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CAN REPROGRAMMING OF OVERALL EPIGENETIC MEMORY AND SPECIFIC PARENTAL GENOMIC IMPRINTING MEMORY WITHIN DONOR CELL-INHERITED NUCLEAR GENOME BE A MAJOR HINDRANCE FOR THE SOMATIC CELL CLONING OF MAMMALS? – A REVIEW*

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Abstract

Successful cloning of animals by somatic cell nuclear transfer (SCNT) requires epigenetic transcriptional reprogramming of the differentiated state of the donor cell nucleus to a totipotent embryonic ground state. It means that the donor nuclei must cease its own program of gene expression and restore a particular program of the embryonic genome expression regulation that is necessary for normal development. Transcriptional activity of somatic cell-derived nuclear genome during embryo pre- and postimplantation development as well as foetogenesis is correlated with the frequencies for spatial remodeling of chromatin architecture and reprogramming of cellular epigenetic memory. This former and this latter process include such covalent modifications as demethylation/re-methylation of DNA cytosine residues and acetylation/deacetylation as well as demethylation/re-methylation of lysine residues of nucleosomal core-derived histones H3 and H4. The main cause of low SCNT efficiency in mammals turns out to be an incomplete reprogramming of transcriptional activity for donor cell-descended genes. It has been ascertained that somatic cell nuclei should undergo the wide DNA cytosine residue demethylation changes throughout the early development of cloned embryos to reset their own overall epigenetic and parental genomic imprinting memories that have been established by re-methylation of the nuclear donor cell-inherited genome during specific pathways of somatic and germ cell lineage differentiation. A more extensive understanding of the molecular mechanisms and recognition of determinants for epigenetic transcriptional reprogrammability of somatic cell nuclear genome will be helpful to solve the problems resulting from unsatisfactory SCNT effectiveness and open new possibilities for common application of this technology in transgenic research focused on human biomedicine.

Key words: somatic cell nuclear transfer, cloned embryo, DNA methylation, histone acetylation/methylation, architectural remodeling, epigenetic reprogramming, parental genomic imprinting

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Is the mechanism of donor chromatin/genome-wide epigenetic marking alterations crucial to the dynamic regulation for gene activation and/or gene silencing during somatic cell nuclear remodeling/reprogramming in mammalian cloned embryos?

The basic assumption of somatic cell cloning is the fact that the donor cell nucleus has to be completely reprogrammed by specific oocyte factors in such a way as to support the development of the reconstituted embryo to term. It is now believed that the chief cause of low developmental potential of nuclear-transferred embryos is abnormal adaptation of transplanted somatic nuclei to the biochemical conditions of the oocyte cytoplasmic microenvironment (Dean et al., 2003; Bonk et al., 2007; Whitworth and Prather, 2010; Sepulveda-Rincon et al., 2016). In other words, it is their incomplete and/or defective remodeling/reprogramming in the cytoplasm of enucleated oocyte (ooplast), that gives rise to problems. Moreover, no consistent definition of donor cell nuclear reprogramming has been provided so far. It can be assumed, however, that this process comprises all the changes to which cell nuclei are subjected after introduction into ooplasts, and which lead to structural and functional assimilation of these nuclei to zygote pronuclei (Mann and Bartolomei, 2002; Renard et al., 2002; Yang et al., 2007; Esteves et al., 2011). The remodeling of introduced cell nuclei would then include consequent transformations, occurring within somatic chromatin, of its spatial conformation collectively defined as denomination of constitutional and metabolic rearrangement of nuclear genetic apparatus (Han et al., 2003; Moreira et al., 2003; Reik et al., 2003 a; Shi et al., 2003 a; Wang et al., 2018). As has been mentioned, the somatic cell nuclei that have been remodeled due to artificial activation of reconstructed oocytes (arrested at the metaphase II/MII meiotic division block) not only resemble morphologically but also imitate cytophysiologically interphase nuclei which are formed after oocyte fertilization. That is why, in the somatic cell nuclear transfer (SCNT) embryos at the 1-cell stage they are very often designated as pseudopronuclei or apparent pronuclei as well as spurious pronuclei and presumptive/pretended pronuclei (Kim et al., 2002; Novak et al., 2004; Yamanaka et al., 2009; Lorthongpanich et al., 2010; Liu et al., 2018). But, in spite of undergoing the series of ultrastructural and biochemical changes such as nuclear envelope break-down (NEBD), dispersion of nucleoli, premature chromosome condensation (PCC) before oocyte activation, and also chromosome decondensation, nuclear envelope restoration as well as intensive nucleologenesis and nuclear swelling, after oocyte activation, these pseudopronuclei are not yet fully reprogrammed. They are consequently unable to direct the entire pre- and/or postimplantation development of cloned embryos and foetuses (Shi et al., 2004; Campbell and Alberio, 2003; Cezar et al., 2003; Iurlaro et al., 2017). It therefore follows from this that functional reprogramming of remodeled somatic cell nuclei is not a one-step (a single-phase) biochemical process, but rather a multi-stage one, and it takes place in the blastomere nuclei in cycles of all preimplantation phases of embryogenesis. The epigenetic reprogramming can be defined as any meiotic or mitotic alteration that does not result in a change in DNA nucleotide sequence but will have a significant impact on the ontogenetic development of the organism (Moreira et al., 2003; Wrenzycki and Niemann, 2003; Corry et al., 2009; Zhao et al., 2010). Epigenetic

