Annotation and comparative analysis of kinetoplastid protein kinases defines core kinomes with relevance for drug discovery and reveals an evolutionary reduction in kinome size in animal-infective trypanosomes compared to their free-living ancestor.

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The kinetoplastids are diverse organisms, comprising free-living species such as *Bodo saltans*, monoxenous species such as *Paratrypanosoma confusum* and *Blechomonas ayalai* that infect only arthropods, and a range of dixenous species that infect animals and/or humans and are spread by arthropod vectors, including the pathogenic "TriTryps" (*Trypanosoma brucei, Leishmania* spp. and *Trypanosoma cruzi*) and other pathogenic animal trypanosomes (*T. congolense, T. evansi* and *T. equiperdum*), as well as the usually non-pathogenic *T. grayi, T. melophagium, T. rangeli* and *T. theileri* species. Given their diversity and that protein kinases are key signalling molecules with significant potential as drug targets, we wanted to compare the protein kinomes of all these species to i) shed light on the evolution of the kinetoplastid protein kinome ii) identify a core kinome for pathogenic species that might have relevance for drug discovery efforts and iii) to identify species-specific kinases that might reflect unique aspects of biology in each organism. Only the kinomes of the TriTryps had previously been annotated, some 20 years ago[1], so we used a similar approach to annotate the kinomes of the additional species since their genomes are publicly available at TriTrypDB[2].

Compared to the mono- and dixenous species, free-living *B. saltans* was found to possess significantly more protein kinase genes, with particular enrichment for genes encoding Sterile (STE) kinases, calcium/calmodulin-dependent-kinases (CAMK), CAMK kinases and NIMA-related kinases (NEKs), indicating an evolutionary reduction in protein kinome size in the animal-infective kinetoplastids. Only small numbers of species-specific kinases identified in any of the animal kinetoplastids, in stark contrast to *B. saltans*. Across all of the kinetoplastids, a core kinome of some 60 ePKs, common to all species analysed, was identified. A larger shared kinome was identified amongst *Trypanosoma* species causing human African trypanosomiasis (HAT) or animal trypanosomiases (135 kinases), and a shared kinome of ~105 kinases was identified between all of the dixenous pathogenic kinetoplastids, suggesting that targeting of essential kinases within this cohort may have potential for developing new pan treatments that would have effectiveness against HAT, animal trypanosomiasis, *Leishmaniasis* and Chagas disease.

1 Parsons *et al.*, 2005 BMC Genomics 6:127

2 Alvarez-Jarreta *et al.*, 2024 Nucleic Acids Research 52:D808–D816