Medical Xpress

Study uncovers relationship between HIV-1 infection and neurodegeneration

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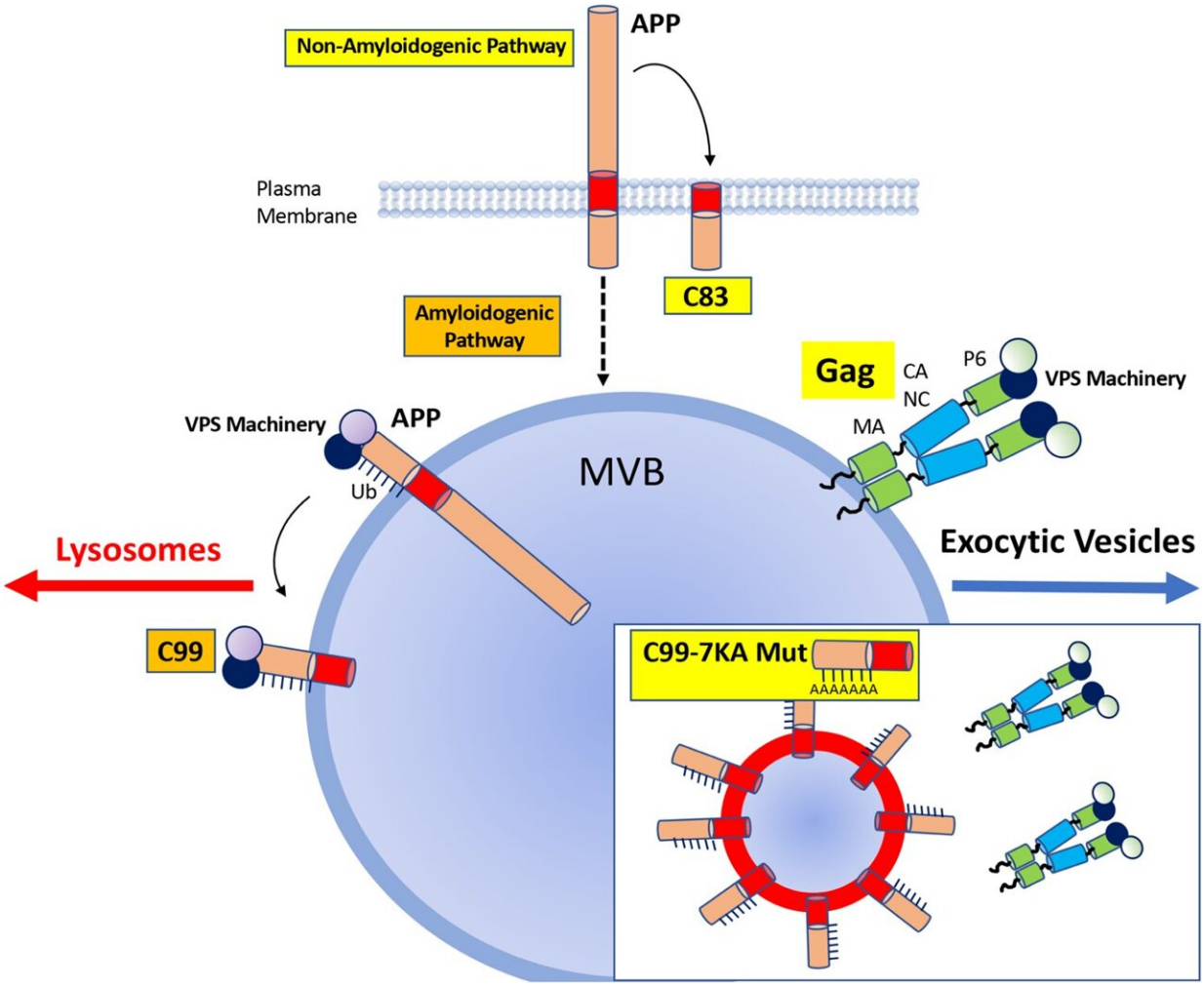

Model for how Gag and C99 compete for control of vesicular sorting pathways. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-40000-x

Northwestern Medicine scientists have discovered how HIV hijacks intracellular processes to proliferate and contribute to neurodegeneration, according to a new study published in *Nature Communications*.

More than 39 million people globally were living with HIV at the end of 2022, according to data from the World Health Organization. Treatment for people living with HIV currently consists of anti-retroviral medications which reduce the amount of the virus in the body, but do not necessarily prevent the spread of or cure the infection.

In addition to causing acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus type 1 (HIV-1) enters the central nervous system in around 80% of infected individuals, resulting in neuronal damage that often leads to HIV-associated neurocognitive disorders (commonly abbreviated as HAND), said Mojgan Naghavi, Ph.D., professor of Microbiology-Immunology and senior author of the study.

"Although HIV-1 does not infect neurons, it does infect brain-resident myeloid cells such as macrophages and microglia. However, how and why HIV-1 infection causes conditions such as HAND has remained enigmatic," said Naghavi, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Previous research from the Naghavi laboratory revealed that amyloid precursor protein (APP) is highly expressed in macrophages and microglia and restricts HIV-1 replication. To counteract this, HIV-1 promotes APP processing which ultimately results in the production of toxic beta-amyloids that contribute to HAND, according to Naghavi's previous research.

Buildup of beta-amyloids is thought to be a major contributor to

neurodegeneration in a variety of dementia-associated diseases, including Alzheimer's, but how and why beta-amyloid is produced in HIV-infected patients and its contribution to HAND had remained a mystery, Naghavi said.

In the current study, Naghavi and her collaborators sought to identify the underlying mechanisms of APP's antiviral function.

"We addressed these questions and in doing so, bridge a second fundamental question in disease biology by providing insights into unique yet poorly understood aspects of HIV-1 replication in specific immune cell types," Naghavi said.

Naghavi and her collaborators found that the processing of APP occurs within subsets of multivesicular bodies (MVBs) that are also required for HIV-1 replication, according to the study.

Under normal conditions, amyloidogenic processing sorts these MVBs to lysosomes, organelles that dispose of cellular waste. This clears amyloids and represses HIV-1 replication. To counter this, HIV-1 diverts MVB sorting from lysosomes to exocytic pathways that support its replication but also increases beta-amyloid secretion.

After making this discovery, Naghavi and her collaborators treated cultured cells with a clinically approved inhibitor of the APP processing pathway and found that it successfully blocked HIV-1's access to the MVBs, thereby suppressing viral replication in microglia and macrophages.

The findings point to this pathway as a potential therapeutic target for HIV-associated neurocognitive disorders, Naghavi said.

Naghavi noted that the findings have the potential to inform the use of

clinically approved inhibitors that might someday be used to treat HAND. Moving forward, Naghavi and her collaborators will continue to study the relationship between HIV-1 and APP.

"We are currently trying to understand how HIV-1 and APP influence each other's vesicular localization and function, and thereby the fate of infectious virus and toxic amyloid production," Naghavi said.

More information: Feng Gu et al, HIV-1 promotes ubiquitination of the amyloidogenic C-terminal fragment of APP to support viral replication, *Nature Communications* (2023). DOI: 10.1038/s41467-023-40000-x

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