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Novel Anti-Retroviral Drug Targets: Interfering siRNA and Mitochondrial TERT Expression

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Abstract

Telomerase can be touted as the miracle anti-aging enzyme that reverses the age-related attrition of telomere ends. The catalytic subunit of telomerase, TERT telomerase reverse transcriptase, is known to function as an RNA dependent DNA polymerase in the nucleus (TERT-TERC), as an RNA dependent RNA polymerase, an RdRP (TERT-RMRP), in mitochondria, and, as TERT alone interacting with master regulators for cell and organellar protection to promote global survival and rejuvenation potential. TERT shows conservation of the viral polymerase structure, and like viral polymerases, is capable of producing cDNA, double stranded RNA, and like HIV reverse transcriptase, is inhibited by some HIV reverse transcriptase inhibitors. TERT also shows promiscuous partnering with RNA elements, RMPR, tRNA, and TERC. TERT, with its versatile viral-like functions, seems like a valuable hostage for viral infection. Telomerase is inhibited by viral proteins. When the role of telomerase in HIV infection is reviewed, telomerase modulation emerges as a valuable player in HIV therapy intervention. Induced viral protein and some reverse transcriptase HIV drugs promote TERT deficit which might be counteracted by TERT up regulation, or preference for use of drugs that do not target host reverse transcriptase, in order to preserve the health promotion of TERT pathways especially mitochondrial protection against oxidative stress, and inhibition of pathways that promote immune deficiency. Telomerase "dark side" dysfunctional overexpression might be targeted using an anti-cancer-like vaccine, delivered selectively to viral reservoirs. The use of siRNA's to inactivate proteins that promote viral survival offer promising potential success in anti-retroviral therapy, with the ability to block mico RNAs favorable for viral progression. Strategies and therapy that interfere with the HIV-TAR interaction offer the desirable ability to stop infection before it starts. Mimetics of exercise, hibernation, anti-aging supplements, and mitochondrial targeted antioxidants offer antiviral potential and disease vulnerability from fallout of immune deficiency.

Keywords: Telomerase; MicroRNA; Aptamers; Mimetics; TAR

Introduction

The following three discoveries, identification of master gene regulator targets, small molecules capable of altering gene expression, and availability of drug delivery by viral and non- viral carriers to organ, cell and mitochondrial-sites provide the potential for magic bullets for multiple human pathologies. Despite disease symptomatic differences, fundamental stresses and abnormal gene function are shared and subject to treatment by common drugs. The master gene regulators are identified by their conservation throughout evolution, since nature demands stress resistance for survival. The common stresses are oxidative, hunger, thirst, energy depletion, temperature, and infection. Tolerance strategies and drugs employed to treat the common stresses are candidates to treat HIV. Mimetics of tolerance, and stress resistance agents used to tolerate stress in different organisms are reservoirs for drug intervention [1-3] applicable in HIV therapeutics.

The master regulator, telomerase, is identified by its phylogenetic conservation throughout evolution. Clues from studies of high resolution of telomerase structure, its subunits, and potential interactions reveal its ancient origin and remarkable similarities with retroviruses and HIV, and reveal drug target potentials for HIV therapy. The diversity of functions of telomerase in the nucleus, cytoplasm, nucleolus, and mitochondria, provide a myriad of interactions [4] and potential for interaction sites with HIV amenable to regulation.

The structure and functions of telomerase are reviewed as a platform for HIV interventions of different pathways to regulate disease progression while preserving patient health. Telomerase is now known to be almost universally conserved in eukaryotes [5]. Telomerase is composed of the RNA ligand TERC and it protein catalytic protein TERC. The human telomerase RNA, hTERC, is thought to function as a dimeric complex consisting of two RNAs that interact with each other physically as well as genetically [5]. The yeast telomerase RNA likewise forms dimers in vitro and the dimerization depends on a unique 6-base self- complementary sequence, which closely mimics palindromic sequences that mediate functional dimerization of HIV-1 and other retroviral genomes [6].

