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HIV-Associated Neuropathogenesis: A Systems Biology Perspective for Modeling and Therapy

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Abstract

Despite the development of powerful antiretroviral drugs, HIV-1 associated neurological disorders (HAND) will affect approximately half of those infected with HIV-1. Combined anti-retroviral therapy (cART) targets viral replication and increases T-cell counts, but it does not always control macrophage polarization, brain infection or inflammation. Moreover, it remains difficult to identify those at risk for HAND. New therapies that focus on modulating host immune response by making use of biological pathways could prove to be more effective than cART for the treatment of neuroAIDS. Additionally, while numerous HAND biomarkers have been suggested, they are of little use without methods for appropriate data integration and a systems-level interpretation. Machine learning, could be used to develop multifactorial computational models that provide clinicians and researchers with the ability to identify which factors (in what combination and relative importance) are considered important to outcome.

Keywords

HIV; brain; neuropathogenesis; macrophages; microglia; microRNA; data integration; machine learning

Introduction

Approximately 40 million people worldwide have been infected with HIV-1. In Western cultures, AIDS was first identified in the early 1980s and has evolved from a deadly to treatable disease, usually requiring close management of drug regimes and careful

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monitoring of biological markers of disease. While treatment has significantly improved and lengthened the lives of those infected with HIV-1, up to half will develop HIV-associated neurological disorder (HAND), which are not effectively treated by combined antiretroviral therapy (cART) and greatly increase morbidity. HAND is a neuroinflammatory disease, a broad term describing a number of events associated with macrophages (the primary immune cell in the brain) in both diseased and aging brains. Biological indicators of neuroinflammation have been identified post-mortem or in animal models; however, little progress has been made in HAND treatment or in the identification of HAND biomarkers for those living with HIV infection. cART is aimed at reducing viral replication, thereby reducing viral load and restoring T-cell counts in lymphoid tissues. However, even with restoration of T cell counts, the role that ongoing macrophage activation plays in HAND is poorly understood. The modulation of macrophage phenotypes via altering host biological pathways is an interesting approach for HAND treatment and has the potential for impacting the brain compartment independent of HIV load measurements. MicroRNAs, small key regulators of cellular machinery, have also been suggested as both potential biomarkers for HAND and as targets for treatment. In this review, we discuss histopathological, cellular, and genetic features of HAND, innovative research aimed at controlling the disease by altering host immune response, and alternative means to supervise or regulate HAND progression. Finally, we discuss how system approaches, computational genomics, and bioinformatics can be used to generate improved classifiers for HAND progression. Furthermore, we discuss how properly mined data and computational modeling could help determine proper therapies for those infected.

1. HIV-associated neurological disorders, past and present

Early in the HIV epidemic, severe neurocognitive conditions, usually resulting in death, were noted in HIV-infected individuals (100). These central nervous system (CNS) conditions were initially identified in persons with advanced HIV-1 infection and called “HIV-Associated Dementia” or HAD (3, 81). At autopsy, histopathological abnormalities in the brains of patients with HAD included disseminated foci of activated microglia, perivascular macrophage infiltration, multinucleated giant cells, and reactive astrogliosis (18-20, 90). Later investigations revealed that milder forms of neurocognitive impairment could be detected in HIV-1-infected persons before the onset of advanced systemic disease (42). Post-mortem findings most strongly associated with HAD severity were the number of activated macrophages present within affected areas of the brain (41). In addition, dendritic loss (72), neuronal loss (7), and brain HIV viral load (13) were relevant for HAD severity however, these did not occur independently of macrophage infiltration.

