

## 審査の結果の要旨

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Pluripotent cells such as ES and iPS cells offered powerful potential for therapeutic purposes such as tissue engineering, drug screening, and disease modeling. Considering the importance of understanding the pluripotent cells at the molecular level, Ms. Razak focused on profiling miRNA expression pattern in various types of pluripotent and non-pluripotent cells, encompassing both human and mouse cells. MicroRNA profiling had been done by using qRT-based microRNA array, and the findings are listed as follows:

1. Ms. Razak carefully refined the protocol to prepare iPS and ES cells to serve miRNA array. It was revealed that the contaminated cDNA from feeder cells reduced sensitivity and stability of detection and affected the miRNA expression profile. The importance of cell sorting to purify iPS cells that were cultured on MEF feeder cells was found, and a protocol was established.
2. The miRNA expression profile of various pluripotent and non-pluripotent cells were analyzed by several analytical methods. The hierarchical clustering (HC) and non-negative matrix factorization (NMF) analyses revealed clear separation of two major clusters, ES/iPS cells and other cell group in both human and mouse.
3. Principal components analysis (PCA) identified miR-187, 299-3p, 499-5p, 628-5p, and 888 as new miRNAs that specifically characterized human ES/iPS cells. In mouse, several new miRNAs were also suggested to define ES/iPS cells.
4. By using these HC, NMF and PCA, new miRNAs to distinguish pluripotent and non-pluripotent cells were identified.
5. Detailed direct comparisons of miRNA expression levels identified several miRNAs including chromosome 19 miRNA cluster that were more strongly expressed in iPS cells than in ES cells. Several miRNAs were also found to be ES/iPS cell-specific, suggesting that miRNAs are differentially expressed in pluripotent cells and can be used as a signature to define cells type.

6. By analyzing miRNA in human and mouse pluripotent cells, it was revealed that ES/iPS specific miRNAs are abundantly expressed in pluripotent cells and specific to the species, suggesting that pluripotent cells expressed a high level of miRNAs that control important pathways specific to the species.

7. Time course tracing of miRNA levels during embryoid body formation revealed drastic and different patterns of changes in the miRNA expression levels. The result showed that miRNAs are an important molecule to regulate iPS cells self-renewal and differentiation.

With crucial thought placed on the experimental procedure, this paper managed to identify new miRNAs to define pluripotency in human and mouse, and can be utilized for regulation of cells reprogramming, maintenance of self-renewal and cells differentiation. The miRNA profiling also revealed the expression pattern of miRNAs covering both human and mouse providing insight to miRNA expression network that exist between those two species. The findings are important to provide a better understanding of miRNAs regulation particularly in the pluripotent cells. Therefore, it is considered worthy of award of degree.