Drug resistance in *Leishmania* : lessons for successful adaptation

Leishmania donovani causes up to 300,000 new cases of visceral leishmaniasis (VL) each year in the Indian subcontinent (ISC), with an estimated case fatality rate above 10%. The parasite population in the ISC underwent a major evolutionary bottleneck in the 60's during the DDT spraying campaigns and caused a massive epidemic after their interruption. Afterwards, this antroponotic parasite was submitted to drug pressure, (i) initially with antimonials (SSG), up to their replacement a decade ago because of resistance and toxicity and (ii) nowadays with miltefosine (MIL) in the frame of a regional control program. *L.donovani* from the ISC thus constitutes a unique model for studies of 'real-time' evolution of parasites and its clinical implications. Next generation sequencing demonstrates that the parasite has a great potential of genome flexibility, essentially at structural level: gene dosage, among others through aneuploidy or the formation of episomes, likely takes part of the adaptation strategies of the parasite. Flexibility is also highlighted by phylogenetic studies which suggest multiple and independent events of SSG resistance emergence, likely involving different adaptive mechanisms. Experimental studies support this hypothesis: on one hand, *Leishmania* can counter the 'direct' damage of the drug inside the parasite (i.e. through drug efflux from the parasite or protection against stress); on the other hand, the parasite can have an 'indirect effect' and manipulate its host cell, still through different mechanisms (i.e. upregulation of the drug efflux from the macrophage, interference with signaling system of the macrophage and down-regulation of the oxidative/nitrosative stress). Metabolomic studies reveal additional adaptive skills of SSG-resistant parasites, like the modulation of their membrane physiology or the preparation of energy stocks for their intracellular life. Interestingly, this set of adaptations has provided SSG-resistant parasites with an increased fitness: they are much more infectious than sensitive parasites and, in absence of the drug, they are still most abundant in natural populations of the ISC. Possible consequences in terms of drug development, clinical management and epidemiological monitoring will be discussed