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The following is the abstract of the article discussed in the subsequent letter:

Lavrentyev EN, He D, and Cook GA. Expression of several genes participating in regulation of fatty acid and glucose utilization and energy metabolism in the rat heart during development. *Am J Physiol Heart Circ Physiol* 288: H2035–H2042, 2004; 10.1152/ajpheart.00372.2004.—The heart is a unique organ that can use several fuels for energy production. During development, the heart undergoes changes in fuel supply, and it must be able to respond to these changes. We have examined changes in the expression of several genes that regulate fuel transport and metabolism in rat hearts during early development. At birth, there was increased expression of fatty acid transporters and enzymes of fatty acid metabolism that allow fatty acids to become the major source of energy for cardiac muscle during the first 2 wk of life. At the same time, expression of genes that control glucose transport and oxidation was downregulated. After 2 wk, expression of genes for glucose uptake and oxidation was increased, and expression of genes for fatty acid uptake and utilization was decreased. Expression of carnitine palmitoyltransferase I (CPT I) isoforms during development was different from published data obtained from rabbit hearts. CPT Iα and Iβ isoforms were both highly expressed in hearts before birth, and both increased further at birth. Only after the second week did CPT Iα expression decrease appreciably below the level of CPT Iβ expression. These results represent another example of different expression patterns of CPT I isoforms among various mammalian species. In rats, changes in gene expression followed nutrient availability during development and may render cardiac fatty acid oxidation less sensitive to factors that influence malonyl-CoA content (e.g., fluctuations in glucose concentration) and thereby favor fatty acid oxidation as an energy source for cardiomyocytes in early development.

A Case of Mistaken Identity

To the Editor: I read the article "Expression of several genes participating in regulation of fatty acid and glucose utilization and energy metabolism in the rat heart during development" by Lavrentyev et al. (1) with great interest. The authors describe the developmental regulation of several genes, including fatty acid transports, involved in cardiac lipid metabolism using cDNAs from rat hearts and real-time PCR. One of the rat genes, which regulation is discussed in more detail, has GenBank accession no. D85100 and is identified by the authors as the rat ortholog of human and mouse fatty acid transport protein (FATP)6.

My group has been working with the FATP gene family for several years, and I was surprised by the Cook's group finding that "It appears that FATP6 may function mostly during the fetal and early newborn period rather than in the adult," because we clearly demonstrated (2) expression of this protein in the adult mouse heart. So I took the liberty of aligning rat protein D85100 with their mouse and human counterparts using the ClustalW algorithm (3).

To my astonishment, I found that D85100 is most homologous with mouse and human FATP2 (also known as SLC27A2, VLACS) (4) and not FATP6, as is convincingly illustrated by the provided unrooted tree and percent identity table (Fig. 1). In fact, 93% of the amino acids in D85100 are identical to mouse FATP2 (82% identical to human FATP2), whereas only 50% are identical to murine FATP6 (48% to human FATP6). Furthermore, a search of the nonredundant GenBank database at NCBI's protein-protein BLAST site using the published murine FATP6 protein sequence showed that another rat protein (GenBank accession no. XP225919) is 82% identical to mouse FATP6 (71% to human FATP6) and therefore most likely the correct rat FATP6 orthoglog.

While the finding that rat FATP2 is regulated in the developing heart is still of interest, some of the key conclusions of the Lavrentyev et al. study (1) regarding fatty acid transporters are clearly incorrect due to this case of mistaken identity and deserve clarification.

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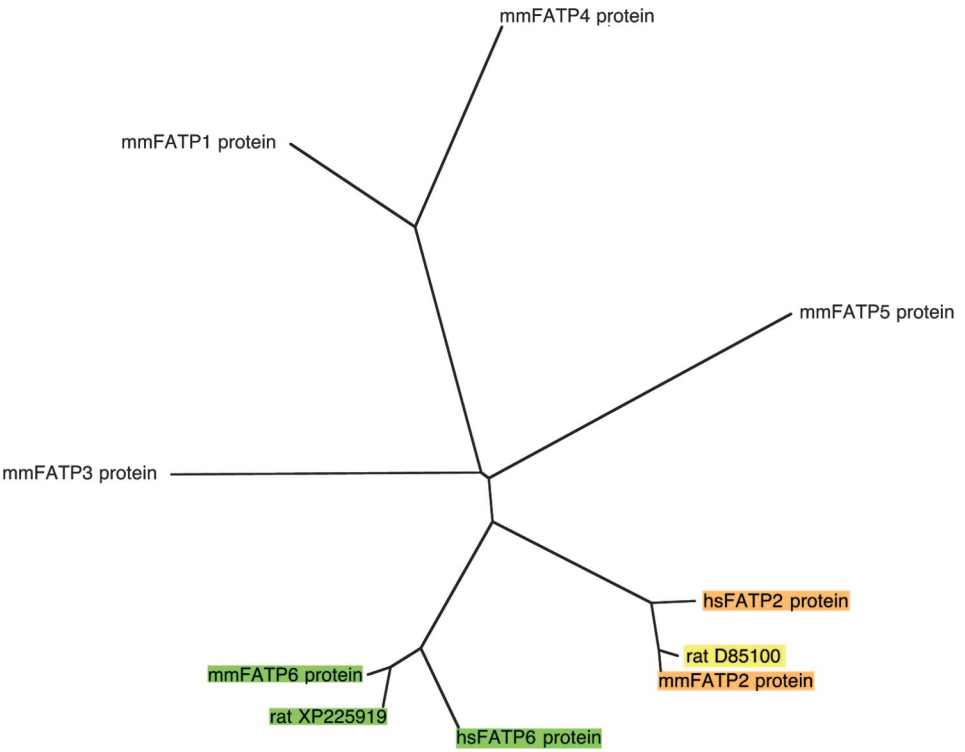
REPLY

Mistaken Identity or Yet Another Case of Species Difference?

