

HIV-1 Exploits Cellular miR-2909 RNomics to Initiate and Ensure AIDS Disease

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Opinion

Human immune cells have evolved with a membrane trafficking pathway called Autophagy, responsible for engulfing the invading pathogens and thereby equipping these cells with the innate and adaptive immune responses against numerous pathogens. On the other hand, the various pathogens have developed strategies to either block or use the autophagy mechanism to their own advantage [1]. Human immunodeficiency virus type 1 (HIV-1) infects mainly CD4⁺ T-lymphocytes and macrophages through the interaction of the viral (Env) glycoproteins (Gp120 and Gp41) with CD4 as well as co-receptor, mainly CCR5, expressed at the surface of the target cells. Such type of interaction induces a structural rearrangement in glycoprotein 41 and the insertion of its N-terminus fusion peptide into the target cell membrane, leading to the cellular endocytosis of the HIV-1 viral particles [2]. The HIV-1 replication cycle is governed in two phases: the early phase, from viral entry to provirus integration with cellular genome, and the late phase, from transcription of viral genes to the release of new particles [2].

Autophagy and HIV-1: Cross Talk

The mechanism that governs the crosstalk between autophagic process and HIV-1 within virally challenged cell type remains to be elucidated. Current data suggest that HIV-1 has evolved mechanism to subvert its autophagic degradation within infected immune cells and thereby replicate efficiently in such cells [2]. Further, how the HIV-1 infected cells contribute to the depletion of the bystander uninfected CD4⁺ T-cells observed in AIDS disease, remains far from clear. However, evidence exists to suggest that HIV-Gp41 can ensure sustained expression of tumor suppressor p53 protein within the bystander uninfected CD4⁺ T-cells leading to their depletion either through p53- induced pro-apoptotic factor Puma and Bax or Beclin-1 initiated autophagic death [3,4]. Several pieces of evidence support the view that p53 protein controls the activity of mammalian target of rapamycin (mTOR) which is a highly conserved serine/threonine kinase recognized to play crucial role in cell homeostasis, regulation of cell growth, metabolism and autophagy in response to the environmental stress [5]. The relevance of mTOR pathway governed autophagic process, assumes importance because its deregulation is observed in several viral diseases including that in AIDS disease [6]. The mTOR has evolved to participate in two distinct functional complexes, mTOR Complex 1 (mTORC1) and mTOR Complex 2

(mTORC2). The mTORC1 is the regulator of cell growth and protein translation, whereas mTORC2 governs the actin cytoskeleton and cell survival by phosphorylating AKT1 [7]. Both these protein complexes are closely controlled by various feedback mechanisms that activate and repress mTOR in response to different intra- and extracellular stimuli. Because mTORC1 inhibits autophagy to end in cell death and mTORC2 promotes cell survival [7], this phenomenon makes the net contribution of mTOR-pathway to the mechanism of CD4⁺ T-cell depletion apparently more complex to decipher. This view is supported by the *in vivo* evidence that mTOR blockade with rapamycin does not influence HIV-1 induced CD4⁺ T-cell death [6]. However, this finding does not rule out the fact that HIV-1 infected cell induced depletion of the bystander uninfected CD4⁺ T-cells, may be mediated through p53-induced apoptotic pathway involving Puma and Bax [3,4] within CD4⁺ T-cells.

hiv-1-miR-H1 & mTOR – Pathway

The discovery of the novel microRNA (designated as hiv-1miR-H1) encoded by HIV-1 genome and its ability to selectively and conspicuously suppresses human cellular apoptosis antagonizing transcription factor (AATF, also known as che-1), added up a new dimension to the pathogenesis of HIV-1 infection [8]. Human cellular AATF gene is located on the chromosome 17, a region of the genome that is home to genes (including tumor suppressor p53) implicated in a wide range of human genetic diseases [9]. In the recent years, AATF protein has not only emerged to behave like a “Master Epigenetic Switch” that regulates cell cycle progression, check point and apoptosis, but also as a nucleolar stress sensor that monitors and maintains ribosome biogenesis and nucleolar integrity [9]. A new dimension was added to the AATF biology by the finding that revealed its crucial role in the regulation of mTOR activity in response to the stress [7]. AATF protein has shown to have inherent capacity to induce the expression of genes coding for p53, Deptor and REDD-1 [4,7]. The Deptor gene-product is known to inhibit mTORC1 and thereby promote autophagy, whereas REDD-1 gene-product induces mTORC2 to ensure cell survival [7]. Further, AATF protein has the ability to inhibit the p53-dependent transcriptional expression of pro-apoptotic genes, such as Puma, Bax and Bak [4]. All these findings taken together point to the fact that HIV-1 genome encoded hiv1-miR-H1 has the capacity to inhibit cellular autophagic process through the inhibition of AATF gene expression (Figure 1).

