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AATF RNome: Cellular Antiviral Armour

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Summary

A common target of all viruses in general and RNA viruses in particular is nucleolus, a dynamic sub-cellular organelle that employs the apoptosis-antagonizing transcription factor (AATF) as its surveillance sensor. It is in this context the AATF RNome, that holds AATF coding transcript and regulatory non-coding miR-2909 within its fold, assumes importance because of its ability to tailor cellular response against a given sensed viral-dependent host-cell nucleoli subversion. This phenomenon is exemplified by the ability of HIV-1 to conspicuously target AATF RNome that ensures cellular antiviral defense through the initiation of CCL5 and RIG-1 signaling response as well as by regulating chromatin dynamics to restrict HIV-1 latency.

AATF RNome: Evolution & Surveillance Nature

Human AATF/ Che-1 RNome finds its origin from the genomic-segment of about 108 Kb size that maps on Chromosome 17 at 17 q11.2- q12. Interestingly in the same chromosomal region, there are several genes encoding proteins that either have binding affinity for nucleic acids or act as chemokine's including CCL5 [1]. AATF RNome assumed importance because it holds AATF coding transcript and regulatory non-coding micro-RNA designated as miR-2909 within its fold to exhibit circadian rhythmical behavior [2-4] as a result of epigenetic cross-talk between RNome and master-genes responsible for the regulation of host immunity, energy metabolism and cellular oncogenic/oncostatic activities [2-6] (Figure 1). AATF encoding transcript gives rise to phosphoprotein, containing 558 amino acids, that not only is highly conserved from yeast to man but is expressed in all human tissues with stronger expression in brain, heart, thymus, kidney and placenta [1,7].

A new dimension was added by the finding that established a direct link between the ultra-structural features of AATF-mutated embryos and paucity of ribosomes, polyribosomes and rough endoplasmic reticulum [8] thereby raising the possibility that AATF protein may be involved in one more aspect of the ontogenic control governing the embryonic development. Further, the conspicuous presence of AATF protein within nucleus especially co-localized with nucleoli reinforced the view that AATF protein may also function as a nucleolar stress-sensor [9] for tailoring the cellular response against a given sensed stress.

Several studies have indicated a crucial role of AATF in the cellular DNA damage response (CDDR) responsible for the maintenance of genomic integrity through the cell cycle arrest followed by DNA repair and promote necroptosis if the damage is too severe [7,10].

AATF protein has been shown to act as a molecular-switch that connects the pathways regulating cell cycle progression, arrest and survival by inhibiting the p53 dependent transcription of pro-apoptotic genes, such as *Puma*, *Bax* and *Back* [11,12]. However, AATF protein is required for p53 transcription as well as the stability of p53 protein [13,14]. Ectopic expression of the AATF protects cells from endoplasmic reticulum (ER) stress – mediated apoptosis whereas its depletion increases the percentage of apoptotic cells as a result of ER-stress [7].

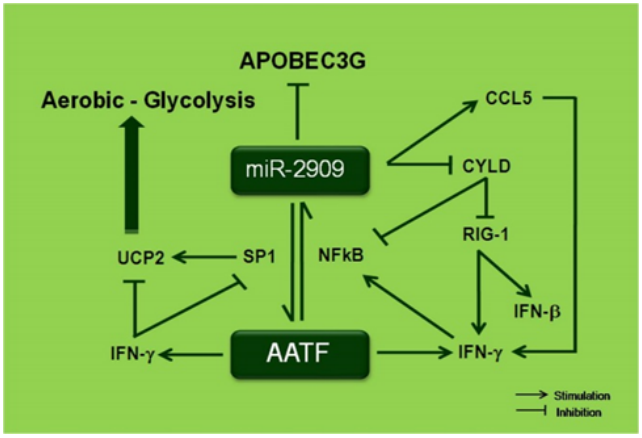

Figure 1: Regulatory "Cross-Talk" between AATF genome encoded AATF protein and miR-2909 is mediated through their effecter master-genes responsible for the regulation of cellular energy metabolism and host immune response. AATF protein ensures sustained expression of miR-2909 by NFkB activation through its ability to induce Akt gene expression directly as well as Bmi-1 gene indirectly. AATF protein also ensures sustained expression of IFN-γ that indirectly controls the expression of miR-2909 leading to the modulation of its effecter genes coding for Rig-1, CCL5, IFN-γ & β, UCP2 & APOBEC3G. The miR-2909 also ensures sustained expression of NFkB & RIG-1 pathway through its ability to repress CYLD gene expression.

