Cell Mol Neurobiol (2018) 38:769–774
https://doi.org/10.1007/s10571-017-0514-0

BRIEF COMMUNICATION

Chromosome 21-Encoded microRNAs (mRNAs): Impact on Down's Syndrome and Trisomy-21 Linked Disease

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Received: 19 May 2017 / Accepted: 20 June 2017 / Published online: 7 July 2017

Abstract Down's syndrome (DS; also known as trisomy 21; T21) is caused by a triplication of all or part of human chromosome 21 (chr21). DS is the most common genetic cause of intellectual disability attributable to a naturally-occurring imbalance in gene dosage. DS incurs huge medical, healthcare, and socioeconomic costs, and there are as yet no effective treatments for this incapacitating human neurogenetic disorder. There is a remarkably *wide variability* in the 'phenotypic spectrum' associated with DS; the progression of symptoms and the age of DS onset fluctuate, and there is further variability in the biophysical nature of the chr21 duplication. Besides the cognitive disruptions and dementia in DS patients other serious health problems such as atherosclerosis, altered lipogenesis, Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), autoimmune disease, various cancers including lymphoma, leukemia, glioma and glioblastoma, status epilepticus, congenital heart disease, hypotonia, manic depression, prostate cancer, Usher syndrome, motor disorders, Hirschsprung disease, and various physical anomalies such as early aging occur at elevated frequencies, and all are part of the DS 'phenotypic spectrum.' This communication will review the genetic link between these fore-mentioned diseases and a small group of just five stress-associated microRNAs (miRNAs)—that include let-7c, miRNA-99a, miRNA-125b, miRNA-155, and miRNA-802—encoded and clustered on the long arm of human chr21 and spanning the chr21q21.1-chr21q21.3 region.

Keywords 42 Amino acid amyloid-beta (Aβ42) peptide · Alzheimer's disease (AD) · Down's syndrome · MicroRNA (miRNA) · Small non-coding RNAs (sncRNAs) · Systemic inflammation

Introduction

Linking the chr21 gene dosage imbalance in Down's syndrome (DS) with the considerable variability of the DS phenotype has been an elusive goal in the study of trisomy 21 (T21) activity, function, genetics, and epigenetics (Hattori et al. 2000; Antonarakis 2017; Castro et al. 2017; Max Plank Institute 2017; NCBI 2017; Vega Genome Browser 54: Homo sapiens 2017). Interestingly, a single copy gene encoding the 770 amino acid beta amyloid precursor protein, the precursor to the 42 amino acid amyloid beta (Aβ42) peptide that accumulates in both familial and sporadic Alzheimer's disease (AD) and DS brains is encoded at chr21q21.3; virtually all DS patients exhibit AD-type pathological change as they age, including progressive Aβ42 peptide accumulation (Castro et al. 2017a; Hithersay et al. 2017). Evidence associating a specific gene or chr21 domain to a particular phenotype has

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been restricted and relatively limited in chr21 genomic studies (Hattori et al. 2000; Antonarakis 2017; Castro et al. 2017; Hithersay et al. 2017). Another understudied and perhaps underappreciated area of T21 gene triplication are the potential contribution of chr21-encoded micro RNAs (miRNAs), their DS-associated increase in abundance (because of the extra chr21 copy—a gene dosage effect), and their enormous potential to shape and regulate the DS transcriptome, and hence alter both pathogenic and global gene expression patterns (Hattori et al. 2000; Li et al. 2012; Ghorai and Ghosh 2014; Hithersay et al. 2017).

