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Light Shed on Differential Effectiveness of Aminoglycosides Against Parasitic Protozoa

By BiotechDaily International staff writers

Posted on 20 Aug 2013

Previously unknown factors have now been identified as important in the differential effectiveness of various aminoglycosides in being used or developed to treat leishmaniasis, with similar implications for treating human diseases caused by other parasitic protozoa.

Aminoglycosides (AGs) are well known as highly potent, broad-spectrum antibiotics and have been extensively investigated as such. The homologous site of AG action (known to be or putatively the decoding "ribosomal A site") in eukaryotes highlights the potential of some AGs for treating relevant human genetic disorders as well as parasitic infections caused by lower eukaryotes, such as in leishmaniasis, trypanosomiasis, giardiasis, and amoebiasis. However, too few studies have been done to characterize AG activity in eukaryotes.

The new findings, from the laboratories of Prof. Timor Baasov and Prof. Noam Adir of the Technion – Israel Institute of Technology (Haifa, Israel), Prof. Charles Jaffe of the Hebrew University (Jerusalem, Israel), and Assistant Prof. Jiro Kondo of Sophia University (Tokyo, Japan), examined the molecular mechanism as well as inhibition activity of AGs in *Leishmania* as a model organism for eukaryotes in general and for parasitic protozoa in particular. Some AGs have recently been clinically approved and are currently used worldwide for the treatment of leishmaniasis, such as geneticin and, particularly, paromomycin, to which parasite resistance is also on the rise.

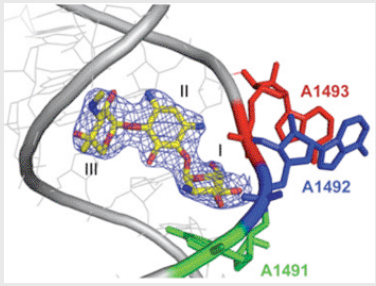

Image: Crystal structure visualization of [geneticin (G418)] – [leishmanial A-site rRNA] complex (Photo courtesy of Prof. Baasov and Prof. Adir of Technion – Israel Institute of Technology – via PNAS).

Five AGs were chosen for comparison in terms of the anti-leishmanial activity part of the study, performed with a growth-inhibition assay (LC50) on *Leishmania* promastigotes in culture: paromomycin and neomycin B of one class, gentamicin and geneticin of another class, and apramycin of another. Two *Leishmania* species were used for these susceptibility assays – *L. major*, causing cutaneous disease, and *L. donovani*, causing fatal visceral disease if not diagnosed and treated in time. Two AGs were chosen for comparison in terms of the structural mechanism part of the study, performed with X-ray crystallography based modeling: geneticin (also known as G418) due to its high potency for the treatment of leishmaniasis, and apramycin due to its lack of anti-leishmanial activity yet being a strong binder of the leishmanial ribosome. The crystal structures were made of the AGs bound to rRNA duplex constructs mimicking their putative leishmanial binding site.

Analyses of the combined structural and physiological data provide important new insight into the anti-leishmanial activities, or lack thereof, of certain AG structural derivatives. The physiological, parasite susceptibility data indicate, for example, that geneticin is more potent than paromomycin, which is more potent than gentamicin and neomycin. This is in agreement with previous work reporting, for example, lower treatment potency of neomycin compared with paromomycin. Notably, the AGs were more effective against *L. major* growth than *L. donovani*, which might be due to species differences that affect AG permeability. Apramycin did not appear here to inhibit growth. The structural data indicate, for example among several, that ability of an AG (here, geneticin) to induce the ON-state conformation is highly important for its observed potency as an anti-Leishmania agent, thus implying the significance of translatory miscoding events in the killing mechanism.

The study was published in the journal *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* online, ahead of print, July 29, 2013.

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