Analysis of metabolic networks controlled by microRNAs in zebrafish

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Abstract

MicroRNAs regulate gene expression at posttranscriptional level. The potential target of a miRNA can be computationally individuated, through a comparison of sequences. Here are presented the preliminary data obtained from a bioinformatic retrieval of the miRNAs involved in the regulation of the arginine metabolism in zebrafish, through the web resource MicroCosm Target (EBI). The potential "key miRNAs" individuated (miR-194b, miR-738 and miR-132*) in this pathway should be considered for an experimental validation.

Introduction

MicroRNAs (miRNAs) are small non-coding RNAs involved in posttranscriptional regulation. The 2-7 nucleotides of a miRNA sequence (the "seed") is complementary to a site located in the 3'UTR of the target mRNA, avoiding its translation [1]. A single miRNA can potentially inhibit several hundred targets, and many mRNAs are targeted by more than one miRNA. The reliable identification of targets is a major problem related to the study of miRNAs [2]. The application of sequence mining methods can be useful in determining the potential target of miRNAs, providing a basis to the experimental validation. In this paper, we use a computational protocol in order to determine, in zebrafish, the miRNAs that are likely to regulate the expression of proteins involved in the arginine metabolism and the nitric oxide (NO) synthesis [3].

Materials and Methods

Enzymes and transport molecules of interest have been identified from the literature and using as a reference the pathway dre00330 of the Kyoto Encyclopedia of Genes and Genomes (http://www.genome.jp/kegg/) [4]; using the web resource MicroCosmTarget (http://www.ebi.ac.uk/enright/software.html) [5], the selected mRNAs were analyzed as potential targets of miRNAs.The results were analyzed in order to highlight the recurring miRNAs (and seeds), as they are likely to be "key mRNAs" for the regulation of the arginine metabolism and the NO synthesis.

Results

The pathway related to the NO production, in a synthetic representation (de novo the synthesis of arginine is typical of non-nervous cells, while the NOS-1, CAT-4 transporter to the cationic amino acids and glutamate NMDA receptor

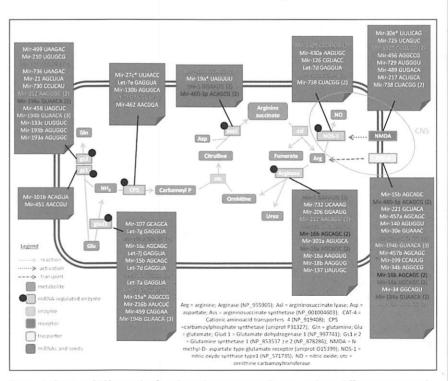


Figure 1. Some miRNAs can be found regulating potentially two or three different target in this pathway

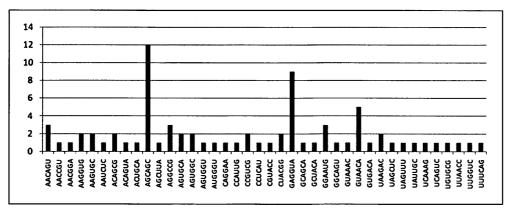


Figure 2. The seeds AGCAGC and GAGGUA are very represented in the miRNAs potentially regulating the selected pathway.

Some cues indicate also a relationship between a pathway and some seed sequences, and this would deserve further investigation. The use of integrated computational protocols allow for planning an experimental validation on a limited number of target reducing time and costs of pilot validation.

are typically neuronal), and the predicted involved miRNAs are shown in Fig. 1. The abundance of each seed sequence represented in the miRNAs highlighted from our research are shown in Fig. 2.

Discussion

All the predicted miRNA-mRNA interactions need an experimental validation, and the zebrafish model can be use for some experimental approach [6]. Among the miRNAs we identified the miR-194b, that could act on GLUD1, GS2 and CAT-4; two different miRNAs (miR-738 and miR-132*) could regulate both NOS-1 and the glutamate NMDA receptor, two molecules that are functionally linked [7]. In this perspective, single miRNA reveals potentially able to mediate more points of the same metabolic pathway.

References

- [1] Jidong L. 2008. Control of protein synthesis and mRNA degradation by microRNAs. Curr. Opin. Cell Biol., 20:214–221.
- [2] Brennecker J., Stark A., Russell R.B., Cohen S.M. 2005. Principles of microRNA-target recognition. PLOS Biol., 3(3): e85.
- [3] Wiesinger H. 2001. Arginine metabolism and the synthesis of nitric oxide in the nervous system. Prog. Neurobiol., 64: 365-391.
- [4] Kanehisa M., Goto S., Sato Y., Furumichi M., Tanabe M. 2012. KEGG for integration and interpretation of large-scale molecular data sets. Nucleic Acids Res., 40(Database issue): D109-114.
- [5] Maziere P., Enright A.J. 2007. Prediction of microRNA targets. Drug Discov. Today, 12(11-12): 452-458.
- [6] Fjose A., Zhao X.-F. 2010. Exploring microRNA functions in zebrafish. New Biotechnol., 27: 250-255.
- [7] Manzoni O., Bockaert J. 1993. Nitric oxide synthase activity endogenously modulates NMDA receptors. J. Neurochem., 61: 368-370.