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Programmed cell death in trypanosomatids: is it an altruistic mechanism for survival of the fittest?

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Abstract

The protozoan parasites *Leishmania*, *Trypanosoma cruzi* and *Trypanosoma brucei* show multiple features consistent with a form of programmed cell death (PCD). Despite some similarities with apoptosis of mammalian cells, PCD in trypanosomatid protozoans appears to be significantly different. In these unicellular organisms, PCD could represent an altruistic mechanism for the selection of cells, from the parasite population, that are fit to be transmitted to the next host. Alternatively, PCD could help in controlling the population of parasites in the host, thereby increasing host survival and favoring parasite transmission, as proposed by Seed and Wenk. Therefore, PCD in trypanosomatid parasites may represent a pathway involved both in survival and propagation of the species.

Programmed cell death in trypanosomatids

The unicellular protozoan parasite *Leishmania*, *Trypanosoma cruzi* and *Trypanosoma brucei* are the causative agents responsible for human leishmaniasis, Chagas disease, and African sleeping sickness, respectively. These trypanosomatid parasites have complex life cycles that involve multiple hosts. Inside the insect vector or mammalian host, these parasites undergo differentiation and multiplication phases. By some unknown signals/mechanisms, some individuals in the total population differentiate into non-dividing but infectious forms, predisposed to live inside the next host. However, the fate of the remaining non-infectious forms is not known. Are these cells eliminated by a process akin to programmed cell death?

Recently, several reports have provided evidence for a form of programmed cell death (PCD) in the trypanosomatid parasites *Leishmania*, *Trypanosoma cruzi* and *Trypanosoma brucei* [reviewed in ref. [1]]. We and others have shown that several features of PCD described in higher eukaryotes were also found in these trypanosomatid parasites [reviewed in ref. [1]]. These features include depolarization of mitochondrial membrane potential, release of cytochrome C, activation of proteases, phosphatidyl serine exposure, loss of plasma membrane integrity and DNA fragmentation. Such features have been observed in parasites in culture in vitro either upon treatment with various stimuli i.e. H_2O_2, staurosporine, amphotericin B, or in late stationary phase cultures [reviewed in ref. [1]]. Further, some of the regulatory and effector molecules that have similarity to known PCD factors in either higher eukaryotes or unicellular organisms also have been identified in trypanosomatids [reviewed in ref. [1]]. In addition, evidence of PCD has also been observed in vivo e.g. in dying *T. brucei rhodesiense* inside the midgut of tsetse flies [2] or in *Leishmania donovani* amastigotes inside macrophages isolated from patients that were treated with antileishmanial drugs [3].

Although some similarities with apoptosis of mammalian cells can be drawn, it is believed that the type of PCD observed in unicellular trypanosomatids is different from that described in higher eukaryotes [[1], references there in]. Whether these differences reflect the remains of an ancient form of PCD in trypanosomatids that evolved into the sophisticated apoptosis process in mammalian cells or the necessary adaptation of unicellular parasites to survive inside their various hosts remains to be elucidated. The important question still remaining is what could be the role of PCD in trypanosomatid parasites. In order to address this question, it is fair to assume that if unicellular parasites have retained such a PCD pathway during evolution, it is because this pathway must be beneficial or essential for survival of the species or population.

In the case of *Leishmania*, inside the gut of the sandfly vector, the procyclic promastigote forms of the parasite multiply and differentiate into several intermediate forms and ultimately into infectious metacyclic promastigotes. Only the infectious metacyclics are transmitted into the mammalian host and have the ability to successfully differentiate into amastigotes and establish an infection. Since not all the promastigotes differentiate into metacyclic forms inside the gut of the insect, we believe that the remaining procyclic forms may undergo PCD, as seen in stationary phase culture in vitro [1]. Such an elimination process of procyclic forms would be beneficial for the rest of the population (i.e. metacyclics) since these parasites would not utilize the limited supply of essential nutrients such as purines or heme (that they are not able to synthesize de novo) present in the insect gut. Therefore, PCD in the *Leishmania* promastigote stage may represent an altruistic mechanism for the selection of parasites that are fit to transmit the disease to the mammalian host, which is a critical step for the propagation of parasites.

Inside the mammalian host, there is a slow multiplication phase of *Leishmania* amastigotes (over weeks in the hamster model, or years in the case of human visceral leishmaniasis) leading to an accumulation of infected macrophages in the spleen and liver. During this chronic phase of the disease, one can assume a continuous release of amastigotes in the infected organs due to the bursting of infected macrophages. The free extracellular amastigotes are then phagocytosed by new macrophages inside which they multiply. This reinfection cycle occurs without triggering an overwhelming immune response by the host, which would be detrimental for the parasite survival. PCD might play a role in this silencing of the host immune response since recent findings showed that uptake of apoptotic T lymphocytes by macrophages infected with *T. cruzi* increases parasite growth inside these macrophages [4]. Such uptake of apoptotic T cells renders the macrophages refractory to inflammatory cytokines, a process probably mediated by transforming growth factor-beta production, and allowing parasite survival and growth. Since *L. donovani* amastigotes (axenically grown) can enter a PCD pathway [1], it is possible that "apoptotic-like" amastigotes in vivo could also play a role in silencing the host immune response when they enter the macrophages along with non-apoptotic amastigotes. Such a process could maintain the parasite growth in the infected tissues during the chronic phase of the disease. Further, this increased survival of parasites through the programmed sacrifice of some would improve the probability of completing their life cycle through the bite of a sandfly and ultimately resulting in the propagation of the species.

Such an altruistic behavior of a trypanosomatid parasite is also proposed by Seed and Wenk in this current issue. These authors argue that the transition from long slender (LS) to short stumpy (SS) forms of African trypanosome parasites in the mammalian host has evolved in part to help control the parasitemia and to increase host survival time. These authors show that after transformation from LS to SS, only a fraction of SS parasites undergo apoptotic-like events, which lead to their cell death and their stimulation of the host immune system. Unlike *Leishmania*, stimulation of the host immune system by SS trypanosomes undergoing PCD leads to elimination of most of the parasite population from the host and selection of minor LS variant and new infective SS forms, which favor parasite transmission for a longer time by keeping the host alive.

In conclusion, in order to successfully demonstrate the real purpose of the PCD, whether altruistic or otherwise, in *Leishmania* and other trypanosomatid parasites, it is essential to first establish PCD in vivo, in an infected host. In addition, the molecular characterization of effector molecules that are critical for the parasite PCD pathway is essential because such process could be exploited for novel therapeutic intervention.

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