modifications serve as an extension of the information content by which the underlying genetic code seems to be interpreted. In contrast to genetic information that is recorded in the nucleotide sequence of nuclear and mitochondrial genomes, epigenetic memory is encoded in the structure and functions of covalent modifications of both genomic DNA and histones mainly forming nucleosomal core of nuclear chromatin. These modifications mark genomic regions and act as heritable and stable instructions for the configurational and multifunctional specification of chromatin biochemical organization (Mann et al., 2003; Bortvin et al., 2003; Liu et al., 2004; Eilertsen et al., 2007; Agrawal et al., 2018). So far, the results of many investigations have confirmed that a complete and correct reprogramming process in cloned embryos is affected by epigenetic transformations of the somatic cell-descended genome. These epigenomic changes give rise to alterations in the frequency and extent of expression of multiple embryonic genes as a result of silencing (repression) or enhancing (stimulation) of their transcriptional activity (Kourmouli et al., 2004; Novak et al., 2004; Pfister-Genskow et al., 2005; Anckaert and Fair, 2015). The most important epigenetic rearrangements of donor cell-derived nuclear DNA and chromatin appear to be methylation (or rather hemimethylation) of DNA cytosine residues and post-translational modifications (i.e., deacetylation and methylation) of *N*-terminal lysine residues within histones H3/H4 of nucleosomal core. The latter are crucial processes that are responsible for regulation of DNA transcription by gene silencing pathways throughout development of mammalian nuclear-transferred embryos (Bonk et al., 2008; Deshmukh et al., 2011; Wang et al., 2011; Ma et al., 2015; Jullien et al., 2017).

Recapitulation of dynamic epigenomic changes during somatic cell genome-wide reprogramming, i.e., selective demethylation and subsequent re-methylation states of developmentally-important genes in early nuclear-transferred embryos

