Adoption of PERILIPIN as a unifying nomenclature for the mammalian PAT-family of intracellular lipid storage droplet proteins

Alan R. Kimmel,†,* Dawn L. Brasaemle,† Monica McAndrews-Hill,§ Carole Zsraly,** and Constantine Londos*

Laboratory of Cellular and Developmental Biology,* National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, Bethesda, MD; Department of Nutritional Sciences,† Rutgers, The State University of New Jersey, New Brunswick, NJ; and the Jackson Laboratory,** Bar Harbor, ME

Abstract The PAT family of proteins has been identified in eukaryotic species as diverse as vertebrates, insects, and amebaitos. These proteins share a highly conserved sequence organization and avidity for the surfaces of intracellular, neutral lipid storage droplets. The current nomenclature of the various members lacks consistency and precision, deriving more from historic context than from recognition of evolutionary relationship and shared function. In consultation with the Mouse Genomic Nomenclature Committee, the Human Genome Organization genomic nomenclature committee, and conferes at the 2007 FASEB conference on lipid droplets: metabolic consequences of the storage of neutral lipids, we have established a unifying nomenclature for the gene and protein family members. Each gene member will incorporate the root term PERILIPIN (PLIN), the founding gene of the PAT family, with the different genes/proteins numbered sequentially.—Kimmel, A. R., D. L. Brasaemle, M. McAndrews-Hill, C. Zsraly, and C. Londos. Adoption of PERILIPIN as a unifying nomenclature for the mammalian PAT-family of intracellular lipid storage droplet proteins. J. Lipid Res. 2010. 51: 468–471.

Supplementary key words perilipin • adipocyte differentiation-related protein • adipophilin • tail-interacting protein of 47 kDa

PAT derives from names of three proteins, PERILIPIN, ADRP, and TIP47, with each having highly related N-terminal sequences and common affinity for intracellular neutral lipid storage droplets (1). Of these, PERILIPIN comes closest to incorporating a biological connection into its name (2). The PERILIPIN appellation is also, without alternative.

PERILIPIN was originally identified as the most highly phosphorylated protein in lipolytically-activated adipocytes (3) and was subsequently shown to localize specifically to the surfaces of intracellular neutral lipid storage droplets [LSDs (2, 4)]. Although perilipin mRNA and protein expression is largely restricted to adipocytes (5) and steroidogenic cells (6), when ectopically expressed, it is exclusively found on LSDs, regardless of cell type (7–9). Indeed, the name “perilipin” derives from περί λίπος, “surrounding lipid”.

ADRP (10), adipocyte differentiation-related protein, is now appreciated to be a misnomer (11). Although ADRP mRNA is upregulated during the differentiation of cultured preadipocytes (10, 11), ADRP protein is rapidly degraded during differentiation and is undetected in mature adipocytes (11, 12). Although additional studies showed that ADRP is expressed in most other cell types (11, 13), when human ADRP was later found to associate tightly with lipid droplet surfaces, human ADRP was named adipophilin (14). Unfortunately, the term “adipophilin” inaccurately implies a specific association with adipose tissue. Further confusion of the acronym “ADRP” with autosomal dominant retinitis pigmentosa (adRP) led to another oft-enused designation, ADFP.

TIP47 (15), also referred to as PP17 (16), was identified by two groups in separate functional studies. TIP47, tail-interacting protein of 47 kDa, was found in a yeast two-hybrid screen for proteins that interacted with the C-terminal...
The group also characterized several TIP47/PP17 splice variants. The close sequence similarity of ADRP and TIP47 prompted a reexamination of the subcellular distribution of TIP47 (17–19). Like perilipin and ADRP, TIP47 is now a recognized member of the PAT protein family that binds to LSDs.

Based upon sequence similarities and functional associations with LSDs, two additional PAT proteins are documented in mammals, S3-12 (20, 21) and PAT1/LSDP5/OXPAT/MLDP (1, 22–24).

The genes for the five PAT proteins share a common underlying structural organization and are acknowledged to define a novel gene family (see Table 1). Moreover, the genes for TIP47, LSDP5, and S3-12 reside within a 200 kb region of murine chromosome 17, with Lspa5 and S3-12 separated by <2kb.

