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Role of ACOT7 in Arachidonic Acid Production and Inflammation

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1. Introduction

Acyl-CoA Thioesterases (ACOTs) perform a wide range of cellular functions by catalysing the thiolytic cleavage of activated fatty acyl-CoAs. Substrates of ACOTs include short to long-chain acyl-CoAs as well as a range of methyl-branched, and dicarboxylic bile acid-CoAs (M. C. Hunt & Alexson, 2008). Expression of ACOTs have been detected in both prokaryotes and eukaryotes with expression in higher organisms being detected in cytosol, mitochondria, peroxisomes and endoplasmic reticulum (J. Yamada, 2005).

Within the ACOT enzyme family, one member in particular, ACOT7 has recently been identified as playing a role in inflammation through the production of arachidonic acid (AA). It was recently proposed that ACOT7-mediated AA production may provide a complementary source of AA to the well characterised phospholipase A₂ (PLA₂) pathway (Satoru Sakuma, Usa, & Fujimoto, 2006); see Table 1 for review of Acot substrate specificity. Evidence for these observations was through experimental data showing that ACOT7 possessed high substrate specificity for AA-CoA; the gene encoding ACOT7 was highly expressed in macrophages and up-regulated when stimulated by lipopolysaccharide (LPS); and that over-expression of the enzyme lead to an increase in prostaglandin production. Together, these observations highlight a novel role of ACOT7 in inflammation through the production of arachidonic acid from the thiolytic cleavage of activated polyunsaturated omega-6 fatty acid C20:4-CoA (Forwood et al., 2007).

2. Cellular production of arachidonic acid (C20:4)

Arachidonic acid has a number of important cellular roles, namely in cell signalling, regulation of metabolic and signalling enzymes, and inflammation. Despite its importance, its methods of cellular production are not fully understood. The most well characterised cellular pathway for arachidonic acid involves its release from membrane phospholipids via the action of PLA₂, an enzyme responsible for the catalysis and hydrolysis of phospholipids at the *sn*-2 position (Sakuma et al, 2006) (see Figure 1).

Expression of PLA₂ is regulated according to the requirement for arachidonic acid and well understood. Rapid activation of PLA₂ is achieved via posttranslational modification, and enzyme activity is activated by phosphorylation (controlled by mitogen-activated protein), while prolonged expression is regulated at a transcriptional level by cytokines and growth factors such as macrophage colony stimulating factor, tumor necrosis stimulating factor-

Acot Homologue	Preferred acyl-CoA substrate
Acot1	Lauroyl and palmitoyl-CoA
Acot2	Lauroyl and palmitoyl-CoA
Acot3	Palmitoyl-CoA
Acot4	Succinyl-CoA
Acot5	Decanoyl-CoA
Acot6	Not determined
Acot7	Arachidonoyl-CoA
Acot8	Bile acids
Acot9	Myristoyl-CoA
Acot10	Myristoyl-CoA
Acot11	Not determined
Acot12	Acetyl-CoA
Acot13	Aromatic acyl-CoAs

Table 1. Substrate specificities for acyl-coA thioesterases.

alpha and glucocorticoid (Jiang et al., 2001; Satoru Sakuma, et al., 2006). While PLA₂ is well known for its role in generating AA from the cleavage of the acyl bond of membrane phospholipids in a range of cell types, several lines of evidence have recently developed to suggest that PLA₂ may not be solely responsible for controlling AA levels. For example, it was shown that AA-CoA can supply AA for prostaglandin (PG) synthesis (S. Sakuma et al., 1994), and that a novel enzymatic pathway exists whereby thioesterase cleavage of AA-CoA is responsible for supplying free AA to be utilised in the synthesis of prostaglandins (S. Sakuma, et al., 1994). A similar mechanism has also been described for controlling cellular levels of AA where it was demonstrated that AA levels were under the control of competing actions of an acyl-CoA thioesterase and synthetase, independent of the classical PLA₂ cascade (Maloberti et al., 2005). In further support of these observations, when competition on AA levels were reduced through inhibition of an AA acyl-CoA synthetase (ACS; the opposite reaction that is catalysed by Acot7), substantial increases in PG levels were observed (Castilla et al., 2004); and moreover, in an independent study, overexpression of an acyl-CoA synthetase was been shown to cause a marked increase in synthesis of AA-CoA, increased 20:4 incorporation into membrane phospholipids, reduced cellular levels of unesterified 20:4, and reduced secretion of prostaglandin E2 (PGE2) while inhibition of the ACS resulted in increased release of PGE2 (Golej et al., 2011). Thus, it is emerging that inflammation is a complex cellular process, and PLA₂ is unlikely to be the sole enzymatic pathway responsible for regulating AA levels, typically kept low due to the potent biological actions of the eicosanoids (Flesch, Schonhardt, & Ferber, 1989; Irvine, 1982), and that complementary pathways exist to contribute to AA generation and synthesis of eicosanoid inflammatory mediators during an immune response. That ACOT7 is abundantly expressed in macrophages and upregulated during an immune response; has high specificity for AA-CoA; and its over-expression in LPS-simulated macrophages cause