After the introduction of cART, the incidence of HAD declined dramatically (11), but milder forms of HIV-associated neurological disorders became highly prevalent, identified in up to 50% of HIV-infected individuals (46). The increased prominence of mild impairment in 2007 led to a new disease nosology called “HIV-Associated Neurocognitive Disorders” (HAND). cART-treated patients with HAND differed from pre-cART patients in many ways. In their cerebrospinal fluid (CSF), they are less likely to have detectable HIV-1 RNA or have high levels of certain inflammatory biomarkers (73), and at autopsy, they are less likely to manifest florid neuropathological changes (24, 30). These observations have

led to a re-evaluation of the pathogenic mechanisms of HAND, including interest in persistent CNS inflammation, persistent viral reservoirs, and neurotoxicity, all of which are associated with the roles of activated macrophages during long-term HIV infection (2, 9, 32, 57, 66, 107). Importantly, cART does not entirely clear the CNS of HIV-1 (122). In part, this is due to poor drug penetration of some regimens (67). However, the preference of HIV-1 to reside in CNS macrophages and microglia, which harbor a large reservoir of provirus and unintegrated DNA that is unaffected by cART, is also a likely factor (122). Thus, progressive neuronal loss/dysfunction and CNS inflammation can be measured even in well-suppressed patients on long-term therapy (44).

2. The HIV infected brain and cells of the CNS

The brain is an important viral reservoir, a source of viral escape (12) and a barrier to full HIV-1 eradication (80). Brain tissues are difficult to target with current therapies because of the Blood-Brain-Barrier (BBB) and also because it is possible that any current therapies could cause more damage to the brain than the virus itself (80). HIV can enter the brain during early infection (26, 40); however, it is unclear if this is always the case. Moreover, while there have been an abundance of studies on the topic, it remains uncertain if virus entering the brain during early infection can effectively prime the environment for long-term, low-grade inflammation during cART, or if viruses which have evolved and adapted to macrophage-tropic environments (gut, lung, atherosclerotic plaque, bone marrow) are perhaps more apt to set up a significant inflammatory response in the brain (21, 101). Using the SIV-infected simian model for neuroAIDS and green fluorescent staining, researchers have observed that subpopulations of SIV-infected monocytes (precursors of tissue macrophages) in bone marrow travel into brain tissues (21, 116). In a viral evolutionary study, it was demonstrated that the onset of HIV-associated simian encephalitis directly correlated with an increase in viral populations size from bone marrow (101). These findings not only help elucidate how and where neurotropic forms of HIV might evolve before they travel to the brain, but they also indicate that there may be tissues, outside of the brain compartment, that could be targeted with specific therapies aimed at reducing the potential for HAND.

In the brain, subpopulations of blood derived migrant monocytes, macrophages, and resident microglia are infected with HIV (117) (Figure 1). Circulating monocytes enter the CNS and differentiate into macrophages (33, 59). These cells inhabit perivascular, fluid-filled canals that surround perforating arteries and veins in the parenchyma of the brain. Monocyte derived macrophages (MDMs) are phagocytic and antigen-presenting cells that, when activated, can produce a large number of soluble substances important in the pathogenesis of HAND. They are relatively short-lived cells that act as a subtle interface between the systemic circulation and the brain tissues; their population can expand during infection and they can be continually replenished by new blood derived MDMs (115). When healthy brains are examined via autopsy, very few MDMs are present, however in the brains of HAD or HAND patients, MDMs are abundant. Fundamentally, activated macrophages should be considered a major driver of HIV inflammation-associated neuropathogensis and an important target for intervention.

Microglia are resident macrophages of the brain that participate in homeostasis during development, adulthood and ageing. These are long-lived cells that interact closely with neurons and astrocytes (36). They survey the CNS to identify, correct or degrade any sub-optimal functioning cells. Similar to macrophages, microglia also police the CNS for infectious agents or defective cells. They can morph into many different shapes depending on their precise location within the CNS. HIV can also infect Microglia, but it is important to note that microglia do not replicate in the brain, so that they do not represent the bulk of cells that occupy pathologic areas of disease wherein MDMs are prevalent. However, because of their role brain housekeeping processes, HIV infection or destruction of resident brain microglia likely contributes HAND pathogenesis (55, 75). Once activated, microglial cells essentially change morphology and become phenotypically and morphologically indistinguishable from MDMs (88).