In early developmental stages of mammalian cloned embryos, two-step changes in the somatic tissue-specific pattern of donor genomic DNA and constitutive heterochromatin methylation occur, which are related to epigenetic nuclear reprogramming (Renard et al., 2002; Mann and Bartolomei, 2002; Prather et al., 2009; Selokar et al., 2015). After reconstruction (by intraooplasmic karyoplast/whole cell microinjection or nuclear donor cell-ooplast couplet electrofusion) and artificial activation of clonal nuclear-ooplasmic hybrids (clonal cybrids), advanced processes of active (replication-independent) and passive (replication-dependent) demethylation of somatic cell-inherited DNA, which are accompanied by hyperacetylation and hypomethylation of lysine residues within histones H3 and H4, take place. All these processes persist until the nuclear-transferred embryos will have reached the blastocyst stage (Cezar et al., 2003; Kang et al., 2003; Kim et al., 2004; Seki et al., 2005; Masala et al., 2017). This first phase of genome wide reprogramming in preimplantation cloned embryos may be a prerequisite for removing somatic cell-inherited epigenetic information in order to allow embryonic gene expression and restore totipotency of cell nuclei. In turn, this last phenomenon is essential for the formation of pluripotent stem cells that are important for the later development and differentiation of many somatic cell lines in cloned embryos (Kang et al., 2002; Shi et al., 2003 a; Santos and Dean,

2004; Iurlaro et al., 2017). After implantation of reconstituted embryo, DNA hypomethylation status is perpetuated in the cells of extraembryonic tissues derived from trophectoderm (Simonsson and Gurdon, 2004; Dindot et al., 2004; Kim et al., 2004; Liu et al., 2004; Anckaert and Fair, 2015). In the second cycle of donor genome transcriptional reprogramming (during gastrulation), DNA of epiblast-derived somatic cell lines is largely methylated *de novo*, which is also reflected in the enhancement of deacetylation and remethylation within histones H3 and H4 of nucleosomal core (Enright et al., 2003; Liao et al., 2015; Sepulveda-Rincon et al., 2016). After increase of the overall genomic methylation extent, not only selective demethylation of DNA cytosine residues, but also selective hyperacetylation of histone lysine moieties are initiated throughout the processes of commitment and differentiation of various somatic cell lines. All these epigenetic alterations are associated with subsequent onset or cessation of tissue- and organ-specific gene expression or suppression in developing cloned conceptuses (Wrenzycki and Niemann, 2003; Santos et al., 2003; Seki et al., 2005; Pfister-Genskow et al., 2005; Koike et al., 2016; Zhang et al., 2018).

Dependence of monoallelic (paternally- or maternally-inherited) transcriptional activity/suppression of imprinted genes in cloned embryos on the gametic imprinting of somatic cell-derived genome

Preimplantation progressive erasure and postimplantation differential (epigenetically-asymmetric or sex-specific) restoration of methylation imprint memory on the donor genomic DNA parental alleles throughout germ cell lineage commitment/differentiation in somatic cell cloned embryos

A significant molecular mechanism of epigenetic transcriptional reprogramming of donor genomic DNA is also erasure ("zeroing/nulling") and later re-establishment (i.e., recapitulation) of genomic parental (gametic) imprinting (uniparental expression) phenomenon in the postimplantation cloned embryos (Inoue et al., 2002; Lorincz et al., 2002; Dean et al., 2003; Lee et al., 2003; Jullien et al., 2017). Genomic imprinting is an epigenetic system by which alleles of some genes in the mammalian genome are marked in the differentially methylated regions/domains (DMRs/DMDs) to be active or inactive in somatic tissues of the offspring, depending on parental (paternal or maternal) origin (Yamazaki et al., 2003; Ruddock et al., 2004; Lucifero et al., 2002, 2004; Park et al., 2004; Sim et al., 2017). In the first reprogramming cycle that occurs in the preimplantation nuclear-transferred (NT) embryos, progressive reduction of the overall DNA methylation level does not significantly affect the imprinted patterns of epigenetic gene marking system (Obata and Kono, 2002; Fernandez-Gonzales et al., 2004; Paoloni-Giacobino and Chaillet, 2004; Masala et al., 2017). This denotes that genes being subjected to expression from either parental genome preserve their methylation status so well that epigenetically programmed cellular memory of the way in which they have been marked, is kept (Inoue et al., 2002; Mann et al., 2003; Ogawa et al., 2003; Shi et al., 2003 b; Jafarpour et al., 2017). In this stage of embryogenesis, transcriptional apparatus seems to be insensitive to imprinted methylation degree of genes, but generally speaking, we have to do with biallelic (biparental) gene expression (Young et al., 2003; Jouneau and