High resolution structure of the protein reverse transcriptase subunit of telomerase, TERT, revealed four conserved domains: RNA-binding domain; fingers, palm, and thumb organized into a ring configuration that shares common features with retroviral reverse transcriptase, viral RNA polymerases, bacteriophage B-family DNA polymerases and DNA associations that are remarkably similar to those observed for retroviral reverse transcriptase, suggesting common mechanistic aspects of DNA replication between the two families of enzymes [7-9]. Human TERT is capable of both type 1 and 2

processivity with the capacity of extending primers by hundreds of nucleotides. Inhibitors of telomerase include chain termination nucleoside analogues which bind to the dNTP site, and NNRT1 which bind to pocket nestled between palm and thumb domain, and lined in part by the grip domain like HIV reverse transcriptase, though TERT has another pocket in the thumb domain [10]. The basic nucleotide transfer and elongation mechanisms of TERT are nearly identical to conventional reverse transcriptase; several conserved motives near the end of the RT domain, provide recognition of diverse RNA structures in multiple diverse organisms [5]. Therefore some reverse transcriptase drugs that target HIV reverse transcriptase likely target TERT as well. The ability of TERT to interact with multiple RNAs implies a potential for human TERT to interact with HIV RNAs. Although much is known about viral protein interactions with TERT, little is known about how host human TERT interacts with viral RNA reverse transcriptase. The TERT multifaceted transcriptase interactions in support of metabolic functions are reviewed here to highlight its potential in HIV therapy, for appropriate up or down regulation for the beneficial and detrimental roles in HIV pathology and associated diseases.

The gap in scientific knowledge is a focus on how human reverse transcriptase function is altered by HIV infection and available therapy, not only by alteration of telomere maintenance, but by alteration of the other TERT subunit roles in global resistance, health, and survival. Figure 1

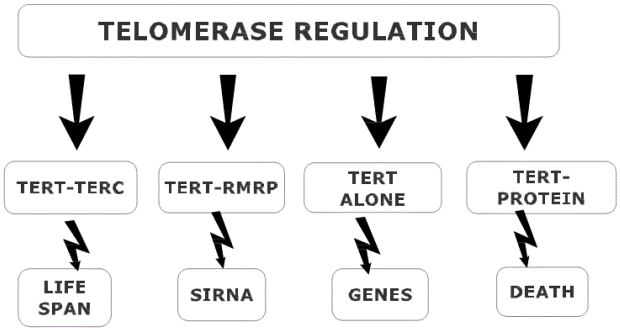

Figure 1: Highlighting telomerase here, in HIV infection, illuminates strategies for HIV drug intervention, drug preferences, and complimentary additions to compensate for certain drug induced deficits and alternative options for drug resistant patients.

The reverse transcriptase protein subunit, TERT, with the RNA moiety TERC, acts as an RNA dependent DNA polymerase capable of replacing tandem short DNA sequences at telomere ends of eukaryote chromosomes [11]. The catalytic subunit, with its RNA ligand TERC, extends the replicative potential and prevents replicative senescence [12]. Each telomerase subunit has health related functions. TERC deficiency exhibits impaired glucose tolerance due to impaired glucose-stimulated insulin secretion from pancreatic islets of reduced islet size, impaired replication, insulin secretion and glucose intolerance that identifies a role of telomerase in diabetes [13]. Viral or intervention therapy that inhibits the TERT-TERC complex then is likely to promote diabetes.

Genetically engineered telomerase-deficient mice show wide-spread endogenous DNA damage, tissue atrophy, stem cell depletion, organ system failure and impaired tissue response that mimic age related changes [14, 15]. Telomere dysfunction activates p53-mediated cellular growth arrest, senescence and apoptosis to drive progressive atrophy of stem cells [14, 15]. The reversal of tissue degeneration in aged telomerase deficient mice by genetically engineered inducible telomerase activation shows unprecedented evidence for global major participation of telomerase in regeneration of organ systems [16]. Telomerase reverse transcriptase alters chromatin state, and DNA damage response [17]. In the absence or low levels of telomerase, telomeres shorten at each cell division; show associated double strand breaks, senescence, replicative division cessation, apoptosis [18]. Therefore, either HIV infection, or therapy-induced telomerase inhibition, would be expected to promote global tissue atrophy that mimics senescence.