Recently, AATF has been demonstrated to protect cells from apoptosis induced by hyper-osmotic stress, hypoxia, glucose deprivation and ER-stress [7]. AATF protein was found to have dual role in the cell cycle regulation because of its ability to displace HDAC1 not only from the Rb-E2F complex resulting in E2F-dependent cell cycle progression but also from SP1 transcription factor responsible for p21 expression thereby ensuring cell proliferation from G1-S phase as well as growth arrest at G1-phase of the cell cycle [1]. AATF Interactome also contains transcriptional co- activator acetylase p 300 which has the capacity not only to acetylate p53 on its lysine residues to prevent MDM2 –induced degradation of p53 protein but also to enhance transactivation of several steroid hormones receptors in a hormone–dependent manner [15,16] .

Using STAT3 as an interacting partner, AATF was found to induce the transcriptional expression of Akt1 gene which, in turn, was responsible for regulating genes coding for KLF4, MDM2, C-myc, NFkB and IFN-γ [17-21]. Interestingly, the transcriptional factors E2F and C-myc were found to induce the expression of AATF and polycomb group protein Bmi-1 [22,23]. It is pertinent to note here that Bmi-1 ensured sustained NFkB activation [24]. KLF4 was found to suppress SP1-dependent genes [23,25] coding for AATF, Bmi-1 and mitochondrial uncoupling protein (UCP2). One arm of the AATF RNome encoding for AATF protein ensures sustained expression of miR-2909 by the activation of NFkB through Akt as well as Bmi-1 gene-products [26,27]. Bmi-1 protein also influences p53 protein stability whereas, the second arm of AATF RNome depicted by miR-2909 ensures regulation of genes coding for Bmi-1, AATF, UCP2, CCL5, CYLD, RIG-1, IFN-γ, IFN-β and APOBEC3G [2-6].

AATF RNome & HIV-1: "Victor" or "Victim" Game

The most conspicuous human intra-cellular structure that is subverted by RNA viruses is the nucleolus, a dynamic sub-nuclear structure responsible for ribosome biogenesis, cell-stress responses and the regulation of cell growth [28]. one of the most well-studied viruses in terms of viral-dependent host-cell nucleoli subversion is HIV which has well define cytoplasmic and nuclear replication strategies involving reverse transcription of positive–sense RNA genome within the cytoplasm follow by trafficking into the nucleus, where the new genome is transcribed and trafficked back to the cytoplasm [29].

Several evidences exist to support the view that RNA viruses use the nucleolus to enhance viral replication, either by interacting directly with proteins such as nucleolin, or altering host cell transcription, translation and possibly the cell cycle [28,29]. Nucleolin is the most characteristic protein of nucleolus and has been shown to shuttle from nucleolus to the nucleoplasm, cytoplasm and the plasma membrane [28] through its Ability to undergo many post-translational modifications, including phosphorylation, glycosylation and acetylation [28,29]. In addition to nucleolin's role in ribosome biogenesis in the nucleolus , it participates in many essential cellular processes, such as chromatin remodeling, DNA recombination and replication, RNA transcription and processing, mRNA metabolism, cell proliferation, , cytokinesis and apoptosis [29]. Nucleolin plays an important role during different life cycle stages of both RNA and DNA viruses thereby contributing to the virus associated pathogenesis [28,29].