Renard, 2003; Srivastava et al., 2003; Mann et al., 2004; Dindot et al., 2004). In contrast, in the postimplantation cloned embryos undergoing gastrulation, the second epigenetic reprogramming cycle of donor genomic DNA leads to intensive changes in the level of imprinted methylation patterns in differentiating the germ cell line and somatic cell lines within the epiblast cell lineage. In the primordial germ cells, genome hypomethylation status that has been established during preimplantation phase of embryogenesis is maintained and, additionally, methylation imprinting the genes undergoing uniparental (monoallelic) expression is obliterated (Fournier et al., 2002; Reik et al., 2003 a, b; Han et al., 2003; Iurlaro et al., 2017). "Vanishing" of the sex specific parental imprints in the somatic cell-inherited genome of reconstituted embryos contributes to the gradual removal of epigenetic markers that imprint uniparentally-exprimed (uniparentally-expressed) alleles of many genes of paternal or maternal origin. Therefore, this process brings about the reduction of a number of methylated forms of 5'-cytidine-3'-monophosphate-5'-guanosine-3' (^{Me}CpG) islands/motifs (Dean et al., 2003; Lucifero et al., 2004; Park et al., 2004; Allegrucci et al., 2005; Miki et al., 2005). This process is continued until shift of the specific dynamic homeostasis in epigenetic marking system towards hyperdemethylation (Lorincz et al., 2002; Fournier et al., 2002; Srivastava et al., 2003; Mann et al., 2004; Reik, 2007; Liu et al., 2018). The reversal of original imprinting in either allele, induced by the above-mentioned process, makes chromosomes derived from both parents to become of equal rank. During almost all the gametogenesis gene expression is then biallelic (Lee et al., 2003; Reik et al., 2003 b; Enright et al., 2003; Han et al., 2003; Anckaert and Fair, 2015). But, in the late gametogenesis stages of cloned specimens, chromosomes are epigenetically marked *de novo* according to the previous imprinting pattern suitable for a given sex, and DNA methylation level reaches a high degree in both of sexes (Ruddock et al., 2004; Kang et al., 2003; Jouneau and Renard, 2003; Fernandez-Gonzales et al., 2004; Miki et al., 2005). In contrast to primordial germ cells, in the somatic cell lines of postimplantation NT embryos increase of overall genome methylation level is observed. However, this phase of epigenetic reprogramming does not involve the sequence-specific repeated CpG dinucleotides/islands of donor genomic DNA and non-marked alleles of the genes undergoing expression from one parental genome (Inoue et al., 2002; Ogawa et al., 2003; Mann et al., 2003; Ruddock et al., 2004; Sim et al., 2017). Sex-specific parental imprints of genes modified during total genome methylation will be erased selectively depending on differentiation pathway of somatic cell lines (Park et al., 2004; Mann et al., 2004; Young et al., 2003; Zhang et al., 2014; Prokopuk et al., 2017).

Expression profiles of several imprinted genes (among others insulin-like growth factor-2/*Igf2* gene, Igf2 receptor/*Igf2r* gene, *H19* foetal liver mRNA gene, small nuclear ribonucleoprotein N/*Snrpn* gene) have been analysed in both cloned and *in vitro*-produced (IVP-derived) pre- and postimplanted embryos and foetuses of such mammalian species as mice, cattle and sheep. Imprinting of parental genome is correlated with the methylation marking of normally unmethylated CpG islands in the DMRs of the uniparentally-exprimed alleles of the nuclear DNA genes (Obata and Kono, 2002; Shi et al., 2003 a; Reik et al., 2003 a; Lucifero et al., 2002, 2004; Jafarpour et al., 2017). For that reason, genes expressed exclusively from the maternal

