The Editorial

Molecular Interactions of lncRNAs: Cellular Fate Determination and Tissue Regeneration

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Summary

LncRNAs (long non-coding RNAs), defined as non-coding RNAs with length ≥200 nt, are responsible to control the degradation process, RNA stability, orchestration, inhibition, transcription and histone modification etc. These RNAs have been termed as the key agents of several vital mechanisms such as development, organogenesis and regeneration of damaged tissues etc. They interact with a number of partner molecules either proteins, RNAs or DNAs. They also control the cellular behaviour of stem cells such as differentiation or self-renewal or their paracrine effects. This editorial is discussing the significance of lncRNAs as therapeutic target in stem cell therapy field.

***Keywords*:** LncRNAs, Regeneration, Molecular interactions, Stem cell fate, Differentiation

LncRNAs (long non-coding RNAs) are defined as the transcripts of greater than 200 nucleotides that lack ORF (open reading frames) and perform a lot of important functions other than coding proteins. RNA polymerase II transcribe them and then they spliced and polyadenalated (Rinn and Chang, 2012). It has been discovered that they are involved in the generation of variety of other nucleic acids such as miRNAs, other-ncRNAs etc (Ogawa et al., 2008; Rogler et al., 2014). LncRNAs have been found to be involved in many known process with interaction of other molecules such as, they are involved in (1) the degradation process when interact with miR-9 (Leucci et al., 2013), (2) enhanced BACE mRNA stability while interacting with miR-485-5p (Faghihi et al., 2010), (3) participates in the orchestration of an intrachromosal loop while interacting with RUNX1 promoter and enhancers (Wang et al., 2014), (4) tether with DNA to recruit inhibitor proteins (Wang et al., 2008), (5) dissociate the preinitiation complex when bind with DHFR promoter (Ponting et al., 2009), (6) form histone modification complex by bridging with PRC2 and the lysine demethylase LSD1 (Tsai et al., 2010), (7) activate the *Dlx5/6* enhancer when cooperate with *Dlx2* homeodomain protein (Feng et al., 2006) and etc.

It has been confirmed that lncRNAs control some vital functions in the development, organogenesis and regeneration of damaged tissues. Their role has been identified in the differentiation and terminal differentiation of somatic stem cells to improve wound healing in traumatic injuries (Beasley et al., 2015; Kretz et al., 2013). It has been discovered that these lncRNAs are involved in the maintenance of stem cells state and to determine the stem cell fate, which lineage it has to adopt and either it has to differentiate or terminally differentiate. As we have discussed here they have very strong molecular interactions with almost all kind of RNAs, DNAs and proteins to play their vital role in cellular behaviour. Every lncRNA has its own specific molecular partners where they interact each other and control the cell fate. A number of cellular mechanisms controlled by lncRNAs in coordination with their partner molecules have been shown in table 1.

Table 1. LncRNAs and their interacted partner molecules to control cellular fate (Flynn and Chang, 2014).

Sr. No.	LncRNA	Partner Molecules	Targeting Cells
1	TUNA/megamind	PTBP1, NCL, hnRNP-K	Neuronal Cells
2	Dix1as	?	Neurons
3	Six3os1	?	Oligodendrocytes
4	TINCR	STAU1	Differentiated Keratinocytes
5	ANCR	?	Skin Stem Cells
6	Braveheart	PRC2	Cardiocytes
7	Fendrr	PRC2 or MLL	Cardiac and Lung Cells
8	Yam1	YY1	Muscle Stem Cells
9	Linc-MD1/miR133	AGO and HuR	Muscle Tisses

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Considering the molecular interactions of lncRNAs and their role in stem cell fate determination and to regulate tissue regeneration, it can be concluded that lncRNAs have been named as the centrally controlling molecules for tissue regeneration. Full and detailed networking maps of these lncRNAs should be discovered so that these RNAs can be used as targeted therapeutic agents in clinics.

References:

1. Beasley S. M., Plikus M. V., Spitale R. C. and Pedersen I. M. (2015) The emerging functions of regulatory RNA species in skin biology. Experimental Dermatology 24:827-828.
2. Faghihi M. A., Zhang M., Huang J., Modarresi F., Van der Brug M. P., Nalls M. A., Cookson M. R., St-Laurent G. and Wahlestedt C. (2010) Evidence for natural antisense transcript-mediated inhibition of microRNA function. Genome Biology 11:R56.
3. Feng J., Bi C., Clark B. S., Mady R., Shah P. and Kohtz J. D. (2006) The Evf-2 noncoding RNA is transcribed from the Dlx-5/6 ultraconserved region and functions as a Dlx-2 transcriptional coactivator. Genes and Development 20:1470-1484.
4. Flynn R. A. and Chang H. Y. (2014) Long noncoding RNAs in cell-fate programming and reprogramming. Cell Stem Cell 14:752-761.
5. Kretz M., Siprashvili Z., Chu C., Webster D. E., Zehnder A., Qu K., Lee C. S., Flockhart R. J., Groff A. F. and Chow J. (2013) Control of somatic tissue differentiation by the long non-coding RNA TINCR. Nature 493:231-235.
6. Leucci E., Patella F., Waage J., Holmstrøm K., Lindow M., Porse B., Kauppinen S. and Lund A. H. (2013) microRNA-9 targets the long non-coding RNA MALAT1 for degradation in the nucleus. Scientific Reports 3.
7. 7- Ogawa Y., Sun B. K. and Lee J. T. (2008) Intersection of the RNA interference and X-inactivation pathways. Science 320:1336-1341.
8. Ponting C. P., Oliver P. L. and Reik W. (2009) Evolution and functions of long noncoding RNAs. Cell 136:629-641.
9. Rinn J. L. and Chang H. Y. (2012) Genome regulation by long noncoding RNAs. Annual review of biochemistry 81.
10. Rogler L. E., Kosmyna B., Moskowitz D., Bebawee R., Rahimzadeh J., Kutchko K., Laederach A., Notarangelo L. D., Giliani S. and Bouhassira E. (2014) Small RNAs derived from lncRNA RNase MRP have gene-silencing activity relevant to human cartilage–hair hypoplasia. Human Molecular Genetics 23:368-382.
11. Tsai M.-C., Manor O., Wan Y., Mosammaparast N., Wang J. K., Lan F., Shi Y., Segal E. and Chang H. Y. (2010) Long noncoding RNA as modular scaffold of histone modification complexes. Science 329:689-693.
12. Wang H., Li W., Guo R., Sun J., Cui J., Wang G., Hoffman A. R. and Hu J. F. (2014) An intragenic long noncoding RNA interacts epigenetically with the RUNX1 promoter and enhancer chromatin DNA in hematopoietic malignancies. International Journal of Cancer 135:2783-2794.
13. Wang X., Arai S., Song X., Reichart D., Du K., Pascual G., Tempst P., Rosenfeld M. G., Glass C. K. and Kurokawa R. (2008) Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature 454:126-130.

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