Molecular & Biochemical Parasitology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Molecular & Biochemical Parasitology

The origin and evolution of the acidocalcisome and its interactions with other organelles

Roberto Docampo [a,b,*]

[a] Center for Tropical and Global Emerging Diseases and Department of Cellular Biology, University of Georgia, Athens 30602, USA
[b] Departamento de Patología Clínica, Universidade Estadual de Campinas, São Paulo 13083-877, Brazil

ARTICLE INFO

Article history:
Received 27 August 2015
Received in revised form 4 October 2015
Accepted 19 October 2015
Available online xxx

Keywords:
Acidocalcisome
Calcium
Polyphosphate
Trypanosome
Malaria
Toxoplasma
Vacuole

ABSTRACT

Acidocalcisomes are acidic calcium stores that have been found from bacteria to human cells. They are rich in phosphorus compounds in the form of orthophosphate (P_i), pyrophosphate (PP_i), and polyphosphate (polyP) and their acidity is maintained by proton pumps such as the vacuolar proton pyrophosphatase (V-H^+-PPase, or VP1), the vacuolar proton ATPase (V-H^+-ATPase), or both. Recent studies in trypanosomatids and in other species have revealed their role in phosphate metabolism, and cation and water homeostasis, as suggested by the presence of novel pumps, transporters, and channels. An important role in autophagy has also been described. The study of the biogenesis of acidocalcisomes as well as of the interactions of these lysosome-related organelles with other organelles have uncovered important roles in calcium signaling and osmoregulation.

Significantly, despite conservation of acidocalcisomes across all of cellular life, there is evidence for intimate integration of these organelles with eukaryotic cellular functions, and which are directly relevant to parasites.

1. Introduction

We named these membrane-bounded organelles as acidocalcisomes when we first found them in trypanosomes [1,2]. We later realized that, as early as in the nineteenth century [3], similar structures had been described in bacteria, and were named metachromatic [3] or volutin [4] granules. There was some initial discrepancy on the presence or absence of a surrounding membrane in these bacterial granules [5] until we described at least two species of bacteria in which a surrounding membrane is present [6,7]. These volutin granules were also described early in the twentieth century in a number of unicellular protists, like trypanosomatids [8], coccidians [9], and sarcosporidia [10] among others, although they were considered granules rather than organelles and were renamed as polyphosphate (polyP) bodies when it was found that this polymer was abundant within the acidocalcisome-like vacuole of yeast [11]. More recently polyP, which is a polymer from 3 to thousands of orthophosphate units bound by high-energy phosphoanhydride bonds, was found in membrane-bounded acid calcium stores [12] from mammalian cells such as human platelet dense granules [13] and mast cell and basophil granules [14], which were then considered as acidocalcisome-like organelles. Taken together, these studies revealed that acidocalcisomes are membrane-bounded organelles that, together with the lipid droplets [15], are the only organelles conserved from bacteria to human cells.

Early reviews [16–18] described the morphological and biochemical characteristics of acidocalcisomes of different species. In this review we will limit our discussion to the most recent work on the origin, biogenesis, and function of these organelles.

2. Origin of the acidocalcisome

Although most cell biology textbooks (see, for example [19]) still state that prokaryotes lack intracellular compartmentalization, many intracellular membrane-bounded organelles have been reported in several bacterial species (Table 1) [20]. Some of

Abbreviations: AP, acid phosphatase; AP-3, adaptor protein 3; AQP, aquaporin; CVC, contractile vacuole complex; IP_3, inositol 1,4,5-trisphosphate; LRO, lysosome-related organelle; Pho91, phosphate transporter 91; PI3K, phosphatidyl inositol 3-kinase; PDE, phosphodiesterase; polyP, polyphosphate; PP_i, pyrophosphate; RVD, regulatory volume decrease; TOR, target of rapamycin; VP1 of H^+-PPase, vacuolar H^+-pyrophosphatase; V-H^+-ATPase, vacuolar H^+-ATPase; VSP, vacuolar soluble pyrophosphatase; VTC, vacuolar transporter chaperone complex; VIT, vacuolar iron transporter.

* Corresponding author at: Center for Tropical and Emerging Global Diseases and Department of Cellular Biology, University of Georgia, 350A Paul D. Coverdell Center, 500 D.W. Brooks Dr., Athens, GA 30602, USA. Fax: + 1 706 542 9493.
E-mail address: rdocampo@cb.uga.edu

http://dx.doi.org/10.1016/j.molbiopara.2015.10.003
0166-6851/

Table 1
Some of the organelles described in prokaryotes.

Name	Membrane	Content	Present in	Evidence of membrane	Reference
Acidocalcisome	Lipid bilayer, proteins	PolyP, cations	*A. tumefaciens R. rubrum*	Biochemical, EM	[6,7]
Magnetosome	Lipid bilayer, proteins	Magnetite (Fe_3O_4) Greigite (Fe_3O_4)	Magnetotactic bacteria (gram-negative)	Biochemical, EM	[21]
Photosynthetic Membranes (thylakoids, chlorosomes, chromatophore membranes)	Lipid mono or bilayer, proteins	Photosynthetic reactions	Purple photosynthetic bacteria Cyanobacteria Green photosynthetic bacteria	Biochemical, EM	[22]
Anammoxosome	Ladderan lipids, proteins	Anaerobic ammonium oxidation pathway	Planctomycetes	Biochemical, EM	[24]
Polyhydroxyalkanoate granules	Lipid, proteins (phasins)	Hydroxyalkanoates, Mercaptoalkanoates	Many bacteria	Biochemical, EM	[25]
Pyrellulosome	Lipid bilayer	DNA (nucleoid)	Planctomycetes	EM	[23]
Lipid droplet	Lipid monolayer	Lipids	Most bacteria	Biochemical, EM	[15]
Carboxysome	Protein	RuBisCO, CA	Actinobacteria, Cyanobacteria, Proteobacteria	Genetic, EM	[26]
Pdu compartment	Protein	Propanediol utilization	Actinobacteria, Firmicutes, Fusobacteria, Proteobacteria Spirochaetes, Synergistetes	Genetic, EM	[26]
Etu microcompartment	Protein	Ethanolamine utilization	Firmicutes	Genomic, EM	[26]