Other brain cells such as astrocytes, oligodendrocytes, and neurons are impacted but not necessarily infected by HIV. The literature concerning active HIV infection of astrocytes is conflicting. Studies have suggested that astrocytes are non-productively infected (82), that astrocytes can translate early HIV proteins such as env, nef and tat and that later HIV structural proteins are blocked (84), and that the infection of brain astrocytes compromises the BBB (29). There is minimal evidence for active HIV infection/replication in either neurons or oligodendrocytes, although viral proteins have occasionally been detected in these cells. However, neurons and oligodendrocytes are affected by MDM associated neuroinflammation and neurotoxicity, both directly (from individual neurotoxic viral proteins shed by HIV-1 infected cells), and indirectly (from neurotoxic soluble products in the HIV-1-infected environment) resulting in cognitive, motor, and behavioral changes (1).

3. Macrophage activation and signaling

A comprehensive understanding of HIV-infected macrophages and their effects in the brain may assist in the discovery of therapeutic interventions that are less CNS-toxic than current strategies. Most HIV-1 is transported across the BBB in $CD14^+/CD16^+$ monocytes (7). Once differentiated into perivascular macrophages, these cells can infect new cells by forming tight cell-to-cell contacts using a matrix metalloproteinase-9 mechanism (79). MDMs, the true driver of HIV-1 infection in the brain, have three different macrophage activation states: 1) M1 is the IFN-γ classically activated macrophage that displays a pro-inflammatory response, 2) M2 is the macrophage activated by IL-4 and IL-13 that displays an anti-inflammatory response and, 3) dM represents a macrophage deactivated by IL-10 which leads to immune suppression (47). Activation of macrophages into M1 and M2 phenotypes mediates an effective immune response against invading pathogens; however, during HIV-1 infection, the system is reversed and the virus uses M1 and M2 pathways to facilitate viral dissemination and pathogenesis (22). Inflammatory M1 macrophages, recruited to sites of infection, typically have a short half-life and may cause tissue damage. Non-inflammatory M2 macrophages produce immunosuppressive cytokines that counteract M1 signaling (22, 71, 96). Macrophages are extremely plastic and some suggest that the phenotypes overlap, resulting in a spectrum of macrophage populations based on their functions (76). Whether macrophages are HIV-1 infected, or uninfected but activated, they still produce soluble substances that contribute to an increasingly toxic, inflammatory, and dysregulated CNS

environment (8, 16). Substantial amounts of unintegrated HIV-1 DNA can persist for long periods in macrophages and can support transcription of viral genes such as *nef* and *tat*, and can induce neurotoxic cytokines such as CXCL9 and CXCL10 (103, 119). Exposure to Nef and Tat, and/or platelet-activating factor stimulates macrophages to produce the neurotoxin quinolinic acid in physiologically relevant concentrations (99). The soluble products of HIV-exposed macrophages inhibit long-term signal transmission between neurons in brain slices, indicating yet another possible mechanism for HAND (118).

4. Towards novel therapies for HAND: modulating macrophages via gene targets

An enormous amount of literature describes the interactions of macrophages in the context of inflammation, including hypotheses that implicate macrophages in specific HIV-associated pathologies, such as HAND, lymphoma and atherosclerosis (60-64, 91, 92); however, two important questions remain to be answered in the context of HIV-associated neurocognitive disorders: Can the potential for HAND development be measured? Is there a way to modulate the immune response during cART to reduce the occurrence of HAND? Due to the sensitivity of the brain environment, ideal therapies for HAND would modulate known biological pathways that contribute to macrophage activation outside of the brain, rather than introduce foreign substances into the brain.