In the mitochondria, promiscuous TERT, can partner with another RNA ligand, namely, the RNA component of mitochondrial RNA processing endoribonuclease (RMRP). TERT- RMRP is the only known RNA dependent RNA polymerase in eukaryotes (RdRP) [19]. The double stranded RNA can be processed into small interfering RNA, siRNA in a Dicer-dependent manner, capable of mitochondrial based regulation of gene expression as an option. TERT-RMRP activity enhances cell proliferation via small interfering RNA generated by RdRP now available for splicing into small interfering RNAs [20]. TERT can act as an RNA dependent DNA polymerase by production of mitochondrial tRNAs [4]. The ability of promiscuous TERT to partner with different RNA ligands was predicted from its structure [10] and implies a potential for TERT to interact with HIV's RNAs.

In control of other master regulators, TERT protein is associated with transcriptional control of the Myc-Wnt developmental program [21] and Wnt/catenin signaling stem cells [22,23]. The role of TERT in gene expression was recently reviewed [4,24]. In the cytoplasm, TERT binds with stress protein particles and initiates signaling interactions. Telomerase directly regulates NF-κB-dependent gene expression by binding to the NF-κB p65 subunit, and recruitment of a subset of NF-κB promoters such as those of IL-6 and TNF-α, cytokines that are critical for inflammation and cancer progression [25, 26]. NF-κB can also regulate telomerase [27] revealing cross-talk between the two regulators. In fully differentiated neurons, the largest pool of cytoplasmic TERT associates with TIA1 positive RNA granules, where it binds the messenger RNA of the cyclin kinase inhibitor p15INK4B [28]. TERT expression activates resistance to P151NKAb cyclin inhibitor and allows proliferation [29]. Thus telomerase should be a potent pro-survival regulator for support of immune cell proliferation.

Within the nucleus, the nucleolus is a membrane-less nuclear compartment originally known only as the site for ribosomal RNA and ribosome biogenesis. The nucleolus is now known as the hot spot for viral infection [30]. In HIV infection, the nucleolus is the site for transcriptional regulation, cell cycle control, transient nucleolar trafficking of both Tat and HIV-1 viral transcripts [31]. Tat expression specifically results in the nucleolar enrichment of proteins collectively participating in ribosomal biogenesis, protein homeostasis, metabolic pathways, and stress response, that promotes a cellular environment supporting robust HIV-1 production [31]. HIV overtakes the nucleolus cell factory for production of viral propagation.

In the nucleolus, telomerase associates with the signalling protein 14-3-3 active in the sub-cellular shuttling of several proteins [32] and is induced by TNF alpha [33] and DNA damage [34]. Telomerase activation in human T lymphocytes does not require increase in telomerase reverse transcriptase, TERT protein, but is associated with TERT phosphorylation and nuclear translocation [35]. TERT

suppresses apoptosis at a premitochondrial step by a mechanism requiring reverse transcriptase activity and 14-3-3 protein-binding ability [36].

In response to oxidative stress, TERT shuttles from the nucleus to the mitochondria and protects mitochondria from apoptosis and mitochondrial DNA damage [37-39] via BCL-1 pathways [40]. The mitochondria, aside from their function as the site of energy generation, are now known to be critical for organelle signaling, regulation of multiple diseases, and the decision between cell proliferation or cell death [41-43]. Drugs that target antioxidants to mitochondria [43] increase mitochondrial function in normal cells and intervene in otherwise unrelated pathologies, like diabetes, Alzheimers disease, neurological disorders, stroke, heart, attack, and wound healing [43]. Mitochondria targeted antioxidants may be candidates for resistance to oxidative stress associated with of HIV pathology and related diseases.

