Human immunodeficiency virus (HIV) is a lentivirus that targets CD4+ cells in vivo, including a subset of lymphocytes (CD4+ T cells) and a broad range of mononuclear phagocytes, including monocytes, dendritic cells, tissue macrophages and brain microglia. The destruction of CD4+ T cells and immune dysfunction results in a progressive immunodeficiency called acquired immunodeficiency syndrome (AIDS), which in the absence of treatment leads to opportunistic infections and malignancies [1]. Although immune system disorders have been focused on the most, HIV infection also has significant effects on the central nervous system (CNS), as the virus both infects and affects the brain [2]. The associated neuropsychopathology or CNS dysfunction results in a group of cognitive and behavioral changes now termed HIV-1-associated neurocognitive disorders (HAND) or neuroAIDS. NeuroAIDS encompasses a broad range of neurological abnormalities, including asymptomatic neurocognitive impairment, HIV-associated mild cognitive motor disorder and the most severe disease, HIV-1-associated dementia (HAD) [3].

The advent of combined antiretroviral therapy (cART; previously referred to as highly active antiretroviral therapy, HAART), however, has significantly changed the dynamics of HIV neuropathogenesis [4]. Severe dementia now affects less than 7% of infected people during the latter stages of disease. Because of the increasing longevity of HIV-1-infected individuals, the incidence of HAD, as well as the other cognitive and motor abnormalities associated with HIV-1 infection, has declined, although the overall prevalence of neuroAIDS has increased [1,3,5-7]. The most severe cognitive, motor and behavioral impairments are now supplanted by milder, less profound cognitive impairment that can nevertheless cause significant problems in individuals' daily lives [8]. HIV-related CNS disease is no longer a result of continuous productive viral infection and activation of brain macrophages and microglia, but rather a result of more limited infection and neuroinflammation [9]. Although widespread use of cART in places where resources are sufficient has increased life expectancy for virus-infected individuals, with a concomitant decrease in disease morbidities [10,11], neurological complications continue to persist. This may be attributed to viral mutation and cART resistance, failure of drugs to access viral sanctuaries, toxicities of cART and poor compliance to complex cART regimens [12-15]. Abuse of illegal drugs [16] and lack of cART availability [17] may also influence neurological disease manifestations. Many aspects of neuroAIDS pathogenesis are well covered in recent reviews [18,19].

Early in the course of infection, HIV enters the CNS and remains detectable throughout the course of infection. Although HIV does not infect neurons, it attacks the monocyctic lineage in the brain: macrophages and microglia [20-23]. The neurotoxicity arising from HIV infection therefore results from an indirect mechanism, possibly involving toxic viral proteins or inflammatory mediators produced by activated macrophages and microglia [24-28], as well as the adaptive immune

Abstract
Diagnosing neurodegenerative diseases, monitoring their progression and assessing responses to treatments will all be aided by the identification of molecular markers of different stages of pathology. Protein biomarkers for HIV-associated neurocognitive disorders that have been discovered using proteomics include complement C3, soluble superoxide dismutase and a prostaglandin synthase. Metabolomics has not yet been widely used for biomarker discovery, but early work shows that it has great potential.
response to the virus in the brain [29,30]. Although studies on the brain can be problematic in humans, an excellent animal model, simian immunodeficiency virus (SIV) infection of nonhuman primates, recapitulates well many aspects of HIV pathogenesis, including neuroAIDS [31–35].

A critical gap in the field of neuroAIDS research is the identification of reliable molecular markers; these could provide valuable insights into the mechanisms of neuro-pathogenesis and response to therapies, and they could aid in the prediction of development of disease.

Biomarkers are biological parameters that are objectively measured and quantifiable and that indicate changes in physiological states due to pathogenic processes or therapeutic intervention. In addition to being invaluable clinically, they have an increasingly prominent role in drug development and medical research [36,37].

