Gene 538 (2014) 366–372

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Novel transcriptome data analysis implicates circulating microRNAs in epigenetic inheritance in mammals

Abhay Sharma *

CSIR-Institute of Genomics and Integrative Biology, Council of Scientific and Industrial Research, Sukhdev Vihar, Mathura Road, New Delhi 110025, India

ARTICLE INFO

Article history:
Accepted 20 January 2014
Available online 29 January 2014

Keywords:
Transgenerational inheritance
Extracellular microRNA
Transcriptomic

ABSTRACT

Experimental evidence supports a role of mobile small non-coding RNAs in mediating soma to germline hereditary information transfer in epigenetic inheritance in plants and worms. Similar evidence in mammals has not been reported so far. In this bioinformatic analysis, differentially expressed microRNAs (miRNAs) or mRNAs reported previously in genome level expression profiling studies related to or relevant in epigenetic inheritance in mammals were examined for circulating miRNA association. The reported sets of differentially expressed miRNAs or miRNAs that are known to target the reported sets of differentially expressed genes, in that order, showed enrichment of circulating miRNAs across environmental factors, tissues, life cycle stages, generations, genders and species. Circulating miRNAs commonly representing the expression profiles enriched various epigenetic processes. These results provide bioinformatic evidence for a role of circulating miRNAs in epigenetic inheritance in mammals.

1. Introduction

Epigenetic inheritance of induced effects on the phenotype across generations, increasingly being uncovered in plants and animals alike, has recently emerged as an exciting new field in biology (Brasset and Chambeyron, 2013; Daxinger and Whitelaw, 2012; Grossniklaus et al., 2013; Holeski et al., 2012; Lim and Brunet, 2013; Walker and Gore, 2011). In the unconventional mode of germline-dependent inheritance that does not involve primary DNA sequence change, and hence defies Mendelian genetics, phenotypic effects induced in the generation exposed to the stimulus are found to persist, in the same or variant forms, in future unexposed generations. The non-genetic transfer of phenotypic information is considered to involve epigenetic means including chromatin associated factors such as DNA methylation and histone modifications and trans-acting and non-nuclear factors like RNA. Of Lamarckian flavor, the epigenetic inheritance of acquired characteristics is most challenging as it confronts the Weismann barrier, the established dogma that genetic information can only be transmitted from germline to soma, not in reverse (Liu, 2007; Liu and Li, 2012; Noble, 2013; Seki, 2013; Sharma, 2012; Zeybel et al., 2012). Surprisingly, discovery of mobile small non-coding RNA mediated cell–cell communication challenges the germ plasm theory, with evidence supporting a role of systemic RNAs in epigenetic inheritance in plants and worms (Ashe et al., 2012; Buckley et al., 2012; Burton et al., 2011; Chitwood and Timmermans, 2010; Fire et al., 1998; Gu et al., 2012; McCue et al., 2012; Rasmann et al., 2012; Saze, 2012).

Also found in mammalian species, circulating small non-coding RNAs, particularly miRNAs, irrespective of existing uncertainties over their biological significance, are of considerable current interest in human health and disease (Duttagupta and Jones, 2013; Etheridge et al., 2013; Leslie, 2013; Sarkies and Miska, 2013; Turchinovich et al., 2012; Turchinovich et al., 2013). To test the hypothesis that extracellular, circulating miRNAs may also play a role in epigenetic inheritance in mammals, existing genome level expression data related to or relevant in non-genetic inheritance in mammals were analyzed in order to examine if an association between the two is supported. The analysis is based on reported genome level miRNA or mRNA profiling studies on environmental factor induced epigenetic inheritance or on environmental effects with a potential to cause epigenetic inheritance. The differentially expressed miRNAs reported by the original authors in the miRNA profiling studies were directly tested for circulating miRNA enrichment. For mRNA studies, the enrichment was tested indirectly by identifying miRNAs that are known to target the reported sets of differentially expressed genes. miRNAs are highly conserved across mammalian species (Kiezun et al., 2012). Extensive functional homology is considered to exist between human and mouse miRNAs, for example (Artzi et al., 2008; Kiezun et al., 2012; Selth et al., 2012). A similar profile of circulating miRNAs has also been demonstrated in these species (Selth et al., 2012). Survey of recent compilations of circulating miRNAs reveals that orthologues of 50% of them in mouse (Dhahbi et al., 2013) are represented in human (Russo et al., 2012). This allowed for cross species comparison of circulating miRNA enrichment in the present analysis. Given the availability of a high quality, manually curated set of human circulating miRNAs (Russo et al., 2012), human orthologues of differentially expressed sets of miRNAs and genes were used in this bioinformatic analysis.

Abbreviations: miRNA, microRNA; HDL, high density lipoprotein; AGO2, argonaute2.

* Tel.: +91 11 26932421; fax: +91 11 27662407.
E-mail address: abhaysharma@igib.res.in.

0378-1119/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gene.2014.01.051

2. Methods

2.1. Expression profiles

Published literature on miRNA and mRNA expression profiling was identified through PubMed search on the 20th of August 2013, first using the key word combination "(trans-generational or transgenerational or multi-generational or multigenerational or inter-generational or intergenerational) (microarray or microarrays or miRNA or mi-RNA or microRNA or micro-RNA or mRNA or transcriptome or transcriptomic)". Papers reporting genome level mammalian studies pertaining to environmental effects in one or more generations were selected. References therein were also curated and relevant ones selected. Additionally, as epigenetic effects of endocrine disrupting chemicals and dietary factors on future generations have been commonly reported, the key word combinations "endocrine disrupting (gestation or gestational) (microarray or microarrays or miRNA or mi-RNA or microRNA or micro-RNA or mRNA or transcriptome or transcriptomic)" and "(diet or dietary or nutrition or nutritional) (inheritance or inherited) (microarray or microarrays or miRNA or mi-RNA or microRNA or micro-RNA or mRNA or transcriptome or transcriptomic)" were also used to screen literature. These searches together identified a total of 6 papers that described 11 individual miRNA profiles and 18 papers that described 50 individual mRNA profiles. Complete lists of differentially expressed genes or miRNAs identified by the authors were mostly retrieved from these papers or from the associated supplementary materials. Wherever unavailable, the authors were requested to provide the same through personal communication. If still unavailable, partial gene lists given in the paper or in the supplementary materials were used.