an increase in prostaglandin production, is consistent with the role of ACOT7 in inflammation through the production of AA-derived inflammatory mediators.

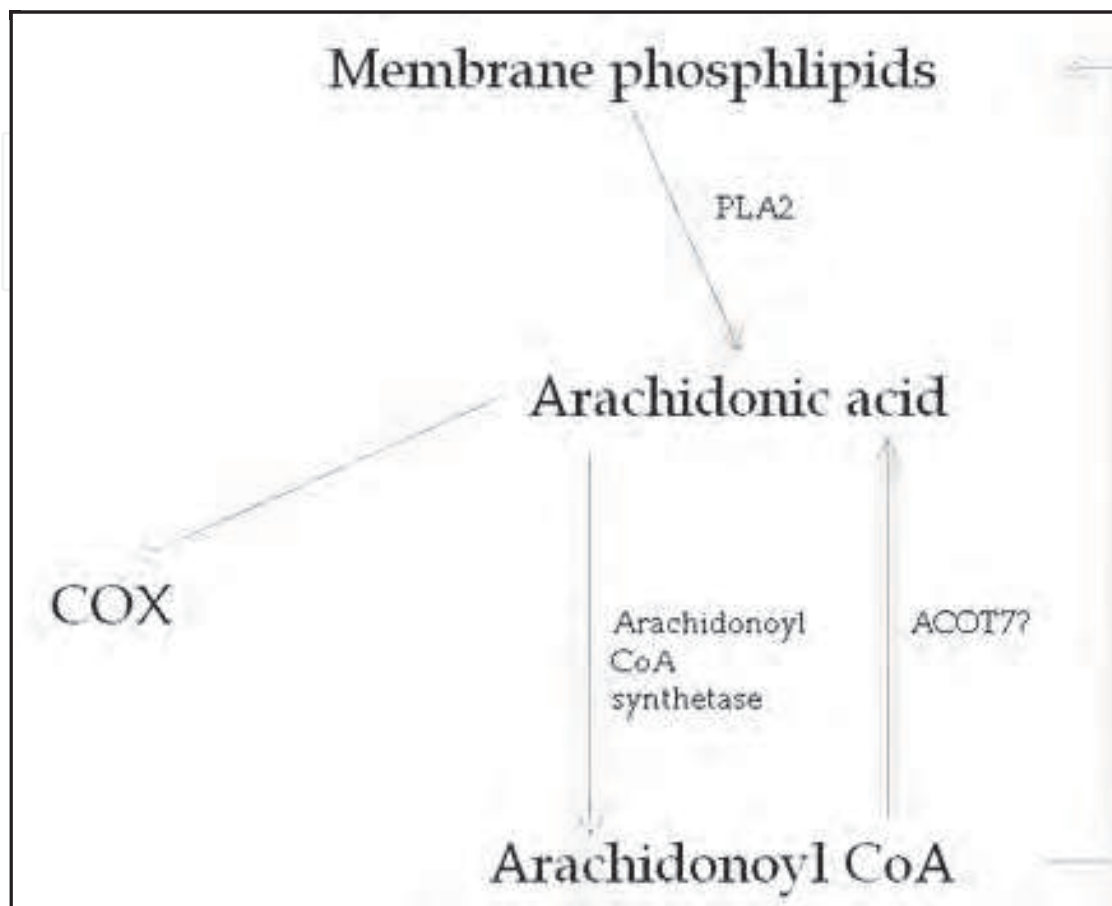


Fig. 1. The cellular pathway of arachidonic acid release involves the phospholipaseA2, and other AA-producing pathways.