**Nomenclature**

Researchers within the lipid droplet field have debated nomenclature confusion regarding the multiple names of the various PAT proteins. Formal reexamination of PAT nomenclature was initiated at the FASEB Summer Research Conference—Lipid Droplets: Metabolic Consequences of the Storage of Neutral Lipids, with encouragement by the Mouse Genomic Nomenclature Committee (MGNC) and consultation with the Human Genome Organization Genomic Nomenclature Committee (HGNC). The nomenclature recommendations were agreed upon without dissent (Table 1).

Nomenclature based upon variations of the most obvious terms, PAT, LSD, etc., suffer from alternative and prior usage. For example, LSD also designates Lysine Specific Demethylase; these LSD complexes regulate histone methylation and dynamic aspects of chromatin structure and transcriptional control (25). We, thus, selected PERILIPIN as the founding root term based on its precision and elegance, with the gene symbols Plin and PLIN, for the murine and human genomes, respectively. The MGNC and HGNC have approved this nomenclature.

Following the Plin/PLIN gene symbol, each family member is numbered sequentially in the order PLIN1 for PERILIPIN, PLIN2 for ADFP, PLIN3 for TIP47, PLIN4 for S3-12, and PLIN5 for LSDP5. Both new and old terminologies (e.g., PLIN2/ADFP) may be of use in the short-term, but we strongly discourage continuous reference to additional alternatives, such as adipophilin, PP17, PAT1, OXPAT, MLDP, and LSD.

As standard for human and rodent nomenclature, human gene symbols are fully capitalized, whereas for mouse, only the first letter is upper case. For both systems, gene symbols are italicized, whereas full-length gene names are nonitalics, lower case. Protein symbols are nonitalics, upper case for both human and mouse.

**SPlice Variants**

The murine Plin1 gene organization is the most fully characterized of the Plin gene family (1). There are four splice variant transcripts. As well, closely situated alternative 5’-transcriptional start sites have been described. The mRNA splice variants are predicted to encode four distinct proteins, previously termed perilipin A, B, C, and D; three of these proteins have been confirmed (5, 6). Lower case letters will now denote alternative protein forms PLIN1a, PLIN1b, PLIN1c, and PLIN1d, with Plin1a, Plin1b, Plin1c, and Plin1d as their respective mRNAs. Alternative 5’-starts would be noted as the mRNA variants Plin1a_v1, Plin1a_v2, etc. Similar nomenclature will follow for the other members.

**Evolutionary Relationships Among Plin Gene Family Members**

Sequence similarity argues strongly for orthologs of PLIN1, PLIN2 (ADFP), and PLIN3 (TIP47) in Osteichthyes and Amphibia. Multiple PLIN family members are present in Insecta, and one is found in Dictostelium (1, 19). These nonvertebrate proteins clearly associate with lipid storage droplets, even when expressed in mammalian cells (19), but their current nomenclatures derive from an LSD protein root (e.g., LSD or LSDP). Nonetheless, the common exon/intron gene organizations among the murine Plin1, murine Plin2/Adfp, and Drosophila LSDP-1 genes

---

**Table 1.** A unified nomenclature for the mammalian perilipin-related, PAT-family of intracellular, lipid storage droplet proteins

| Approved Human Symbol | Approved Name | Previous Aliases | Human Entrez GeneID | Chr. Location | Mouse Entrez GeneID | Chr. Location |
|-----------------------|--------------|------------------|---------------------|--------------|---------------------|--------------|
| PLIN1                 | perilipin 1  | perilipin, PERI, PLIN | 5346                | 15q26        | 103968              | 7 D3         |
| PLIN2                 | perilipin 2  | ADRP, ADFP, adipophilin | 123                | 9p22.1      | 11520               | 4 38.9 cM    |
| PLIN3                 | perilipin 3  | TIP47, PP17, M6PRBP1 | 10226              | 19p13.3     | 66905               | 17 D         |
| PLIN4                 | perilipin 4  | S3-12            | 729559              | 19p13.3     | 57435               | 17 D         |
| PLIN5                 | perilipin 5  | PAT1, LSDP5, OXPAT, MLDP | 440503             | 19p13.3     | 66968               | 17 D         |
indicate an ancient evolutionary origin for the entire PLIN gene family (1). In addition, the insect proteins exhibit lipolytic regulation of LSDs that are comparable to that of mammalian PLIN family members (26–28).

