Exploring the cellular targets of anti-leishmanial natural product analogues

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Abstract

The dehydrodieugenol family of natural products has specific activity against all *Leishmania* species tested[1, 2]. This prompted synthesis of related analogues, with improved potency comparable to Miltefosine[3]. Elucidating the mechanism of action of these compounds could validate the "goodness" of target and aid drug development efforts. Initial evidence suggested these compounds affect the mitochondrion, however evidence was weak and the protein target(s) are unknown.

We have developed an active analogue with both cross-linking and click capabilities which allows access to various techniques for target identification. As a first approach, we attach a fluorescent azide using *in situ* click to visualise fluorescence localisation of the compound in *L. mexicana*. We show that photo cross-linking using a diazirine on the small molecule is necessary to prevent compound wash-out during the click protocol. Click-conjugated fluorescence appeared mitochondrial, which we have confirmed using colocalisation with a tagged mitochondrial protein.

These analogues are also a powerful toolkit for photo-affinity protein pull-downs and related techniques. Combining this with parallel approaches, including selecting for drug resistant mutants and transcriptomic analysis of treated cells, will allow us to evaluate protein targets of this family of compounds.

References

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