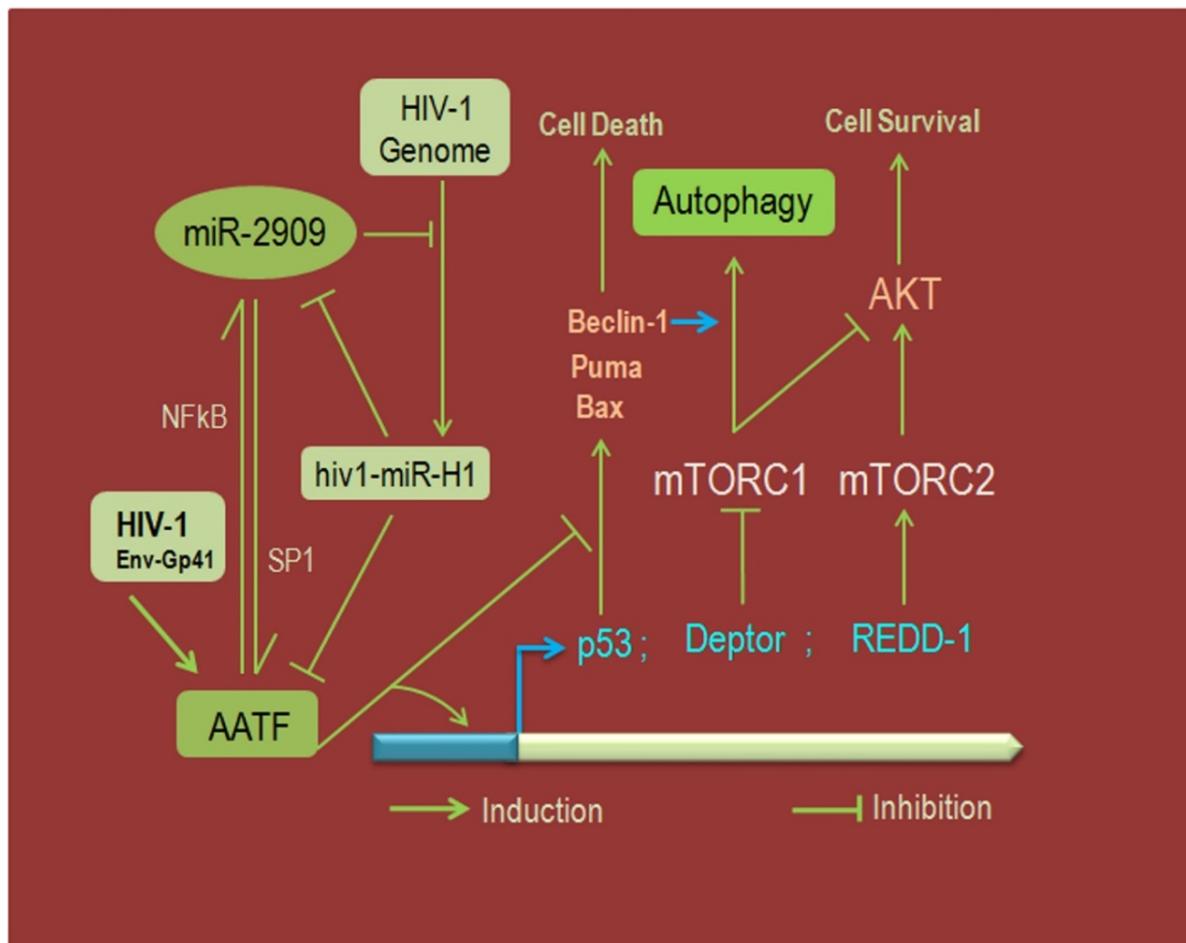


Figure 1: Inhibition of AATF gene expression.

Cellular miR-2909 RNomics & HIV-1 Infection

The ability of hiv-miR-H1 to also target the intronic region that separates exon-11 and 12 of the AATF genome, intrigued us to explore this region for the existence (if any) of a novel cellular microRNA that could have the ability to target HIV-1 genome. Such a study, indeed, revealed the existence of a microRNA (initially named by us as hmiR-che-1 and now widely known as miR-2909) that has the ability to target region (within HIV-1 genome) that encodes hiv1-miR-H1 [10,11]. Interestingly, higher expression of miR-2909 in the lymphocytes from asymptomatic AIDS subjects was always accompanied by the lower expression of hiv1-miR-H1, whereas it was vice-versa in the lymphocytes from the symptomatic AIDS subjects [10]. Hence, the cellular AATF genome has evolved to hold AATF protein coding-transcript and regulatory non-coding miR-2909 within its fold in a fashion that ensures their mutual regulation. AATF protein ensures higher expression of miR-2909 through the activation of NFkB, whereas miR-2909 RNomics ensures increased AATF expression through up-regulation of SP1 transcription factor [11-13].

There exists a general recognition of the fact that cellular autophagy and exosome secretion are two coordinated mechanisms responsible for the cellular defense against any kind of stress [14]. Consequently, it is reasonable to assume that for HIV-1 to sustain its replication cycle,

the host cellular autophagic process has to be considerably reduced to allow release of exosomes (hiv1-miR-H1) to initiate death within HIV-uninfected bystander CD4⁺ T-cells through the down-regulation of AATF gene expression (Figure 1) leading to AIDS disease. Such a phenomenon would have been impossible to achieve if the HIV-1 encoded hiv1-miR-H1 was not able to exploit miR-2909 RNomics (Figure 1) to regulate host cellular autophagic process. This view is in conformity with the finding that revealed higher expression of both AATF and miR-2909 within lymphocytes from asymptomatic AIDS subjects as compared to lymphocytes from the symptomatic AIDS subjects [10]. There is reason to believe that HIV-1 has evolved strategy to up-regulate cellular miR-2909 RNomics for the sustenance of its replication cycle and to down-regulate miR-2909 RNomics within uninfected bystander CD4⁺ cells exposed to exosomes (enriched with hiv1-miR-H1) secreted by viral infected immune cells (Figure 1). Hence, it would be pertinent to explore if antagomiR-against hiv1-miR-H1 could be used as a therapeutic strategy against the AIDS pathogenesis.

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