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Invited Review

Acetate formation in the energy metabolism of parasitic helminths and protists

Aloysius G.M. Tielens [a,*], Koen W.A. van Grinsven [b,1], Katrin Henze [c], Jaap J. van Hellemond [a], William Martin [c]

[a] Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[b] Department of Biochemistry and Cell Biology, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 2, 3584 CM Utrecht, The Netherlands
[c] Institute of Botany III, Heinrich Heine University, Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany

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ABSTRACT

Formation and excretion of acetate as a metabolic end product of energy metabolism occurs in many protist and helminth parasites, such as the parasitic helminths *Fasciola hepatica, Haemonchus contortus* and *Ascaris suum*, and the protist parasites, *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis* as well as *Trypanosoma* and *Leishmania* spp. In all of these parasites acetate is a main end product of their energy metabolism, whereas acetate formation does not occur in their mammalian hosts. Acetate production might therefore harbour novel targets for the development of new anti-parasitic drugs. In parasites, acetate is produced from acetyl-CoA by two different reactions, both involving substrate level phosphorylation, that are catalysed by either a cytosolic acetyl-CoA synthetase (ACS) or an organellar acetate:succinate CoA-transferase (ASCT). The ACS reaction is directly coupled to ATP synthesis, whereas the ASCT reaction yields succinyl-CoA for ATP formation via succinyl-CoA synthetase (SCS). Based on recent work on the ASCTs of *F. hepatica, T. vaginalis* and *Trypanosoma brucei* we suggest the existence of three subfamilies of enzymes within the CoA-transferase family I. Enzymes of these three subfamilies catalyse the ASCT reaction in eukaryotes via the same mechanism, but the subfamilies share little sequence homology. The CoA-transferases of the three subfamilies are all present inside ATP-producing organelles of parasites, those of subfamily IA in the mitochondria of trypanosomatids, subfamily IB in the mitochondria of parasitic worms and subfamily IC in hydrogenosome-bearing parasites. Together with the recent characterisation among non-parasitic protists of yet a third route of acetate formation involving acetate kinase (ACK) and phosphotransacetylase (PTA) that was previously unknown among eukaryotes, these recent developments provide a good opportunity to have a closer look at eukaryotic acetate formation.

1. Introduction

Most parasites have a complex life cycle, which can include free-living stages as well as distinct stages inhabiting one or more host organisms. Oxygen availability is often limited during all or part of the parasite life cycle, therefore they must possess pathways of ATP synthesis that are independent of O_2 as the terminal electron acceptor. The formation of acetate from acetyl-CoA as a metabolic end product is a metabolic route that is present in many parasites, especially in those that inhabit or encounter hypoxic or anoxic habitats (Table 1) (Köhler, 1985; Tielens, 1994; Sanchez and Müller, 1996; Tielens et al., 2002). Furthermore, acetate production is also present in many non-parasitic eukaryotes, including flowering plants (Zeiher and Randall, 1990) and marine invertebrates (De Zwaan, 1991), but it is absent in mammals. Since acetate is an important end-product of energy metabolism among many parasites but not among their mammalian hosts, acetate formation is an attractive target for the development of novel anti-parasitic drugs.

Thus far, four different chemical reactions have been identified in which acetate is produced from acetyl-CoA, catalysed by either (i) a CoA-transferase, (ii) a synthetase, (iii) a hydrolase or (iv) a phosphate-acetyltransferase in combination with a kinase reaction (Fig. 1).

For all four reactions, corresponding enzymes can be found among the eukaryotes. In parasites, however, only acetyl-CoA synthetases (ADP-forming) and acetate:succinate CoA-transferases (ASCTs) have been identified to date. Therefore, this review will only briefly address the characteristics of acetate kinases and acetyl-CoA hydrolases and will focus on acetyl-CoA synthetases (ADP-forming) and ASCTs present in parasites. The similarities and differences in acetate formation between parasites will be discussed, as well as the biochemical characteristics, the sub-cellular localisations, and some remarks will be presented on the evolutionary origins of the enzymes responsible for acetate production.

* Corresponding author. Tel.: +31 10 703 2193; fax: +31 10 703 3875.
E-mail addresses: a.tielens@erasmusmc.nl, a.g.m.tielens@uu.nl (A.G.M. Tielens).
[1] Present address: Department of Molecular Cell Physiology, Faculty of Earth and Life Sciences, Vrije Universiteit Amsterdam, de Boelelaan 1085, 1081 HV Amsterdam, The Netherlands.

