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Molecule of the month: miRNA and Down's syndrome

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The pathogenesis and molecular biology of Down's syndrome are under intense study and advances have been made in the care of patients with Down's syndrome. Patients with Down's syndrome may exhibit cognitive impairment and developmental cognitive disorder; post-mortem brain tissue from patients who were older than 40 years may show senile plaques and neurofibrillary tangles as found in Alzheimer's disease. Skeletal and soft tissue abnormalities appear as well. Particular patients may have only mild cognitive disability; however, some patients may exhibit psychiatric disorders including autism and major depression. Most often, Down's syndrome is a noninherited chromosome disorder caused during meiosis by chromosome 21 nondisjunction. This leads to chromosome 21 trisomy. However, there is also an inherited form of Down's syndrome that is due to translocation of a fragment of chromosome 21 onto chromosome 14. The chromosome 21 fragment is from the 21q22 band-region and causes a triplication of that 1,000 bp portion of chromosome 21. However, there are indications that the two types of Down's syndrome are clinically indistinguishable **[1, 2]**

MicroRNAs(miRNAs) are noncoding RNAs that are involved in gene expression regulation. They have been identified in several cell processes including DNA damage, synapse formation, neurotransmission, neural network plasticity, and CNS (central nervous system) development. MiRNA levels change during neurodegeneration. **[3]** MiRNAs have been studied in several diseases that exhibit intellectual disability (ID) including Fragile X syndrome and Down's syndrome **[4].**

Much work is being done, focused on the involvement of miRNAs in the pathogenesis of Down's syndrome. For example, as of 8-11-2013, 2,042 miRNAs were identified in humans, 1,281 in *Mus musculus*, and 580 in *Pan troglodytes*. However, miRNA densities per 10 megabases in humans vary from 7.42 on chromosome 1, 29.26 on chromosome 19, and 5.40 on chromosome 21. There are 26 miRNAs that have been localized on human chromosome 21 and five of these actually are associated with Down's syndrome: let-7c, miR-99a, miR-155, miR-125b-2, and miR-802. Just to indicate a few interactions of miRNAs and their targets are that miR-155 interacts with MeCP2 (methyl CpG base pair 2) and CFH (complement factor H) and miR-199b with SIRT1 (sirtuin 1) **[4, 5].**

In greater detail, the genes that are perturbed by changes in the expression of the above five miRNAs in Down's syndrome include the following proteins: methyl CpG binding protein 2 (MeCP2), complement factor H (CFH), sirtuin 1 (SIRT1) ,phosphatidylinositol-binding clathrin assembly protein (PICALM), cyclin-dependent kinase inhibitor 2A (CDKN2A), glutamate receptor, ionotropic, N-methyl d-aspartate subunit 2A, (NR2A), Ephrin type A receptor 4 (EPHA4), Nestin (NES), transforming growth factor-β (TGF-β), toll-like receptor 7 (TLR7), cortactin-binding protein 2 (CTTNBP2), ankyrin 2 (ANK2), sodium-calcium exchanger 1 (Ncx1), tyrosine-(Y)-phosphorylation regulated kinase 1A gene (Dyrk1a), and nuclear factor of activated T-cells (NFAT).

Is it possible to correct or reverse the pathogenesis of Down's syndrome? We conclude this brief report with a few remarkable findings related to chromosome inactivation that indicate it may be just a matter of time prior to being able to cure this complex disease/syndrome.

Human females, diploid in the X chromosome, utilize the Xist gene (X-chromosome inactivation specific transcript (non-protein coding) for expression suppression (inactivation,

transcription silencing) of one of the X chromosomes. The X chromosome location of the Xist gene is at cytogenetic band Xq13.2 **[6].** In addition, it should be noted, remarkably, that the RNA gene product of this gene is non-coding. The X chromosome silencing is effected by Xist non-coding RNA and is associated with chromatin modification. This serves as the canonical mechanism of chromosome inactivation **[7].** Recent work has remarkably applied this model of transcriptional silencing to the problem of supernumerary gene expression in Down's syndrome. Pluripotent stem cells from Downs's syndrome patients were used as follows. Via editing zinc finger nucleases on chromosome 21 in these cell cultures, a Xist non-coding transgene was inserted into the DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A) locus. This step itself is notable as it amounts to the genetic reengineering of a specific chromosome. The chromosome 21 location of DYRK1A is at cytogenetic band 21q22.13 **[6].** The mechanism of transcriptional silencing due to the Xist transgene appears to involve coating chromosome 21 with Xist RNA that results in stable modification of heterochromatin. Barr body formation and DNA methylation ensue. The silencing of one chromosome 21 in these cell cultures has distinct biological effects as this procedure releases cells from inhibition of cell propagation and promotes neural rosette formation **[8].**

The development and utilization of Down's syndrome tissue and cell culture banks is of great assistance in the defeat of this disease. Several such banks in existence support progress in the medical field. A few examples are provided **[9, 10].** In addition, ethical considerations are maintained at a high level of discussion and practice **[11-14].** On a continued hopeful note, chromosome therapy and re engineering, gene therapy, gene manipulation, and reversing and preventing Down's syndrome disease appear on the horizon.

Figures 1A & 1B illustrate the gene expression and protein networks involving the proteins that interact with miRNAs in Down's syndrome as mentioned above.) This is a large set of proteins with complex series of interactions. These proteins include MeCP2, CFH, SIRT1, PICALM, CDKN2A, NR2A, EPHA4, NES, TGF-β, TLR7, CTTNBP2, ANK2, Ncx1, Dyrk1a, and NFAT **[3, 4, 5]. Figure 1C** indicates the input interactions among Xist and two proteins with which it interacts. The two protein are NXF1 (nuclear RNA export factor 1) and CTCF (CCCTC-binding factor zinc finger protein). **Figure 1D** shows the output interactions resulting from Xist, NXF1, and CTCF. **Figures 1C & 1D** indicate a few of the genes implicated in chromosome 21 expression and the application of X chromosome inactivation mechanisms to chromosome 21 gene duplication and expression control abnormalities as mentioned above.