Despite substantive research efforts, the mechanisms underlying cognitive impairment resulting from HIV infection are far from understood. However, the advent of high-throughput strategies such as genomics, transcriptomics, proteomics and metabolomics has revolutionized biological investigations and brought great insights. This especially holds true for mass spectrometry (MS)-based proteomics and metabolomics, which have generated immense interest and which offer different but complementary insights into the full complexity of the disease phenotype. In addition to allowing the unbiased identification of molecular markers for disease states, these approaches also enable a greater understanding of the processes underlying them.

Neuroproteomics and biofluids profiling

Cerebrospinal fluid biomarkers for neuroAIDS

Neuroproteomics reveals complex protein expression, function, interactions and localization in cells of the nervous system. Although ideally one would analyze the brain itself, obtaining brain biopsy specimens is not usually practical. Profiling of biofluids is therefore ideal, and the relative ease of obtaining data from the same animals or people over time also means that longitudinal molecular analyses of changes during the course of neurological diseases can be conducted. Of the biofluids, the cerebrospinal fluid (CSF) is close to the site of neuropathology and can reflect the biochemical milieu of the CNS. There is a growing consensus that the CSF is the best material for biomarker discovery and for understanding the ongoing pathological processes associated with neurodegeneration [38,39]. The protein component of CSF consists of brain-derived proteins as well as many proteins that are also abundant in plasma [40].

The complexity and great dynamic range of protein concentrations as well as protein heterogeneity in the CSF create significant challenges to the existing proteomic technologies [41]. To address these challenges (which are not unique for CSF and also apply to blood-based tests on plasma and serum), advances have been made on two fronts: enrichment of potential proteins of interest expressed at lower levels by immunodepletion of abundant proteins [42], and an improved ability to separate the great number of peptides resulting from protein digestion using multi-dimensional chromatography before MS [43].

One recent study used immunodepletion followed by two-dimensional difference gel electrophoresis (2D-DIGE) to identify differentially expressed features and then MS to identify the proteins that differentiated individuals with HAD from HIV-infected individuals without CNS disease [44]. This method required a certain amount of protein, because of which only 6 of the 38 available samples (16%) could be assessed. Nevertheless, this study was successful in identifying six putative biomarkers: vitamin D binding protein, clusterin, gelsolin, complement C3, procollagen C-endopeptidase enhancer 1 and cystatin C. Of these, vitamin D binding protein was upregulated and the other five proteins were downregulated in the CSF of HAD patients.

A separate study from our lab [45] used a more streamlined approach to identify differentially expressed proteins in the CSF of SIV-infected monkeys, comparing the CSF from the same animals before infection and during CNS disease. This technique bypassed immunodepletion or other manipulations and used small amounts of protein isolated by organic extraction followed by limited pre-fractionation using a liquid chromatography tandem MS (LC-MS/MS) approach. Among the proteins differentially expressed in the SIV-infected monkeys, complement C3 was identified but found to be upregulated in the CSF of infected monkeys. The difference between the two studies [44,45] can be attributed to numerous factors, including looking at a human disease or a monkey model, the different sites of CSF removal, the study designs and other aspects of experimentation.

We also investigated [45] whether the increase in C3 reflected synthesis in the brain or leakage across the blood-brain barrier. Quantitative real-time PCR revealed that the mRNA level of C3 was indeed increased in the brains of diseased animals. This increase corroborates other studies in which an increase in C3 in astrocytes, microglia and, to a lesser extent, neurons was found in SIV encephalitis (SIVE) [46]. Furthermore, increased C3 has been found in other human CNS disorders, including Alzheimer’s disease and multiple sclerosis [47]. The enhanced complement synthesis may reflect immune activation in the brain, leading to the formation of molecules such as the anaphylatoxins C3a and C5a, which act as chemoattractants and activators of macrophages and microglia and may act through these cells or
other mechanisms to protect [48-50] or damage [51-54] the brain. Thus, in the case of SIVE, increased C3 probably contributes to SIV-induced damage to the brain.

