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Short communication

Cyclic nucleotide specific phosphodiesterases of the kinetoplastida: A unified nomenclature

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There are numerous infections of humans and domestic animals that are mediated by a variety of trypanosomatids. Despite the significant loss of life and the debilitating economic impact of these diseases, the pallet of medications for treatment of these trypanosomatid infections is still quite limited. The last decade has seen numerous attempts to define and characterize new potential drug targets in these organisms [1–3]. In human pharmacology, cyclic nucleotide specific phosphodiesterases (PDEs) have long been established as attractive drug targets, and some inhibitors of PDEs are proving to be very effective in the relief of a number of maladies. A number of these PDE-inhibitor based drugs are already on the market, and many more are in the various stages of development. All 11 human PDEs are currently being explored as potential drug targets for a variety of ailments. In striking contrast, very little is still known about the kinetoplastid PDEs, and about cyclic nucleotide signalling in these organisms at large [4]. Our laboratories have recently begun to study the PDEs of various kinetoplastid parasites, both as potential targets for the development of novel and effective anti-parasitic drugs and as important players in cellular signal transduction. Several PDEs from three kinetoplastid species have been experimentally explored [5–12], and the gene sequences for several more are accessible, as three kinetoplastid genome projects have recently been completed [13–15]. All kinetoplastid PDEs identified to date belong to the class I PDEs [16] that also include the 11 families of human PDEs, one of the two PDEs of fungi, such as *Saccharomyces* or *Candida*, and several PDEs from the slime mold *Dictyostelium*. Class I PDEs share a conserved catalytic domain of ~270 amino acids. All kinetoplastids for which genomic sequencing projects are completed [13–15] or are still in progress appear to be equipped with the same set of four different class I PDE families (Fig. 1). Inevitably, different laboratories have applied different nomenclatures to the various kinetoplastid PDEs, which has not contributed to greater clarity in the field. An additional level of confusion is generated by the fact that the current hodgepodge naming of kinetoplastid PDEs does not fit with the nomenclature of the human PDEs (http://depts.washington.edu/pde/pde.html; [17]). In the human field, the PDE nomenclature is defined as given in the following example: HsPDE4Al is a human PDE, member of family 4 (cAMP-specific), gene A (four genes A–D are present in the human genome), splice variant 1. As this numbering system

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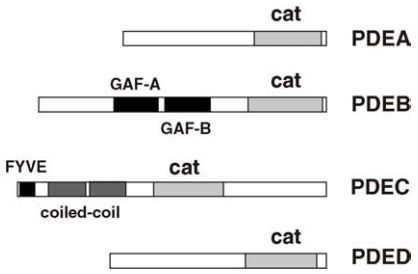

Fig. 1. Schematic domain structure of the four kinetoplastid PDE families, cat: Class I PDE catalytic domain, pfam00233: GAF-A, GAF-B: pfam01590; FYVE: smart00064.

is firmly established, the current proliferation of kinetoplastid PDEs with different designations is particularly confusing in the dialogue with collegues who are active in the human PDE field. As an example: human HsPDEl is a Ca^{2+}/calmodulin-activated dual-specificity PDE with preference for cGMP [17], while TcPDEl from *Trypanosoma cruzi* is a cAMP-specific, low-K_m PDE with two N-terminal GAF domains [9], whereas TbPDEl from *Trypanosoma brucei* is a high-K_m, cAMP-specific PDE with no discernible functional domains besides the catalytic region [5]. In view of this confusion, we wish to propose a unified nomenclature for kinetoplastid PDEs that should clarify the situation within the field, and that should also facilitate the discussion with collegues studying PDEs in mammals or other organisms. We realize that the proposed solution will have to restrict itself to the kinetoplastida, and will not be applicable to the many PDEs of other unicellular eukaryotes, such as the apicomplexa, the yeasts or *Dictyostelium*.

We here propose a nomenclature for kinetoplastid PDEs based on the following considerations:

1. In keeping with the proposed three-letter gene and protein nomenclature for kinetoplastids [18], all PDE genes should be assigned the three letter code, “PDE”, preceded by a three letter code for the organism (e.g. *TbrPDE*). Gene designations are set in italics.
2. The consistent use of a three-letter identification code for the organism should eliminate ambiguities concerning the species.
3. In order to avoid confusion with the mammalian PDE nomenclature, the gene identifiers for kinetoplastid PDEs should be followed by a single letter that designates the PDE gene family concerned (e.g. *TbrPDEB*). This code is followed by a number in those cases where the gene family contains more than one member (e.g. *TbrPDEBl*). Should splice variants or

Table 1
Classification of class I PDEs from *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania* major

