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Unstable amplification of two extrachromosomal elements in α -difluoromethylornithine-resistant *Leishmania donovani*

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We describe the first example of unstable gene amplification consisting of linear extrachromosomal DNAs in drug-resistant eukaryotic cells. α -Difluoromethylornithine (DFMO)-resistant *Leishmania donovani* with an amplified ornithine decarboxylase (*ODC*) gene copy number contained two new extrachromosomal DNAs, both present in 10 to 20 copies. One of these was a 140-kb linear DNA (ODC140-L) on which all of the amplified copies of the *ODC* gene were located. The second was a 70-kb circular DNA (ODC70-C) containing an inverted repeat but lacking the *ODC* gene. Both ODC140-L and ODC70-C were derived from a preexisting wild-type chromosome, probably by a conservative amplification mechanism. Both elements were unstable in the absence of DFMO, and their disappearance coincided with a decrease in *ODC* activity and an increase in DFMO growth sensitivity. These results suggest the possibility that ODC70-C may play a role in DFMO resistance. These data expand the diversity of known amplification mechanisms in eukaryotes to include the simultaneous unstable amplification of both linear and circular DNAs. Further characterization of these molecules will provide insights into the molecular mechanisms underlying gene amplification, including the ability of linear amplified DNAs to acquire telomeres and the determinants of chromosomal stability.