The hematopoietic stem cell as a parasitological niche responsible for antileishmanial treatment failure

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Amongst the parasitic diseases, visceral leishmaniasis (VL) belongs to one of the deadliest, yet most neglected diseases of the world. Treatment options are scarce, have many limitations and post-treatment relapse is common while there is no effective test-of-cure.

Recently, long-term hematopoietic stem cells (LT-HSC) in the bone marrow were identified as a sanctuary niche where parasites can survive drug treatment by transitioning through a quiescent state, serving as source of systemic parasite spread and relapse. A vast number of parasites reside within this hospitable niche that is characterized by low oxidative burst levels and a unique transcriptional signature, named *StemLeish*, significantly overlapping with human VL and HIV co-infected blood transcriptomes. Silencing of the various *StemLeish* genes pinpointed a pivotal role of *Cxcr4* in shaping the LT-HSC niche.

Parasites that transitioned through quiescence displayed an increased cellular infectivity and high transmission capacity through the *Lutzomyia longipalpis* sand fly vector, emphasizing the risk of propagation of enhanced phenotypes following post-treatment relapse. Transcriptional profiling of quiescent parasites revealed a novel set of markers and potential drivers, several with predicted involvement as regulators of cell cycle progression and of gene expression at various levels.

Collectively, this work delivers unprecedented insights regarding post-treatment relapse during VL, providing novel biomarkers and drug targets for both host-directed and anti-parasite therapeutics targeting differential genes in quiescent amastigotes and in the hematopoietic niche.

Keywords: visceral leishmaniasis, bone marrow, hematopoietic stem cells, quiescence, relapse

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