of pre-labeled sperm mitochondria, indicated by asterisk. Signal intensity profile shows higher H3K9 acetylation and lower H3K9 methylation in the paternal pronucleus, in contrast with maternal pronucleus (B).

N-methyltransferase 1 and 2 (EHMT1, EHMT2, also GLP and G9A, respectively), SET domain bifurcated 1 and 2 (SETDB1, SETDB2) and mixed lineage leukemia family (MLL/SET) enzymes transfer the methyl group to lysine in the N-terminal tail of histones and establish heterochromatin marked by H3K9me2/3 modification (Rea *et al.*, 2000; Tachibana *et al*., 2001; Völkel and Andgrad, 2007; Park *et al*., 2011; Shao *et al.*, 2014; Golding *et al*., 2015).

The above mentioned SUV39H1 is an established key factor for facultative heterochromatin formation, genome stability and regulation of gene expression by transcription factors (Firestein *et al*., 2000; Nielsen *et al.*, 2001; Peters *et al*., 2001; Vaquero *et al*., 2004). The activity of this enzyme is important for embryogenesis and determination of embryonic cell lineage (Park *et al.*, 2011; Shao *et al*., 2014). Heterochromatin formation mediated by SUV39H1 involves the linkage of multiple proteins, such as heterochomatin proteins HP1α and HP1β. Cross-linking of SUV39H1 and HP1 is associated with centromeric regions. The constitution of an SUV39H1-HP1 methylation system is important for chromosome segregation (Aagaard *et al*., 2000) and H3K9 methylation (Bannister *et al*., 2001; Lachner *et al*., 2001; Nakayama *et al*., 2001; Jacobs and Khorasanizadeh, 2002; Maison and Almouzni, 2004; Park *et al*., 2011).

The formation of the SUV39H1-HP1-H3K9me2/3 complex is associated with other marks of genome stability, such as DNA methylation (Johnson *et al.*, 2002; Lehnertz *et al*., 2003; Peters *et al*., 2003; Peters and Schubeler, 2005; Yeo *et al*., 2005). Therefore, DNMT1 and DNMT3B seem to be strictly downstream factors of SUV39H1 on pericentromeric chromosome loci in embryonic stem cells, where DNMTs form complexes with HP1 isoforms (Lehnertz *et al*., 2003). Moreover, DNMT1 interacts directly with histone H3 methyl transferase G9A at the replication fork, resulting in H3K9 methylation (Cheedipudi *et al.*, 2014; Esteve *et al*., 2005), and a positive feedback loop is indicated. Methylated H3K9 also recruits co-factors of other DNA methyltransferases (Karagianni *et al*., 2008).

In summary, SUV39H1 exerts a positive effect on early embryonic development. In accordance with this assumption, understanding molecular mechanisms leading to SUV39H1 activation will facilitate further progress in ART. Recent studies point to non-histone substrates of NAD^+-dependent histone deacetylates, sirtuins, targeting a wide spectrum of factors with cumulative effects resulting in histone methylation following their direct deacetylation (Vaquero *et al.*, 2007a; Li *et al.*, 2009; Bosch – Presegue *et al*., 2011).

Sirtuins: the favourite histone deacetylase

The family of histone deacetylases (HDACs) is responsible for histone deacetylation on lysine residues (Allfrey, 1964; Fujimoto, 1972). Based on the original description, the HDACs are divided into three classes: Rpd3p (class I), Hda1p (class II) and Sir2p (class III). An important group within this family is the NAD^+-dependent class III of HDACs, together called the sirtuins. The sirtuin family comprises 7 members (SIRT1 - 7), collectively identified as key regulators of lifespan and longevity in various organisms. Sirtuin activity has been linked to protection against DNA damage and repair of DNA strand breaks (Haigis and Guarente, 2006; Kim and Um, 2008; Canto and Auwerx, 2009; Milner, 2009; Herranz *et al*., 2010). Beneficial effects of sirtuins during gametogenesis and early embryo development have been described (Coussens *et al*., 2008; Kawamura *et al*., 2010; Kwak *et al*., 2012a, 2012b; Bell *et al.*, 2014; Di Emidio *et al*., 2014; Zhang *et al*., 2014). One possible explanation of sirtuins‘ protective role is their ability to deacetylate histone H1 on K26, H3 on K9, K14, K26 and K56, and H4 on K8, K12 and K16 (Vaquero *et al*., 2004; Vaquero *et al*., 2007b; Oberdoerffer *et al*., 2008; Das *et al*., 2009; Chen *et al*., 2010). These deacetylations lead to a greater abundance of methylated histones, acting as heterochromatin marks. Histone methylation requires lysine residue release and activation of multiple methyltransferases (Vaquero *et al*., 2004; Yuan and Zhu, 2013).