The critical role of mitochondria in innate and adaptive immunity has recently been reviewed [44]. Mitochondria are necessary for establishing immune cell phenotype in order to fulfil the appropriate metabolic demands of different immune cells. The immune cells are so effective because of their ability to rapidly respond to stress and decide to participate as an effector cell promoting inflammation, or suppressor cell to control inflammation. The effector cell increases uptake of glucose and glutamine to supply ATP for cloning cells with mitochondria as the anabolic hub. Cd8 memory cells use catabolic metabolism of fatty acids to generate fuel for survival and localization of immune regulatory proteins on the outer mitochondrial membrane [44]. Mitochondria must play a critical role in HIV progression.

While the protective role of telomerase is well documented, there is also a dark side. Overexpression of TERT in cancer neutralizes ROS production, improves mitochondrial function, inhibits apoptosis [45], and protects against DNA damage [46]. Telomerase reverse transcriptase inhibitors are effective anticancer drugs that target only cancer cells, not normal cells. In HIV infected monocyte derived macrophages (MDM), viral reservoirs show over expression of telomerase, likely participating in safeguarding HIV viral reservoirs, and are therefore a target for selective HIV intervention [47]. Successful reservoir destruction has the potential for minimizing the need for long-term HIV therapy.

The universal cancer vaccine is a cancer peptide-based therapeutic vaccine against telomerase and eradicates established tumour [48]. The vaccine targets antitumor CD4 helper cells with universal tumour reactive helper peptides derived for telomerase [49]. The activated CD4 cells then selectively destroy the cancer cells. The "dark side" overexpression of TERT in monocyte reservoirs may reflect a "different" TERT. Alternative splicing affects ~95% of eukaryotic genes, greatly expanding the coding capacity of complex genomes. TERT mRNA is subject to an atypical alternative spliced mRNA. It is known that misregulation of telomerase splicing is a hallmark of nearly all cancers, though details of this process are incomplete [50]. TERT-induced overexpression may be also be alternatively spliced in HIV reservoirs. There may be potential for a "universal antiviral vaccine" that selectively targets TERT in MDM cells without interfering with the positive role of TERT in immune cell proliferation.

Clues of telomerase protection against HIV infection emerge from studies of non- progressor hosts of HIV infection, versus patients that show progressive HIV infection pathology. Vpr viral protein inhibits telomerase by increase ubiquitination targeting telomerase for disposal [51]. Viral protein Vpr redirects the host ubiquitination pathway to trash cell regulators [52]. A Vpr mutant protein, identified in HIV-1-infected long-term nonprogressors failed to promote TERT destabilization [51], and provides the host with resistance to viral progression. The mutant Vpr protein may be a therapeutic agent in HIV progression intervention therapeutics.

Telomerase activity of HIV-1-specific CD8+ T cells show constitutive up regulation in non-progressive controllers HIV patients. Blockade of programmed cell death ligand 1 is associated with immunosuppression found in patients progressive viral infections. Telomere shortening contributes to functional deficiencies of HIV-1-specific CD8+ T cells in chronic progressive infection, while high constitutive telomerase correlates with maintenance of polyfunctional HIV-1-specific CD8+ T cells from HIV-1 controllers [53]. Therapeutic increase of telomerase expression in HIV progressors may intervene in telomere loss and reduce HIV pathology.

Up regulation of telomerase has a beneficial effect in HIV pathology intervention. Ectopic hTERT expression extends the life span of human CD4+ helper and regulatory T-cell clones by induced resistance to oxidative stress-induced apoptosis [54]. Although immune cells up-regulate telomerase in concert with activation, during aging and chronic HIV-1 infection, there are high proportions of dysfunctional CD8+ CTL, crucial effector cell type responsible for intervention in HIV infection, with short telomeres. Exposure of CD8+ T lymphocytes from HIV-infected human donors to a small molecule telomerase activator (TAT2) (cycloastragenol) a Chinese herb, modestly retards telomere shortening, increases proliferative potential, and enhances cytokine/chemokine production and antiviral activity [55].