To the Editor: Six highly homologous proteins of the fatty acid transport family (FATP) family have been identified in human and mouse genomes (FATP1–6), and their expression in human and mouse tissues have been studied to different extents (5, 8, 9). Very little is known about the rat FATP family.

The FATP1 gene was the first of the FATP family to be identified (7), and it is the best studied in the human and mouse. FATP1 is known as the major FATP in adipose tissue, but it is also found in the heart and skeletal muscle (2, 8). FATP2 in the mouse and human is found almost exclusively in the liver and kidney cortex (5). Very little is known about FATP3, but it has an expression pattern with notably high mRNA and protein levels in the lung (5). FATP4 is the only FATP expressed in the small intestine (10). FATP4 and FATP1 are the predominant FATPs in the brain (3). FATP5 is a liver-specific isoform (5). FATP6 has recently been recognized as the predominant FATP family member expressed in the human and mouse heart (4, 9). It was also proposed that, in the human heart, FATP6 is colocalized with another protein involved in fatty acid transport known as fatty acid translocase (FAT/CD36) (4). FAT/CD36 is not homologous with the FATP family but seems to be important in the process of fatty acid transport into several tissues (1, 4). At present, much less is known about the mechanistic and functional aspects of each of the FATPs than about their expression (9).

When we began our study of the perinatal expression of genes involved in fatty acid and glucose transport and metabolism (6), we wanted to examine expression of the most abundant mRNAs of the fatty acid transporters found in the rat



1	2	3	4	5	6	7	8	9	10		
	49.8	82.4	48.2	37.6	93.4	41.3	34.4	42.7	50.2	1	rat D85100
		48.1	70.6	36.0	45.1	42.8	33.7	40.9	82.1	2	rat XP225919
			50.5	38.5	82.6	42.4	34.5	42.1	52.6	3	hsFATP2 protein
				36.2	47.8	45.1	36.0	40.1	77.9	4	hsFATP6 protein
					36.2	37.8	56.0	36.4	37.3	5	mmFATP1 protein
						41.5	33.9	42.9	50.3	6	mmFATP2 protein
							29.9	37.1	39.7	7	mmFATP3 protein
								32.8	35.0	8	mmFATP4 protein
									38.0	9	mmFATP5 protein
										10	mmFATP6 protein

Percent Identity

Fig. 1. Relatedness of known fatty acid transport proteins (FATPs) to rat genes XP225919 and D85100. Full-length sequences for the indicated genes were aligned using the ClustalW algorithm. On the basis of this alignment, an unrooted dendrogram and percent identities were calculated. FATP6 family members are highlighted in green, known FATP2 genes in magenta, and D85100 in yellow.

heart. On the basis of previous work in humans and mice, we expected to find that FATP6 and FAT/CD36 would be most prominent mRNAs. In making real-time PCR primers for our study of rat genes, we made primers that detected a cDNA designated as GenBank accession no. D85100, which is now clearly designated by UniGene (PubMed/NCBI web site) as rat FATP2, but which we thought at the time was similar to mouse FATP6 (50.2% similarity). Expression of FATP2 has not been shown in the human or mouse heart. We found the expression of this gene relatively high in the rat heart (6). On the other hand, when we tested for the presence of the mRNA corresponding to the protein proposed by Dr. Stahl to be rat FATP6 because of 82% identity to mouse and 71% to human FATP6, we found extremely low, even questionable, expression in the rat heart. This protein sequence (XP_225919) is listed in UniGene as "similar to rat very long-chain acyl-CoA synthetase, homolog 1." This points out another confusing aspect of the FATP genes–their close relationship to very long-chain acyl-CoA synthases because of an AMP-binding domain, which may be a part of the fatty acid transport function in some cases.

Assuming that D85100 is truly the rat homolog of FATP2 and XP_225919 is truly the rat homolog of human FATP6, we recently reexamined the relative abundance all adult rat heart mRNAs related to fatty acid transport using real-time PCR as described in our study (6). We found the highest abundance of mRNA for FAT/CD36 (50x) followed by FATP1 (10x) > FATP2 (10x) > FATP4 (x) > FATP3 (0.3x) > FATP6 (0.08x, questionable expression) ≫ FATP5 (not expressed) (where FATP2 is D85100 and FATP6 is XP_225919). These data suggest that in the rat heart, FATP6 (XP_225919) is not expressed as it is in the human and mouse, whereas both FATP1 and FATP2 (D85100) are highly expressed in the rat heart. We believe that the surprisingly high expression of FATP2 (D85100) in the rat heart could be explained as a difference between species and that rat FATP2 (D85100) likely plays a significant role in rat heart for long-chain fatty acid uptake as FATP6 does in the human and mouse. Especially interesting is the fact that changes in rat FATP2 (D85100) expression are closely related to changes in rat FAT/CD36 expression during heart development. These results also confirm what has been found for expression of the carnitine palmitoyltransferase I isoforms–that different isoforms may be the predominant isoform in different species or different tissues. The reasons for these species differences can only be determined by further research. Obviously, the FATP family requires much more work to identify FATP family members and clarify their regulation and functions.

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