Research concerning macrophage-associated biomarkers to track the progression of HAND has identified some surrogate and some potentially causal agents such as quinolinic acid, proinflammatory cytokines and metalloproteinases (39). Some monocyte activation markers in the CSF (sCD14, IL-6, IL-8, CCL2, CCl3, CSCL10, and IFN-γ) are elevated in patients on cART regardless of neurocognitive status, while other appear more strongly associated with HAND (sCD14)(54). However, while these studies show promise, functional proteins are still very difficult to predict from genomic measurements alone and no clear biomarker forerunner for HAND has emerged. The complexity of biomarker development was recently highlighted in a proteomics study where, using only two distinct sets of samples, 3608 proteins from HIV infected and uninfected macrophages were identified, 420 of which were significantly altered upon HIV-1 infection (45).

Macrophage activation states have been modified in animal models using humoral factors. For example, the protein activin A promotes a proinflammatory macrophage phenotype (98). C-reactive protein has been shown to inhibit macrophage transformation to the M2 phenotype (27). Thioredoxin-1 and adiponectin also promote anti-inflammatory macrophages of the M2 phenotype (28, 69). Recently, control of the CSF-1 signaling pathway in macrophages has been suggested as a means to develop inhibitors to treat diseases where infiltrating macrophages contribute to their progression (77, 87). Modulation of transcription factor networks may also represent a means to modulate macrophage polarization. For example, peroxisome proliferator-activated receptors (PPARs) are ligand-activated factors that control lipid and glucose metabolism, as well as the inflammatory response (14). Reactive oxygen species (ROS), derived from NADPH-oxidases, compose a network signaling system known as “redox regulation” that impacts the inflammatory response. Formation of redox signals in classically versus alternatively activated

macrophages, their action and interaction at the level of key targets, and the resulting physiology is just beginning to be understood and could represent another approach in modulating biological pathways to inhibit HAND development (17). Targeted inhibition of an enzyme called MLK3 has been presented as a strategy to reverse HAND and rebuild synaptic architecture (37). sCD163 is a marker of HIV activity in both acute and chronically infected patients; in the macaque model for neuropathogenesis, levels of sCD163 correlate with monocyte expansion and can predict those animals that will have more rapid and severe neurological disease (21). A novel candidate drug called PA300 was described recently that decreases the number of activated macrophages in the hearts of macaques with cardiac disease (112). PA300 is a polyamine synthesis inhibitor currently under evaluation only in animal models and its effect in the brain compartment remains unknown.

5. Towards novel therapies for HAND: modulating microRNA pathways

Recent advances in understanding how microRNAs (miRs) might impact the cellular function may yield new insights into an emerging target (macrophages) for regulation of HIV associated diseases such as HAND. MiRs are found in animals, plants, and viruses. They are small, naturally occurring, non-coding RNAs that are key regulators of host machinery because they alter protein expression, which, in turn, can impact a variety of critical cell functions including control of cellular proliferation, apoptosis, and differentiation. Putative miR targets are believed to regulate 10-30% of protein-coding messenger RNAs (mRNA) (10, 48, 51). miRs function post-transcriptionally via the RNA-induced silencing complex (RISC) containing an Argonaut (Ago1-4) protein (10, 34, 52). The general steps of miR regulation, including pre-miR processing and interactions with Dicer, Drosha and RISC have been described extensively in the literature (5, 10, 48, 52). More than 2,000 mature human miRs have been validated and new targets of these regulatory RNAs are continually discovered. miR profiling has been used to detect various human diseases including cancer, as well as organ transplant rejection (70, 86, 102). These discoveries have led to a broader use of miR profiling for biomarker development in a variety of diseases including HAND. Therapeutic strategies related to miRs are also being developed; miR antagonists, such as anti-miRs, can inhibit miRs that acquire a gain-of-function in the diseased tissue, whereas miRs that show a loss-of-function can be restored by using miR mimics. Specific miRs are highly expressed in brain tissues where they play an important role in fine-tuning the balance between the transcriptome and proteome in cells (95).

