Kinetoplastid Biology and Disease BioMed Central

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The role of apoptotic mimicry in host-parasite interplay: is death the only alternative for altruistic behavior?

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Published: 25 June 2003

Kinetoplastid Biology and Disease 2003, **2**:6

Received: 10 June 2003
Accepted: 25 June 2003

This article is available from: http://www.kinetoplastids.com/content/2/1/6

Multicellular organisms can clearly benefit from the non-inflammatory elimination by apoptosis of unnecessary and potentially harmful cells. Recently accumulated data show that unicellular organisms such as pathogenic trypanosomatids can also take advantage of different apoptotic features [1]. As a matter of fact, similarities between multicellular organisms and the multicellular organization of unicellular organisms in the control of very basic mechanisms in cell physiology are not restricted to apoptosis, but extend to different cell biological phenomena such as cell-cycle control, multiplication, and differentiation [2]. Indeed, examples of mammalian-derived cytokines able to induce cell multiplication, protein phosphorylation, and protection from death in unicellular pathogenic trypanosomatids have been described [3,4]. These examples allow the postulation that the usage, by a population of unicellular parasites, of cellular and molecular processes normally operating in the host, is an efficient adaptive strategy. One such example is the capacity of different members of the genera *Trypanosoma* and *Leishmania* to take advantage of different features of the apoptotic process to establish a host-parasite relationship, without death as the necessary outcome. This will be the subject of the present commentary.

Indeed, we have described that amastigotes [5] and metacyclic promastigotes (manuscript in preparation) of *Leishmania L. amazonensis* display phosphatidylserine (PS) on the outer leaflet of their cellular membrane. This molecular moiety induces an anti-inflammatory response of the macrophages through the activation of a specific receptor [6]. Macrophages are the obligatory habitat of *Leishmania* spp in the mammalian hosts and, paradoxically, are also the effector leishmanicidal cells when properly stimulated by the adaptive immune response of the host [7]. The PS-dependent anti-inflammatory response is characterized by inhibition of nitric oxide synthesis and activation of TGFβ and IL-10 production; the net result is an increase in internalization and a facilitated intramacrophagic proliferation of the parasite [5]. PS exposure is one of the most precocious and widespread features of a cell primed for apoptosis; it is essential for the non-inflammatory disposal of dying cells [8], and thus allows apoptosis to occur without disturbing normal organogenesis and normal adult cell renewal. This same feature, in an apoptotic-mimicry fashion, seems to be important for the establishment of *Leishmania* spp as an obligatory intramacrophagic parasite of mammalian hosts. In the present context, two alternative explanations for the capacity of exposing PS can be formulated. PS exposure can be viewed as a property of genes that have been selected in ancestors of present day *Leishmania* spp. due to coding for advantageous features which were – and still are – not necessarily part of the very complex phenomena of programmed cell death. However, they might have played a role in the establishment and maintenance of the present day Leishmania/host parasitic relationship by allowing for the survival of the parasite within its mammalian hosts. Alternatively, PS exposure by the parasite might really be part of a cell death program. Indeed, in our hands, if the PS-exposing amastigotes are kept *in vitro* at 34°C, they undergo typical apoptotic oligonucleososmal DNA cleav-

age (unpublished result). This strongly suggests that the complete mechanism of cell death is present, and eventually operational, in this unicellular organism. Our present data cannot, of course, distinguish between both of the phylogenetic alternatives described above. Neither can it answer to the question of whether PS exposure by the parasite is an independent phenomenon or is part of the molecular demands of a fully operational cell death program. To start with, we still have no clear-cut evidence whether the PS in the parasite's surface is synthesized by the parasite itself, or is derived from the host. The following are strong evidence indicating that the former is the case: (a) it is a fact that axenically grown metacyclics expose PS; (b) plasma membrane translocases, which are capable of regulating PS exposure, have been described in promastigotes of *Leishmania tropica* [9]; and (c) amastigotes derived from susceptible Balb/c mice systematically expose more PS on their outer surface than amastigotes derived from resistant C_{57}Bl/6 mice (manuscript in preparation). In addition, considering that the source of the exposed PS is the parasite itself, we do not know whether PS exposure occurs only when the amastigote is released from the macrophage, or if it already occurs inside the phagolysosome. This latter possibility is very interesting and enables us to hypothesize that a quorum sensing mechanism defines the moment of PS exposure and subsequent macrophage rupture. If this is true, PS exposure on the outer membrane leaflet defines a metacyclic amastigote. We are currently investigating this possibility. Finally, and central to the present discussion, it is not clear either if the PS-exposing parasites are the truly infective forms, or if they only contribute to infectivity due to their PS-depended macrophage inactivation properties. If, indeed, PS exposure is part of a cell death program, and the PS positive parasites are the infective ones, they must be rescued from death within the phagolysosomal environment. This is, by itself, a fascinating biological question. If, on the contrary, the infective forms are the PS negative ones, with the PS positive forms facilitating infectivity, a truly cooperative system is operating here. In both situations, however, PS exposure, with its consequent macrophage inactivation, is the relevant phenotype for parasite persistence in the host. Parasite death by apoptosis is, in the present situation, just a side effect. Interestingly, *Trypanosoma cruzi*, a parasite displaying just a transient intramacrophagic phase in the vertebrate host, is endowed with the capacity of inducing apoptosis in the host's T lymphocytes [10]. This parasite, which displays only traces of PS in its lipid composition, takes advantage of the interaction with the macrophages of the PS exposed by the T lymphocytes, in a very similar way to what *Leishmania L. amazonensis* does with PS on its own surface.

Except for the differential usage of apoptotic features in the two examples discussed above, different apoptosis-like features (e.g. morphological changes, DNA cleavage, caspase activation, etc) have been described in unicellular parasites in a wide variety of working conditions, with parasite death as the final read out [11]. In all such cases, discussion is focused on the biological significance of this type of death: is it just the end point of the parasite's life-cycle, or does it have any beneficial consequence for the parasite population and can thus be considered an altruistic type of death? Furthermore, these descriptions have raised arguments supporting that the phylogenetic origin of programmed cell death predates multicellularity. The postulation that forces imposed by the demands of a parasitic life-style have selected cell death or any other feature of the apoptotic process in those vertebrate infective eukaryotes seems to us a very reasonable alternative. The development of molecular biology and the increasing progress in the competence for genome sequencing and for searching molecular phylogenies will certainly bring new answers to such exciting questions.

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