Response to Comment on "Transcription Factor FOXO3a Mediates Apoptosis in HIV-1-Infected Macrophages"

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LETTERS TO THE EDITOR

Comment on “Transcription Factor FOXO3a Mediates Apoptosis in HIV-1-Infected Macrophages”

We read with interest the recent article by Cui et al. (1) in which they show that HIV-1 infection of monocyte-derived macrophages (MDM) induces dephosphorylation and nuclear translocation of the proapoptotic transcription factor FOXO3a. This extends their previous work showing that TRAIL-mediated apoptosis of HIV-infected MDM is dependent on phosphorylation of Akt-1 upstream of FOXO3a (2). However, their interpretation in the present report suggests that HIV-1 infection directly induces apoptosis of macrophages. This misrepresents an extensive body of literature that finds no direct cytopathic effect of HIV infection in MDM (3) and indeed their own earlier results in which apoptosis is induced only after stimulation with recombinant human TRAIL (2). We are also engaged in study of HIV-1 infection in MDM and find no evidence on the basis of cell viability or genomic transcriptional profiling for direct induction of apoptosis or necrosis (see Fig. 1). The significance of this is that HIV-1 cannot establish a reservoir of infection in long-lived cells that may contribute to viral persistence. The possibility that HIV-1 infection can prime MDM for apoptosis is of significant interest but should be placed in context with evidence that HIV-1 may protect macrophages from apoptosis (4, 5) and that HIV-infected macrophages can induce apoptosis of bystander cells contributing to T cell or neuronal death (6, 7).

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Recent comments by Noursadeghi et al. show that HIV-1 BaL establishes uniform infection of monocyte-derived macrophages (MDM) and does not induce apoptosis or necrosis based on cell viability and genomic transcriptional profiling (1). These comments, together with our recent publications (2, 3), highlight the dynamic process of HIV-1 infection of macrophage populations. HIV-1 establishes a reservoir of infection in macrophages that may contribute to viral persistence in vivo (4–6). However, we have extensively studied macrophage apoptosis in vitro and found remarkable cytopathic effect and apoptosis 5–7 days after infection, the peak of productive infection in our MDM system (2). Accordingly, HIV-1 does not induce significant apoptosis at earlier time points (<5 days) except following stimulation with recombinant human TRAIL (3). We have also compared primary HIV-1 isolates with laboratory strains, and a similar course of infection and cell loss were found (Fig. 1). The data presented...
by Noursadeghi et al. raise a few questions such as whether typical syncytia were observed in MDM following infection with BaL (not apparent in provided image), whether cell viability and genomic transcriptional profiling was performed throughout the infection course, and whether DNA fragmentation was absent throughout the course of infection. One additional point is that in vitro HIV-1 infection is unlikely to be a “uniform” process, where all cells in the culture are in the same status of infection, but rather a heterogenous culture of variably infected primary cells, particularly early in the infection.

HIV-1 alters apoptotic processes in host cells in an effort to survive and proliferate. As stated by Cui et al.: “a large number of macrophages in the brain and lung are infected with HIV-1 during late stage disease. Although macrophages are usually resistant to HIV-1-mediated cell death, targeted cell death of infected macrophage in tissue is likely a host immune response . . . ” (2). Studies have shown that HIV-encoded proteins are able to manipulate apoptotic pathways, modifying the cellular machinery that regulates host cell death in either a pro- or anti-apoptotic manner (9). RNA transcription in infected macrophages indicates a conflicted state where proapoptotic and antiapoptotic cascades are modified as the cells respond to HIV infection. Death factors such as TRAIL, TNF, and Fas are up-regulated and the anti-apoptotic factors BCL-2, NAIP, and Akt-3 are significantly down-regulated 5 days postinfection, but survival factors including XIAP, MDM2, and SOD2 are up-regulated (N. Erdmann et al. manuscript in preparation). The MDM system represents a unique model of HIV-1 infection, allowing the evaluation of human cells and various isolates of HIV-1. Study of the survival-apoptotic equilibrium in HIV-1-infected MDM should continue, and identifying a comprehensive list of factors and cascades could bring further understanding of HIV-1 pathogenesis. Although macrophages in vivo are resistant to induction of apoptosis, the clinical course of disease may be subject to modification with appropriate intervention of macrophage survival.

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References