Super-enhancer LncRNA Microarrays

- The master gene regulators unmasked

Highlights

- Powerful SE-lncRNA collection to simultaneously profile all SE-lncRNAs, target genes, transcription factors and oncogenes.
- Detailed annotations of SE-lncRNAs, super-enhancers, and targets.
- Unambiguous and reliable SE-lncRNA isoform detection.
- Best solution for sensitive detection of labile SE-lncRNAs, powered by efficient labeling.

Introduction

Super enhancers are the transcription regulatory regions consist of constituent enhancers often clustered within 12.5 kb distance [1]. Super-enhancers produce long-noncoding RNAs (SE-lncRNAs) which are the hallmark of their activity. SE-lncRNAs, together with super-enhancers, activate the gene expression by multiple mechanisms. SE-lncRNAs are increasingly found to *trans*-activate target genes beyond *cis*-activation by typical enhancers [2](Fig. 1). SE-lncRNAs play master regulator roles in diverse gene expression programs that ultimately determine the cell types, cell identities, and diseases. SE-lncRNAs are also disease regulators and intimately involved in cancers.

Expression profiling of SE-lncRNAs provides a comprehensive view of the differential expressed SE-lncRNAs and what super-enhancers have turned active. Due to the very high tissue/cell/disease specificity restricted in only a few cell types, SE-lncRNAs can be an excellent class of biomarkers.

Powerful SE-lncRNA collection

Arraystar Super-Enhancer LncRNA microarrays are the first commercially available solution for sensitive and accurate SE-lncRNA profiling (Fig. 2). The SE-lncRNAs are compiled on the foundation of Arraystar Gold standard & Reliable lncRNA collections and authoritative super-enhancer databases. "Super lncRNAs", a special class of SE-lncRNAs forming RNA:DNA:DNA triplex with the super-enhancers, are also included [3].

To experimentally observe, analyze, and correlate with the super-enhancer associated target gene expression, the nearest protein coding genes are simultaneously profiled on the same array. As super-enhancers are intimately related with transcription factors and oncogenes, all known transcription factors and oncogenes are collected, regardless in *cis* or *trans* with the super-enhancers.

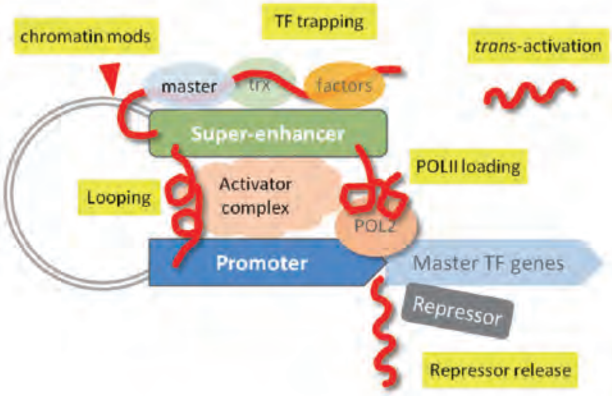


Fig. 1. Super-enhancer lncRNA activates the target gene promoter by multiple mechanisms.

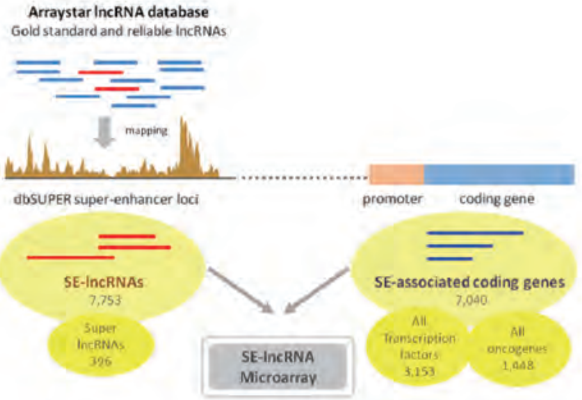


Fig. 2. Arraystar Human Super-enhancer LncRNA microarray features rich content and analysis of SE-lncRNAs, super lncRNAs, associated target genes, all transcription factors and oncogenes.

Detailed annotation and rich analyses

- **Nearby target genes:** To quickly locate nearby coding mRNA genes overlapping with or within 50-kb distance of the SE-lncRNAs as the potential *cis*-targets of the SE-lncRNAs.
- **"Super-lncRNAs":** A special class of SE-lncRNAs that form RNA:DNA:DNA triplex with the super-enhancers [3], which warrant special research on their mechanisms on super-enhancers.
- **Subcellular localization:** An important clue in knowing the functional sites and mechanisms of the SE-lncRNAs, which are tightly coupled with the subcellular localization.
- **Tissue and cell type specificity:** The key links to the high degrees of tissue or temporal specificity exhibited by super-enhancer activities.
- **Cancer and disease SE-lncRNAs:** Association with clinical or translational medicine sourcing databases such as Lnc2Cancer database and lncRNADisease.