miRNAs represent a novel and intriguing group of endogenous small non-protein-coding RNAs (sncRNAs) that are evolutionarily conserved and widely distributed amongst all species so far studied in both the plant and animal kingdoms (Guo et al. 2010; Eichhorn et al. 2014; Hruska-Plochan et al. 2015; Zhao et al. 2015a, b; Hill and Lukiw 2016; Liu et al. 2017). Interestingly, a single miRNA can regulate multiple target genes dispersed throughout all somatic chromosomes, indicating that miRNAs may regulate multiple signaling pathways and participate in numerous physiological and pathological processes. The major mode of action of these sncRNAs is to interact, via base-pair complementarity, with the 3′-untranslated region of their target messenger RNAs (mRNAs), and in doing so decrease the expression of that particular target mRNA, and hence act as negative regulators of target gene expression. Ribosome profiling and RNA sequencing have shown that up-regulated miRNAs act predominantly to decrease their target mRNA levels, and miRNA-mediated destabilization of mRNAs is the main reason for the observed reductions in gene expression that are characteristic of both AD and DS brains (Guo et al. 2010; Codocedo et al. 2016; Liu et al. 2017).

Consisting of 48 million base pairs (Mbps) and representing ~1.5% of total cellular DNA, chr21 contains a relatively low number of identified genes (~225), for example, compared with the 545 genes reported for the 49 Mbp chromosome 22 (chr22; Hattori et al. 2000). Equally under-represented is the small number of just five miRNAs encoded and clustered around the long arm of chr21 spanning the chr21q21.1-chr21q21.3 region (compared to the ~46 miRNAs encoded on chr22; Dunham et al. 1999; "Vega Genome Browser 54: Homo sapiens 2017; http://atlasgeneticsoncology.org/Indexbychrom/idxg_22.html). Chr21 encoded miRNAs include let-7c, miRNA-99a, miRNA-125b, miRNA-155, and miRNA-802. Together specific members of this small miRNA family (i) have been found to be readily detectable in control brains and significantly up-regulated in both AD and DS brains (Zhao et al. 2015a, b; Hill and Lukiw 2016), (ii) are observed to be up-regulated more than gene-dosage effects alone would predict (Li et al. 2012), (iii) includes a subset of miRNAs including miRNA-99a, miRNA-125b, and miRNA-155 that are inducible and under NF-kB regulatory control (Lukiw 2007, 2012; Prasad 2017; unpublished observations), and (iv) are known to down-regulate the expression of key innate-immune regulatory and anti-inflammatory genes in AD and/or DS (Pogue et al. 2010; Lukiw et al. 2012; Maciotta et al. 2013; Hill et al. 2015; Hill and Lukiw 2016; Nadim et al. 2017). For example, gene dosage mediated increases in the chr21-encoded miRNA-155 have been shown in part to down-regulate the expression of complement factor H, an important soluble, innate-immune regulatory glycoprotein in AD and DS tissues and in primary brain cell models of AD, and be centrally involved in pathogenic signaling pathways that include inflammatory neurodegeneration (Li et al. 2012; Lukiw 2012; Zhao et al. 2015a, b; Hill and Lukiw 2016).

Concluding Remarks

As research into the molecular-genetics of DS (T21) progresses, more and more neurological (and non-neurological) diseases have been shown to be significantly linked to the T21 phenotype. This 'Short Communications' paper provides four novel findings hitherto unrecognized or undocumented in the research field involving the molecular-genetics of T21: (i) for the first time we point out that the five miRNAs encoded on the extra copy of chromosome 21 in DS have potential to regulate the expression of over 3600 genes (see Table 1 and text), (ii) largely due to the containment of five miRNAs encoded on chromosome 21, and the fact that DS is the most common genetic cause of intellectual disability attributable to a naturally occurring imbalance in gene dosage; this communication provides the first example of what was classically considered a neurological-developmental-dementing disorder as also a serious contributor to the development of disease in other major organ systems including the heart, lung, blood, bladder, prostate, thyroid and circulatory system, GI tract, as well as predisposition to many types of cancer, (iii) for the first time we point out the hitherto unappreciated regulatory potential of chromosome 21 in the development of a very broad clinical spectrum of potentially fatal human disease, and (iv) that further study and analysis of these chr21-encoded miRNAs, their mRNA interactions and induction of pathogenic biological pathways provides a greatly expanded list of potential therapeutic targets which would ultimately define the basis for more effective treatments in the clinical management of secondary maladies associated with development of chr21-linked disease.

