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Life after death: are trypanosomatids programmed to die for the survival of their partners?

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In the year 1315, on the battle field of Morgarten, a Swiss hero named Winkelried, stabbed himself with lances he grabbed from the wall of armed Austrian soldiers. His sacrifice, was thus essential to open the way for the victory of the Swiss army. In his mind, there was a clear suicide plan under which action was taken towards a goal, that is, the survival of his colleagues. Such a suicide plan is found at the cellular level in metazoa, namely in their cell death program. Programmed cell death (PCD), is a suicidal pathway that has clear benefits for multicellular organisms, whereby, cells that are damaged, infected, or no longer required are eliminated. Considering the importance of PCD in metazoa, it is reasonable to ask if such a predetermined mechanism of behavior, or operations, exists in phylogenetically ancient, single cell organisms, such as, pathogenic trypanosomatids.

In this issue, Seed and Wenck make comments relating to the role of the long slender (LS) to short stumpy (SS) transition in the life cycle of the African trypanosomes. The authors quote several different reports describing the presence of PCD in trypanosomatids. There is strong evidence to suggest that cell death in Trypanosoma exhibits some morphological features of PCD common to higher eukaryotes. However, these morphological changes are not yet definitive proof of a program or coded set of instructions. Thus far, genes, that are involved in metazoan PCD, have not been functionally characterized in trypanosomatids. Furthermore, it is likely that the Kinetoplastida genomes do not encode caspases, suggesting that, if programmed cell death does exist, it is not an apoptotic process but an apoptotic-like mechanism. Such apoptotic-like programs have already been described in higher eukaryotes. The observations that these death features are visible under stress or during differentiation of parasites into the infectious stages are, however, interesting. In the infectious stage, the parasite will encounter its host and be exposed to the hosts' immune system. From this point onwards, the parasite may either, survive by controlling or escaping the immune system of the host, or alternatively, be killed. In the latter case, it is advantageous for the parasite to expose phosphatidylserine and be phagocytized as for any metazoan cell undergoing death. In *Leishmania mexicana*, it has been shown that antigens can be presented to T cells by macrophages harbouring dead organisms but not by cells harbouring live parasites [1]. Such observations, however, do not imply, *de facto*, that the parasite is acting altruistically. In their analysis on the role of LS and SS forms of *T. brucei*, Seed and Wenck conclude that some parasites of <<...the SS stages during the apoptosis-like process are acting altruistically >>...and also <<give their lives to insure the long-term survival of the host, and insure renewed growth of the minor LS variants and new infective SS forms...for a successful transmission of the trypanosomes to a new host>>. According to the authors' conclusion, one ends up with the feeling that some short stumpy (SS) forms of the African trypanosomes are programmed to die and that this program is altruistic.

We do not contest the authors' comments concerning the different roles of the LS and SS forms, however, we feel that interpretation of the data concerning the altruistic role of the SS should be taken with more caution. There is strong evidence suggesting that quorum sensing exists in bacteria, therefore, cross-talk between protozoan parasites may also take place, and thereby controlling the virulence and genetic competence of the parasite. These processes

are, however, designed for the survival of the pathogen and not for its programmed elimination. We therefore feel that the authors may have gone one step too far by asserting that the death of some SS parasites is due to an altruistic program. The question concerning the role of cell death in trypanosomatids is still pending. Some recent reports suggest that promastigotes of *Leishmania* parasites may undergo autophagy when exposed to specific peptides [2]. This process differs from the cell death program observed when parasites are exposed to stress conditions such as exposure to H_2O_2, suggesting that parasites could die using varying mechanisms. It is likely that the immune response of the host will then differ depending on which pathway is used.

In conclusion, most of the "ingredients" are presently available to better understand the mechanism(s) of death in trypanosomatids. However, the pathways of cell death in these parasites require much further dissection. Once this has been achieved we may have some ideas to the definitive role of a cell death program(s) in trypanosomatids and its potential relevance to the immune response of the host.

References

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