The $CD8^+$ T-cell-depleted and SIV-infected macaque is frequently used for studying the pathogenesis of HIV, especially as it pertains to neuropathogenesis. $CD8^+$ T-cell depletion results in the inability to control viral replication and these macaques rapidly progress to SIV-associated encephalitis. To highlight the use of the macaque model to study miR expression during SIV-induced neuropathogenesis, we used a deep sequencing approach to generate libraries of miR sequences from the temporal lobe of a CD8-depleted macaque during early SIV infection and before the onset of neurological complications ($SIVE^-$) and a CD8-depleted macaque at end-stage disease with SIV-associated encephalitis ($SIVE^+$) (Supplemental material). We subsequently compared these libraries to, 1) a database of known lymphoid-derived macaque (mml) miRs in order to identify miRs that could serve as

potential neurodegenerative biomarkers, 2) variation between $SIVE^{-}$ to $SIVE^{+}$ macaque miRs to identify any changes during progression to SIVE, and 3) miRs derived from humans that are associated with neurological disorders in order to determine their presence and relative abundance (53). Of the 486 published mml-miRs (miRBase release 18), a subset of 315 was identified in brain tissues. Ninety-six of these were found at ≤5.0 RPM. Seventeen upregulated miRs and 27 down-regulated miRs above ≥100 RPM and with a ≥1.5 fold change were identified between early and late samples. Of these, miRs with >200 RPM are shown in Table 1 and were further examined using TarBase (110). TarBase contains more than 65,000 experimentally validated miR-gene interactions (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index).

The highly expressed and up-regulated miRs included miR-153, a miR known to target an anti-apoptotic protein and may increase viral production (BCL-2)(35), miR-98 that targets a protein involved in suppressing cytokine signaling (SOCS)(49), miR-148b that targets a protein (HLA-G) that induces HLA synthesis in response to stressful conditions such as infection (58), miR-26a that targets a protein (EZH2) involved in cell fate decisions (93) and may play a role in central nervous system functions (15), miR-204 that targets homeobox proteins (MEIS1, HOXA10) and may regulate gene expression and hematopoiesis (6), miR-23b that targets chemokine ligand 12 (CXCL12) and is involved in driving lymphocyte cell migration to sites of injury (106) and miR-148a that targets a protein (CDC25B) involved in regulating cell division (68). Six highly expressed and down-regulated miRs also targeted proteins associated with infection. For example, miR-27b targets the Notch pathway, which is involved in controlling gene regulation in the brain during HIV infection (43), miR-30d targets GNAI2, which is known to be increased during HIV infection and associated with increased in CCR5 binding (121), miR-30a-5p targets Beclin1, which is involved in neurodegeneration (78), both miR-30c and miR-30e target UBE2I that modifies ubiquitin, which interacts with HIV-1 nef (50), miR-124a has multiple known targets proteins (EZH2, ROCK2, MPTN, SYCP1, MAPK1, CAV1) that play a role in the nervous system, miR-29c targets BACE1, which is involved in the development of amyloid plaques (97), an early feature of Alzheimer's disease, and miR-222 that targets a protein (CDKN1B) involved in cell-cycle inhibition (25). Even though Tarbase describes experimentally validated targets, it is important to note that any reported targeting may be tissue/time specific. Interestingly, up-regulated miRs generally targeted mRNAs of genes involved in cell fate decisions/apoptosis and the immune response whereas down-regulated miRs generally targeted mRNAs of genes involved in cell cycle, neurodegeneration, protein degradation, and maintenance of the nervous system.

Specific miRs have been identified with differential expression in the brain during various neurodegenerative diseases (Table 2) (52). Some interesting miR targets in Table 2 include BACE1, which is involved in cerebral deposition of amyloid beta peptide, an early feature of Alzheimer's disease (31), Pitx3, which is involved in a negative feedback circuit that regulates midbrain function (56) and P250GAP, which plays a key role in the development and refinement of neuronal circuitry (114). Because viruses alter host protein synthesis signaling pathways in cells in order to ensure that ribosomes are recruited to viral messenger RNAs (113), several studies have concluded that HIV/SIV infection also alters miR expression patterns and contributes to neurodegenerative disease (23, 105, 120).