allele (i.e., paternally-methylated) such as *Igf2r* or *H19* should be represented by a higher relative abundance of transcriptional products in parthenogenetic embryos, whereas paternally-expressed genes (i.e., maternally-methylated) such as *Igf2* or *Snrpn* should be correlated with a higher gene expression in IVP-derived and cloned embryos carrying one paternal and one maternal allele (Inoue et al., 2002; Han et al., 2003; Mann et al., 2003; Shi et al., 2003 a, b; Sepulveda-Rincon et al., 2016). Aberrations in the methylation status (i.e., inappropriate epigenetic reprogramming) and faithful expression of imprinted genes, which are developmentally important, are thought to be involved in the Large Offspring Syndrome (LOS) and the Large Placenta Syndrome (LPS; placentomegaly) (Reik et al., 2003 b; Fernandez-Gonzales et al., 2004; Hossain et al., 2014; Zhang et al., 2014; Sim et al., 2017). The LOS and LPS are frequently observed in offspring derived from IVP-derived and cloned embryos that have been exposed to specific culture conditions (the use of foetal bovine serum/FBS-supplemented medium or co-culture system) before their transfer into recipient females (Young et al., 2003; Inoue et al., 2002; Lee et al., 2003; Shi and Wu, 2009). It causes important late foetal losses not only in IVP-derived embryos, but also the considerable decrease of the overall efficiency of somatic cell cloning in mice and ruminants (Chavatte-Palmer et al., 2002; Dean et al., 2003; Anckaert and Fair, 2015; Selokar et al., 2015). In these syndromes, perinatal deaths are associated with abnormal placental development that involves, among others, hydrops/hydroallantois, placental hypertrophy, anomalies in the formation of spongiotrophoblasts and the labyrinthine layers in murine placentas, enlarged edematous placentomes in reduced numbers in bovine and ovine placentas (De Sousa et al., 2001; Young et al., 2003; Masala et al., 2017; Liu et al., 2018). Another typical malformations of the *in vitro* cultured cloned embryos that are related to LOS and LPS are excessive foetal growth and thereby increased birth weight as well as asynchronous growth of organs (Chavatte-Palmer et al., 2002; Fernandez-Gonzales et al., 2004; Iurlaro et al., 2017). There is higher incidence of LOS and LPS in clones generated using somatic cells or embryonic stem (ES) cells as nuclear donors compared with clones generated using non-cultured embryonic cells and in all clones compared with IVP-derived embryos (Ogawa et al., 2003; Inoue et al., 2002; Han et al., 2003; Sim et al., 2017). This raises the question of whether the high incidence of LOS/LPS-related gestation losses after embryonic cell cloning or somatic cell cloning is mainly triggered by either *in vitro* culture conditions or associated reprogramming effects for the imprinting memory of donor genome in NT-derived and IVP-derived embryos. The recent studies show that increasing evidence has pointed towards epigenetic deregulation of imprinted genes due to incomplete or abnormal resetting donor DNA methylation and/or histone acetylation patterns during embryonic and foetal development (Mann et al., 2003; Lee et al., 2003; Enright et al., 2003; Koike et al., 2016). It has been reported that epigenetic alteration of the imprinted (maternally-expressed) *Igf2r* and *H19* DMR segments and thereby abnormal expression (i.e., decreased transcription or suppression) of the corresponding genes have been detected in both ovine LOS/LPS foetuses derived from IVP-derived embryos and murine LOS/LPS foetuses produced by nuclear transfer of somatic or embryonic stem cells. In contrast, the transcription of *P0* that is a placental-specific transcript variant of *Igf2* increased at more than four times in

