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Molecule of the month: miRNA and HIV-1 TAR

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A recent publication analyzed MicroRNAs (miRNAs) globallyinhumans **[1]**. Here, we summarize several key concepts from this article. Apparently during evolution, there were several origins of miRNAs and the authors embarked on a detailed and specific analysis of these events. In fact, the authors analyzed 1,433 extant human miRNAs that originated 15 times during evolution. These steps correspond to the evolutionary progression of the following species: avians, *Prototheria* platypus, *Metatheria* opossum / wallaby, *Atlantogenata*, *Laurasiatheria*, rodents / rabbits, tupai, lemur / galago, tarsier, marmoset, rhesus monkey, gibbon ape, orangutan, gorilla, chimpanzee, and humans. The rates of origin of miRNAs was greatest (most accelerated) in two periods, during the *Atlantogenata-Laurasiatheria* transition / origin period and during the monkey-gibbon ape transition / origin period. Across all 15 originations, the extents of expression are lower for the younger miRNAs **[1].** It should be noted that the process of miRNA integration, stabilization, and expression in an organism's transcriptome takes 60 million years. In addition, there is an ongoing process of miRNA expression increase during that time **[2].** It is noteworthy that the HIV-1 antecedent viruses may have evolved among the primates during this most recent resurgence of miRNAs.

Considering the complexity of miRNAs that we are just beginning to appreciate, it is remarkable that HIV-1 has evolved the capacity to interact with and damage human cells and cause severe disease. HIV-1 is a nine-kilobase single stranded RNA virus with nine genes.There is thus a great difference in number of HIV-1 genes compared to the approximately 20-30,000 genesthat humans have **[3].**

The origin of HIV-1 is a difficult and complex issue. HIV-1 entered human beings and became the virulent virus it is known to be, at least by 1959. Thus, it has caused continued havoc for more than 50 years. Since HIV-1infected humans and was derived from other primates, it was probably by this time primed and ready to invade the human ecosphere / genosphere. HIV-1 has a tremendous capacity to evolve rapidly. This has been studied extensively **[4, 5].**

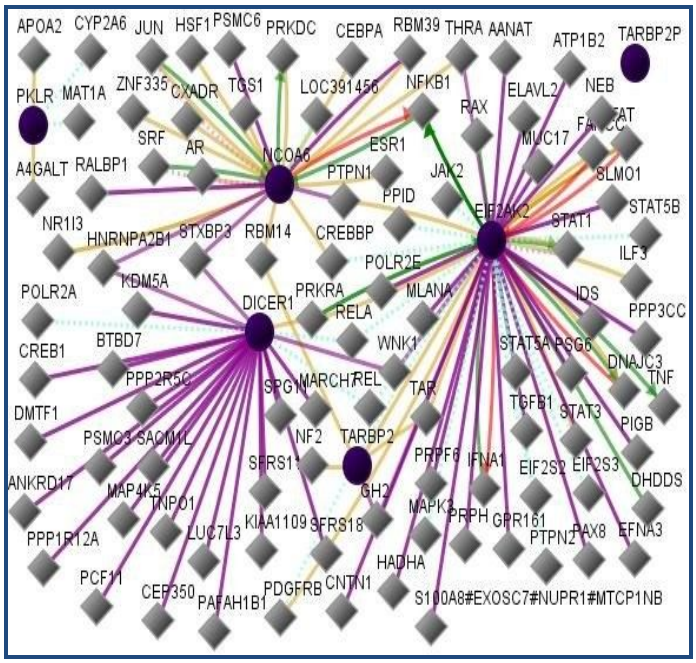

Figure 1: Network of input proteins (TARBP2, TARBP2P, NCOA6, PKLR, EIF2AK2, and DICER1) and the input neighbors of these proteins.Consequent to HIV-1 infection, expression of these proteins may be modulated by miRNAs. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regu*lation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[9].**

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Previously, we analyzed the involvement of HIV-1 Tat protein in cellular gene networks and aspects of its interaction with miRNAs **[6].** In addition, we discussed HIV-1 viral protein R (Vpr) that interacts with miRNAs and its involvement in gene expression networks **[7].** In the current paper, we briefly relate a few themes related to the TAR RNA sequence of HIV-1 from a recent publication **[8]**.

