Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (Print) 1744-8352 (Online) Journal homepage: informahealthcare.com/journals/iero20

CHI conference on microRNAs: dramatic expansion of research tools and discoveries

Clark D Jeffries

To cite this article: Clark D Jeffries (2010) CHI conference on microRNAs: dramatic expansion of research tools and discoveries, Expert Review of Molecular Diagnostics, 10:5, 555-557, DOI: 10.1586/erm.10.47

To link to this article: https://doi.org/10.1586/erm.10.47

Published online: 09 Jan 2014.

EXPERT REVIEWS

CHI conference on microRNAs: dramatic expansion of research tools and discoveries

Expert Rev. Mol. Diagn. 10(5), 555–557 (2010)

Clark D Jeffries

University of North Carolina at Chapel Hill Eshelman School of Pharmacy and Renaissance Computing Institute, NC, USA
Tel.: +1 919 260 6576
Fax: +1 919 962 1380
clark_jeffries@med.unc.edu

Cambridge Health Institute's Sixth Annual Conference on microRNAs

Cambridge, MA, USA, 22–24 March 2010

The Cambridge Health Institute's sixth annual conference on microRNAs integrated exceedingly diverse academic and commercial interests. Included were novel technologies for microRNA profiling and nucleic acid sequencing, drug delivery technologies using gene therapy, and promising diagnoses and treatments for various diseases, especially types of cancer. The conference format comprised 42 presentations, each 25 min in length. This article gives telegraphic descriptions of ten of the presentations, to illustrate the range of conference topics. At least two other mutually nonintersecting choices of ten could have been used with equal effect.

Nanotechnology

Shana Kelley (University of Toronto, Canada), described progress toward specifically detecting RNA or genomic DNA sequences with a multiplexed microelectronic chip that features a 'nanostructured microelectrode'. The electrode is composed of gold with an overcoating of palladium. The prospect is disposable-chip, hand-held, 30-min detection of ten microRNA (miRNA) molecules per 1 µl with 5:1 specificity against a second miRNA differing by a single nucleotide, and 10:1 specificity against the precursor miRNA (pre-miRNA) [1].

Research converging to a small set of miRNAs

Scott Valastyan of Robert Weinberg's laboratory, MIT/Whitehead Institute for Biomedical Research (MA, USA), reported that miR-31 levels are specifically reduced in metastatic breast cancer cells and inversely correlated with onset of metastasis [2,3]. From four previous studies, ten miRNAs were selected for investigation, including miR-31. In a limited study involving collaborators from Brigham and Women's Hospital (Boston, MA, USA), samples from patients were partitioned according to low- or high-miR-31 levels. A review of records revealed that all high miR-31 patients remained metastasis-free for 80 months, but over half of low-miR-31 patients experienced metastasis. Of the 200 genes reported to be miR-31 targets, 16 were found to be motility-related, of which six were experimentally validated as direct downstream targets. Notably, re-expression of three of the genes (*ITGA5*, *RDX*, *RHOA*) reversed miR-31 inhibition of metastasis in rodent models.

Kai-Christian Sonntag (McLean Hospital, Harvard Medical School, MA, USA), reported implications of networks of mRNAs and miRNAs in Parkinson's disease (PD). Samples were obtained by laser microdissection of dopamine neurons from post-mortem midbrain regions (substantia nigra) of sporadic PD patients. Samples were age-matched with controls and also across genders. miRNA profiling using high-throughput RT-qPCR revealed a distinct expression pattern in the dopamine neurons, regardless of disease or gender. miRNAs were negatively correlated with predicted targets from previous Affymetrix microarray data on the same dopamine neurons, which demonstrated profound downregulation of gene expression in signaling pathways relevant to PD pathogenesis, including a bias in men. This produced a short list of 'PD-specific' miRNAs distinguished by case and control. Significantly, bioinformatic analysis further revealed association of these miRNAs with gene-expression networks known to be dysregulated in PD [4].