Perhaps most importantly, miRNA–mRNA integration mapping, in depth RNA sequence analysis using complementarity algorithms and bioinformatics evaluation

Table 1 miRNAs encoded on human chr 21, location, Genbank accession, function/disease association, and references

micro RNA	Chromosomal location/Genbank sequence	Number of potential mRNA targets*	Function/disease association	References
let-7c	chr21q21.1/ NR_029480	~700	Tumor suppressor/arsenite-induced, gastric, lung and colorectal cancers; Moyamoya disease	Lee and Dutta (2007), Lukiw (2007), Sethi and Lukiw (2009), Wang et al. (2013), Cappuzzo et al. (2014), Crowley et al. (2014), Jiang et al. (2014), Zhang et al. (2015), Zhao et al. (2015a, b) and Regazzo et al. (2016); http://www.genecards.org/cgi-bin/carddisp.pl?gene=MIRLET7C&keywords=mir-let7c
miRNA-99a	chr21q21.1/ NR_029514.1	~665	Lung cancer, multiple myeloma, head and neck squamous cell carcinoma, anaplastic thyroid and prostate cancer	Feng et al. (2015), Hou et al. (2015), Huang et al. (2015), Wu et al. (2015), Yu et al. (2015) and Regazzo et al. (2016); http://www.genecards.org/cgi-bin/carddisp.pl?gene=MIR99A&keywords=mir-99a
miRNA-125b-2	chr21q21.1/ NR_029694.1	~900	NF-kB inducible miRNA; involved in astrogliosis, glial cell proliferation, Alzheimer's disease (AD), age-related macular degeneration (AMD), breast, gastric, gallbladder, lung, squamous cell and colorectal carcinoma, intellectual disabilities, glioma, glioblastoma; status epilepticus	Lukiw (2007), Pogue et al. (2010), Risbud and Porter (2013), Siew et al. (2013a, b), Feng et al. (2015), Ferlazzo et al. (2016), Moss et al. (2016), Regazzo et al. (2016), Wang et al. (2017) and Zhang et al. (2017); http://www.genecards.org/cgi-bin/carddisp.pl?gene=MIR802&keywords=mir-802
miRNA-155	chr21q21.3/ NR_030784.1	~700	NF-kB inducible miRNA; adenocarcinoma, Alzheimer's disease (AD); age-related macular degeneration (AMD), B cell lymphoma, bacterial pneumonia, peritonitis, colitis, squamous cell carcinoma, Down's syndrome (DS), hepatic fibrogenesis, bladder cancer, multiple sclerosis (MS), status epilepticus	Pogue et al. (2010), Li et al. (2012), Lukiw et al. (2012), Maciotta et al. (2013), Risbud and Porter (2013), Devier et al. (2015), Bofill-De Ros et al. (2015), Asim et al. (2015), Hill et al. (2015), Siew et al. (2013), Feng et al. (2015), Ferlazzo et al. (2016), Moss et al. (2016), Regazzo et al. (2016), Lu et al. (2017), Lutz et al. (2017) and Mikamori et al. (2017); http://www.genecards.org/cgi-bin/carddisp.pl?gene=MIR155&keywords=mir-155
miRNA-802	chr21q22.12/ NR_030414.1	~665	Breast cancer, Down's syndrome and DS murine models, biliary hyperplasia type 2 diabetes, cholesteatoma, osteosarcoma	Cao et al. (2013), Li and Qin (2014), Wang et al. (2014), Higuchi et al. (2015), Yuan and Wang (2015), Bofill-De Ros et al. (2015) and Church et al. (2016);www.genecards.org/cgi-bin/carddisp.pl?gene=MIR802&keywords=mir-802
Summary	chr21q21.1-chr21q21.3/various	~3630	A surprisingly broad range of human diseases including many cancers and neurological disorders such as DS, AD, AMD and MS	Multiple (see text and above)