The HIV-1 Tat protein as well as host cell proteins interacts with the TAR sequence on HIV-1 RNA for the control of HIV-1 translation. The TAR sequence is 59 nucleotides in length and is present on all HIV-1 transcripts. Three host cell proteins that are in interactive networks are included among those that are involved in the regulation of HIV-1 translation. These proteins are TAR RNA binding protein (TRBP), dsRNA-dependent kinase (PKR), and Ribonuclease III, double-stranded RNA-specific endoribonuclease (Dicer) **[8].**

On the one hand, the secondary structure in the TAR sequence due to ponderal forces can hamper translation by impeding translation initiation factors, prevent 5'-CAP access, and by PKR activation. On the other hand, HIV-1 translation is enabled by TRBP binding and relaxing of the TAR secondary structure as well as overpowering the triggering of PKR. Moreover, Sanghvi et al indicate that since TRBP is a cofactor of DICER miRNA processing, the arrogation by TAR of TRBP is a forceful opposing measure evolved by HIV-1 to obstruct antiviral cellular processes. The authors indicate that once PKR actuation is blocked, inhibiting TRBP has no further effect on virus production. However, the authors state that these processes do not affect miRNA-muzzling pathways **[8].**

When TRBP, PKR, and DICER were entered into the GenePro program **[9]** then TRBP mapped to multiple symbols TARBP2, TARBP2P, and NCOA6, PKR mapped to multiple symbols PKLR and EIF2AK2, and DICER mapped to DICER1. The protein interactive networks were analyzed as seen in (**Figures 1 & 2)**, and the protein input list became TARBP2, TARBP2P, NCOA6, PKLR, EIF2AK2, and DICER1.

We note that semantics is not always consistent across all databases. This is a relevant issue to analyze and will be done **[10].** Suffice it to say as a general caveat, individual researchers should ascertain the semantics of their terms.

The figures illustrate various gene interactions among the proteins mentioned above. It is left as a puzzle for the interested reader to identify the various genes and their functions in the figures **[11, 12]**.

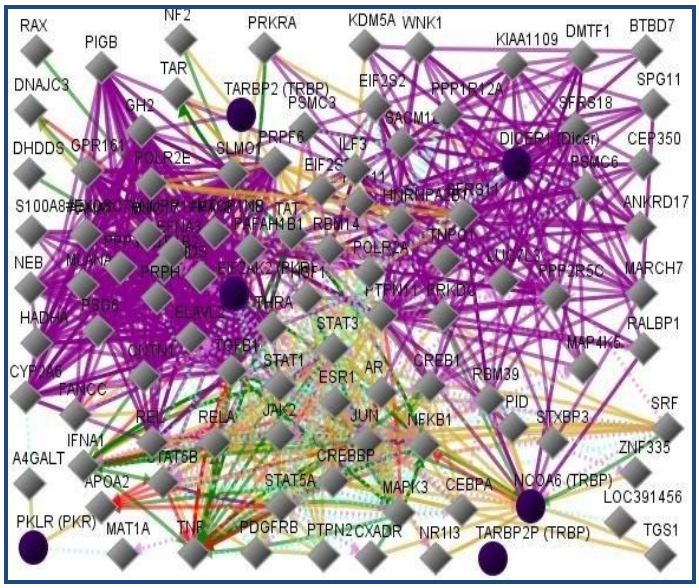

Figure 2: Network of neighbor interactions of the input proteins (TARBP2, TARBP2P, NCOA6, PKLR, EIF2AK2, and DICER1) with the various networks through which they interact. Consequent to HIV-1 infection, expression of these proteins may be modulated by miRNAs. In this figure, line-colors and various interactions 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 **[9]**.

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