The above mentioned SUV39H1 methyltransferase is activated by deacetylation of K266 within its catalytic SET domain by SIRT1 (Rea *et al*., 2000; Vaquero *et al.*, 2007a), which accumulates in the zygotic pronuclei (Figure 2). In addition to induction of deacetylating activity, SIRT1 may protect and prolong the half-life of SUV39H1 by suppressing its proteasomal degradation promoted by polyubiquitination via MDM2 E3-type ubiquitin ligase (Bosch – Presegue *et al*., 2011). Therefore, H3K9me2/3 increases in the presence of activated SIRT1 (Peters *et al.*, 2003; Vaquero *et al*., 2004; Vaquero *et al.*, 2007a). The H3K9me2/3 is able to protect H3 against proteasomal degradation due to HP1α recognition followed by ICBP90 binding (Karagianni *et al*., 2008). This complex enables heterochromatin establishment and maintenance, relevant for epigenetic regulation of mammalian development (Peters *et al*., 2003; Matoba *et al*., 2014).

In addition to histone code modification, SIRT1 is capable of affecting signalling mediated by transcriptional factors, such as p53, proteins of the Forkhead box O-class family (e. g. FOXO1, FOXO3A), and p65, a subunit of NF–κB (Kawahara *et al*., 2009; Kawamura *et al*., 2010; Wang *et al*., 2012; Shinozaki *et al.*, 2014). Expression of p53 negatively determines the blastocyst quality and plays a role

in response to DNA damage during embryogenesis. The aforementioned ubiquitin ligase MDM2 is involved in proteasomal degradation of p53 (O'Neill *et al*., 2012; Tollini et al., 2014) and cross-talk between MDM2 and p53 regulates proteasomal degradation of FOXO3A (Fu *et al*., 2009). Regulation by MDM2 and/or the marking-up of deacetylated lysine residues in FOXO for ubiquitination are two possible ways of SIRT1 signalling leading to improved embryonic development due to FOXO regulation (Chen *et al.*, 2010; Wang *et al*., 2012, 2014; Chao *et al*., 2014; Sparks *et al*., 2014; Tseng *et al*., 2014).

In addition to MDM2 signalling, SIRT1 affects various cell survival-related functions, including mitochondrial metabolism, apoptosis and maintenance of telomere length (Palacios *et al*., 2010; Wang *et al*., 2013; Zhang *et al*., 2015). The extensive spectrum of SIRT1 targets indicates its complex effect, with the prospect of utilisation for improvement of *in vitro* embryo production. However, many non-histone targets and exact SIRT1 molecular mechanisms in early embryonic development remain undefined.

Significance of SIRT1 understanding for assisted reproduction and *in vitro* embryo production

The multiplicity of cellular pathways involving SIRT1 signalling (Figure 3) accounts for the well-known pro-survival effect of resveratrol, a strong activator of sirtuin favouring SIRT1 (Hubbard *et al.*, 2013; Lakshminarasimhan *et al.*, 2013). The positive effect of SIRT1 activation on oocyte maturation, early embryonic development and blastocyst rate has been described in numerous studies (Lee *et al.*, 2010; Kwak *et al*., 2012a; Giaretta *et al*., 2013; Sato *et al*., 2014; Takeo *et al*., 2014;