The PLIN-based nomenclature is sufficiently flexible and unifying to allow inclusion of all members of this evolutionarily diverse gene family and we encourage all genome annotating organizations to consider the use of PLIN in their current and future nomenclatures. Hence, the single Dictyostelium PLIN member LSD1/DdLSD (DBD- G0279791) would now be cross-referenced as Plin. As with other orthologous genes, particularly in distantly related species, identical nomenclature (e.g., PLIN1) would not imply a common function.

OTHER LIPID STORAGE DROPLET BINDING PROTEINS

The defining characteristics of PLIN proteins include a conserved PAT-domain (1) and an 11-mer repeating helical organization (29). Although, the extreme N-terminal ~100 amino acids are the most conserved in PLIN1, 2, 3, and 5 proteins, similarity extends through ~250 amino acids. PLIN4/S3-12 is somewhat distinct, with a highly expanded (>75n) 11-mer repeat region. Although structurally similar 11-mer motifs (29) are found in other lipid-associated proteins (e.g., apolipoproteins and α-synuclein), their sequences are unrelated to the PLIN family and are not classified as PAT domains. Although the lipid droplet-binding protein CIDE/CSP27 (related family members) shares some limited sequence similarity to PLIN1, it has an unrelated genomic organization (30, 31). Additional lipid storage droplet proteins, such as the plant oleosins, hepatitis C virus core protein, caveolins, and METTL7A/B, which possess other domains for lipid intercalation or transient localization to lipid droplets, but reserved for proteins with an evolutionary relationship that yields conservation of the primary amino acid sequence. We also recognize that PLIN-family member functions may not be solely restricted to their lipid-binding character.

CONCLUSION

In summary, we recommend adoption of PLIN nomenclature for lipid droplet binding proteins within the PERILIPIN gene family. This nomenclature will reduce confusion over the multiplicity of names for the individual members of the family.

We are extremely grateful to the insightful comments of the attendees at the 2007 FASEB Summer Research Conference - Lipid Droplets: Metabolic Consequences of the Storage of Neutral Lipids, the Mouse Genomic Nomenclature Committee (http://www.informatics.jax.org/mgihome/nomen/index.shtml), the HUGO Genomic Nomenclature Committee (http://www.genenames.org), and participants in an online nomenclature discussion. The following individuals, listed in alphabetical order, contributed to the online discussion, the discussion at the FASEB conference site, or both: William Ackerman, Thomas Alsted, Sadie Bartholomew, Mathias Beller, Perry Bickel, Pontus Boström, Patricia Bozza, Deborah Brown, William Brown, Anna Bulankina, Jorge Caviglia, Benny Chang, Rosalind Coleman, Barbara Corkey, Knut Tomas Dalen, Sadie Demignot, Robert Fares, Joel Goodman, Andrew Greenberg, ZengKui Guo, Hans Heid, Matthijs Hesselink, Kai Hsieh, Sepp Kohlwein, Ronald Kuhnlein, Dominique Langin, Soazig LeLAY, Lei Li, Laura Listenberger, Clarissa Maya-Monteiro, James McManaman, Pamela Mertz, Sheila O’Byrne, Paul Pilch, Vishwajiet Puri, Tanya Russell, Stephen Sturley, John Tansey, Nandor Than, Michael Welte, Nathan Wolins, Tomohiro Yamaguchi, Liqing Yu, and Rudolf Zechner. We apologize for omission of any discussion participants.