New name	Earlier name	Reference	Experimentally determined characteristics	Protein accession number	Gene identification number in GeneDB	Chrom. number
TbrPDEA	TbPDE1	[5]	cAMP-specific, high-K_m	AAL58095	Tbl0.389.0510	10
TbrPDEBl	TbPDE2C	[7]	cAMP-specific, low-K_m, 2 N-terminal, GAF domains	AAK33016	Tb09.160.3590	9
TbrPDEB2	TbPDE2B	[6,10]	cAMP-specific, low-K_m, 2 N-terminal, GAF domains	[a]	Tb09.160.3630	9
TbrPDEC			N-terminal, FYVE domain		Tb03.27C5.640	3
TbrPDED			n.i.a.		Tb03.3K10.420	3
TcrPDEAl[b]			n.i.a.		Tc00. 1047053509805.20	n.i.a.
TcrPDEA2[b]			n.i.a.		Tc00. 1047053511269.40	n.i.a.
TcrPDEBl		[12]	2 N-terminal, GAF domains	**AY099403**		n.i.a.
TcrPDEB2	TcPDEl	[9,12]	cAMP-specific, low-K_m, 2 N-terminal, GAF domains	**AAP49573**	Tc00.1047053508277.110	n.i.a.
TcrPDEC-1[b]; **TcrPDEC-2**[b]		[20,21]	N-terminal, FYVE domain, dual-specificity PDE	**AJ889575**; **AJ889576**	Tc00.1047053506697.20	n.i.a.
TcrPDED-1[b]; **TcrPDED-2**[b]			n.i.a.		Tc00.1047053508153.260; Tc00.1047053510323.50	n.i.a.
LmjPDEA				**AAR88144**	LmjF18.1090	18
LmjPDEBl	LmPDEB2	[11]	cAMP-specific low-K_m 2 N-terminal GAF domains	**AAR88146**	[c]	15
LmjPDEB2	LmPDEBl	[11]	cAMP-specific low-K_m 2 N-terminal GAF domains	**AAR88145**	[c]	15
LmjPDEC			N-terminal FYVE domain		LmjF29.2680	29
LmjPDED			n.i.a.		LmjF29.2440	29

n.i.a., no experimental information available.

[a] The sequence deposited in GenBank with the nucleotide sequence accession number **AF192755** [6] contains an assembly error. The correct sequence is contained in GeneDB under the access code TbO9.160.3630.

[b] The *T. cruzi* strain CL Brener used for generating the genome database is a hybrid which is heterozygous for many loci and contains extensive duplications in its genome [15]. Correspondingly, single-copy genes may be represented twice.

[c] The relevant locus on chromosome 15 in GeneDB contains an assembly error. The correct version, containing both genes is given in Johner et al. [11].

postranslational cleavage products be detected at a later time, the respective protein designators can be complemented by a small letter following the number (e.g. TbrPDEB la). Following the established rules of kinetoplastid genetics [18], alleles will be indicated by a hyphenated number that follows the gene name (e.g. *TcrPDEC-1*).

4. The nomenclature scheme proposed below (see also Table 1) is based on overall sequence similarities and the presence of distinct functional domains in the various PDEs (Fig. 1). The experimental data that are already available for several of the kinetoplastid PDEs [5–12] support the proposed definition of the PDE families.

PDEA: A high-K_m (>200 μM), cAMP-specific PDE of about 620 amino acids. The polypeptide contains no discernible structural elements other than the PDE catalytic domain, which is located in the C-terminal part of the polypeptide. *PDEA* is a single copy gene. The experimentally characterized prototype for PDEA is **TbrPDEA** (earlier designation TbPDEl; GenBank **AAL58095**; [5]).

PDEB: A low-K_m (1–10 μM), cAMP-specific PDE containing two GAF domains in its N-terminal part. Two closely related genes are tandemly arranged. The first and the second gene of the cluster are designated as B1 and B2, respectively. Prototypes for which experimental evidence is available are: **TbrPDEBl** (previous designation: TbPDE2C; GenBank **AAK33016**; [7]); **TbrPDEB2** (TbPDE2B; [6]); **TcrPDEB2** (TcPDEl; GenBank **AAP49573**; [9]); **LmjPDEBl** (LmPDEB2; GenBank **AAR88146**; [11]); **LmjPDEB2** (LmPDEBl; GenBank **AAR88145**; [11]).

PDEC: An intermediate-K_m, dual-specificity PDE of 900–1000 amino acids. The N-terminal contains a FYVE-variant domain [19], followed by two coiled-coil domains. The PDE catalytic region is located in the middle of the polypeptide chain. A prototype for which experimental evidence is available is **TcrPDEC**, which is coded for by two slightly different alleles, *TcrPDEC-1* and *TcrPDEC-2* (GenBank **CAI63255** and **CAI63256**; [20,21]).

PDED: A predicted PDE of about 700 amino acids containing the PDE catalytic domain in the C-terminal part of the polypeptide. No other functional domains are predicted. *PDED* is a single copy gene.

The proposed new nomenclature covers all published kinetoplastid PDEs of *T. brucei*, *T. cruzi* and *Leishmania major* deposited in GenBank (http://www.ncbi.nlm.nih.gov/) and in the respective kinetoplastid databases (http://www.genedb.org/) as given in Table 1. A complete set of homologues is also present in the genomes of *L. infantum*, *T. congolense* and *T. vivax*. Should additional PDEs be identified and characterized, their nomenclature should follow the same concept. We believe that the proposed nomenclature, applied to the PDEs of all kinetoplastid species, will provide a clear and unambiguous identification of the various kinetoplastid PDE families. The scheme is sufficiently open so that it can be easily expanded should novel PDEs be discovered, e.g. proteins with PDE activity that do not fall into the canonical classes I–III [22], and thus cannot be predicted from the genome sequence databases.

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