World Academy of Science, Engineering and Technology
International Journal of Biotechnology and Bioengineering
Vol:17, No:12, 2023

Targeting Peptide Based Therapeutics: Integrated Computational and Experimental Studies of Autophagic Regulation in Host-Parasite Interaction

Authors : Vrushali Guhe, Shailza Singh

Abstract : Cutaneous leishmaniasis is neglected tropical disease present worldwide caused by the protozoan parasite Leishmania major, the therapeutic armamentarium for leishmaniasis are showing several limitations as drugs are showing toxic effects with increasing resistance by a parasite. Thus identification of novel therapeutic targets is of paramount importance. Previous studies have shown that autophagy, a cellular process, can either facilitate infection or aid in the elimination of the parasite, depending on the specific parasite species and host background in leishmaniasis. In the present study, our objective was to target the essential autophagy protein ATG8, which plays a crucial role in the survival, infection dynamics, and differentiation of the Leishmania parasite. ATG8 in Leishmania major and its homologue, LC3, in Homo sapiens, act as autophagic markers. Present study manifested the crucial role of ATG8 protein as a potential target for combating Leishmania major infection. Through bioinformatics analysis, we identified non-conserved motifs within the ATG8 protein of Leishmania major, which are not present in LC3 of Homo sapiens. Against these two non-conserved motifs, we generated a peptide library of 60 peptides on the basis of physicochemical properties. These peptides underwent a filtering process based on various parameters, including feasibility of synthesis and purification, compatibility with Selective Reaction Monitoring (SRM)/Multiple reaction monitoring (MRM), hydrophobicity, hydropathy index, average molecular weight (Mw average), monoisotopic molecular weight (Mw monoisotopic), theoretical isoelectric point (pI), and half-life. Further filtering criterion shortlisted three peptides by using molecular docking and molecular dynamics simulations. The direct interaction between ATG8 and the shortlisted peptides was confirmed through Surface Plasmon Resonance (SPR) experiments. Notably, these peptides exhibited the remarkable ability to penetrate the parasite membrane and exert profound effects on Leishmania major. The treatment with these peptides significantly impacted parasite survival, leading to alterations in the cell cycle and morphology. Furthermore, the peptides were found to modulate autophagosome formation, particularly under starved conditions, suggesting their involvement in disrupting the regulation of autophagy within Leishmania major. In vitro, studies demonstrated that the selected peptides effectively reduced the parasite load within infected host cells. Encouragingly, these findings were corroborated by in vivo experiments, which showed a reduction in parasite burden upon peptide administration. Additionally, the peptides were observed to affect the levels of LC3II within host cells. In conclusion, our findings highlight the efficacy of these novel peptides in targeting Leishmania major's ATG8 and disrupting parasite survival. These results provide valuable insights into the development of innovative therapeutic strategies against leishmaniasis via targeting autophagy protein ATG8 of Leishmania major.

Keywords : ATG8, leishmaniasis, surface plasmon resonance, MD simulation, molecular docking, peptide designing, therapeutics
Conference Title : ICA 2023 : International Conference on Autophagy
Conference Location : Rome, Italy
Conference Dates : December 11-12, 2023