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Editorial

Cell death pathways in retroviral infection

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Viruses mercilessly exploit their host cells with the exclusive aim of assuring their own survival and propagation. In fact, viruses control all facets of the host cell biology, subverting its metabolism, influencing the cell division cycle and regulating the apoptotic machinery. Viruses target the cell death program at different levels, following a three-layered strategy. First, viruses must avoid the rapid death of freshly infected cells, which constitutes one of the most ancient antiviral defense mechanisms. For example, retroviruses can trigger the DNA damage response as a correlate of retroviral DNA integration,[1] and obviously cell death induced at this stage would abort viral infection. Second, viruses can actively kill the infected target cell, at late stages of the viral life cycle, to ensure its liberation and propagation to adjacent cells. Induction of host cell death may also induce a tolerogenic type of cell death, apoptosis (as opposed to necrotic lysis), thus subverting the host's immune response. Third, viruses can induce the death of noninfected inflammatory or immune cells. This 'bystander killing' is induced with the scope of paralyzing the host's innate and cognate defense systems.

As a result, viruses employ multiple strategies to manipulate (induce or inhibit) cell death. The present Special Issue of *Cell Death and Differentiation* specifically deals with the regulation of cellular demise by retroviruses, in particular by the human immunodeficiency virus (HIV), which has infected an estimated 60 million people worldwide.[2] Owing to the widespread use of the highly active antiretroviral therapy (HAART), the incidence of AIDS is now declining in the developed West, although the number of HIV-infected individuals still increases.[2] Since viral escape from HAART is increasingly frequent, HIV-1 infection thus will continue to constitute a major epidemiological, medical and scientific problem.

HIV kills human cells of different types by a cornucopia of different mechanisms.[3] HIV is particularly malicious since it primarily infects cells from the cognate and innate immune systems (in particular, $CD4^+$ T cells and monocytes), in which it manipulates apoptosis through direct effects.[3] In addition, HIV uses cell-exposed proteins (such as the Envelope glycoprotein complex, Env)[4] or secreted proteins including Vpr to induce cell death in a variety of different cell types.[5] To kill cells, HIV profoundly influences the cell biology, including the cytoskeleton,[6] by acting on multiple cellular receptors, not only the classical HIV-1 receptor CD4 with its chemokine coreceptor.[7] In addition, HIV-1 may induce subtle tactics to induce the death of HIV-1-specific immune effectors, for instance by inducing the expression of CD95//Fas on infected cells, which then engages the CD95/Fas death receptor on $CD8^+$ T cells.[8–10] Although the detailed mechanisms accounting for T-cell death *in vivo* are not known, HIV-1 infection profoundly influences the T-cell repertoire, both in $CD4^+$ and in $CD8^+$ T cells *in vivo*.[3] Animal models such as the infection of macaques by simian immunodeficiency virus (SIV) may be important for the elucidation of the exact molecular mechanisms of the apoptotic pathways participating in the pathogenesis of AIDS.

Importantly, HIV-1 provokes a neuropathological response involving all cell types in the brain. The incidence of the so-called HIV-1-associated dementia (HAD) is increasing, and its pathogenesis is likely to be complex, involving multiple direct and indirect apoptosis-inducing mechanisms culminating in neurodegeneration.[11–13] Soluble viral products such as gp120 and Tat as well as inflammatory responses play a major role in HAD.[12] Moreover, direct mechanisms leading to the formation of synctia may contribute to HAD. The apoptotic response of synctia is likely to involve the activation of p53,[4,12] illustrating how host cell-intrinsic factors can contribute to viral pathogenesis.

Human T-cell leukemia virus type 1 (HTLV-1) is responsible for adult T-cell leukemia/lymphoma, as well as progressive demyelinating neurodegenerative disease termed HTLV-associated myelopathy/tropica spastic paraparesis. HTLV-1 encodes the viral oncogene Tax, which can inhibit apoptosis through the activation of the NF-κB pathway.[14] In addition, HTLV-1 encodes for a protein, p13II, which can sensitize for apoptosis induction, presumably through a direct effect on the mitochondrial inner membrane.[15] How and to which extent p13/II contributes to the HTLV-1-mediated disease states remains on open conundrum.

Antiretroviral agents used for the treatment of AIDS can modulate host cell apoptosis, even in the absence of retroviruses.[16,17] Thus, HIV-1 protease inhibitors can both inhibit and induce apoptosis, depending on the dose and on the cell type investigated.[16] It may thus be speculated that such drugs may become useful in clinical applications in which apoptosis modulation is a therapeutic goal.[17]

We do hope that the readers of *Cell Death and Differentiation* will appreciate the present compendium of articles on retroviral and antiretroviral modulation of cell death pathways. May the ideas shared by the authors stimulate further debate and experimentation. It appears reasonable to anticipate that a detailed comprehension of cell death modulation by retroviruses will open new therapeutic avenues that may reduce viral reproduction, boost antiretroviral immune responses or, alternatively, dampen deleterious host cell loss, for instance in the central nervous system.

M Piacentini[1,2] and G Kroemer[*,3]*

[1] National Institute for Infectious Diseases IRCCS 'L. Spallanzani', Via Portuense 292, Rome, Italy
[2] Department of Biology, University of Rome 'Tor Vergata', Rome, Italy
[3] CNRS-UMR8125, Institut Gustave Roussy, 39 rue Camille-Desmoulins, Villejuif, France
* Corresponding author: G Kroemer, CNRS-UMR 8125, Institut Gustave Roussy, Pavillon de Recherche 1, 39 rue Camille-Desmoulins, F-94805 Villejuif, France. Tel: +33 1 42 11 60 46; Fax: +33 1 42 11 60 47; E-mail: kroemer@igr.fr

1. Skalka AM and Katz RA (2005) Cell Death Differ. 12: 971–978
2. Girardi E *et al.* (2005) Cell Death Differ. 12: 837–844
3. Gougeon M-L (2005) Cell Death Differ. 12: 845–854
4. Perfettini J-L *et al.* (2005) Cell Death Differ. 12: 916–923
5. Muthumani K *et al.* (2005) Cell Death Differ. 12: 962–970
6. Matarrese P and Malorni W (2005) Cell Death Differ. 12: 932–941
7. Ritsou E *et al.* (2005) Cell Death Differ., in press
8. Petrovas C *et al.* (2005) Cell Death Differ. 12: 859–870
9. Hurtrel B *et al.* (2005) Cell Death Differ., in press
10. Kaul M *et al.* (2005) Cell Death Differ. 12: 878–892
11. Mattson MP *et al.* (2005) Cell Death Differ. 12: 893–904
12. Nardacci R *et al.* (2005) Cell Death Differ. 12: 855–858
13. Corasaniti MT (2005) Cell Death Differ. 12: 999–1001
14. Kfoury Y *et al.* (2005) Cell Death Differ. 12: 871–877
15. d'Agostini DM *et al.* (2005) Cell Death Differ. 12: 905–915
16. Badley AD (2005) Cell Death Differ. 12: 924–931
17. Fischer U and Schulze-Osthoff K (2005) Cell Death Differ. 12: 942–961