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Long non-coding RNAs, "the dark matter of the genome", as powerful regulators of cellular fate and reprogramming

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Recent global analyses of the transcriptional output of the genome of higher eukaryotes points to the existence of a very large number of previously unknown long non-coding transcripts. While intense research has demonstrated their involvement in a diverse range of cellular functions, whether they can act as dominant determinants or "master regulators" of cellular function has remained uncertain. To address this pivotal question, we have analyzed the function of highly tissue-specific long non-coding RNAs which are almost exclusively expressed in neurons in both mouse and human, focusing on a promising example of this group of transcripts. The RNA is strongly upregulated during the differentiation of pluripotent cells into neurons and blocking this upregulation prevented neuronal differentiation in several model systems. On the other hand, its forced overexpression led to enhanced neuronal differentiation. Interestingly, forced overexpression of the RNA in non-neuronal cells of myoblastic and fibroblastic origin led to reprogramming of both cell types into neurons, indicating that the RNA is a master regulator of neuronal differentiation, able to induce neuronal transdifferentiation in mesodermal cells as a single gene. The efficiency of neuronal reprogramming for myoblasts and fibroblasts was 65% and 35%, respectively, significantly higher than what has been previously observed with the use of a cocktail of 3-5 protein factors. Taken together, these findings indicate that long non-coding RNAs can indeed play critical roles as master regulatory switches in differentiation and cell fate specification and provide the first instance of cellular reprogramming mediated by a long non-protein-coding RNA.

Biography

Saba Valadkhan has completed her M.D. at the age of 23 from Iran University of Medical Sciences and her Ph.D. at the age of 29 from Columbia University under the supervision of Dr. James Manley. After completion of her Ph.D. she joined Case Western Reserve University School of Medicine as a faculty member in 2004. She has received several national and international awards including the Young Scientist Award from the AAAS and GE Healthcare and the Harold Weintraub award and has been named a Searle Scholar. She was a founding member of the Rosalind Franklin Society in 2006.

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