placenta of cloned mouse foetuses at day 12.5 of gestation as compared to the control conceptuses. Control conceptuses originated from embryos produced by pronuclear transfer in such a manner that karyoplasts containing pronuclei had been isolated from zygotes generated by *in vitro* fertilization (IVF) of MII-stage oocytes and were subsequently transferred into enucleated ova (Ogawa et al., 2003; Inoue et al., 2002; Mann et al., 2003; Young et al., 2003). By contrast, expression of *Igf2* gene was not changed in foetal tissues of clones. Rather than acting/responding to signals that are transmitted by the anchorage of the insulin-like growth factor type-2 ligands (IGF2 agonists) to the IGF2 receptor (IGF2R) proteins located in the extracellular surface of plasma membrane, the IGF2R proteins are believed to immobilize, inactivate, remove and/or biodegrade the IGF2 polypeptides (Chavatte-Palmer et al., 2002; Lee et al., 2003). In these conditions, the peripheral concentration of IGF2 molecules would be expected to be higher and acting to increase growth of cloned foetuses (Shi et al., 2003 a; Reik et al., 2003 b; Sepulveda-Rincon et al., 2016; Zuo et al., 2017).

The impact of donor genome-associated architectural remodeling and epigenetic reprogramming for developmental disorders following somatic cell nuclear transfer

High incidence for positive correlation between spatial configuration defects of somatic chromatin, nuclear DNA and nucleosomal histone epigenetic modification-related errors in the gene expression/repression patterns, and impaired developmental potential of cloned embryos, foetuses as well as neonates

Incorrect and/or incomplete transcriptional reprogramming of methylation as well as acetylation patterns of donor cell genomic DNA and chromatin nucleosome-derived histones, respectively, can lead to morphological failures in preimplantation cloned embryos that develop *in vivo* or *in vitro* to the blastocyst stages with low cytological quality rates and a paucity of structural integrity arising from aberrant allocations of inner cell mass (ICM) and trophectoderm cells (Koo et al., 2002; Mann and Bartolomei, 2002; Santos et al., 2003; Anckaert and Fair, 2015). Moreover, inefficient reprogramming of epigenomic memory can result in early peri/post-implantation gestational deficiencies in nuclear-transferred embryos/foetuses and extrafoetal (placental) tissues (Kang et al., 2002, 2003; Pfister-Genskow et al., 2005; Zhang et al., 2014; Hörmanseder et al., 2017; Sim et al., 2017). Some epigenetic disturbances will be tolerated during embryogenesis and foetogenesis and these will induce lethal or sublethal changes in phenotype that will be exhibited at a later stage of ontogenetic development (De Sousa et al., 2001; Chavatte-Palmer et al., 2002; Liao et al., 2015; Jullien et al., 2017). Therefore, epigenetically-descended developmental retardation and abnormal placentation can cause not only mid- and/or late-gestation foetal losses, placental insufficiency, but also peri- and/or postnatal mortality/morbidity of somatic cell cloned foetuses and resultant offspring (Hill et al., 2002; Cezar et al., 2003; Dindot et al., 2004; Park et al., 2005; Hossain et al., 2014). An important characteristic that distinguishes epigenetic modifications or epimutations from genetic modifications or mutations is their reversibility. Epigenetic marking is normally erased in the germ line. Nonetheless, incomplete “vanishing”/”nulling” of

both donor nuclear DNA methylation/hypermethylation and chromatin deacetylation/hypoacetylation status can adversely bring about epigenetic inheritance (Kang et al., 2003; Reik et al., 2003 a; Yamazaki et al., 2003; Simonsson and Gurdon, 2004; Iurlaro et al., 2017). Another pathway of epigenetic rearrangements to be transmitted to the next generation of cloned specimens takes place when they occur after oocyte reconstruction by somatic cell nuclear transfer (SCNT), but before specification of/commitment to the germ line (Shi et al., 2004; Sarmento et al., 2004; Allegrucci et al., 2005; Seki et al., 2005; Masala et al., 2017).