Two studies have used surface enhanced laser desorption ionization (SELDI) to examine the CSF. In one, nine proteins were identified uniquely in the CSF of individuals with HIV-associated cognitive impairment [55]. These included soluble superoxide dismutase (SOD1), which for which western blot analysis verified its increase. SOD1 is an antioxidant and migration inhibitory factor secreted by macrophages during inflammation and an inhibitor of the protein kinases that are upregulated in the CSF of individuals with cognitive impairment.

The other recent study also used SELDI to identify increases in chitinase 3-like 1 (CHI3L1, also known as HCGp39 and YKL-40) in the CSF as a biomarker of SIVE/HIV encephalitis (HIVE) [56]. Microglia and macrophages were found to produce CHI3L1. It displaced extracellular matrix-bound basic fibroblast growth factor and inhibited the mitogenic activity of its receptor. This may contribute to neurodegeneration through lack of ability of this growth factor, and possibly other factors bound to the extracellular matrix, to support neurons. Independent studies corroborate its upregulation. Our previous microarray study of SIVE found increased levels of CHI3L1 mRNA in the brain [57], and in our CSF proteomics study [45] this protein was elevated in SIVE.

Proteomics has also been used to identify modifications of proteins in the CSF, providing clues to the pathogenesis of neuroAIDS; in particular, nitrosative/oxidative stress has been examined [58]. Levels of proteins modified by nitric oxide, nitrate and 3-nitrotyrosine (3-NT) were assessed in the CSF of 46 patients with HIV infection classified according to their neurocognitive status and whether they had a history of intravenous drug abuse. Although the levels of nitrates and nitrites were increased in individuals with HAD and a history of drug abuse, this did not reach significance. However, CSF from these individuals had significantly elevated levels of 3-NT-modified proteins [58]. Subsequent analysis by immunoprecipitation and LC-MS/MS identified lipocalin-type prostaglandin D synthase (L-PDGS), an enzyme involved in the prostaglandin biosynthesis pathway, to be one of the major 3-NT-modified proteins in the CSF of HAD individuals with a history of drug abuse. Prostaglandins, which regulate many physiological functions, have been suggested to be involved in the pathogenesis of HAD [59]. Further analysis by immunoassay revealed a significant reduction in the enzymatic activity of L-PDGS, a reduction that was due to 3-NT modification. This correlation with HAD may be functionally important, suggesting that L-PDGS is a potential biomarker for neuroAIDS in this population.

Plasma biomarkers for neuroAIDS

Although CSF is ideal for neuroproteomics, its relative unavailability and the limited amount of protein it contains makes such studies difficult. By contrast, blood plasma is a much more accessible biofluid and can contain markers relevant for prediction, diagnosis and/or further investigation into the cause and effects of neurological disorders. Despite the ease of obtaining plasma, a major challenge associated with its analysis is that it has a highly complex proteome, similar to that of CSF. The relatively high expression of abundant proteins such as serum albumin and immunoglobulins, which together constitute more than 85% of the total protein content, masks the less abundant proteins, which could be biomarkers.

Another necessary and informative step in protein biomarker discovery is to detect quantitative alterations of a protein in different disease and control conditions. Development of new quantitative proteomics approaches has greatly enhanced proteomics technologies. One of these, already mentioned above, relies on identifying the different levels of intact proteins separated by electrophoresis followed by protein identification by MS. An alternative strategy is to identify all proteins in a sample by MS and use data from the MS for quantification. Label-free methods such as used in [45] are possible, but chemical reactions to introduce isotopic tags at specific functional groups on amino acids have also been found to provide excellent methods of quantification. One such method is known as isobaric tag for relative and absolute quantitation (iTRAQ) [60]. In an iTRAQ experiment, different samples from control and experimental groups are labeled with different tags and up to eight conditions can be assessed simultaneously.

