

Advances in Virus Research—Volume 81

Edited by

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Cover Illustration: Possible routes of entry of soluble Vpr to the central nervous system. Within the periphery, lymphocytes (green) and cells of the monocyte-macrophage (blue) lineage (MML) are major HIV-1 carriers, although the number of infected undifferentiated monocytes is low. After traversing the blood-brain barrier (BBB), monocytes differentiate into short-lived monocyte-derived macrophages (MDMs) capable of seeding infection, releasing Vpr throughout the CNS. Lymphocytes can also traverse the BBB after antigen presentation by local infected perivascular phagocytic cells, thus are a source for Vpr release once activated. Brain-resident cells microglial cells (red/maroon) represent the primary susceptible and permissive HIV-1 target, possibly releasing/secreting newly synthesized Vpr on activation in response to pathogens within the CNS. Resting microglia can support only low levels of viral transcription, therefore are not a main source of Vpr. Brain microvascular endothelial cells (BMVEC) (orange) are also infected by HIV-1 and may be responsible for disseminating Vpr into the CNS. Astrocytes (yellow) are the most abundant cells in the CNS, but their frequency of infection and level of permissivity are likely lower than cells of the MML. During late stages of disease, the number of HIV-infected astroglial cells increases, seeding infection and participating in Vpr release. Neurons (pink) are not known to be infected by HIV-1.

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ACADEMIC PRESS

An imprint of Elsevier
elsevierdirect.com

ISBN 978-0-12-385885-6



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