Additionally, miR regulation during HIV infection may be quite different than non-infectious neurological disease because HIV encodes the protein TAR, which is capable of sequestering the gene TRBP, an important co-factor in Dicer-mediated miR processing (94) and Tat, which deregulates the levels of several miRs (23).

Most neurodegenerative human miRs (ND-miRs) were identified in the macaque temporal lobes, with the exception of four miRs with very low or no expression (Table 2). Some ND-miRs were highly expressed; however, only two of these miRs showed a fold change of ≥1.5 with >200 reads per million (RPM) (Bold Rows, Table 2). In both cases, miR up- or down-regulation was opposite to reports concerning their expression during Alzheimer's disease. The identification of specific brain miRs associated with neurological disease helps to narrow the field of potential neurodegenerative miR biomarkers that might be missed in routinely collected clinical specimens, such as blood and cerebral spinal fluid, which likely contain a significantly more complex set of miRs associated with multiple and unrelated biological processes.

Certain human miRs are involved in the processes of activating macrophages and microglia during inflammation. During active inflammation in the CNS, both microglia and macrophages express M1 markers and have low levels of miR-124, while macrophages in normal CNS or during disease recovery upregulate miR-124 (89). miR-414, miR-155, and miR-124 also contribute to the generation of monocytes in bone marrow (74). miR-155 is significantly upregulated in macrophages in response to lipopolysaccharide, suggesting that it is important for macrophage activation (83). MiR-124 was altered threefold in the simian experiment described above. In another study, interleukin-27 treated human macrophages induced the expression of novel miRs with antiviral properties (104). These studies clearly demonstrate that miRs contribute to the adaptation of macrophages to the local environment and the regulation of inflammation. Since activation of macrophages is the most predominant feature of HAND, the use of anti-inflammatory miRs such as miR-124 and inhibitors for pro-inflammatory miRs such as miR-155 that modulate macrophage activation could be useful for controlling HAND in HIV-infected individuals.

6. Summary

There is considerable interest by medical research agencies to fully understand HIV brain infection/inflammation and to develop novel treatment methods in the context of HIV eradication. In the National Center for Biontechnology Information's (NCBI) BioSystems database (https://www.ncbi.nlm.nih.gov/biosystems/), 1419 genes and over 3000 proteins are associated with the macrophage inflammatory response. In NCBI's Geo Proteins database, over 150,000 genes are associated with macrophage response to virus infection and each record has links to profile and sequence neighbors (http://www.ncbi.nlm.nih.gov/geo/). The National NeuroAIDS Tissue Consortium (NNTC) (http://www.nntc.org/) recently performed brain gene expression arrays to elucidate the pathophysiologies of HIV-1-associated neurocognitive disorders and profiled 24 human patients with varied degrees of HAND and controls and found that over 1,900 gene probes were regulated (38). The Macrophage research is inundated with literature that describes various aspects of the inflammatory process but fails to link them in a universal fashion that has clinical translation

as its central goal (111). Furthermore, proteomic studies often incorporate *in vitro* experiments when *in vivo* work may reveal an entirely different set of outcomes. The NNTC and the AIDS and Cancer Specimen Resource (ACSR) (http://acsr.ucsf.edu/)(4) are important biorepositories for HIV-infected human biospecimens from a wide spectrum of HIV-related or associated diseases, including cancer, and from appropriate HIV-negative controls that were established as a resource for investigators working in the fields of HIV/AIDS immunology and pathology—such resources are instrumental for investigators to further the field. Biobanks and tissue repositories for studies with HIV-infected animal models are also needed in the research community (108, 109).