the membranes are lipid based as in, for example, acidocalcisomes [6,7], magnetosomes [21], photosynthetic membranes (thylakoids, chlorosomes, and chromatophore membranes) [22], pyrellulosomes [23], anammoxosomes [24], lipid droplets [15], and polyhydroxyalkanoate granules [25], while others are protein based such as in carboxysomes, 1,2-propanediol use (Pdu) compartment, and ethanol use (Etu) microcompartment [26]. The existence of such compartmentalization, which includes the discoveries that the planctomycete *Gemmata obscuriglobus* has its chromosome surrounded by a double membrane with similarities to a nuclear membrane [27] and that it has an endocytosis-like protein uptake [28] support an autogenous origin of these organelles rather than an endosymbiotic one, although convergent evolution in their appearance cannot be ruled out [26,29].

It has been claimed that acidocalcisomes could be present in all domains of life, including archaea, and may thus date back as far as to the last universal common ancestor [30]. On the other hand, acidocalcisomes of trypanosomes share characteristics with organelles known as lysosome-related organelles (LROs) such as human platelets dense granules and mast cell granules, which are also considered acidocalcisome-like organelles [18,14]. For example, adaptor protein 3 (AP-3), a protein complex involved in transport of membrane proteins to LROs of mammalian cells [31] is involved in the biogenesis of acidocalcisomes of *Leishmania major* [32] and *Trypanosoma brucei* [33]. This does not necessarily suggest a different origin of acidocalcisomes in eukaryotes but a potential further adaptation in these cells. The point here is that similar membrane-bounded polyP-containing acidic calcium stores are present in both prokaryotes and eukaryotes and they could have appeared either autogenously or by convergent evolution.

Recent articles have reported the presence of acidocalcisomes and acidocalcisome-like organelles in a number of bacteria and eukaryotic species. The marine sulfide-oxidizing bacteria *Beggiatoa* was reported to accumulate polyP together with cations in well-delimited granules enclosed by a lipid layer with similarity to acidocalcisomes, although not particularly acidic [34]. Similar polyP and cation storage structures (small granules) were found in the gram-negative sporulating bacterium *Acetonema longum* [35]. PolyP also accumulates in acidocalcisome-like vacuoles of the arbuscular mycorrhizal fungus *Rhizophagus* sp. [36]. Typical acidocalcisomes were recently found in the midgut of the caterpillar *Anticarsia gemmatalis*, although they were called spherites [37]. Acidocalcisomes have recently been described in other eukaryotes such as *Eimeria acervulina*, and *Eimeria tenella*, parasites that infect poultry flocks all over the world [38], and in the egg yolk of the insect *Rhodnius prolixus* [39], one of the insect vectors of *Trypanosoma cruzi*. Mast cell granules and human basophil granules were also shown to contain polyP, calcium and an acidic pH and together with their elemental composition have the characteristics of typical acidocalcisomes [14]. PolyP released by mast cells and basophils could be important mediators of their pro-coagulant and pro-inflammatory activities [40].

3. New insights into the chemical and enzymatic composition

Recent biochemical and proteomic studies in trypanosomatids and in other species have identified new components of acidocalcisomes that clarify their role in phosphate and cation homeostasis, and in cell signaling.

Acidocalcisomes of *Chlamydomonas reinhardtii* [41] were found to contain copper, which becomes available for the synthesis of plastocyanin [42]. Copper trafficking to acidocalcisomes was proposed as a strategy for preventing mismetallation during zinc deficiency enabling efficient cuproprotein metallation or remetallation upon zinc resupply [42]. Copper accumulation was also detected in acidocalcisomes (spherites) of the midgut of the carterpillar *A. gemmatalis* [37] and in acidocalcisome-like vacuoles of *Euglena gracilis* [43].

PolyP is the polymer that defines acidocalcisomes and new information became available about its synthesis in eukaryotes. PolyP synthesis in eukaryotes was unclear until it was demonstrated that the *Sacharomyces cerevisiae* vacuolar transporter chaperone 4 (ScVtc4p) is a polyP polymerase that uses ATP to generate polyP [44] (Fig. 1). The Vtc complex in *S. cerevisiae* consists of 4 proteins (Vtc1-4) that form hetero-oligomeric complexes that couple synthesis and translocation of polyP to the acidocalcisome-like vacuole and prevents its toxicity when in the cytosol [45]. This polyP import requires an electrochemical gradient as a driving force [45]. A similar acidocalcisome localization of Vtc4 protein was

Please cite this article in press as: R. Docampo, The origin and evolution of the acidocalcisome and its interactions with other organelles, Mol Biochem Parasitol (2015), http://dx.doi.org/10.1016/j.molbiopara.2015.10.003