 10.1586/ERM.10.47 ISSN 1473-7159

Delia Mezzanzanica (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy) reported correlations of miRNA expression with response to frontline treatment of patients presenting advanced-stage epithelial ovarian carcinoma. Experiments with specimens collected at time of primary surgery from two independent case materials revealed that poor prognosis was strongly associated with downmodulation of a set of miRNAs located on chromosome Xq27.3, including miR-506, -508–3p, -514, -509-3p and -513a-5p [5]. These findings obviously invite further research.

Diagnostics

Anna Schwarzbach (Asuragen, Inc., TX, USA) described development of a two miRNA-based RT-qPCR test to aid in differential diagnosis and management of pancreatic ductal adenocarcinoma, now available. In a blinded validation on formalin-fixed paraffin-embedded specimens, this test achieved approximately 95% sensitivity and specificity, with 21 cases and 39 controls. Asuragen produced this laboratory developed test by identifying miRNA expression changes between a benign condition of chronic pancreatitis and pancreatic ductal adenocarcinoma, followed by selection of the two top performing candidates. Asuragen was reported to use a similar approach to generate novel miRNA-based laboratory developed tests for other human cancer indications.

Alternative biomarkers

Dirk P Dittmer (Lineberger Comprehensive Cancer Center, North Carolina Cancer Hospital, NC, USA) presented work on the provocative hypothesis that pre-miRNAs might be more informative biomarkers than mature miRNAs. As hairpins are generated in the nucleus, pre-miRNAs are causally upstream of mature miRNAs, and hence are faster to react. The technology employed in his research is RT-qPCR with SYBR and regular primers. Detecting approximately 70 nucleotide pre-miRNAs is inherently more specific than detecting mature miRNAs only a third as long. Also ameliorated are problems stemming from variable 5′ and 3′ ends of mature miRNAs, ambient unusually short RNAs, and SNPs in the mature miRNA. As an application, pre-miRNA assays were reported to define progressive stages of endothelial cell transformation culminating in Kaposi sarcoma [6].

Therapy

An integration of miRNA science and gene therapy was presented by Brian Brown, Mount Sinai School of Medicine. He showed how synthetic miRNA target sites could be incorporated into gene-transfer vectors to make the vector subject to endogenous miRNA regulation. One application of this was to de-target the expression of a therapeutic transgene from hematopoietic cells [7]. This was done by utilizing target sites for the pan-hematopoietic miRNA, miR-142. After multiple miR-142 target sites were added to a lentiviral vector, vector expression was suppressed in hematopoietic cells, but not hepatocytes, and this enabled robust, stable and corrective expression of a factor IX transgene in hemophilia B mice [8]. Additional work was presented on the use of synthetic target sites to sponge or decoy miRNAs for loss-of-function studies [9,10].

In cardiac therapy, Bill Marshall of miRagan Therapeutics proposed catheter delivery of miRNA mimics and miRNA inhibitors to regulate protein expression in the heart. Cardiomycetes efficiently uptake oligonucleotides, and apparently even more so in cardiac hypertrophy. Catheter delivery enables efficient, target-specific dosage with respect to heart and vascular disorders. Anti-miR-15 was reported to reduce infarct size and anti-miR-208 was reported to counter hypertrophy and improve cardiac function in rodent models.

Surprising use of miRNA signatures

CD Atreya (Center for Biologic Evaluation and Research, US FDA), described miRNA profiling in search of quality genomic biomarkers for stored blood cells [11,12]. Recent literature suggests that both red blood cells and platelets have abundant and diverse miRNAs. Since both cell types are anucleate, it is hypothesized that the miRNAs identified in these cells must be the terminal carryover miRNAs of biogenesis that occurred in their erythroblast and megakaryocyte progenitors. Stored blood cells (red blood cell and platelets) undergo storage lesions, that is, morphological, biochemical and functional derangements during storage. It is speculated that miRNA–mRNA interactions could play a role in the storage lesion process. At present, there is no single *in vitro* biomarker predictive of *in vivo* quality and function of stored blood cells. In this report, it was demonstrated that in stored blood cells, a few selected miRNAs had significant alterations, which could form a basis to undertake robust studies on miRNA profiling of stored blood cells as genomic biomarkers towards identifying quality-assessment technologies.