Down syndrome (DS) or trisomy 21 (T21) results from a gene dosage imbalance that translates into a surprisingly broad clinical spectrum. DS is the most common genetic cause of intellectual disability attributable to a naturally occurring imbalance in gene dosage—a major objective in the study of DS is the identification of functional genetic elements that impact alterations and variations in the DS phenotype. Indeed DS is a primary human model for studying imbalances in gene dosage and provides a unique opportunity to elucidate the molecular and pathogenic consequences of extra chromosomal copies; note that: (i) DS is also associated with multiple other serious age-related human maladies (see text and table column function/disease association), (ii) the majority of the disease associations listed above are the result of the mis-regulation of let-7c, miRNA-99a, miRNA-125b, miRNA-155, and/or miRNA-802 abundance and expression, (iii) all five chr21-encoded miRNAs are located within the relatively narrow domain on the long arm of chr21 from chr21q21.1 to chr21q21.3, (iv) all five chr21-encoded miRNAs have strong genome-wide regulatory effects, (v) miRNA-99a, miRNA-125b and miRNA-155 are inducible and under NF-kB regulatory control (Hill et al. 2015; unpublished observations), and (vi) at least three of these miRNAs encoded on chr21 are significantly increased in expression in AD and/or DS (miRNA-125b, miRNA-155 and miRNA-802; Lukiw 2007; Li et al. 2012; Devier et al. 2015; Zhao et al. 2015a, b; Castro et al. 2017). Interestingly, of the 2650 human miRNAs so far identified, only about 35–40 are highly expressed in the human brain and retina, and of these highly expressed miRNAs, miRNA-125b and miRNA-155 are encoded on chr21 (in comparison chr21 miRNAs let-7c, miRNA-99a and miRNA-802 are less highly expressed; Hattori et al. (2000); Li et al. (2012); Zhao et al. (2015a, b); Antonarakis (2017); unpublished observations)

*The number of potential miRNA–mRNA interactions was assessed using the MicroCosm Targets Version 5 (miRBase; EMBL-EBI) algorithm

indicate that these five chr21-encoded miRNAs have the remarkable capacity to potentially regulate the expression approximately 3630 protein-coding genes (Table 1). This rather large number of protein-coding genes targeted by chr21-encoded miRNAs and the chr21 miRNA-mediated potential down-regulation of vast numbers of mRNAs may in part explain the tremendous diversity and complexity of human maladies associated with DS. This knowledge should be useful in targeting miRNA-mediated molecular mechanisms that cause or modify the development and propagation of different DS phenotypes. For example, employing anti-miRNA-based therapeutic strategies directed toward a single or a few chr21 specific miRNAs: (i) could be of therapeutic use in the restoration of essential and homeostatic mRNA and gene expression patterns in DS patients, and/or (ii) may ultimately provide more effective treatments in the clinical management of ancillary maladies associated with the T21 phenotype (Lukiw 2013; Antonarakis 2017; Castro et al. 2017; Zhao et al. 2016).

Acknowledgements This Research Work was presented in part at the Alzheimer Association International Congress 2016 (AAIC 2016) Annual conference 21–27 July 2016 in Toronto Canada and at the 13th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD 2017) 29 March–2 April in Vienna Austria. Thanks are also extended to the many neuropathologists, physicians and researchers of the US, Canada, and Europe for helpful discussions and who have provided high quality, short post-mortem interval (PMI) human CNS, extracted tissue fractions and/or bioinformatics data for scientific analysis and study and to Drs. Christoff Eicken, Chris Hebel, Kyle Navel, Aileen Pogue and Darlene Guillot for expert technical assistance, organization and medical artwork. Research on the pro-inflammatory and pathogenic signaling in the Lukiw laboratory involving the innate-immune response, neuroinflammation, and amyloidogenesis in AD, PD, DS, retinal and prion disease, and in other neurological diseases was supported through an unrestricted grant to the LSU Eye Center from Research to Prevent Blindness (RPB); the Louisiana Biotechnology Research Network (LBRN) and NIH grants NEI EY006311, NIA AG18031, and NIA AG038834.

Author Contributions PNA, MEP and WJL discussed the genomic data and scientific implications of these ideas; WJL researched and wrote this paper; the authors are sincerely grateful to colleagues and collaborators for helpful discussions and for sharing unpublished data.

Compliance with Ethical Standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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