Pivotal factors affecting and mechanisms underlying epigenetic remodeling and reprogramming of somatic cell nuclei in mammalian cloned embryos – a final and general overview

Impact of mitotic/meiotic cycle phase coordination status between donor cell and recipient ooplast (i.e., compatibility degree of nuclear-cytoplasmic interactions) on the epigenetic complementation of somatic genome methylation/acetylation reprogramming in developing cloned embryos

The dynamic, several-step epigenetic modifications of donor genome after SCNT (i.e., clonal cybrid reconstruction) include, among others, processes of chromatin architectural remodeling (Vignon et al., 2002; Bortvin et al., 2003; Yamanaka et al., 2009; Narbonne et al., 2012), global changes in overall DNA methylation status (Cezar et al., 2003; Bonk et al., 2007, 2008; Deshmukh et al., 2011; Zuo et al., 2017), uniparental (monoallelic) expression of imprinted genes (Mann et al., 2003; Yang et al., 2007; Rodriguez-Osorio et al., 2012; Sim et al., 2017), restoration of telomere length (Cui et al., 2003; Shi et al., 2003 b; Armstrong et al., 2006), and also X chromosome inactivation in female clones (Eggan et al., 2000; Wrenzycki et al., 2002; Jeon et al., 2008). All these events that take place synchronously with donor nuclear cycle progression in the cytoplasmic microenvironment of embryonic cells give rise to global rearrangement of the somatic genetic apparatus at various stages of pre- and postimplantation development (Campbell and Alberio, 2003; Samiec and Skrzyszowska, 2005; Eilertsen et al., 2007; Esteves et al., 2011; Agrawal et al., 2018).

The remodeling and reprogramming of somatic cell-inherited nuclear apparatus is a result of interaction of factors accumulated in the nucleoplasm and attached/anchored to the chromatin (configured in the form of metaphase plate as a consequence of appropriate rearrangement of its spatial structure and nucleosome repression) with protein factors descended from recipient oocyte cytoplasm (Kim et al., 2002; Reik et al., 2003 b; Xie et al., 2016; Wang et al., 2018). This shows that these processes, crucial for somatic cell cloning of mammals, are not a direct effect of conformance of the exogenous genetic material to cytophysiological conditions of metaphase II-stage ooplast (Kourmouli et al., 2004; Novak et al., 2004; Yan et al., 2011; Sepulveda-Rincon et al., 2016). That is why, the nuclei of somatic cells have a tendency towards minimizing the manifestation degree of developmental program of their own after its introduction into foreign cytoplasm of allogenic origin (Renard et al., 2002; Hiendleder et al., 2004; Burgstaller et al., 2007; Yan et al., 2010). In turn, the low contribution of realizing the somatic cell-derived genetic program in the

preimplantation development of reconstituted embryos should be revealed in preservation through exogenous nuclear apparatus of the competence for easy adaptation to the program of pseudomeiotic, and then mitotic control of restriction points of cell cycle, forced upon it by cytoplasmic microenvironments of enucleated oocytes and dividing clonal cybrids (Campbell and Alberio, 2003; Jouneau and Renard, 2003; Bowles et al., 2007; Prokopuk et al., 2017). However, the abilities of transplanted cell nuclei to completely direct the developmental program of reconstructed embryos stem most likely from a correct course of molecular processes accompanying both nuclear chromatin remodeling and reprogramming of somatic cell-descended genome (Hiendleder et al., 2004; Novak et al., 2004; Burgstaller et al., 2007; Liao et al., 2015; Huang et al., 2016). Proper rearrangement of exogenous genetic apparatus induces only the program of active action of donor genomic DNA on the hybrid cytoplasm of reconstituted oocyte and on the mitochondrial DNA (mtDNA) molecules of heteroplasmic origin and from ooplasmic/maternal inheritance (Figure 1) (Samiec, 2005; Hiendleder, 2007; Yan et al., 2010, 2011; Srirattana et al., 2011).