Overview presentation

Perhaps the presentation with broadest impact at the conference was that of Carlo Croce (Ohio State University, OH, USA). He recounted the difficult, multi-year work that went into research reported in the 2002 *Proceedings of the National Academy of Sciences* paper that identified genomic deletion of two miRNAs as strongly associated with chronic lymphocytic leukemia [13]. This was a stem cell of a paper that has proliferated and differentiated into numerous lines of research connecting miRNAs and cancer, including many subsequent discoveries of the Croce laboratory itself, as summarized in his presentation.

Concluding remarks

The Cambridge Health Institute conference updated accelerating miRNA research and development that will enable human transformation of mystery to knowledge and sickness to health. It coalesced the talents of many professions and interests. What a splendid time to be engaged in molecular genetics!

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Soleymani L, Fang Z, Sargent EH, Kelley SO. Programming the detection limits of biosensors through controlled nanostructuring. *Nat. Nanotechnol*. 4(12), 844–848 (2009).

2 Valastyan S, Reinhardt F, Benaich N *et al.* A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. *Cell* 137(6), 1032–1046 (2009).

3 Valastyan S, Benaich N, Chang A, Reinhardt F, Weinberg RA. Concomitant suppression of three target genes can explain the impact of a microRNA on metastasis. *Genes Dev*. 23(22), 2592–2597 (2009).

4 Sonntag K-C. miRNAs and deregulated gene expression networks in neurodegeneration. *Brain Res*. 1338, 48–57 (2010).

5 Mezzanzanica D, Bagnoli M, De Cecco L, Valeri B, Canevari S. Role of microRNAs in ovarian cancer pathogenesis and potential clinical implications. *Int. J. Biochem. Cell Biol.* (2010) (Epub ahead of print).

6 O'Hara AJ, Chugh P, Wang L *et al.* Pre-micro RNA signatures delineate stages of endothelial cell transformation in Kaposi sarcoma. *PLoS Pathog.* 5(4), e1000389 (2009).

7 Brown BD, Venneri MA, Zingale A, Sergi Sergi L, Naldini L. Endogenous microRNA regulation suppresses transgene expression in hematopoietic lineages and enables stable gene transfer. *Nat. Med*. 12(5), 585–591 (2006).

8 Brown BD, Cantore A, Annoni A *et al.* A microRNA-regulated lentiviral vector mediates stable correction of hemophilia B mice. *Blood* 110(13), 4144–4152 (2007).

9 Gentner B, Schira G, Giustacchini A *et al.* Stable knockdown of microRNA *in vivo* by lentiviral vectors. *Nat. Methods* 6(1), 63–66 (2009).

10 Brown BD, Naldini L. Exploiting and antagonizing microRNA regulation for therapeutic and experimental applications. *Nat. Rev. Genet*. 10(8), 578–585 (2009).

11 Kannan M, Mohan KV, Kulkarni S, Atreya C. Membrane array-based differential profiling of platelets during storage for 52 miRNAs associated with apoptosis. *Transfusion* 49(7), 1443–1450 (2009).

12 Kannan M, Atreya C. Differential profiling of human red blood cells during storage for 52 selected microRNAs. *Transfusion* DOI: 10.1111/j.1537-2995.2010.02585.x (2010) (Epub ahead of print).

13 Calin GA, Dumitru CD, Shimizu M *et al.* Frequent deletions and down-regulation of micro-RNA genes *miR15* and *miR16* at 13q14 in chronic lymphocytic leukemia. *Proc. Natl Acad. Sci. USA* 99(24), 15524–15529 (2002).