It is left as a puzzle for the interested reader to identify the additional various genes and their functions in the figures **[6, 15, 16]**

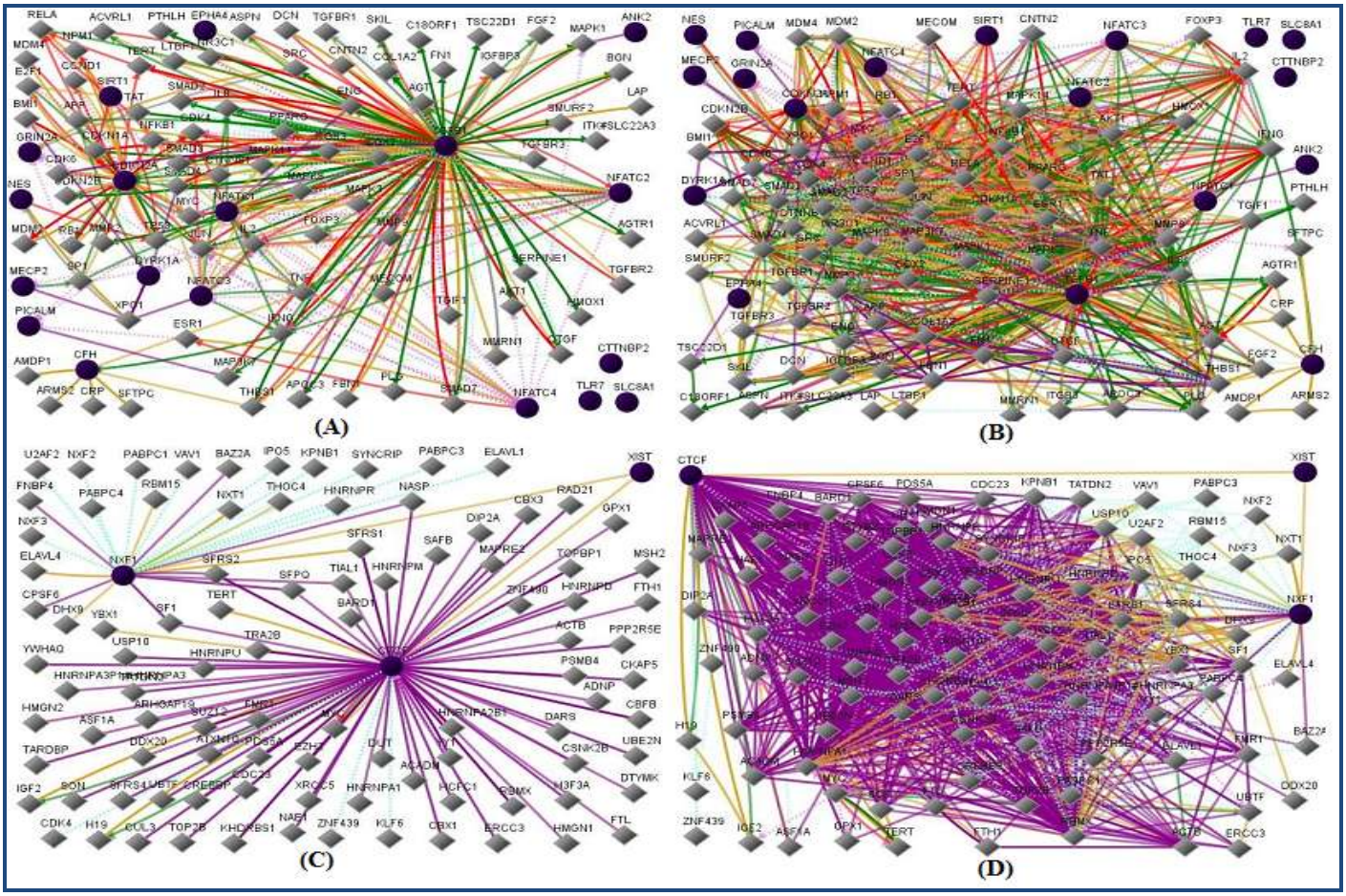

Figure 1: A) Network of input MeCP2, CFH, SIRT1, PICALM, CDKN2A, NR2A, EPHA4, NES, TGF-β, TLR7, CTTNBP2, ANK2, Ncx1, Dyrk1a, and NFATwith immediate input neighbors. In this figure, line-colors and various interactions with other genes are

red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[15].** The genes shown interacting with the above genes are immediate interactions; **B)** Network of MeCP2, CFH, SIRT1, PICALM, CDKN2A, NR2A, EPHA4, NES, TGF-β, TLR7, CTTNBP2, ANK2, Ncx1, Dyrk1a, and NFAT with output neighbors. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation. (15) This figure is a continuation of the genes shown in Figure 1A and shows additional levels of interactions among the genes; i.e. many of these are downstream from the first level shown in Figure 1A; **C)** Network of input non-coding RNA and proteins Xist, NXF1, and CTCF with immediate input neighbors. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[15].** The gene networks shown are immediate interactions; **D)** Network of non-coding RNA and proteins Xist, NXF1, and CTCF with additional output neighbors. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[15].** This figure is a continued analysis of the genes shown in Figure 1C and shows additional levels of interactions among the genes; i.e. many of these are downstream from the first level shown in Figure 1C.

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