Using such a platform, afamin, a member of the albumin superfamily [61], was recently found by our group to be significantly downregulated after SIV infection only when CNS disease was developing [62]. Another study using 2D-DIGE-based MS [63] also found afamin to be downregulated (by 2.25-fold [63] compared with 2.77-fold [62]) when comparing HIV-infected individuals with dementia and those without CNS disease. Afamin has been shown to be a specific binding protein for vitamin E [64]. The central role of vitamin E, which comprises eight related tocopherols and tocotrienols, is to maintain physiological cellular and tissue function through the antioxidant properties of these compounds. Further analysis of α-tocopherol (αToCH) levels in the plasma samples of monkeys with SIVE revealed decreases, but to varying extents [62]. However, an identical result was found in animals that did not develop CNS disease. Thus, the decrease in αToCH correlated with infection itself and not the development of CNS disease, in contrast to afamin, which was
processes, including synaptic plasticity, were increased in proteins belonging to the 14-3-3 family (14-3-3ζ and thus abnormal neurotransmission. In addition, two abnormal regulation of the reserve pool of vesicles and expression with HIV-1 infection suggests that there is cytoskeletal proteins and modulates neurotransmitter terminals that regulates synaptic vesicle pools bound to protein protein present primarily in the presynaptic individuals with high HIV loads. SYN1 is a phospho-

functionally important alterations in synaptic proteins, time-of-flight MS, the authors [69] identified potentially the ability to analyze the brain itself is key. A recent study using classical biochemical fractionation isolated synaptosomes (a subcellular fraction of nerve terminals and the synaptic region) from 19 human post-mortem specimens from uninfected and HIV-infected individuals classified by viral RNA load and immunoproteasome (IPS) concentrations as low HIV/low IPS and high HIV/high IPS, of which the latter group had four individuals with HIVE [69]. Using two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) and matrix-assisted laser desorption ionization time-of-flight MS, the authors [69] identified potentially functionally important alterations in synaptic proteins, such as synapsin 1b (SYN1), which was downregulated at early time points on monocytes in monkeys that will develop SIVE [68]. From a therapeutic standpoint, lowering OPN levels or its signaling is one possible strategy to ameliorate neuroAIDS.

Organelle proteomics
Although profiling of biofluids such as CSF and plasma have been useful, the ability to analyze the brain itself is key. A recent study using classical biochemical fractionation isolated synaptosomes (a subcellular fraction of nerve terminals and the synaptic region) from 19 human post-mortem specimens from uninfected and HIV-infected individuals classified by viral RNA load and immunoproteasome (IPS) concentrations as low HIV/low IPS and high HIV/high IPS, of which the latter group had four individuals with HIVE [69]. Using two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) and matrix-assisted laser desorption ionization time-of-flight MS, the authors [69] identified potentially functionally important alterations in synaptic proteins, such as synapsin 1b (SYN1), which was downregulated in individuals with high HIV loads. SYN1 is a phospho-protein protein present primarily in the presynaptic terminals that regulates synaptic vesicle pools bound to cytoskeletal proteins and modulates neurotransmitter release in response to a stimulus [70]. The decrease in its expression with HIV-1 infection suggests that there is abnormal regulation of the reserve pool of vesicles and thus abnormal neurotransmission. In addition, two proteins belonging to the 14-3-3 family (14-3-3ζ and 14-3-3ε), which are crucial for regulation of neuronal processes, including synaptic plasticity, were increased in individuals with high HIV loads. These isoforms have been previously reported to be increased in the CSF of patients with HIV/AIDS, primarily those with HAD [71,72]. The CSF of SIV-infected monkeys also showed higher expression of 14-3-3 proteins in animals with CNS disease [73].