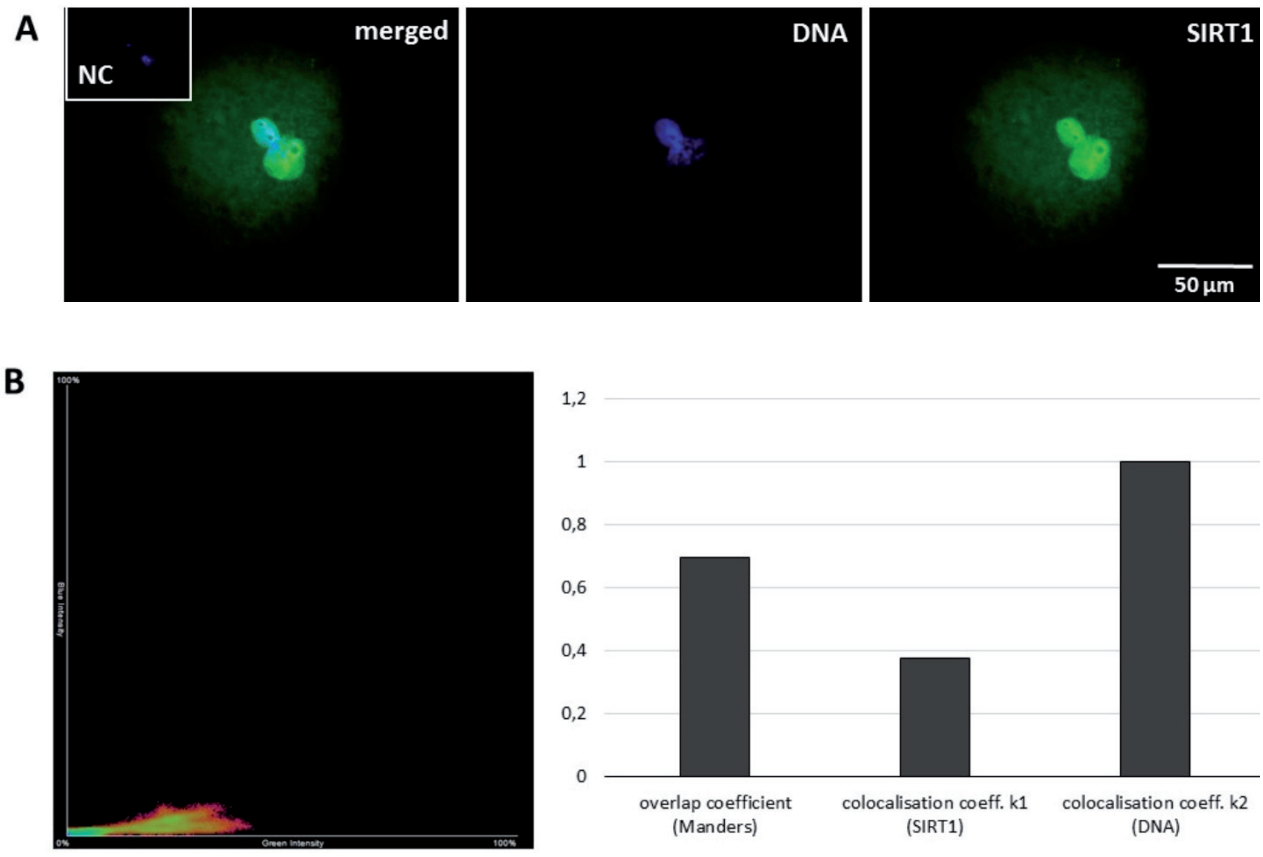

Fig. 2: The SIRT1 protein (green) in porcine zygote. Co-localisation of SIRT1 and DNA indicates SIRT1 accumulation in the pronuclei. Weak SIRT1 signal in cytoplasm is in accordance with existence of SIRT1 non-histone targets (A). Manders' overlap coefficient shows 70 % total signal of SIRT1 in the pronucleus wherein 99 % of chromatin is co-localised with SIRT1 (B). NC: negative control for SIRT1 immunolocalization (anti-SIRT1 antibody was replaced with a non-immune serum during sample processing).

Itami *et al*., 2015). Although SIRT1-improved embryonic development is well known, SIRT1 signalling in embryos is not understood, and research focused on its targets and determinants is still insufficient.