An improved understanding of the systems biology that leads to HAND coupled with the rapidly increasing amount of data being generated on the topic suggests an opportunity to develop molecular biomarkers for HAND, and patient specific treatments for HAND in light of sufficient data (Figure 2). These approaches could make use of machine learning or computational intelligence approaches similar to tools that allow for HIV tropism prediction (65) or microarray analysis (85). However these computational approaches will have to make use of data from largely different sources, over different time scales, at different system levels from genes to miRs to proteins to metabolomics, even demographics. However, the nonlinear classifiers that result have the opportunity to not only assist with improved personalized therapies for patient care but to help elucidate which features (and their combination) that are of most utility for prediction. An understanding of these features establishes a feedback loop of learning that generates more data, additional features, refined modeling, and improved understanding of the systems biology that leads to HIV-associated neuropathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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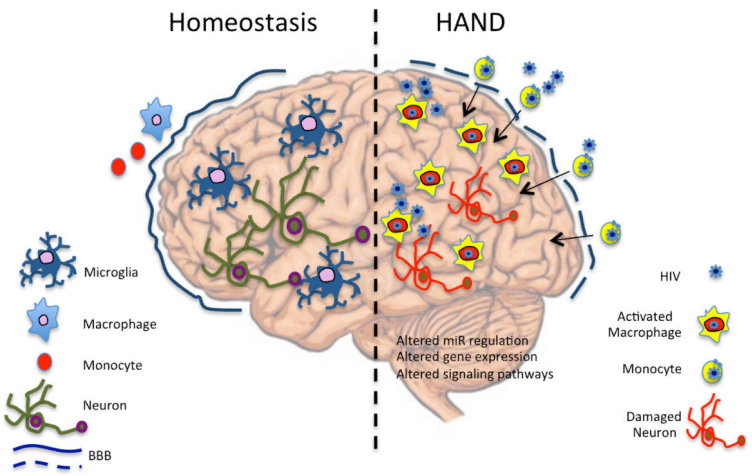

Figure 1. Brain Homeostasis and Infection

In a healthy brain, microglia are the primary immune cell of the brain and few, if any, perivascular macrophages are present. Microglia monitor and communicate with neurons. During HIV infection, HIV-infected monocytes migrate into the brain and differentiate into activated macrophages. Brain microglia become indistinguishable from perivascular macrophages. Neurons and oligodendrocytes become victims of inflammatory chemicals.

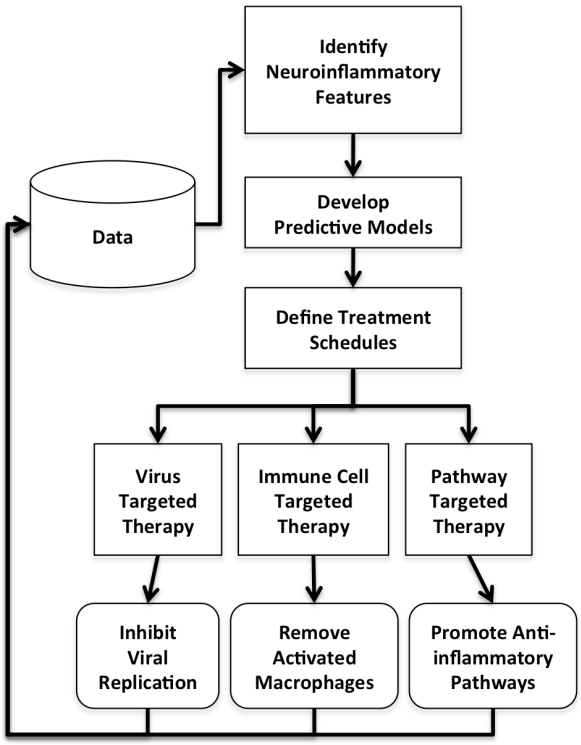

Figure 2. A data-driven systems approach to therapy

In light of sufficient data, predictive models for HAND could be generated using computational intelligence. These models could construct treatment schedules that target the virus, immune cells or biological pathways as needed in light of a complex combination of neuroinflammatory biomarkers. The system would generate additional data on which feature-model-therapy combinations worked best. Repeated cycles of this approach would generate improved therapy and systems that link features to clinical actions. (no color reproduction necessary)

Table 1

Down- and up-regulated temporal lobe Macaque-miRs with greatest fold-change.