A new dimension was added to the nucleolar biology by the finding that AATF has the ability to acts as a novel nucleolar stress sensor [9] and was found to be exclusively localized in the nucleolus , where it co-localized with two well-known nucleolar markers such as nucleolin and B23 [9]. It is pertinent to note that HIV-1 genome encoded microRNA designated as hiv1-miR –H1 (Figure 2) was conspicuously able to suppress AATF gene expression [30] by targeting its exon-1 (Figure 2).

However, an additional target of hiv-1-miR-H1 in the intronic-region between Exon-11 & -12 of the AATF gene intrigued us to explore this region for the existence, if any, of a novel microRNA that many have the ability to target HIV-1 genome. Such a study indeed, revealed the existence of a novel miRNA (initially named as hmiR-Che-1 and now designated as miR-2909) that has the inherent capacity to target HIV-1 genome encoded hiv1-miR-H1 as well as *Vpr* gene [31] (Figure 2). surprisingly, there are not only about ten HIV-1 integration sites within the intronic- region separating Exon-11 from Exon-12 of the AATF gene but also these integration sited are spanning the DNA – sequence that encodes miR-2909 (Figure 2) thereby revealing as to why it is critical for HIV-1 to suppress AATF gene expression together with to neutralize the cellular defense armour in the form of miR-2909 encoded by the AATF genome [31]. At this stage, it is interesting to note that miR-2909 has the inherent capacity to restrict the HIV-1 induced CD4+ lymphopenia, by regulating the expression of antiviral genes coding for APOBEC3G, CCL5, AATF, R1G-1, IFN-β, IFN-γ and UCP2 [2-6,21] (Figure 1).

Several findings have suggested that UCP2 initiates aerobic-glycolysis by shunting pyruvate out of mitochondria through decoupling of glycolysis from aerobic- respiration [32]. Hence it becomes apparent that cyclic regulation of cellular energy metabolism from aerobic respiration to aerobic glycolysis would have been impossible to achieve without the existence of AATF RNome within human cells, which holds AATF mRNA and miR-2909 within its fold. However, flux of aerobic- glycolysis within primary CD4+T-cells not only helps HIV-1 virion production but also increases the sensitivity of the infected cells to the virus- induced cell death. Increased AATF expression ensures sustained expression of miR-2909 as well as IFN-γ which, in turn, ensures aerobic- respiration as well as miR-2909 RNomics contributing to the production of antiviral such as CCL5, R1g-1, IFN-β and IFN-γ [2-6,21] (Figure 1).

This phenomenon explains as to why it is essential for HIV-1 to target AATF gene which has the inherent capacity to restrict this viral entry and replication by its interaction with nucleolar proteins as well as ability to activate cellular antiviral defense armour comprising of CCL5 and Rig-1 signaling required for normal mitochondrial aerobic respiration [2-6,33]. Further, HIV-1 latency has posed major hurdle in devising various prevention or curative measures. Histone deacetylase inhibitors have, recently, shown promise in reactivating HIV-1 reservoirs [34]. In this context also, AATF Interactome assumes importance because AATF is known to displace HDAC and recruit co-activators p300 to various promoters in human genome [15]. Hence HIV-1 dependent suppression of AATF gene may contribute to HIV-1 latency as well as pathogenesis of AIDS.

Concluding Remarks

Human cellular AATF genome has evolved to emerge as a "Master Epigenetic-Switch" that governs major cell decisions involving cell cycle progression, check point control, apoptosis and nucleolus – directed tailored immune response to a given sensed "Alarmin". All viruses in general and RNA viruses in particular, have developed not only fatal affinity for nucleolus but also strategies to disable its antiviral arsenal in the form of AATF genome that encodes AATF transcript and non-coding transcript maturing into miR-2909. This view is in conformity with the love & hate relationship that exists between HIV-1 genome and the host cellular AATF genome (Figure 2). Hence functional stability of AATF genome may provide novel protective armour against RNA viruses.