Epigenetic changes and histone code dynamics are potential subjects of SIRT1 and thus possible targets for further improvement of *in vitro* embryo production, which is inferior to *in vivo* development. In addition to IVF, epigenetic modifications play a key role in assisted reproductive technologies, such as ICSI and SCNT, where SIRT1 activity may be altered (Kwak *et al*., 2012b; Peat and Reik, 2014; Mao *et al*., 2015). Subsequently, varied modifications of the DNA and histone code during zygotic and embryonic development could be responsible for the high failure rates of these techniques.

The involvement of SIRT1 in epigenetic inheritance provides an opportunity for the utilisation of new knowledge based on SIRT1 study. However, comprehensive research needs to be undertaken before its application to *in vitro* techniques and methods of both assisted reproduction in farm animals and human reproduction therapy. Particular efforts in our laboratories will focus on the cross-section of SIRT1 and HDAC-mediated epigenetic regulation with the ubiquitin-proteasome system, which plays important

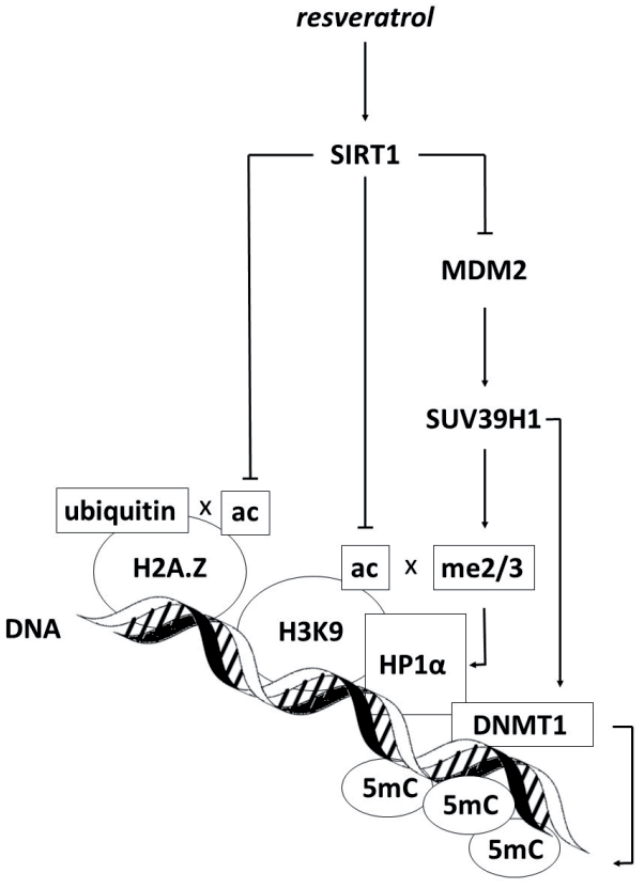

Fig. 3: The involvement of SIRT1 in histone code modifications and heterochromatin establishment. The complex of H3K9me2/3 - HP1α - DNMT1 causes DNA methylation accompanied by the presence of aforementioned histone heterochromatin markers. The SIRT1 protein is able to suppress MDM2 - mediated proteolysis of SUV39H1 and thus increase the presence of heterochromatin markers. Direct deacetylation of histones enables the methylation of H3 as well as ubiquitination and proteolytic degradation of H2A.Z. Altogether, these genome changes can be beneficial for genome stabilisation in zygotic pronuclei and thus improvement of further embryonic development *in vitro*. MDM2: Mouse Double Minute 2 homolog, E3 - ubiquitin ligase; SUV39H1: Suppressor of Variegation 3 - 9 Drosophila, homolog 1, the histone methyl transferase; ac: acetyl group; me2/3: di – or trimethyl group; HP1α: Heterochromatin Protein 1α; DNMT1: DNA Methyl Transferase 1; 5mC: 5'-methylcytosine.

roles in gametogenesis, fertilization and pre-embryo development (Sutovsky, 2003; Mtango *et al*., 2014; Nevoral and Sutovsky, 2015).

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