Likewise, transfection of telomerase cDNA into HIV-specific CD8+ T cells, enhanced antiviral function, increased proliferative potential, and telomere length stabilization in long-term cultures of virus-specific CD8+ T cells established from multiple HIV-1-infected donors [56]. Telomerase expressing CD8+ T cells exhibited enhanced viral suppressive activity, delay or some inhibition of senescence, and prolonged ability to produce IFN-γ and TNF-α in response to stimulation with HIV-1-derived peptides. Reduced expression of the p16INK4a and p21WAF1 cell cycle inhibitors in human TERT-transduced lymphocytes is another possible contributor to TERT mediated promotion of delayed senescence.

In CD4+ T lymphocytes, the viral HIV-1-Tat shows inhibition of telomerase activity in human infected or non-infected T lymphocytes [57]. The inhibition of telomerase by Tat reflected reduction of nuclear telomerase levels and altered TERT phosphorylation, thereby reducing the replicative potential non-infected CD4(+) T cells and promotion of immunodeficiency in AIDS patients [57]. Hematopoietic progenitor cells (HPC) exposed to recombinant viral gp120, showed significantly reduced telomerase [58]. CD 4(+) T lymphocytes infected with human immunodeficiency virus type 1 (HIV-1) showed down regulation of nuclear and cytoplasmic fractions of TERT expression and phosphorylation [59].

Artificially inhibiting TERT, using small interfering RNA-targeting human TERT (hTERT) in HIV-1-infected monocytic U937 cells resulted in the upregulation of HIV-1-induced overexpression of intercellular adhesion molecule-1 via the NfkappaB-regulated mechanism, a pathway known to be regulate by telomerase. Telomerase inhibition by HIV proteins may predispose cells to inflammatory mediators and the disruption of the barrier function at the level of the brain endothelium [60].

TERT dysfunction activates tumour suppressor p53 and the proapoptotic Bcl-2 protein Bax, and in the absence of other proteins, destroys mitochondria. [61]. A consequence of telomerase dysfunction is short telomeres, and activation of DNA damage response associated with p53 expression [14]. Treatment of p53-positive cell lines U2OS and MCF-7 with the DNA damaging drug, doxorubicin, and increases p53 protein level, and induces expression of Ipaf mRNA, a caspase 1 activator [62]. SiRNA of Ipaf RNA down regulated p53-induced Ipaf gene expression and reduces p53-induced apoptosis [62].

In most human lymphoid tissues including tonsil, lymph node, and spleen, the activated and permissive subset of cells represents 5% or less of the total CD4 T cells, while non- permissive quiescent cells represent 95% or more of the targets encountered by HIV. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue via caspase 1 rather than caspase 3 [63]. Since DNA damage activates p53, that activated Ipaf [62] and caspase1 Ipaf inhibition would theoretically block caspase 1 mediated inflammation and depletion of immune cells. The known small hairpin siRNA that down regulates Ipaf and p53- induced apoptosis, [62] may intervene in Ipaf activation of caspase1 induced CD4 cell depletion.

Interferon-γ-inducible protein 16 (IFI16) is a host DNA sensor required for CD4 T cell death due to abortive HIV infection. Regulation of this sensor may play a central role in CD4 T cell depletion during disease progression to AIDS and is currently investigated as target against HIV [64].

In contrast to the detrimental effects of p53, p53 is known to be a host restriction factor against HIV-1 replication. A recent study provides the underlying basis for p53 host protection. In p53 hosts, HIV activates p53, and a double stranded RNA dependent-protein kinase (PKR) that mediates a complex with the viral protein Tat to form the noncanonical P53/PKR/Tat phosphorylation inactivation pathway that blocks the HIV infection. Tat phosphorylation prevents Tat interactions with Tar, Tat cyclin, and nuclear transport [65].

A mutant Tat protein, Null basic, was found to produce instability of the viral apparatus called the reverse transcription complex (RTC). This unique antiviral activity may stimulate development of other viral RTC inhibitors [66]. Since this reverse transcriptase inhibitor targets the viral reverse transcriptase, it likely does not inhibit host TERT reverse transcriptase and stops infection before it starts.

