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Breakthroughs and Views

Low-level illegitimate transcription of genes may be to silence the genes

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Abstract

In yeast and plants, low level transcription of a gene is recently revealed to be required to repress the gene. It may account for the widely low level illegitimate transcriptions of tissue-specific genes reported in mammalian cells. This hypothetical link gives insight into both analysis of transcription-associated evolutionary events and further interpretation of the mechanism of small RNA-mediated transcriptional repression.

Keywords: Illegitimate transcription; Ectopic expression; Low-level expression; RNA-induced transcriptional silencing; Germline; Processed pseudogene

In multicellular organisms, housekeeping genes are expressed in all cells because they provide basic functions needed for sustenance of all cell types. By contrast, tissue-specific genes code for specialized functions, thus were expected to be transcribed only in particular cell types. However, low levels of tissue-specific mRNAs are detected in many, or even in all cell types [1–3]. Analysis of human transcriptomes reveals that the majority of transcripts are present at levels as low as one copy per cell [4]. Gene transcriptions are coupled with strand asymmetric DNA repair and damages [5,6], thus producing strand compositional asymmetry [7] if occurred in germline. Genome-wide analysis of strand asymmetry implies that 71–91% of all human genes may be transcribed in germline cells [8]. Apparently, sustenance of germline cells does not require so many genes.

There are several hypotheses for the low-level expression of apparently unnecessary genes.

The most common one is leaky or stochastic gene expression [2,3,9,10]. Gene repression mechanisms were not viewed to be powerful enough to exhaustively repress the unnecessary genes. This idea is inconsistent with a hypothesis that cell specialization may be advantageous by protecting genes from transcription-associated damages [11]. If the latter idea were correct, there should be selective force for efficient repression of unnecessary genes. Unfortunately, it has not yet obtained experimental supports, so it should not be overrated.

As the understanding of biological systems is progressing, the apparently unnecessary gene expressions may be demonstrated to be functional in the future. The second hypothesis is that the low-level expressions have some undiscovered functions [12]. Low basal level gene expression is functional in bacterial lactose operon in the absence of any specific activation [13]. In addition, low-level transcription and the subsequent degradation of the transcripts make up of a substrate cycle. Other substrate cycles, such as the phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate and its hydrolysis back to fructose 6-phosphate, are now generally accepted to have biological significance [14].

In various organisms, small RNAs can induce DNA methylation and/or heterochromatin (i.e., transcriptional silencing) at the homologous genomic locus [15]. Recent studies in yeast and plants revealed that low-level transcription of a gene is required for initiating (and maybe maintaining) the silenced state of the gene by short interfering

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RNAs ([16,17] and references therein, [18]). After cell specialization, most genes are not required for particular cell. That is, most genes may be repressed involving low-level transcription of themselves. This is a good explanation for the low-level expression of unnecessary genes [1–4,8].

A hypothetical link between illegitimate (or ectopic) transcription and RNA-mediated transcriptional silencing is suggestive to both evolutionary biologists and molecular biologists.

Studies on transcription-associated evolutionary events should give full consideration for low-level illegitimate transcription. The separation between germline expressed genes and genes expressed only in soma becomes meaningless, thus it should be replaced by distinguishing between high-level and low-level expressed genes in germline. Thus, the expected differences between germline expressed genes and soma-tissue-specific genes in both abundance of corresponding processed pseudogenes [19] and frequency of mRNA-mediated intron loss [20] change from present/not to high/low. More abundance of processed pseudogenes from embryonic stem cell-specific genes than somatic tissue-specific genes [21] should be explained by high-level expression in germline cells, rather than presence of embryonic stem cell-specific transcripts in germline cells. Germline-specific transcription factors, if not expressed at high level, are not necessarily more accessible to retrotransposition process than the pancreas- or skeletal muscle-specific genes. GDF3 [21] may be such a case.

Illegitimate transcriptions in mammalian cells use the normal promoters [22] and enable protein synthesis [1]. These implicate that the RNA-mediated transcriptional silencing in mammalian cells may use typical gene expression apparatus, like the fission yeast [18,23]. An unsolved problem in yeast is whether low-level transcription can maintain repression [16]. Initiation of gene repression is unlikely to occur cell by cell. But initiation and maintenance of gene repression together seem to occur cell by cell. "Transcription of any gene in any cell type" [2] indicates that low level transcription of a gene may also involve in maintenance of its silenced state.

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References

[1] G. Sarkar, S.S. Sommer, Access to a messenger RNA sequence or its protein product is not limited by tissue or species specificity, Science 244 (1989) 331–334.

[2] J. Chelly, J.P. Concordet, J.C. Kaplan, A. Kahn, Illegitimate transcription: transcription of any gene in any cell type, Proc. Natl. Acad. Sci. USA 86 (1989) 2617–2621.