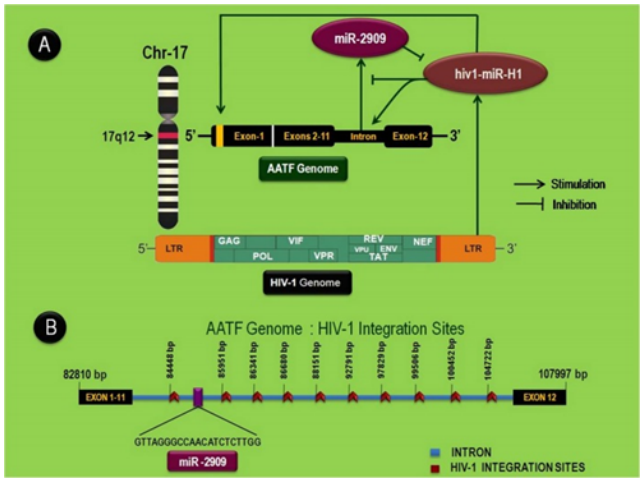

Figure 2: The hiv1-miR-H1, encoded by 3' LTR region of the HIV-1 genome , targets human cellular AATF gene not only at the Exon-1 to suppress its expression but also in the intronic- region separating its Exon-11 from Exon-12. This hiv1-miR-H1 intronic target-region encodes a microRNA designated as miR-2909 that has the inherent capacity to target hiv1-miR-H1 genome. Interestingly, there are about ten HIV-1 integration sites within this intronic-region (of AATF gene) spanning the DNA-sequence that encodes miR-2909.