REFERENCES

1. Lu, X., J. Gruia-Grav, N. G. Copeland, D. J. Gilbert, N. A. Jenkins, C. Londos, and A. R. Kimmel. 2001. The murine perilipin gene: the lipid droplet-associated perilipins derive from tissue-specific, mRNA splice variants and define a gene family of ancient origin. Mamm. Genome. 12:741–749.
2. Greenberg, A. S., J. E. Egan, S. A. Wek, N. R. Garty, E. J. Blanchette-Mackie, and C. Londos. 1991. Perilipin, a major hormonally regulated adipocyte-specific phosphoprotein associated with the periphery of lipid storage droplets. J. Biol. Chem. 266:11341–11346.
3. Egan, J. J., A. S. Greenberg, M. K. Chang, and C. Londos. 1990. Control of endogenous phosphorylation of the major cAMP-dependent protein kinase substrate in adipocytes by insulin and beta-adrenergic stimulation. J. Biol. Chem. 265:18769–18775.
4. Blanchette-Mackie, E. J., N. K. Deyer, T. Barber, R. A. Coxe, T. Takeda, C. M. Rondinone, J. L. Theodorakis, A. S. Greenberg, and C. Londos. 1995. Perilipin is located on the surface layer of intracellular lipid droplets in adipocytes. J. Lipid Res. 36:1211–1226.
5. Greenberg, A. S., J. E. Egan, S. A. Wek, M. C. Moos, Jr., C. Londos, and A. R. Kimmel. 1993. Isolation of cDNAs for perilipins A and B: sequence and expression of lipid droplet-associated proteins of adipocytes. Proc. Natl. Acad. Sci. USA. 90:12035–12039.
6. Servetnick, D. A., D. L. Brasaemle, J. Gruia-Gray, A. R. Kimmel, J. Wolff, and C. Londos. 1995. Perilipins are associated with cholesterol ester droplets in steroidogenic adrenal cortical and Leydig cells. J. Biol. Chem. 270:16970–16975.
7. Tansey, J. T., A. M. Huml, R. Vogt, K. E. Davis, J. M. Jones, K. A. Fraser, D. L. Brasaemle, A. R. Kimmel, and C. Londos. 2003. Functional studies on native and mutated forms of perilipins. A role in protein kinase A-mediated lipolysis of tripalmitoylglycerols. 278:8401–8406.
8. García, A., A. Sekowski, V. Subramanian, and D. L. Brasaemle. 2003. The central domain is required to target and anchor perilipin A to lipid droplets. J. Biol. Chem. 278:625–635.
9. Zhang, H. H., S. C. Souza, K. V. Muliro, F. B. Kraemer, M. S. Ohin, and A. S. Greenberg. 2003. Lipase-selective functional domains of perilipin A differentially regulate constitutive and protein kinase A-stimulated lipolysis. J. Biol. Chem. 278:51335–51342.
10. Jiang, H. P., S. E. Harris, and G. Serrero. 1992. Molecular cloning of a differentiation-related mRNA in the adipogenic cell line 1246. Cell Growth Differ. 3:21–30.
11. Brasaemle, D. L., T. Barber, N. E. Wolins, G. Serrero, E. J. Blanchette-Mackie, and C. Londos. 1997. Adipose differentiation-related protein is an ubiquitously expressed lipid storage droplet-associated protein. J. Lipid Res. 38:2249–2253.
12. Xu, G., C. Szalay, X. Lu, J. T. Tansey, J. Gan, H. Dorward, A. R. Kimmel, and C. Londos. 2005. Post-translational regulation of adipose differentiation-related protein by the ubiquitin/proteasome pathway. J. Biol. Chem. 280:42841–42847.
13. Heid, H. W., M. Schmolzer, and T. W. Keenan. 1996. Adipocyte differentiation-related protein is secreted into milk as a constituent of milk lipid globule membrane. Biochim. J. 320:1025–1030.
14. Heid, H. W., R. Moll, I. Schwetlick, H. R. Rackwitz, and T. W. Keenan. 1998. Adipophilin is a specific marker of lipid accumulation in diverse cell types and diseases. *Cell Tissue Res.* 294: 309–321.

15. Diaz, E., and S. R. Pfeiffer. 1998. TIP47: a cargo selection device for mannose 6-phosphate receptor trafficking. *Cell. 95:* 483–493.

16. Than, N. G., B. Sumegi, G. N. Than, G. Kispal, and H. Bohn. 1998. Cloning and sequence analysis of cDNAs encoding human placental tissue protein 17 (PP17) variants. *Eur. J. Biochem.* 258: 752–757.

17. Barbero, P., E. Buell, S. Zulley, and S. R. Pfeiffer. 2001. TIP47 is not a component of lipid droplets. *J. Biol. Chem.* 276: 24348–24351.

18. Wolins, N. E., B. Rubin, and D. L. Brasaemle. 2001. TIP47 associates with lipid droplets. *J. Biol. Chem.* 276: 5101–5108.

19. Miura, S., J. W. Gan, J. Brzostowski, M. Parisi, C. J. Schultz, C. Wolins, N. E., B. K. Quaynor, J. R. Skinner, A. Tzekov, M. A. Croce, K. G. Londos, B. Oliver, and A. R. Kimmel. 2002. Functional conservation for lipid storage droplet association among Perilipin, ADRP, a component of lipid droplets. *J. Biol. Chem.* 277: 32253–32257.