[3] Y. Kimoto, A single human cell expresses all messenger ribonucleic acids: the arrow of time in a cell, Mol. Gen. Genet. 258 (1998) 233–239.

[4] V.E. Velculescu, S.L. Madden, L. Zhang, A.E. Lash, J. Yu, C. Rago, A. Lal, C.J. Wang, G.A. Beaudry, K.M. Ciriello, B.P. Cook, M.R. Dufault, A.T. Ferguson, Y.H. Gao, T.C. He, H. Hermeking, S.K. Hiraldo, P.M. Hwang, M.A. Lopez, H.F. Luderer, B. Mathews, J.M. Petroziello, K. Polyak, L. Zawel, W. Zhang, X.M. Zhang, W. Zhou, F.G. Haluska, J. Jen, S. Sukumar, G.M. Landes, G.J. Riggins, B. Vogelstein, K.W. Kinzler, Analysis of human transcriptomes, Nat. Genet. 23 (1999) 387–388.

[5] J.Q. Svejstrup, Mechanisms of transcription-coupled DNA repair, Nat. Rev. Mol. Cell. Biol. 3 (2002) 21–29.

[6] M.J. Lippert, J.A. Freedman, M.A. Barber, S. Jinks-Robertson, Identification of a distinctive mutation spectrum associated with high levels of transcription in yeast, Mol. Cell. Biol. 24 (2004) 4801–4809.

[7] A.C. Frank, J.R. Lobry, Asymmetric substitution patterns: a review of possible underlying mutational or selective mechanisms, Gene 238 (1999) 65–77.

[8] J. Majewski, Dependence of mutational asymmetry on gene-expression levels in the human genome, Am. J. Hum. Genet. 73 (2003) 688–692.

[9] S.S. Sommer, G. Sarkar, Response to Are tissues a patch quilt of ectopic gene expression? Science 246 (1989) 261.

[10] C. Finta, P.G. Zaphiropoulos, A statistical view of genome transcription? J. Mol. Evol. 53 (2001) 160–162.

[11] D.K. Niu, J.K. Chen, Evolutionary advantages of cell specialization: save and protect DNA, J. Theor. Biol. 187 (1997) 39–43.

[12] S. Lee, J. Bao, G. Zhou, J. Shapiro, J. Xu, R.Z. Shi, X. Lu, T. Clark, D. Johnson, Y.C. Kim, C. Wing, C. Tseng, M.I.N. Sun, W.E.I. Lin, J.U.N. Wang, H. Yang, J. Wang, W.E.I. Du, C.-I. Wu, X. Zhang, S.M. Wang, Detecting novel low-abundant transcripts in *Drosophila*, RNA 11 (2005) 939–946.

[13] B. Lewin, Gene, eighth ed., Pearson Prentice Hall, Upper Saddle River, NJ, 2004.

[14] J.M. Berg, J.L. Tymoczko, L. Stryer, N.D. Clarke, Biochemistry, fifth ed., WH Freeman and Company, New York, 2002.

[15] M.A. Matzke, J.A. Birchler, RNAi-mediated pathways in the nucleus, Nat. Rev. Genet. 6 (2005) 24–35.

[16] S. Buratowski, D. Moazed, Gene regulation: expression and silencing coupled, Nature 435 (2005) 1174–1175.

[17] M.W. Vaughn, R.A. Martienssen, Finding the right template: RNA pol IV, a plant-specific RNA polymerase, Mol. Cell 17 (2005) 754–756.

[18] V. Schramke, D.M. Sheedy, A.M. Denli, C. Bonila, K. Ekwall, G.J. Hannon, R.C. Allshire, RNA-interference-directed chromatin modification coupled to RNA polymerase II transcription, Nature 435 (2005) 1275–1279.

[19] I. Goncalves, L. Duret, D. Mouchiroud, Nature and structure of human genes that generate retropseudogenes, Genome Res. 10 (2000) 672–678.

[20] D.-K. Niu, W.-R. Hou, S.-W. Li, mRNA-mediated intron losses: evidence from extraordinarily large exons, Mol. Biol. Evol. 22 (2005) 1475–1481.

[21] D. Pain, G.-W. Chirn, C. Strassel, D.M. Kemp, Multiple retropseudogenes from pluripotent cell-specific gene expression indicates a potential signature for novel gene identification, J. Biol. Chem. 280 (2005) 6265–6268.

[22] J. Chelly, J.P. Hugnot, J.P. Concordet, J.C. Kaplan, A. Kahn, Illegitimate (or ectopic) transcription proceeds through the usual promoters, Biochem. Biophys. Res. Commun. 178 (1991) 553–557.

[23] H. Kato, D.B. Goto, R.A. Martienssen, T. Urano, K. Furukawa, Y. Murakami, RNA polymerase II is required for RNAi-dependent heterochromatin assembly, Science 309 (2005) 467–469.