Interference in the Tat-TAR interaction, essential for initiation of HIV infection is a target for HIV intervention. Functional interactions between HIV-1 Tat and TAR are known [67] and inhibitors of the interaction are identified [68]. TAR is a structured RNA located at the 5' end of all transcripts derived from HIV-1 that act as a master switch that turns on HIV replication and alters proapoptosis gene expression [69]. A chimeric small nucleolar RNA-TAR decoy inhibited HIV-1 replication [70]. An anti-HIV Tar-microRNA construct that functioned as dual-function therapeutic agent, serving as a TAR decoy that bind with Tat, with the siRNA delivery vehicle, caused potent inhibition of HIV gene expression when delivered directly, or expressed in HIV infected cells [71].

MicroRNA (miRNA,MiRs, MicroRs), like TAR micro RNA, are small RNA molecules found in plants and animals and viruses involved in RNA silencing and post transcriptional regulation of gene expression [72,73]. Senescence is promoted by specific microRNAs [74-76]. Overexpression of microRNA-335 and microRNA-34a induced premature senescence of young mesangial cells via suppression of SOD2 and Txnrd2 with a concomitant increase in reactive oxygen species (ROS). Using siRNA antisense against these microRNAs, senescence of old mesangial cells was inhibited via up regulation of SOD2 and Txnrd2 with a concomitant decrease in ROS [76]. A specific microRNA that inhibits translation of a cellular factor, VprBP, was found to inhibit HIV infection in monocytes [77].

The processing and release of functional microRNAs from the HIV transactivation response element (TAR) can mediate RNA interference siRNA [78]. MicroRNA-146a and PLZF, its repressor, are major players in the control of hematopoiesis, immune function and cancer, and can be used to prevent HIV-1 infection of leukemic monocytic cell line and CD4(+) T lymphocytes [79]. Micro RNAs in adaptive changes in hibernation have been detected [80] and may provide pivotal microRNAs that promote stress tolerance to disease vulnerability to HIV.

Although siRNA with potential for interference in HIV infection approaches are known [81], delivery of the agent to the specific target is challenging. Aptamers (apto latin for "fit) are small molecules isolated from nucleic acid libraries with desired selective binding properties [82]. The aptamer targeted oligonucleotide therapeutics allows site cell or receptor specific delivery for interference or promotion of metabolic network to alter disease pathology [83]. Cell-type specific anti-HIV aptamers for siRNA delivery are available that target HIV gp120 [84, 85] and HIV protease [86], A recent review documents the advances in HIV and present challenges of aptamer technology in HIV therapeutics [87]. The use of anti-CD4 conjugated immunoliposomes with antiviral drugs provides a "trojan horse" drug delivery system as well [88]. Both RNA aptamers that target mitochondria and mitochondrial targeted antioxidants can be used for drug delivery [89, 43]. Curcumin, the powerful antioxidant has been engineered to be more bioavailable to increase its anti-oxidant potential [90] and available for possible application in HIV therapeutics [90].

Another major pathway impacting HIV infection is regulation of glucose metabolism. Glucose transporter (Glut-1) drives the proinflammatory phenotype [91]. Glucose metabolism regulates T cell activation, differentiation and function [92]. Glut 1 expression both induces and increases glucose uptake as a key factor in T lymphocyte susceptibility to HIV infection. HIV is suppressed by inhibition of Glut-1 signal transduction or siRNAGlut-1downregultion [93].

