Multi-drug tolerance in *Leishmania* persister-like cells

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The ability of microorganisms to resist the killing action of antimicrobial agents is emerging as one of the most serious public health threats and has been observed for antibiotics, antifungals, and antiparasitic compounds. Understanding the mechanisms that allow pathogens to survive chemotherapy is essential. The most extensively studied molecular mechanism is drug resistance caused by acquired, heritable genetic changes. However, microorganisms can also adopt a physiological state of transient quiescence, manifested by non-proliferation and reduced metabolism. Persisters are a small fraction of quiescent cells that are adapted to withstand a variety of environmental assaults, including lethal doses of antibiotics. We present evidence for the existence of persister-like cells in the protozoan parasite Leishmania, induced upon exposure to normally lethal doses of antimonials. We show that Leishmania promastigotes survive lethal doses of antimonials by adopting a quiescence phenotype characterised by reduced proliferation, diminished metabolism and a reduced mitochondrial membrane potential. Importantly, these cells demonstrate cross tolerance to other anti-leishmanial drugs. Depending on the presence of genomic pre-adaptation to antimonial resistance, two types of persister-like cells were observed for *L. donovani* field isolates. In wild-type lines, persister-like cells were transiently tolerant to antimonials and returned to the sensitive state upon removal of drug pressure. Surprisingly, isolates with genetic changes associated with antimony-resistance, acquired a level of hyper-resistance after transient passage through the quiescent state, without further genetic changes. Our results demonstrate extreme versatility of *Leishmania* in adaptation to drug pressure and highlight the need for the development of innovative anti-leishmanials targeting non-proliferative forms.

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