Macaque miRNA	21 dpi RPM	75 dpi RPM	Fold Change
mml-miR-24	839.93	229.02	−3.67
mml-miR-124a	4836.71	1475.22	−3.28
mml-miR-30c	3423.63	1364.89	−2.51
mml-miR-29c	3267.92	1343.23	−2.43
mml-miR-30a-5p	9988.39	4200.96	−2.38
mml-miR-30e	6045.37	2603.58	−2.32
mml-miR-30d	11423.27	5042.82	−2.27
mml-miR-423-3p	605.10	274.08	−2.21
mml-miR-92a	2511.68	1228.58	−2.04
mml-miR-338-3p	2095.77	1025.84	−2.04
mml-miR-126	1051.94	526.20	−2.00
mml-miR-27b	18489.14	10232.94	−1.81
mml-miR-138	785.66	456.89	−1.72
mml-miR-222	2824.62	1671.89	−1.69
mml-miR-149	803.92	485.19	−1.66
mml-miR-181d	336.78	212.56	−1.58
mml-miR-148a	257.66	399.99	1.55
mml-miR-23b	875.94	1507.85	1.72
mml-miR-204	316.50	558.55	1.76
mml-miR-26a	41420.38	73099.72	1.76
mml-miR-148b	345.41	630.46	1.83
mml-miR-98	990.57	2173.84	2.19
mml-miR-153	201.78	476.24	2.36

Table 2

Neurotropic human miRs identified in macaque brain temporal lobe. Values for miRs were normalized as reads per million (RPM). Highlighted miRs indicate instances where the RPM was >200 and Fold Change was >±1.5.

Human Neurodegenerative miRs	Published Findings		Our Findings		
	Downreglated	Upregulated	SIVE− (RPM)	SIVE+ (RPM)	Fold Change
hsa-miR-206	ALS		3.04	0.58	−5.27
hsa-miR-133b	Parkinson's		194.26	51.12	−3.8
hsa-miR-338-3p	Prion		172.96	67.87	−2.55
hsa-miR-138-5p		**AD**	**785.66**	**456.89**	−1.72
hsa-miR-330-3p		Huntington's	53.26	33.21	−1.6
hsa-miR-29b	AD	AD	162.31	103.68	−1.57
hsa-miR-330-5p		Huntington's	290.63	200.72	−1.45
hsa-miR-103	AD		2296.62	1642.43	−1.4
hsa-miR-125b-5p		AD	13200.01	9514.39	−1.39
hsa-miR-29a	AD	AD	290.63	208.52	−1.39
hsa-miR-342-3p		Prion	675.6	504.54	−1.34
hsa-miR-320		Prion	259.69	195.81	−1.33
hsa-let-7b		Prion	2685.65	2015.57	−1.33
hsa-miR-9-1	Huntington's, AD		11470.44	10139.37	−1.13
hsa-miR-132	Huntington's		610.67	644.9	−0.95
hsa-miR-34c	Parkinson's		0	0	0
hsa-miR-494		Prion	0	0.29	0
hsa-miR-328		Prion	121.22	123.32	1.02
hsa-miR-370		Prion	88.76	91.84	1.03
hsa-miR-191		Prion	12214.51	13600.69	1.11
hsa-miR-337-3p	Prion		1.01	1.16	1.14
hsa-let-7d		Prion	22043.12	26685.87	1.21
hsa-miR-107	AD		167.38	222.67	1.33
hsa-miR-23b	**AD**		**875.94**	**1507.85**	**1.72**