Although not anti-HIV drugs, examples of supplements are known to activate protective metabolic networks and upregulation of health and disease resistance, including. Lipoic acid, carnitine, and resveratrol. Lipoic acid has antioxidant activity that preserves the structural and functional integrity of RBC in diabetes. The RBC can then assume a more efficient role as the first line of systemic defence against diabetic complications arising from oxidative stress-induced damage of other agents [94-96]. Acetyl-L-carnitine induces upregulation of heat shock proteins and protects cortical neurons against amyloid-beta peptide 1–42 mediated toxicity [97], and may provide resistance to HIV-induced oxidative damage associated pathologies. Resveratrol is a sirtuin SIRT activator, and HIV-1 Tat protein is a substrate for the deacetylase activity of sirtuin 1 (SIRT1). Resveratrol, a SIRT1 activator inhibited Tat-induced HIV-1 transactivation [98]. Diabetic drugs may also be protective against HIV induced alteration of glucose metabolism.

Stress response is a universal protection strategy conserved throughout evolution, and drugs that increase tolerance to stress have potential in HIV therapy. AICAR, a mimetic of exercise is a drug

already used in humans [99]. AICAR may upregulate host resistance to infection and disease vulnerability and mimic the benefits of exercise. AICAR is used to intervene in multiple diseases including acute trauma of hemorrhagic shock [100]. AICAR was found to inhibit Tat induced HIV transactivation [98].

Hibernation is process that adjust metabolism to tolerate multiple environmental stresses of energy depletion and cold [101]. Hibernation induction trigger initiates stress tolerance pathways that adjust to seasonal changes in transcript requirements [102, 103]. Delta opioid receptor agonists were identified as mimetics of the hibernation trigger that protect against acute trauma of cardiac ischemia, stroke, and hemorrhagic shock [104-108]. Delta opioid receptor agonists modulate T cell proliferation, IL-2 production, chemotaxis, and suppress HIV-1 p24 Ag expression, a marker of HIV infection [109]. Both delta opioid receptor agonists, deltorphin and SNC-80 concentration-dependently inhibited the production of p24 antigen HIV infection marker [109].

Infection with human immunodeficiency virus-1 (HIV-1) often leads to HIV-associated neurocognitive disorders prior to the progression to acquired immunodeficiency syndrome (AIDS). Evidence has accumulated that p38 MAPK may plays crucial roles in various pathological processes associated with HIV infection, ranging from macrophage activation to neurotoxicity and impairment of neurogenesis to lymphocyte apoptosis [110]. Delta opioid agonists inhibit p38 MAPK, and suppress activation of murine macrophages [111]. Thus, p38 MAPK, which has generally been linked to stress-related signal transduction, may be an important mediator in the development of AIDS and be responsive to regulation by hibernation induction trigger mimetic.

Protein structure maintenance is a critical variable required for normal biological function and must adapt to altered stress demands of infection. Recently RBM3, has been found to protect structural plasticity during environmental stress of cooling and rewarming in normal, but not in Alzheimer cells [112]. Protein structure maintenance for cell function is critical for survival and may provide resistance to HIV induced cell dysfunction by preservation of resistance protein structure.

Telomerase	Treatment Goal	HIV Therapy
Telomerase deficiency: and global damage[14,15]	Engineered telomerase regeneration [16]	Telomerase↑ to ↓ oxidative stress, ↓ apoptosis,↑ antiviral [54-56].
Telomerase excess: MDM viral reservoir	Vaccine that activates CD4: ↓ dysfunctional TERT [47]	Try cancer vaccine against TERT. TERT↓ target MDM TERT
Viral proteins [51] ↓ TERT P53 vs TERT [14]	↓ HIV proteins [87]↑ TERT ↓ p53 role ↓ immune loss	Viral protein siRNA TERT↑ to↓p53↓ damage
P53↓ TERT↑	↓caspase 1 [62,63]	↓Ipaf siRNA↓immune deficiency

Table 1: Telomerase in Heath and HIV Therapy.
Proposed intervention in HIV infection and immune deficiency by manipulation of telomerase suggested by data from previous studies documented above.

Table 1 summarizes the suggested novel approaches to HIV therapy when an emphasis is placed on telomerase functions, not only in maintenance of telomere length, but also in oxidative stress and mitochondrial preservation.

