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Selection and biochemical characterization of novel leishmanicidal molecules by virtual and biochemical screenings targeting Leishmania eukaryotic translation initiation factor 4A

Yosser Zina Abdelkrim

Institut Pasteur de Tunis, Tunisia.

Abstract

The identification of novel small and active molecules for the treatment of leishmaniases constitutes a research priority. Here, we expand on previous in silico investigations and virtual screens of small molecules targeting the Leishmania infantum initiation factor 4A (LieIF) as a potential drug target. LieIF belongs to the DEAD-box family of RNA helicases. DEAD-box proteins contain a highly conserved core structure with a dumbbell shape containing two, linked domains with structural homology to that of recombinant protein A (RecA). This core structure confers an ATP-dependent RNA-binding affinity, an RNA-dependent ATPase activity and an ATP-dependent RNA unwinding activity. We used the ATPase activity to establish a colorimetric assay in microtiter plates to screen for molecules that inhibit LieIF. We screened hundreds molecules previously identified by virtual screenings for their ability to bind to sites on LieIF that were important for the enzymatic activity. We discovered an interesting inhibitor: 6-α/β-aminocholestanol with an IC50 value of 150 ± 15 µM for 1 µM of LieIF. This compound also inhibits the RNA helicase activity of LieIF. The helicase assays and the ATPase competition experiments with the individual RecA-like domains and other proteins indicate that there are multiple binding sites on LieIF, and that the primary binding site is on domain 1 involving conserved RNA-binding motifs. Two out of ten identified chemical analogues of 6-α/β-aminocholestanol (6-α-aminocholestanol and 6-ketocholestanol) showed inhibitor effects on the ATPase activity of LieIF. Similar inhibitor effects were observed with mammalian eIF4A, but with different reaction profiles. All three molecules showed an anti-leishmanial activity against the promastigotes and the amastigotes of L. infantum parasites, and they showed non-significant toxicity toward macrophages. This study constitutes a first step towards the validation of LieIF as a drug target. It demonstrates biochemical differences between the Leishmania and mammalian eIF4A proteins, most notably in ATPase assays that show that rocaglamide affects the two proteins differently. To conclude, this work delivers a promising leishmanicidal molecule: 6-aminocholestanol with IC50 value lower than 1 µM on intracellular amastigotes, with little toxicity and with a selectivity index higher than 20. The 6-aminocholestanol constitutes a promising anti-Leishmania molecule that deserves further investigation.

معهد باستور تونس
Institut Pasteur de Tunis

Biography

Yosser Zina Abdelkrim is working as a professor in Institut Pasteur de Tunis in the Department of Parasitology Her field of interest is Pharmaceutical, Biochemistry Parasitology.

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