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Plenary Session 2

Animal models for AIDS research (1)/Immune activation and chemokine biology

Chairpersons: J. Rappaport (Philadelphia, USA)
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Tracking the pathogenesis of HIV CNS disease using an accelerated, consistent SIV/macaque model

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An accelerated and consistent model of SIV-induced AIDS and encephalitis was developed to track the early viral footprints and host immune/inflammatory responses that lead to the later development of CNS disease. Pigtailed macaques were co-inoculated with a well-characterized, cloned, recombinant virus, SIV/17E-Fr, that is macrophage-tropic and neurovirulent, and an immunosuppressive virus swarm, SIV/DeltaB670, isolated from an infected macaque. Over 90% of inoculated animals developed CNS lesions accompanied by neuronal dysfunction and high CNS viral RNA levels by three months post-inoculation (p.i.). Given this high incidence of SIV CNS disease, groups of animals were examined at early time points in infection with the assurance that the great majority of inoculated animals were destined to develop encephalitis. Infected macaques consistently had replicating virus and microglial activation in the brain during acute infection, but viral replication and microglial activation were suppressed at 21 days p.i. By 56 days p.i., viral recrudescence in the brain was detected in two of six infected macaques. CD4+ cells were the predominant lymphocytes in the brain during acute infection whereas CTL and NK cells predominated in macaques with encephalitis. Low levels of peripheral blood NK lytic activity at 10 days p.i., elevated CSF MCP-1 levels at 28 days p.i., and high CSF viral RNA levels at 42 days p.i. predicted macaques that would develop SIV encephalitis. Although animals in this model have accelerated disease progression, the disease follows the natural course of HIV and SIV infection with acute infection characterized by high viral load in plasma, followed by the development of adaptive immune responses that lower plasma viral load and determine viral set-point. Afterwards, an asymptomatic phase ensues with no evidence of clinical disease although virus replication continues in tissues. Finally, terminal disease develops, characterized by AIDS and the development of encephalitis and neuronal damage.

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Animal models for HIV-1 associated dementia: development of new treatment paradigms

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Neuro-immune events leading to HIV-1-associated dementia (HAD) are associated with macrophage (MP) secretory products secreted during HIV-1 encephalitis (HIVE). Virus can persist in the brain following potent anti-retroviral therapy (PART) due to failure of drugs to penetrate the blood-brain barrier (BBB), or because of inflammatory responses instigating viral replication. To study HIV-1 neuropathogenesis, we developed a murine animal model for HIVE. SCID mice inoculated with HIV-1 infected human monocyte-derived macrophages (MDM) into basal ganglia exhibit the hallmarks of HIVE (astrogliosis, activation of macrophages and mouse microglia, and neuronal degeneration). Integrative experiments correlated neuro-cognitive abnormalities with neuronal dysfunction (by ex vivo electrophysiology) and decrease in synaptic density in the brains of HIVE SCID mice. The ability to evaluate the above mentioned parameters makes this model system suitable for testing of diverse therapeutic approaches (anti-inflammatory, anti-retroviral or neuroprotective). HIVE SCID mice treated with anti-inflammatory compounds (PAF and TNF-alpha inhibitors) show a marked reduction in brain inflammation ameliorating neuronal injury. Refinement of the animal model allows demonstration of HIV-1 spread among the inoculated MDM in mouse brains and provides a unique tool to assess penetration of PART drugs across BBB. Analyses of different PART combinations (assessed by measurements of viral load and numbers of infected MDM) provide direct evidence as to which ones are the most efficient in reduction of viral load in HIVE. The ability of HIV-1-infected MP to induce a specific cytotoxic T-lymphocyte (CTL) response was tested in SCID mice reconstituted with human peripheral blood leukocytes (PBL), and subsequent inoculation of HIV-1-infected MDM into the basal ganglia. HIV-1-specific CTL developed within 1 week. CD8 and granzyme B positive T-cells migrated to the sites of human MDM leading to cell-mediated destruction of MDM. The hu-PBL-SCID HIVE mice provide a new means for studies of cellular immune responses against HIV-1-infected brain MP during disease and following vaccination.

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Immune activation and dementia

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The pathogenesis of HIV-associated dementia (HAD) has frequently been viewed as a disease process confined to the brain and instigated primarily, if not exclusively, by HIV replication. This perspective, however, fails to adequately answer such questions as why the abundance of macrophages in brain appears to be a better correlate of HAD than the presence or extent of HIV expression, and why the incidence of HAD appears to have declined in association with the use of protease inhibitors, drugs with poor brain penetrance. New insight into HIV neuropathogenesis may come from looking beyond the brain. Evidence is accumulating which suggests a causal link between immune activation and the development of cognitive impairment. This potential link extends beyond diseases such as Multiple Sclerosis, whose primary pathology is found in the brain, to include autoimmune diseases such as Systemic Lupus Erythematosus and Sjogren's Syndrome, which typically present as disorders of other organ systems. Imaging studies indicate a link between cognitive impairment in these settings, and cerebral white matter changes. The development of this cognitive impairment appears restricted to subsets of individuals with these diseases. Like endstage HIV infection, these diseases are characterized by a generalized immune activation which includes activation and/or functional abnormalities in circulating monocytes. It has been suggested that the pathological correlate of HAD is encephalitis, and clearly, HAD is associated with increased numbers of brain macrophages. This increase could arise via local proliferation and/or an increase in the entry of blood-borne monocytes. We have proposed a model suggesting that an initial critical step in the development of HAD is an increase in monocyte trafficking into the brain. We hypothesize that an activated phenotype facilitates transendothelial migration of these monocytes, and that systemic events occurring outside of the brain are responsible for the activation. Host genetic factors may influence monocyte activation and thereby predispose individuals to cognitive impairment. This model may have relevance to other white matter dementias.

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Astrocyte signaling in brain inflammation

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Astrocytes have important physiological properties as they relate to CNS homeostasis, and also function as immunocompetent cells in the CNS. Astrocytes are capable of responding to and producing a wide array of cytokines and chemokines. Although expression of cytokines and chemokines is limited in the normal CNS, aberrant expression occurs in CNS diseases including Multiple Sclerosis, HIV-1 Associated Dementia, Alzheimer's Disease, brain injury/trauma and Parkinson's Disease.

We have been interested in the stimuli capable of inducing cytokine/chemokine expression by astrocytes. We report that engagement of Death Receptors (DR5 and Fas), and the chemokine receptor CXCR4, leads to chemokine expression in primary astrocytes and a variety of astroglioma cell lines. Engagement of DR5 by recombinant TRAIL leads to the selective induction of IL-8 via activation of NF-kB. Fas ligation leads to the production of a wider array of chemokines (MIP-1a, MIP-1b, IL-8, MCP-1 and IP-10) via activation of the MAPK pathway (ERK 1/2 and p38 MAPK). CXCR4 engagement by its ligand stromal cell derived factor-1 (SDF-1) enhances expression of MCP-1, IL-8 and IP-10 through the ERK 1/2 signaling cascade.

These results indicate that the Fas-FasL and DR5-TRAIL systems may be involved not only in apoptotic processes, but also in the provocation of angiogenic and proinflammatory responses. As well, CXCR4-mediated signaling pathways in astrocytes may be another mechanism for these cells to express chemokines involved in angiogenesis and inflammation.

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