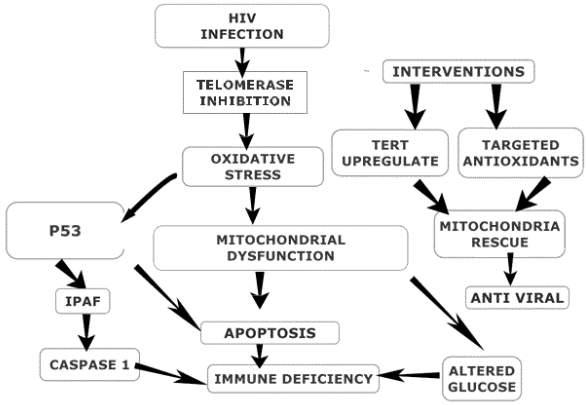

Figure 2: Schematic of Telomerase Roles in HIV Infection. HIV proteins inhibit telomerase with cascading damage to mitochondria and disease vulnerability. Telomerase up regulation and targeted antioxidants should compensate for telomerase deficit.

Discussion

My contention is that there is sufficient preliminary data from studies of others that justify an emphasis in modulation of targeted telomerase therapy to intervene in HIV progression, and to supplement telomerase activation for current effective strategies and drug therapy. Telomerase "dark" role in protection of MDM cell reservoirs by dysfunctional high levels of telomerase may be restricted by targeted telomerase inhibition and thereby perhaps reduction of long term antiviral drug therapy.

The structural similarity between HIV reverse transcriptase and telomerase reverse transcriptase implies that some drugs that target HIV reverse transcriptase, likely target the master gene expression regulator, telomerase, and interfere with its multiple health and longevity pathways documented in this review of eminent scientific studies. The master regulator telomerase, inhibited by viral proteins, and some anti HIV therapy, deplete the host of resistance to stress in general, and increase infection and opportunistic disease vulnerability. Telomerase deficit correlates with HIV progression in infected cells, while sufficient telomerase correlates HIV resistance. Upregulation of telomerase suppresses HIV, and downregulation exacerbates HIV pathology. Telomerase, p53, and glucose regulate HIV progression and are targets for intervention therapy.

The role of overexpression of telomerase in monocyte derived macrophage reservoirs, may be susceptible to a vaccine against telomerase, like the "universal cancer vaccine" developed from telomerase peptides from reservoir of infected cells. Telomerase deficit activates p53, which in turn,, activates Ipaf, which then activates caspase 1 mediated destruction of the immune cell population; the hallmark of AIDS, immune deficiency. Inhibition of Ipaf by siRNA and/or telomerase upregulation may inhibit the caspase1 deadly cascade of immune cell depletion.

The TAR member of the Tat-TAR initiation proves to be a vulnerable target for inhibition of infection. Host and viral micoRNAs emerge as regulators of gene expression susceptible to siRNA control of HIV progression. Aptamers provide the site specific delivery options to cells and organelles to target the nucleolus and mitochondrial organelles where HIV infection "takes over" cell machinery. The recent appreciation of role of glucose and mitochondria in immune cell function provides alternative approaches for up regulation of host resistance. Mimetics of exercise, AICAR, hibernation, and delta opioid receptor agonists, and protein structure regulators, are a class of host resistance drug options with support from previous studies, but virtually untapped in current HIV therapies. Exercise benefit is implied for HIV patients. Anti-aging supplements may also reduce HIV induced telomerase deficits.

Summary

In summary, when the role of telomerase in HIV infection is emphasized, telomerase up regulation emerges as a valuable addition to current HIV therapy. The new technologies, targeted drug delivery, viral and host microRNA roles in viral progression, and siRNA interference, offer unprecedented weapons against the disease. The recent paradigm shifts in the roles of mitochondria, oxidative stress, and glucose metabolism, in immune response, provide alternative strategies to intervene in immune deficiency. Tapping into the environmental adaptations to stress, exercise and hibernation, by known mimetics of stress, can stimulate resistance to infection stress to supplement available HIV drugs. Anti-aging supplements may be of benefit increase resistance to the stresses of HIV infection and reduce vulnerability to other opportunistic diseases.

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