2.2. Circulatory miRNA enrichment

The differentially expressed miRNAs or genes identified by the original authors were used in circulatory miRNA enrichment analysis. For 11 miRNA profiles, the reported sets of differentially expressed miRNAs in the lone human profile or human homologs of the reported sets of differentially expressed miRNAs in the rest non-human mammalian profiles were tested for enrichment of human circulating miRNAs using hypergeometric distribution, with 2578 as the total number of all human miRNAs, documented in release 20 of miRBase (Kozomara and Griffiths-Jones, 2011; miRBase), and 590 as that of circulating mature human miRNAs, documented in version 1.5 of miRandola (miRandola; Russo et al., 2012). Extracellular existence of numerous miRNAs, non-coding RNAs of around 22 nt length that mediate post-transcriptional gene regulation by repressing specific mRNA targets, has been reported in body fluids of mammals including humans and mouse in various studies (Dhahbi et al., 2013; Russo et al., 2012). A comprehensive catalog of human circulating miRNAs is available in the

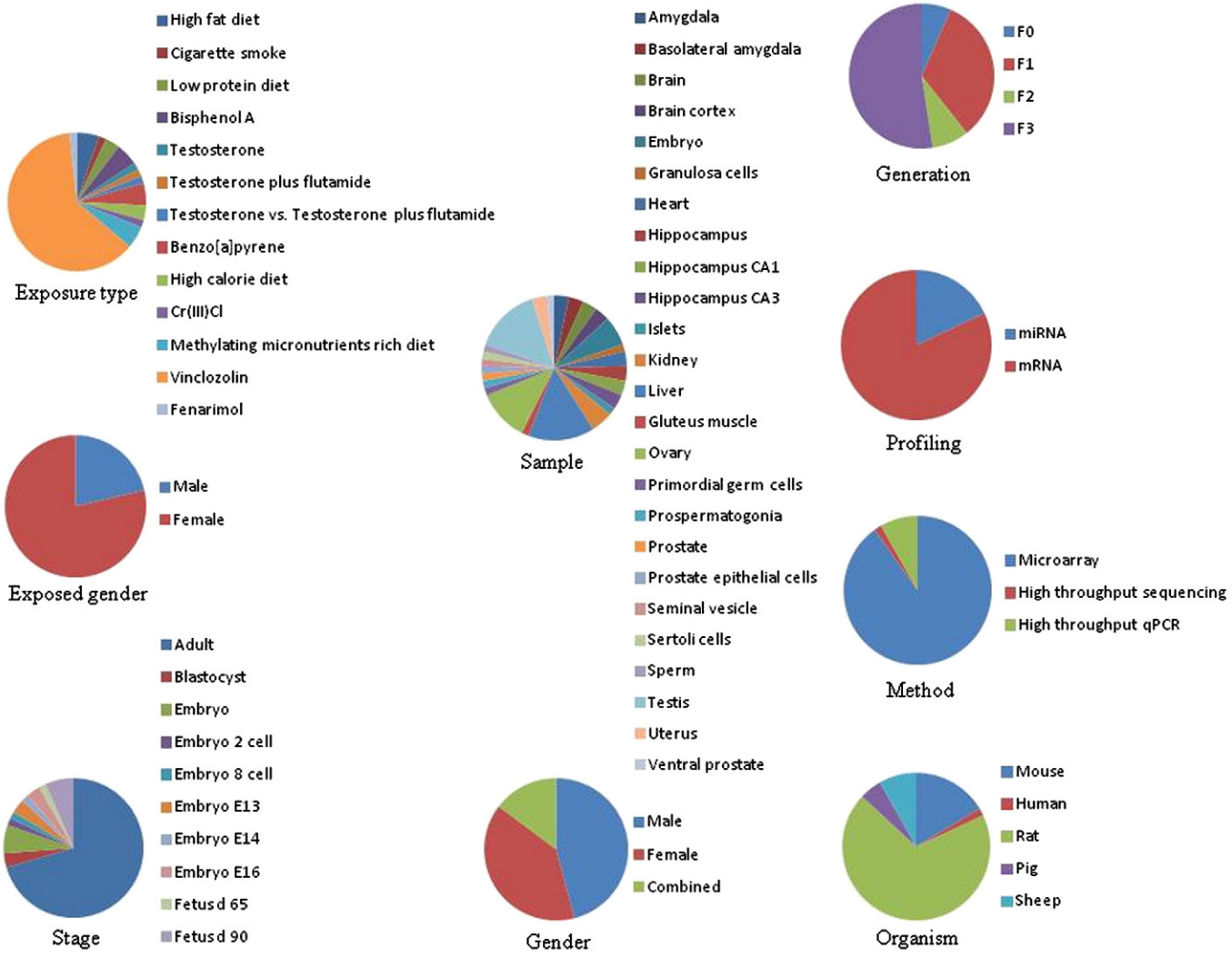

Fig. 1. Metadata of the reported expression profiles. All the 61 profiles covered in the present analysis, 11 miRNA and 50 mRNA, are represented. Stage, gender and generation relate to the source of sample analyzed for expression levels. The details are given in Supplementary Table S1.