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Addenda

Autophagy and CD4+ T Lymphocyte Destruction by HIV-1

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ABSTRACT

The first step of HIV-1 infection is mediated by the binding of envelope glycoproteins (Env) to CD4 and two major coreceptors, CCR5 or CXCR4. The HIV-1 strains that use CCR5 are involved in primo-infection whereas those HIV-1 strains that use CXCR4 play a major role in the demise of CD4+ T lymphocytes and a rapid progression toward AIDS. Notably, binding of X4 Env expressed on cells to CXCR4 triggers apoptosis of uninfected CD4+ T cells. We now have just demonstrated that, independently of HIV-1 replication, transfected or HIV-1-infected cells that express X4 Env induce autophagy and accumulation of Beclin 1 in uninfected CD4+ T lymphocytes via CXCR4. Moreover, autophagy is a prerequisite to Env-induced apoptosis in uninfected bystander T cells, and CD4+ T cells still undergo an Env-mediated cell death with autophagic features when apoptosis is inhibited. To the best of our knowledge, these findings represent the first example of autophagy triggered through binding of virus envelope proteins to a cellular receptor, without viral replication, leading to apoptosis. Here, we proposed hypotheses about the significance of Env-induced Beclin 1 accumulation in CD4+ T cell death and about the role of autophagy in HIV-1 infected cells depending on the coreceptor involved.

INTRODUCTION

HIV-1 infection usually leads to progressive decline in functionality and number of CD4+ T lymphocytes, resulting in AIDS development.1 As early as 1991, T cell apoptosis has been proposed as a possible mechanism responsible for T cell depletion in patients infected with HIV-1,2,3 and an extensive body of literature since then has supported this hypothesis. In addition, there is a correlation between the extent of apoptosis and disease progression,4,5 and highly active antiretroviral therapy (HAART) is associated with a lower level of CD4+ T cell apoptosis in HIV-1-infected patients.6-8

In HIV-1-infected patients, both infected and uninfected cells undergo accelerated apoptosis. However, HIV-1-induced apoptosis in bystander uninfected immune cells is likely the event leading to the depletion of T lymphocytes since the degree of cell loss largely exceeds the number of infected cells. Furthermore, the vast majority of T cells undergoing apoptosis in peripheral blood and lymph nodes of HIV patients are uninfected.9,10

Several HIV-1 proteins, such as HIV envelope glycoproteins (Env), Tat, Vpr, Nef, Vpu and the protease can induce T cell apoptosis. Cumulative data demonstrate a major role of Env in the death of uninfected lymphocytes.11,12 The mature HIV-1 Env is composed of gp120, the exterior envelope glycoprotein, and gp41, the transmembrane one. In most cases, to enter a target cell, HIV-1 must bind two cell surface receptors on its surface. gp120 first interacts with CD4, which triggers conformational changes leading to increased exposure of the gp120 V3 loop that is then able to bind to several coreceptors, essentially CCR5 and CXCR4, determining the tropism of the virus (R5 and X4, respectively) for particular cell types.13 These events trigger the formation of a coiled-coil structure in the gp41 ectodomain that places the hydrophobic amino-terminal region of gp41 in close proximity to the cellular membrane, thereby inducing cell fusion.14 Env receptors (CD4, CCR5 and CXCR4) are able to transduce signals within cells after interaction with their physiological ligands. Thus, HIV-1 Env can be considered as a pathological ligand and constitutes the primary interface between viruses and T cells. It has been shown that binding of HIV-1 Env to either CXCR4 or CCR5 induces CD4+ T cell death.15,16 Whereas the R5 HIV-1 strains are involved in the first steps of infection, the X4 HIV-1 strains are associated with a stronger depletion of CD4+ T lymphocytes and a rapid evolution toward AIDS.17

KEY WORDS

autophagy, apoptosis, HIV-1, HIV-1 envelope glycoproteins, cell signaling, Beclin 1

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Addendum to:

Autophagy Is Involved in T Cell Death after Binding of HIV-1 Envelope Proteins to CXCR4