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Table 1
Acetate-forming enzymes in parasitic helminths and protists. BLAST searches were performed to identify homologs of acetyl-CoA synthetase (ADP-forming) and CoA-transferases of family 1A, 1B and 1C genes in parasites, using acetyl-CoA synthetase (ADP-forming) of *Entamoeba histolytica* (AF286346) and the acetate:succinate CoA-transferases of *Trypanosoma brucei* (EAN79240), *Fasciola hepatica* (ACF06126) and *Trichomonas vaginalis* (XP_001330176), respectively. Identified homologous demonstrated significant homology with *E* values smaller than $1e^{-20}$. (—) indicates not present in a completely sequenced genome, (n.d.) not detected in available databases, (?) no literature or sequence data available.

Organism	Acetate formation from gluocse	Family I CoA-transferases			AcCoA synthetase
		Subfamily IA	Subfamily IB	Subfamily IC	(ADP-forming)
Nematodes					
Ascaris suum[a]	Major end product[e]	BI594619	BI782486	n.d.	n.d.
Haemonchus contortus[a]	Major end product[f]	n.d.	BM138769	n.d.	n.d.
Brugia malayi[b]	?[g,h]	—	XP_001900057	—	—
Onchocerca volvulus	Major end product[g]	?	?	?	?
Strongyloides stercoralis	?	?	BE580065	?	?
Trichostrongylus colubriformis	Major end product[i]	?	?	?	?
Trematodes					
Schistosoma mansoni[b]	No[j]	—	XP_002577003	—	—
Schistosoma japonicum[a]	No[j]	n.d.	AAW27410	n.d.	n.d.
Schistosoma haematobium[a]	No[j]	n.d.	n.d.	n.d.	n.d.
Fasciola hepatica[a]	Major end product[k]	n.d.	ACF06126	n.d.	n.d.
Cestodes					
Ecchinococcus multilocularis[c]	Major end product[l]	n.d.	n.d.	n.d.	n.d.
Echinococcus granulosus[a]	Major end product[l]	n.d.	n.d.	n.d.	n.d.
Taenia taeniaeformis	Major end product[m]	?	?	?	?
Taenia solium[a]	?	n.d.	EL751586	n.d.	n.d.
Moniezia expansa[a]	?	n.d.	FF677706	n.d.	n.d.
Parabasalids					
Trichomonas vaginalis[b]	Major end product[n]	—	—	XP_001330176	—
Tritrichomonas foetus[a]	Major end product[n]	n.d.	n.d.	CX154925	n.d.
Kinetoplastidae					
Trypanosoma brucei (procyclics)[b]	Major end product[o]	EAN79240	—	—	—
Trypanosoma cruzi[b]	Major end product[o]	EAN86067	—	—	—
Leishmania major [b]	Major end product[p]	CAJ06634	—	—	—
Leishmania infantum[d]	Major end product[q]	CAM70089	n.d.	n.d.	n.d.
Phytomonas sp[a]	Major end product[r]	CO723949	n.d.	n.d.	n.d.
Crithidia luciliae[d]	Major end product[o]	n.d.	n.d.	n.d.	n.d.
Archamoebae					
Entamoeba histolytica[b]	Major end product[s]	—	—	—	AF286346
Diplomonads					
Giardia lamblia[b]	Major end product[t]	—	—	—	XM_001705692
Apicomplexa					
Plasmodium falciparum[b]	No	—	—	—	XM_001348495
Toxoplasma gondii[b]	No	—	—	—	—
Theileria parva[b]	No	—	—	—	—
Babesia bovis[a]	No	n.d.	n.d.	n.d.	n.d.
Cryptosporidium parvum[b]	No	—	—	—	—
Blastocystidae					
Blastocystis hominis[a]	?	n.d.	EC648226	EC647239	EC648512
Ciliates					
Nyctotherus ovalis[a]	Major end product[u]	AJ871320	n.d.	n.d.	n.d.
Chlorophyta					
Chlamydomonas reinhardtii[b]	Major end product[v]	—	—	—	—

[a] Expressed sequence tag (EST) database.
[b] Complete genome database.
[c] DNA shotgun database.
[d] Incomplete genome database.
[e] Köhler and Bachmann (1980).
[f] Ward and Huskisson (1978).
[g] MacKenzie et al. (1989) acetate production unknown for *B. malayi*, but *B. pahangi* microfilaria are known to produce acetate as major end product (Rew and Saz, 1977).
[h] Rew and Saz (1977).
[i] Sangster and Prichard (1985).
[j] Tielens et al. (1989).
[k] van Vugt et al. (1979).
[l] McManus and Smyth (1978).
[m] von Brand et al. (1968).
[n] Steinbüchel and Müller (1986).
[o] Cazzulo (1992).
[p] Darling et al. (1989).
[q] Van Hellemond et al. (1997).
[r] Chaumont et al. (1994).
[s] Montalvo et al. (1971).
[t] Lindmark (1980).
[u] Boxma et al. (2005).
[v] Mus et al. (2007).