In addition, changes in proteasomal proteins were found [69]. One proteasomal subunit protein, LMP7, was increased in individuals with high HIV loads, increasing the evidence that disruption of this process is linked to HIV-associated neurodegeneration. To determine whether the altered synaptosomal proteins in HIV/AIDS are histologically related to immunoproteasomal subunits, confocal microscopy was performed, showing co-expression of LMP7 and 14-3-3ζ in punctate neuronal and neuropil markings in brains with high HIV loads [69]. Taken together, these findings [69-72] reflect changes in the synaptodendritic arbor, which have been documented during high HIV loads in the brain [74], and give important insights into how HIV can affect neurons in the brain while not infecting them.

The scope of metabolomics
The use of proteomics to study neuroAIDS has been well documented. Another high-throughput methodology, metabolomics, quantifies all low molecular weight endogenous metabolites in specified cellular, tissue or biofluid compartments and has seen increasing development and use. The measurement of metabolites is fundamental to every aspect of biology, from basic biochemistry to standard tests in clinical medicine. Although high-density data gathering metabolomics technologies are still under development, this methodology may soon become superior to other post-genomic technologies for pattern-recognition analyses of biological samples. A recent review [75] describes the translation of important metabolomics findings on neurological disorders to the clinic. Although early on this field centered around toxicological profiling and inborn errors of metabolism, recent applications have been extended to biomarker discovery, including for neurodegenerative disorders (reviewed in [76]).

Earlier targeted studies had identified changes in specific metabolite levels in CSF. For example, quinolinic acid, part of the kynurenic pathway, was shown to increase in CSF during HIV and SIV infection [77,78]. Similarly, the nitric oxide metabolites nitrate and nitrite were increased in a similar manner in the CSF [26,79,80]. Although these studies used a directed approach, our group has used a global MS-based metabolomics approach to identify differentially regulated metabolites in the CSF of monkeys before and after infection with SIV [81]. We found various metabolites to be up-regulated, including carnitine, acyl-carnitines, fatty acids
(linoleic, palmitic and stearic acids) and phospholipid molecules [81]. In conjunction with gene array analysis, the increase in free fatty acids and lysophospholipids was found to correlate with increased expression of specific phospholipases, PLA1A and PLA2G4C; PLA2G4C can release numerous identified fatty acids. Further, in situ hybridization experiments revealed increased expression of PLA2G4C in monkeys with SIVE. Identification of specific metabolites as well as mechanisms of their increase greatly add to the credibility and potential of MS-based metabolomics and demonstrates its power to identify potential markers for neuroAIDS.

Conclusions

The potential of post-genomic strategies has increased immensely in recent years. In the case of neuroAIDS, proteomics has revealed signs of immune system activation and protective responses. These have added to the clues provided by earlier gene array studies and, importantly, they provide molecules that can be assessed in biofluids in future studies. Proteomics has also identified post-translational modifications that affect protein function. Although proteins carry out most biological events in a cell, the chemical transformations catalyzed by enzymes lead to metabolites that themselves have important physiological roles. In addition to metabolic functions, such metabolic products mediate crucial interneuronal communications in the brain. Combining metabolomics with gene array studies in neuroAIDS has led to discovery of a pathogenic process: phospholipase activation involving an increase in specific lipids in the CNS. This helps to illustrate that although each of these approaches is crucial, long-term success will most certainly depend on integrating them. Additional developments and work in proteomics and metabolomics will enable a better understanding of the physiological alterations leading to disease, as well as providing additional biomarkers for diagnosis and therapeutic intervention.

Abbreviations

2D-DIGE, two-dimensional difference gel electrophoresis; 3-NT, 3-nitrotyrosine; AIDS, acquired immunodeficiency syndrome; CART, combined antiretroviral therapy; CHI3L1, chitinase 3-like 1; CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; HIVE, HIV encephalitis; IP5, immunoproteasome; ITRAQ, isobaric tag for relative and absolute quantitation; L-PDGS, lipocalin-type prostaglandin D synthase; MS, mass spectrometry; OPN, osteopontin; SELDI, surface enhanced laser desorption ionization; SIV, simian immunodeficiency virus; SIVE, SIV encephalitis; SOD1, soluble superoxide dismutase; SYN1, synapsin 1b.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

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