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Panning for Long Noncoding RNAs to Improve Somatic Cell Nuclear Transfer Reprogramming Efficiency: Challenges and Opportunities

Yanjun Huan and Hongbin He*

Dairy Cattle Research Center, Shandong Academy of Agricultural Sciences, Jinan, China.

Commentary

Since the cloned sheep "Dolly" was born in 1997, somatic cell nuclear transfer (SCNT) has been achieved in many species, however, to date, the overall cloning efficiency is still low, and this limits the large-scale application in basic research, agriculture and medicine, etc [1-3]. It is generally believed that low cloning efficiency is mainly due to aberrant epigenetic reprogramming [4]. In cloned embryos, DNA methylation, histone modifications and genomic imprinting, etc, are usually disrupted, and these incomplete epigenetic reprogramming causes continuous expression of tissue specific genes, no effective activation of genes related to early embryo development, and aberrant transcription of imprinted genes, etc, thereby leading to poor cloning efficiency [5-7].

Previous studies have displayed that incomplete epigenetic reprogramming in cloned embryos is due to the disrupted expression patterns of genes related to epigenetic modifications [4,8,9]. Recently, long noncoding RNAs (lncRNAs) have been shown to interact with epigenetic modification related enzymes and further regulate epigenetic reprogramming [10]. LncRNAs are non-protein coding transcripts longer than 200 nucleotides, once considered as dark matter, and confirmed to take part in diverse epigenetic regulatory progresses, including DNA methylation, histone modifications, genomic imprinting, etc [11-13].

It is known that DNA methylation reprogramming is regulated by DNA methylation and demethylation related enzymes, thus, lncRNAs-guided DNA methylation reprogramming includes the interplay between lncRNAs and these enzymes [10,12,14]. For gene activation, promoter-associated noncoding RNAs (pancRNAs) are typical lncRNAs during the progress of lncRNAs-mediated DNA demethylation, and pancRNAs can recruit DNA demethylation related enzymes, such as ten eleven translocation enzymes (Tets), to regulate DNA demethylation [15,16]. Similarly, Dnmt1-interacting RNAs and TARID also inhibit DNA methyltransferases (Dnmts) to block DNA methylation, or recruit DNA demethylation related enzymes to carry out DNA demethylation, thereby promoting gene expression [17,18]. When gene silence, lncRNAs, Dum as an example, interact with Dnmts to establish and maintain DNA methylation [19], and, increased levels of lncRNAs, such as HOTAIR and POU3F3, also promote DNA methylation [20,21]. During the progress of lncRNAs-guided histone modifications, HOTTIP has been shown to recruit Trithorax group (TrxG) proteins, and promote H3K4me3 and gene expression [22], while HOTAIR silences the Hoxc locus through the recruitment of Polycomb group (PcG) proteins and H3K9me3 and H3K27me3 catalyses. Also, other lncRNAs, such as Air and Kcnq1ot1, can recruit epigenetic silencing complexes to inhibit gene expression [23,24]. Thus, lncRNAs mediate histone modifications through TrxG and PcG proteins and regulate gene expression. Overall, the emerging links between lncRNAs and epigenetic modifications confirm that lncRNAs are key epigenetic regulators [10,13,25].

During cellular reprogramming, genome-wide epigenetic dynamics are necessary, and lncRNAs exert critical functions in reprogramming cell fate [26-28]. In induced pluripotent stem cells, lncRNAs have been shown to promote or inhibit somatic cell reprogramming [29,30]. In cloned embryos, H19 and Xist, the best studied lncRNAs, are also known to participate in embryo development, and their disrupted expression patterns result in low cloning efficiency [31,32]. However, due to the limited number of SCNT embryos resulting from the complicated production and poor developmental competence, only a small number of lncRNAs have been identified. In view of the critical role of lncRNAs in the development of cloned embryos, methods for detection at the single-embryo level or at the level of a small number of embryos are needed to identify and characterize lncRNAs required for cellular reprogramming. Currently, available technologies to reveal the functions of lncRNAs in scarce materials, such as early embryos, are coming, and more surprises are to emerge [15,28]. Overall, lncRNAs are a "rich ore" to be mined, and panning for these "treasures" would enhance the developmental competence of cloned embryos.

In conclusion, disrupted epigenetic modifications cause low cloning efficiency, and lncRNAs can regulate epigenetic reprogramming, thus, to reveal the functions of lncRNAs in nuclear reprogramming induced by SCNT will broaden our knowledge of the mechanism underlying cellular reprogramming, and further improve cloning efficiency.

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***Corresponding author:** Hongbin He, Dairy Cattle Research Center, Shandong Academy of Agricultural Sciences, No.159 Industrial North Road, Jinan, Shandong Province, 250100, China, Tel: +86 531 88679268; Fax: +86 531 88679268; E-mail: hongbinh@hotmail.com

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