Tax and Semaphorin 4D Released from Lymphocytes Infected with Human Lymphotropic Virus Type 1 and Their Effect on Neurite Growth

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AIDS RESEARCH AND HUMAN RETROVIRUSES
Volumen: 32
Número: 1
Páginas: 68-79
DOI: 10.1089/aid.2015.0008
Fecha de publicación: JAN 1 2016
Ver información de revista

Resumen

Human lymphotropic virus type 1 (HTLV-1) is a retrovirus causing HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a neurodegenerative central nervous system (CNS) axonopathy. This virus mainly infects CD4(+) T lymphocytes without evidence of neuronal infection. Viral Tax, secreted from infected lymphocytes infiltrated in the CNS, is proposed to alter intracellular pathways related to axonal cytoskeleton dynamics, producing neurological damage. Previous reports showed a higher proteolytic release of soluble Semaphorin 4D (sSEMA-4D) from CD4(+) T cells infected with HTLV-1. Soluble SEMA-4D binds to its receptor Plexin-B1, activating axonal growth collapse pathways in the CNS. In the current study, an increase was found in both SEMA-4D in CD4(+) T cells and sSEMA-4D released to the culture medium of peripheral blood mononuclear cells (PBMCs) from HAM/TSP patients compared to asymptomatic carriers and healthy donors. After a 16-h culture, infected PBMCs showed significantly higher levels of CRMP-2 phosphorylated at Ser(522). The effect was blocked either with anti-Tax or anti-SEMA-4D antibodies. The interaction of Tax and sSEMA-4D was found in secreted medium of PBMCs in patients, which might be associated with a leading role of Tax with the SEMA-4D-Plexin-B1 signaling pathway. In infected PBMCs, the migratory response after transwell assay showed that sSEMA-4D responding cells were CD4(+)Tax(+) T cells with a high CRMP-2 pSer(522) content. In the present study, the participation of Tax-sSEMA-4D in the reduction in neurite growth in PC12 cells produced by MT2 (HTLV-1-infected cell line) culture medium was observed. These results lead to the participation of plexins in the reported effects of infected lymphocytes on neuronal cells.

Palabras clave

KeyWords Plus:RESPONSE MEDIATOR PROTEIN-2; HTLV-1-ASSOCIATED NEUROINFLAMMATORY DISEASE; I HTLV-I; T-CELLS; SPASTIC PARAPARESIS; NEUROLOGIC DISEASE; EXPRESSION; MIGRATION; ACTIVATION; CRMP2

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Financiación

Entidad financiadora	Número de concesión
Fondecyt	Fondecyt 108-0396
CONICYT	24090150 22110639

Ver texto de financiación

Editorial

MARY ANN LIEBERT, INC, 140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, NY 10801 USA

Categorías / Clasificación

Áreas de investigación: Immunology; Infectious Diseases; Virology

Categorías de Web of Science: Immunology; Infectious Diseases; Virology

Información del documento

Tipo de documento: Article

Idioma: English

Número de acceso: WOS:000367335100010

ID de PubMed: 26389656

ISSN: 0889-2229
eISSN: 1931-8405

Información de la revista

- **Impact Factor:** Journal Citation Reports®

Otra información

Número IDS: CZ8FH
Referencias citadas en la Colección principal de Web of Science: 49
Veces citado en la Colección principal de Web of Science: 0