Best and sensitive solution for labile SE-lncRNAs

Enhancer RNAs typically have short half-lives, high turnover rates and low abundance, which pose technical challenges if profiled by RNA-seq. Generic RNA-seq is simply not up for the task. Special techniques, such as GRO-seq are required. However, global run-on labeling of nascent transcripts in *vitro* cell culture is not feasible for tissues or clinical samples.

To sensitively detect and accurately quantify the transient, low level SE-lncRNAs, Arraystar has developed an efficient and robust linear amplification method to generate fluorescent cRNA for use with the microarrays, with a sensitivity > 100-fold higher than conventional methods.

SE-lncRNA Roadmap

As a roadmap to research forward, the differentially expressed SE-lncRNAs can be used to easily indicate the active state of the super-enhancers, study the gain or loss of functions, investigate the mechanisms of action, and explore biomarker applications. The super-enhancer lncRNAs, emerged from hidden just recently, are now a scientific gold mine in the research of any fields of biology and disease (Fig. 4).

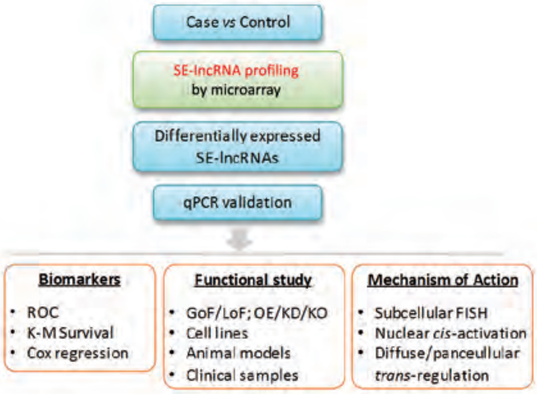
References

[1] Whyte W.A. et al. (2013) Cell [PMID: 23582322]
[2] Alvarez-Dominguez J.R. et al. (2017) Cell Rep [PMID: 28636939]
[3] Soibam B. (2017) RNA [PMID: 28839111]

SE-lncRNA				
TransID	**Subcellular**	**Tier**	**Tissue specificity**	**Cancer**
ENST00000549804	Nucleus		2:pituitary_gland[6.29]	
ENST00000487240			25:nervous_system[275.20]	breast
NR_126491		Gold	7:cardiac_chamber[49.69]	
ENST00000430027	Nucleus		19:nervous_system[196.11]	lung
ENST00000502463	Nucleus		1:mammary_gland_epithelial_cell[5.30]	colon
uc022bbo.1	Cytosol			
uc003ysb.3		Reliable		

SE-lncRNA		Super-Enhancer	Target Gene	
Disease	**Super-LncRNA**	**Genomic**	**Overlapped**	**Proximal**
Angelman syndrome	yes			SNRPN
Alzheimer's disease	yes		DNAJC19	
acute myocardial infarction		chr14:23867308:23891809	MYH7	
split hand/split foot malformation		chr7:96630715:96657145	DLX6	
		chr8:128743538:128752334		MYC
AIDS		chr8:132815762:132873739		EFR3A
		chr8:128180346:128229384		POU5F1B

Fig. 3. A snapshot of comprehensive SE-lncRNA annotations.


Case *vs* Control
SE-lncRNA profiling by microarray
Differentially expressed SE-lncRNAs
qPCR validation

Biomarkers
- ROC
- K-M Survival
- Cox regression

Functional study
- GoF/LoF; OE/KD/KO
- Cell lines
- Animal models
- Clinical samples

Mechanism of Action
- Subcellular FISH
- Nuclear *cis*-activation
- Diffuse/panceullular *trans*-regulation

Fig. 4. Roadmap of super-enhancer lncRNA Research.

Specifications	Human	Mouse
Total Number of Probes	14,873	14,637
SE-lncRNA probes -Arraystar Gold and Reliable lncRNA collections -Mapped to dbSUPER super-enhancer catalog	7,753	8,222
target gene probes -Tfcheckpoint Transcription factors -Cancer genes (allOnco,SBCSSB)	7,040	6,385
Array format	8 ×15K	8 × 15K

Fig. 5. Specifications of Arraystar Super-enhancer LncRNA Microarrays.

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