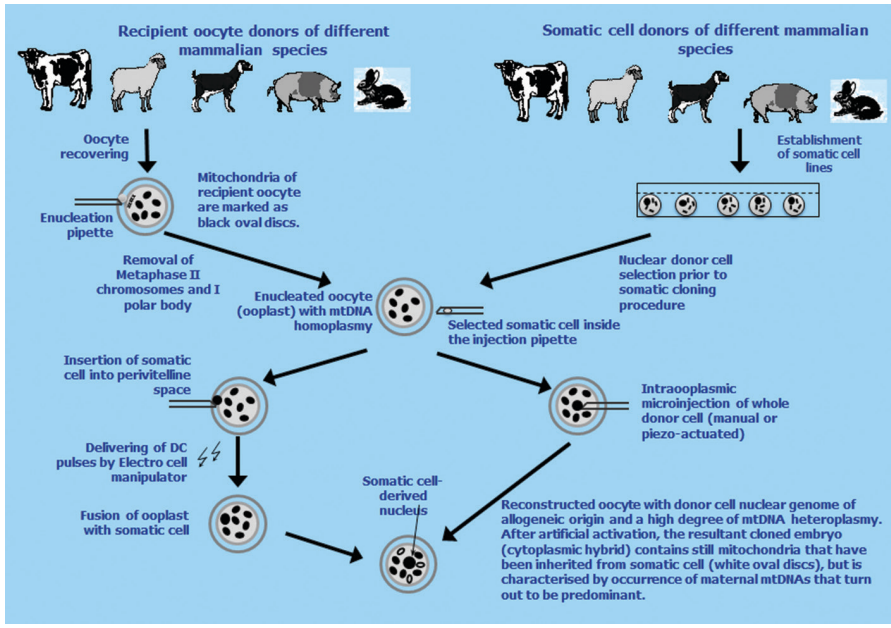

Figure 1. Distribution of donor cell-derived mtDNAs in nuclear-transferred oocytes reconstructed by somatic cell-ooplast couplet electrofusion or whole cell intracytoplasmic microinjection

The expression profiles of different genes of somatic cell nuclear genome that are important for embryonic and foetal development or conceptus survival rate should be studied more closely in the early stages of cloned embryos. So far, however, the precise mechanism for the epigenetic anomalies in the nuclear transfer-derived embryos remains unclear. The characterization of more epigenomic parameters that affect the low developmental competences of the SCNT-derived embryos/foetuses, the

lethal anatomo- and histopathological defects in the foetal and extrafoetal (placental) tissues as well as the high peri-implantation or perinatal mortality rates and immune dysfunctions in resultant abnormal or deceased/stillborn cloned offspring helps the current somatic cell nuclear transfer technology to identify its problems and to address what should be done to resolve them (Yang et al., 2007; Rodriguez-Osorio et al., 2012; Zhang et al., 2018). It is reasonable that preimplantation cloned embryos are one of the most valuable tools for studies focused on the epigenetic remodeling/reprogramming degree of somatic cell nuclei and parentally-dependent expression levels of donor DNA imprinted genes. Therefore, to improve the efficiency of the present animal cloning methods, more extensive investigations should be performed in order to elucidate all the underlying molecular mechanisms and in order to detect/recognize all the intrinsic biochemical factors determining architectural remodeling and transcriptional reprogramming for epigenetic and parental (gametic) imprinting memory of donor cell genome during early embryogenesis (Narbonne et al., 2012; Kungulovski and Jeltsch, 2016; Liu et al., 2018).

Summing up, at the present stage of investigations, biotechnological possibilities of the strategies used for somatic cell cloning of mammals exceeded the understanding of molecular mechanisms underlying epigenetic remodeling and reprogramming of donor cell genome in nuclear transfer-derived oocytes and resultant embryos. Therefore, highlighting the above-mentioned double face of somatic cell cloning, it is beyond any doubt that reprogramming of overall epigenetic memory and specific parental genomic imprinting memory, which are encoded in covalent modifications of somatic cell-inherited DNA, can be found to be one of the most important obstacles for achieving satisfactory effectiveness of SCNT method in different mammalian species. Unfortunately, taking into consideration the current state of the art in this assisted reproductive technology (ART), SCNT efficiency appears to be still characterized by the relatively low rates of the cloned progeny born in relation to the numbers of enucleated oocytes reconstituted with the somatic cell nuclei.

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