20. Scherer, P. E., P. E. Bickel, M. Kotler, and H. F. Lodish. 1998. Cloning of cell-specific secreted and surface proteins by subtractive antibody screening. *Nat. Biotechnol.* 16: 581–586.

21. Wolins, N. E., J. R. Skinner, M. J. Schoenfish, A. Tzekov, K. G. Bensch, and P. E. Bickel. 2003. Adipocyte protein S3–12 coats nascent lipid droplets. *J. Biol. Chem.* 278: 57713–57721.

22. Dallen, K. T., T. Dahl, E. Holter, B. Arntsen, and C. Londos. C. Szalayd, and H. I. Nebb. 2007. LSDP5 is a PAT protein specifically expressed in fatty acid oxidizing tissues. *Biochim. Biophys. Acta.* 1771: 210–227.

23. Wolins, N. E., B. K. Quaynor, J. R. Skinner, A. Tzekov, M. A. Croce, M. C. Gropler, V. Varma, Y. Yao-Borengasser, N. Rasouli, P. A. Kern, et al. 2006. OXPAT/PAT-1 is a PPAR-induced lipid droplet protein that promotes fatty acid utilization. *Diabetes.* 55: 3418–3428.

24. Yamaguchi, T., S. Matsushita, K. Motojima, F. Hirose, and T. Osumi. 2006. MLDP, a novel PAT family protein localized to lipid droplets and enriched in the heart, is regulated by peroxisome proliferator-activated receptor alpha. *J. Biol. Chem.* 281: 14232–14240.

25. Wysocka, J., T. A. Milne, and C. D. Allis. 2005. Taking LSD 1 to a new high. *Cell.* 122: 654–658.

26. Teixeira, L., C. Rabouille, P. Rorth, A. Ephrussi, and N. F. Vanzo. 2003. *Drosophila* Perilipin/ADRP homologue Lsd2 regulates lipid metabolism. *Mech. Dev.* 120: 1071–1081.

27. Gönke, S., M. Beller, S. Fellert, H. Ramakrishnan, H. Jackle, and R. P. Kahnlein. 2003. Control of fat storage by a *Drosophila* PAT domain protein. *Curr. Biol.* 13: 603–606.

28. Patel, R. T., J. L. Soulages, B. Hariharasundara, and E. L. Arrese. 2005. Activation of the lipid droplet controls the rate of lipolysis of triglycerides in the insect fat body. *J. Biol. Chem.* 280: 22624–22631.

29. Bussell, R., Jr., and D. Eliezer. 2003. A structural and functional role for 11-mer repeats in alpha-synuclein and other exchangeable lipid binding proteins. *J. Mol. Biol.* 329: 763–778.

30. Wu, C., Y. Zhang, Z. Sun, and P. Li. 2008. Molecular evolution of Gide family proteins: novel domain formation in early vertebrates and the subsequent divergence. *BMCEvol. Biol.* 8: 159.

31. Pur, V., S. Ranjit, S. Konda, S. M. Nicoloro, J. Straubhaar, A. Chawla, M. Chouinard, C. Liu, A. Burkart, S. Corvera, et al. 2008. Gide is associated with lipid droplets and insulin sensitivity in humans. *Proc. Natl. Acad. Sci. USA.* 105: 7833–7838.

32. Capuano, F., F. Beaudoin, J. A. Napier, and P. R. Shewry. 2007. Properties and exploitation of oleosins. *Biotechnol. Adv.* 25: 203–206.

33. Shavinskaya, A., S. Boulant, F. Penin, J. McLauchlan, and R. Bartenschlager. 2007. The lipid droplet binding domain of hepatitis C virus core protein is a major determinant for efficient virus assembly. *J. Biol. Chem.* 282: 37158–37169.

34. Ostermeyer, A. G., J. M. Paci, Y. Zeng, D. M. Lublin, S. Munro, and D. A. Brown. 2003. Accumulation of caveolin in the endoplasmic reticulum redirects the protein to lipid storage droplets. *J. Cell Biol.* 152: 1071–1078.

35. Zehmer, J. K., R. Barz, P. Liu, and R. G. Anderson. 2008. Identification of a novel N-terminal hydrophobic sequence that targets proteins to lipid droplets. *J. Cell Sci.* 121: 1852–1860.