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Authors

Davies, Karen M
Kühlbrandt, Werner

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Structure of the catalytic F₁ head of the F₁-F₀ ATP synthase from *Trypanosoma brucei*

Karen M. Davies^{a,1} and Werner Kühlbrandt^b

Trypanosoma brucei is the causative agent of sleeping sickness, which is responsible for thousands of deaths per year in developing countries. The single-cell eukaryotic parasite has an elaborate life cycle that involves both an insect vector and a mammalian host. The mitochondrial F₁-F₀ ATP synthase is crucial for cell survival in both stages, making it a key target for designing new drugs to combat trypanosomal infections (1, 2). In our previous work we used electron cryotomography and subtomogram averaging to determine the structure and organization of ATP synthase in mitochondria of procyclic *T. brucei* (3). We discovered that the ATP synthase forms rows of dimers, which curve around the edges of the mitochondrial cristae. Particularly remarkable was the structure of the catalytic F₁ head, which was different from that of all other known ATP synthases. In the low-resolution subtomogram average map, the three catalytic β -subunits looked as expected, whereas the density for parts of the noncatalytic α -subunits was weak or absent. Because it is known that the α -subunit of the *T. brucei* ATP synthase is proteolytically cleaved into two domains of unequal size (2), we proposed that the C-terminal domains of the α -subunits had shifted from their usual position to the three corners of the pyramid-shaped F₁ assembly. Subsequent single-particle cryo-EM studies of isolated *T. brucei* F₁ heads at 3.9-Å resolution (Fig. 1A) conducted by one of us (K.M.D.) indicate that the ($\alpha\beta$)₃ assembly of the trypanosomal F₁ head has in fact a canonical structure, and the three corners are occupied by the euglenozoa-specific F₁ subunit p18. The same finding was obtained independently by Montgomery et al. using X-ray crystallography, as reported in PNAS (4). The analysis of our

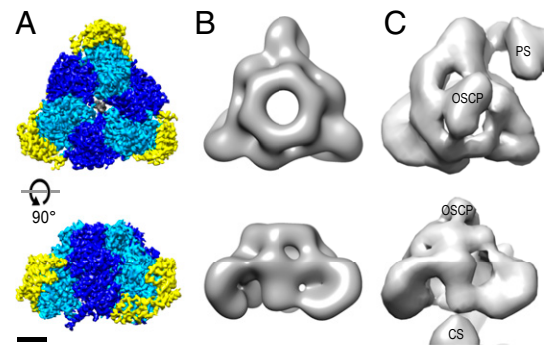


Fig. 1. Comparison of single-particle and subtomogram average cryo-EM maps of the *T. brucei* F₁ head. Top views (Upper); side views (Lower). (A) Single-particle map at 3.9-Å resolution colored by subunit (dark blue, β -subunit; light blue, α -subunit; yellow p18). (B) Single-particle map filtered to 30-Å resolution. (C) Subtomogram average map at 27.5-Å resolution. CS, central stalk; OSCP, oligomycin sensitivity-conferring protein (3); PS, cropped peripheral stalk. (Scale bar, 25 Å.)

original subtomogram average map was carried out with all due care based on the data available to us at the time. The map is consistent with our single-particle map and the structure reported by Montgomery et al. (4), except for a lack of density for part of the α -subunit. The absence of density for the α -subunit appears to be a feature of the subtomogram average map that is reproduced by filtering the single-particle map to 30-Å resolution (Fig. 1B and C). Thus, low-resolution maps of macromolecular complexes can be misleading and their interpretation should be verified whenever possible by higher-resolution structures obtained by single-particle cryo-EM (Fig. 1A) or X-ray crystallography (4).

^aMolecular Biophysics and Integrated Bioimaging Division, Lawrence Berkeley National Laboratory, Berkeley, CA 64720; and ^bDepartment of Structural Biology, Max Planck Institute of Biophysics, 60438 Frankfurt am Main, Germany

Author contributions: K.M.D. designed research; K.M.D. performed research; K.M.D. analyzed data; and K.M.D. and W.K. wrote the paper. The authors declare no conflict of interest.

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¹To whom correspondence should be addressed. Email: KMDavies@lbl.gov.

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- 1 Schnauffer A, Clark-Walker GD, Steinberg AG, Stuart K (2005) The F₁-ATP synthase complex in bloodstream stage trypanosomes has an unusual and essential function. *EMBO J* 24:4029–4040.
 - 2 Zíková A, Schnauffer A, Dalley RA, Panigrahi AK, Stuart KD (2009) The F₀F₁-ATP synthase complex contains novel subunits and is essential for procyclic *Trypanosoma brucei*. *PLoS Pathog* 5:e1000436.
 - 3 Mühleip AW, Dewar CE, Schnauffer A, Kühlbrandt W, Davies KM (2017) In situ structure of trypanosomal ATP synthase dimer reveals a unique arrangement of catalytic subunits. *Proc Natl Acad Sci USA* 114:992–997.
 - 4 Montgomery MG, Gahura O, Leslie AGW, Zíková A, Walker JE (2018) ATP synthase from *Trypanosoma brucei* has an elaborated canonical F₁-domain and conventional catalytic sites. *Proc Natl Acad Sci USA* 115:2102–2107.