References

1. Passananti C, Fanciulli M (2007) The anti-apoptotic factor Che-1/AATF links transcriptional regulation, cell cycle control, and DNA damage response. Cell Div 2: 21.
2. Kaul D, Sharma S (2015) High glucose-induced human cellular immune response is governed by miR-2909 RNomics. Blood Cells Mol Dis 54: 342-347.
3. Kaul D, Sharma S, Garg A (2015) Mitochondrial uncoupling protein (UCP2) gene expression is regulated by miR-2909. Blood Cells Mol Dis 55: 89-93.
4. Sharma S, Singh D, Kaul D (2015) AATF RNome has the potential to define post mortem interval. Forensic Sci Int 247: e21-24.
5. Sharma M, Sharma S, Arora M, Kaul D (2013) Regulation of cellular Cyclin D1 gene by arsenic is mediated through miR-2909. Gene 522: 60-64.
6. Kaul D, Sharma S, Sharma M, Arora M, Arora M (2014) Arsenic programmes cellular genomic-immunity through miR-2909 RNomics. Gene 536: 326-331.
7. Iezzi S, Fanciulli M (2015) Discovering Che-1/AATF: a new attractive target for cancer therapy. Front Genet 6: 141.
8. Thomas T, Voss AK, Petrou P, Gruss P (2000) The murine gene, Traube, is essential for the growth of preimplantation embryos. Dev Biol 227: 324-342.
9. Ferraris SE, Isoniemi K, Torvaldson E, Anckar J, Westermarck J, et al. (2012) Nucleolar AATF regulates c-Jun-mediated apoptosis. Mol Biol Cell 23: 4323-4332.
10. Lord CJ, Ashworth A (2012) The DNA damage response and cancer therapy. Nature 481: 287-294.
11. Hopker K, Hagmann H, Khurshid S, Chen S, Hasskamp P, et al. (2012) AATF/Che-1 acts as a phosphorylation-dependent molecular modulator to repress p53-driven apoptosis. EMBO J 2012 31: 3961-3975.
12. Sharma S, Kaul D, Arora M, Malik D (2015) Oncogenic nature of a novel mutant AATF and its interactome existing within human cancer cells. Cell Biol Int 39: 326-333.
13. Bruno T, Desantis A, Bossi G, Di Agostino S, Sorino C, et al. (2010) Che-1 promotes tumor cell survival by sustaining mutant p53 transcription and inhibiting DNA damage response activation. Cancer Cell 18: 122-134.
14. Calao M, Sekyere EO, Cui HJ, Cheung BB, Thomas WD, et al. (2013) Direct effects of Bmi1 on p53 protein stability inactivates oncoprotein stress responses in embryonal cancer precursor cells at tumor initiation. Oncogene 32: 3616-3626.
15. Peter Leister SB, Leister P, Burgdorf S, Scheidtmann KH (2003) Apoptosis antagonizing transcription factor AATF is a novel co-activator of nuclear hormone receptors. Signal Transduct 3: 17-25.
16. Dornan D, Shimizu H, Burch L, Smith AJ, Hupp TR (2003) The proline repeat domain of p53 binds directly to the transcriptional coactivator p300 and allosterically controls DNA-dependent acetylation of p53. Mol Cell Biol 23: 8846-8861.
17. Ogawara Y, Kishishita S, Obata T, Isazawa Y, Suzuki T, et al. (2002) Akt enhances Mdm2-mediated ubiquitination and degradation of p53. J Biol Chem 277: 21843-21850.
18. Segrelles C, Moral M, Lara MF, Ruiz S, Santos M, et al. (2005) Molecular determinants of Akt-induced keratinocyte transformation. Oncogene 25: 1174-1185.
19. Meng F, Liu L, Chin PC, D'Mello SR (2002) Akt is a downstream target of NF-kappa B. J Biol Chem 277: 29674-29680.
20. Okubo T, Washida K, Murakami A (2010) Phenethyl isothiocyanate suppresses nitric oxide production via inhibition of phosphoinositide 3-kinase/Akt-induced IFN-gamma secretion in LPS-activated peritoneal macrophages. Mol Nutr Food Res 54: 1351-1360.
21. Kaul D, Arora M, Garg A, Sharma S (2015) MALT1 induced immune response is governed by miR-2909 RNomics. Mol Immunol 64: 210-217.
22. Mehrotra A, Joshi K, Kaul D (2010) E2F-1 RNomics is critical for reprogramming of cancer cells to quiescent state. Int J Cancer 127: 849-858.
23. Wang HB, Liu GH, Zhang H, Xing S, Hu LJ, et al. (2013) Sp1 and c-Myc regulate transcription of BMI1 in nasopharyngeal carcinoma. FEBS J 280: 2929-2944.
24. Jiang L, Song L, Wu J, Yang Y, Zhu X, et al. (2013) Bmi-1 promotes glioma angiogenesis by activating NF-IB signaling. PLoS One 8: e55527.
25. Kaul D, Mehrotra A (2007) Functional characterization of AATF transcriptome in human leukemic cells. Mol Cell Biochem 297: 215-220.
26. Ishigaki S, Fonseca SG, Oslowski CM, Jurczyk A, Shearstone JR, et al. (2010) AATF mediates an antiapoptotic effect of the unfolded protein response through transcriptional regulation of AKT1. Cell Death Differ 17: 774-786.
27. Nowak K, Kerl K, Fehr D, Kramps C, Gessner C, et al. (2006) BMI1 is a target gene of E2F-1 and is strongly expressed in primary neuroblastomas. Nucleic Acids Res 34: 1745-1754.
28. Hiscox JA (2007) RNA viruses: hijacking the dynamic nucleolus. Nat Rev Microbiol 5: 119-127.
29. Salvetti A, Greco A (2014) Viruses and the nucleolus: the fatal attraction. Biochim Biophys Acta 1842: 840-847.
30. Kaul D, Ahlawat A, Gupta SD (2009) HIV-1 genome-encoded hiv1-mir-H1 impairs cellular responses to infection. Mol Cell Biochem 323: 143-148.
31. Kaul D, Hussain A (2009) Cellular AATF gene encodes a novel miRNA that can contribute to HIV-1 latency.
32. Xu X, Duan S, Yi F, Ocampo A, Liu GH, et al. (2013) Mitochondrial regulation in pluripotent stem cells. Cell Metab 18: 325-332.
33. Tamamis P, Floudas CA (2014) Elucidating a key anti-HIV-1 and cancer-associated axis: the structure of CCL5 (Rantes) in complex with CCR5. Sci Rep 4: 5447.
34. Smith PL, Tanner H, Dalgleish A (2014) Developments in HIV-1 immunotherapy and therapeutic vaccination. F1000 Prime Rep 6: 43.