AUTOPHAGY IS TRIGGERED BY HIV-1 ENV BINDING TO CXCR4 AND IS INVOLVED IN UNINFECTED CD4⁺ T CELL DEATH

We have recently demonstrated that autophagy is involved in T-cell death after binding of HIV-1 Env to CXCR4. Indeed, independently of HIV replication, transfected or HIV-infected cells that express Env induce autophagy in uninfected CD4⁺ T lymphocytes through CXCR4, and accumulation of Beclin 1 is rapidly observed in these target cells. Furthermore, Env-mediated autophagy is required to trigger CD4⁺ T cell apoptosis because blockade of autophagy at different steps, by either drugs (3-methyladenine or bafilomycin A1) or short interfering RNAs specific for the beclin 1/atg6 and atg7 genes, totally inhibits the apoptotic process. In addition, CD4⁺ T cells still undergo an Env-mediated cell death with autophagic features when apoptosis is inhibited by zVAD. These results suggest that HIV-1-infected cells can induce autophagy in bystander CD4⁺ T lymphocytes through contact of Env with CXCR4, leading to apoptotic cell death, a mechanism most likely contributing to immunodeficiency (see Fig. 1). Naive CD4⁺ T cells, which cannot be productively infected by HIV, may thus take different routes to die after contact with a cell infected by an X4 HIV-1 strain and sequential, but not exclusive, cell death pathways are triggered by Env binding to CXCR4.

What is the signification of Env-induced Beclin 1 accumulation in CD4⁺ T cell death? Beclin 1 is accumulated at the early steps of the Env-induced signaling cascade, and this phenomenon precedes autophagic vacuolization. Accumulation of Beclin 1 has also been reported in response to drugs that trigger cell death with autophagic features. Beclin 1, which is involved in the very early steps of autophagosome formation, was first identified as a Bcl-2 interacting protein. Recently, Pattingre et al. have shown that Bcl-2 negatively regulates Beclin 1-dependent autophagy and Beclin 1-dependent autophagic cell death. This study suggests that the modulation of Beclin 1/Bcl-2 interaction could act as a switch to determine the cell fate between survival and death. Thus the accumulation of Beclin 1 may lead to autophagic cell death. Deciphering the molecular mechanism of Beclin 1 accumulation is a crucial point to understand the role of autophagy in HIV-1 pathogenicity.

What is the role of autophagy in HIV-1 infected cells? Interactions exist between the autophagic pathway and the intracellular multiplication of microorganisms. Even if autophagy is implicated in bacterial clearance in many cases, some bacteria have developed strategies to circumvent this mechanism of innate immunity and are able to divert this cellular process to their own benefit to replicate inside the autophagosomes. Recent studies show that viruses are also able to modulate autophagy. Indeed, it has been shown that RNA viruses such as poliovirus require autophagic membranes to assemble their replication complexes in the host cell cytoplasm. In contrast, autophagy can also be an antiviral mechanism, as demonstrated after Herpes Simplex Virus-1 (HSV-1) infection.

Nothing is currently known, however, about autophagy induced in HIV-infected CD4⁺ T cells. Nevertheless, at least two hypotheses can be suggested (see Fig. 2).

- HIV-1 infection triggers an autophagic program in infected T cells. In this case autophagy may lead to apoptosis. However this seems unlikely because it is known that viruses are able to maintain the viability of infected cells in order to replicate efficiently and produce new infectious particles. The autophagic program may thus be triggered in order to maintain cell integrity, and to permit HIV-1 replication and propagation.
- Alternatively, it is possible that autophagy is not induced in infected cells. In this case, a viral determinant may be involved in the repression of autophagy, to block the death of infected T cells and, consequently, to permit HIV-1 replication and propagation.

Can R5 HIV-1 strains induce autophagy? The R5 HIV-1 strains are found in primary infection while the X4 HIV-1 strains emerge in the late and most aggressive stages of the pathology, leading to AIDS. We have demonstrated that X4 Env expressed on...
HIV-1-infected cells can induce autophagy and cell death in bystander uninfected CD4+ T cells.18 Even if CD4+ T cell infection by the R5 HIV-1 strain can also induce CD4+ T cell death, the putative role of autophagy in this case has not been investigated. It would be important to analyze if the two main coreceptors, CCR5 or CXCR4, present differences in triggering and/or regulating autophagy and if CCR5-dependent autophagy and CXCR4-dependent autophagy have different outcomes on cell survival and cell death. This process may determine the course of the HIV-1 associated pathology.

The emerging development of novel therapeutic strategies based on modulation of autophagy in cancer and neurodegenerative diseases attests to the increasing importance of the autophagy field. A number of essential issues, however, remain to be addressed, especially the connections between autophagy, cell death and viral infections. It appears fundamental to better understand the autophagic process and its regulation in the case of HIV-1 infection in order to develop new and more adapted therapeutics that target not only the viral replication but also the cellular response to infection.

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