2.1 Role of arachidonic acid in inflammation

Cellular production of arachidonic acid is utilized in a range of pathways, including the generation of potent mediators to initiate an inflammatory response. Two well characterised pathways important in inflammation include the cyclooxygenase (COX) and 5-Lipoxygenase pathways, and involve the conversion of arachidonic acid into prostanoids (prostaglandins, thromboxans), and leukotrienes respectively. The prostanoids include a range of arachidonic acid-derived metabolites that function to maintain body homeostasis by acting in a paracrine and autocrine fashion on cells within the vicinity of their release and are targets for the anti-inflammatory drugs including aspirin and derivatives. They typically exert their effect through activation of cell surface specific G-protein coupled receptors (GPCR), of which there are several subtypes for each prostanoid: PGD receptor (DP); PGE receptors EP1, EP2, EP3 and EP4 subtypes; PGF receptor (FP); PGI receptor (IP); and TX receptor (TP). There is also a receptor found on Th2 cells (CRTH2) that reacts to PGD₂ but belongs to the chemokine receptor family (Narumiya, 2009; Wang, Honn, & Nie, 2007). Prostanoid production is increased during the inflammation response, particularly during acute inflammation, prior to the recruitment of leukocytes. There are a number of different

prostanoids produced from the COX pathway, including prostaglandin (PG) D₂, prostaglandin E₂ (PGE₂), prostaglandin F_{2α} (PGF_{2α}), prostacyclin (PGI₂) and thromboxane (TX) A₂ (Narumiya, 2009). Gilroy et al. found that PGE₂ levels are raised only during the initial phases of inflammation whilst PGD₂ becomes the predominant prostanoid during the final stages of the inflammatory response (Gilroy et al., 1999; Tilley, Coffman, & Koller, 2001).

5-lipoxygenase utilises free arachidonic acid in conjunction with 5-lipoxygenase activating-protein (FLAP), the 5-lipoxygenase activating protein, to catalyse the oxygenation of arachidonic acid into hydroperoxy-eicosatetraenoic acid (HPETE). FLAP selectively transfers arachidonic acid to 5-lipoxygenase and enhances the sequential oxygenation of this substrate to produce 5(S)-hydroperoxyeicosatetraenoic acid (5HpETE), as well as dehydration of arachidonic acid to leukotriene A₄ (LTA₄). LTA₄ can then be exported from the cell and undergo transcellular metabolism or be converted into either the pro-inflammatory LTB₄ or into a cysteinyl leukotrienes (cysLTs) LTC₄, LTD₄ or LTE₄. The cysteinyl leukotrienes are a family of bronchoconstrictive, vasoconstrictive pro-inflammatory molecules. The primary signalling method for these leukotrienes is the activation of GPCRs on cell surfaces, namely BLT₁ and BLT₂ for LTB₄, and CysLT₁ and CysLT₂ for CysLT's. Leukotrienes are thought to play a role in innate immune defence as well as a role in antimicrobial host defence. Importantly, they have been shown to play a role in respiratory diseases, such as asthma, allergies, such as anaphylaxis (Ferreira et al., 2008), as well as cardiovascular disease (Evans, Ferguson, Mosley, & Hutchinson, 2008).

Cytochrome P450 is thought to act on endogenous arachidonic acid converting it into epoxy-eicosatrienoic acids (EETs) (Piomelli, 2000). Although found primarily in the liver cytochrome P450 has also been detected in a number of different tissues such as lungs, kidney, skin, adrenal cortex and brain tissues. The implications of P450 in the brain were demonstrated by Nicholson & Renton (2005) by removing astrocytes from rat brains and demonstrating that levels of P450 are modulated by inflammation using LPS stimulation.

Peroxisome-proliferator-activated receptors (PPARs) α and γ regulate the transcription of target genes through agonist binding to the ligand-binding domain (LBD) of these genes. PPARα plays a role in fatty acid regulation, through modulating the expression of target genes, and are characterised by a high lipid catabolic activity. Jiang et al. (2001) found that clofibrate, which activates PPARα, up-regulates the expression of cPLA₂ and COX-2 in preadipocytes. PPARγ has been shown to play a role in the regulation of differentiation of preadipocytes into adipocytes. It was found by Murakami et al. (2001) that fatty acyl-CoA's function as antagonists for PPARα and PPARγ.

3. Acyl-CoA thioesterase activity

Acyl-CoA's perform a wide range of important cellular functions, serving as primary substrates for fatty acid degradation and lipid synthesis as well as regulators of cellular mechanisms such as ion fluxes, vesicle trafficking, protein phosphorylation and gene expression (see Figure 2 for domain organisation of Acot family members).

Most recently, the action of a specific enzyme within the ACOT enzyme family was demonstrated to act on arachidonoyl-CoA, and therefore possibly play a role in arachidonic acid production for the generation of prostanoids and leukotrienes. This is achieved by cleaving the thioester bond of activated C20:4-CoA in the general reaction described in Figure 3.

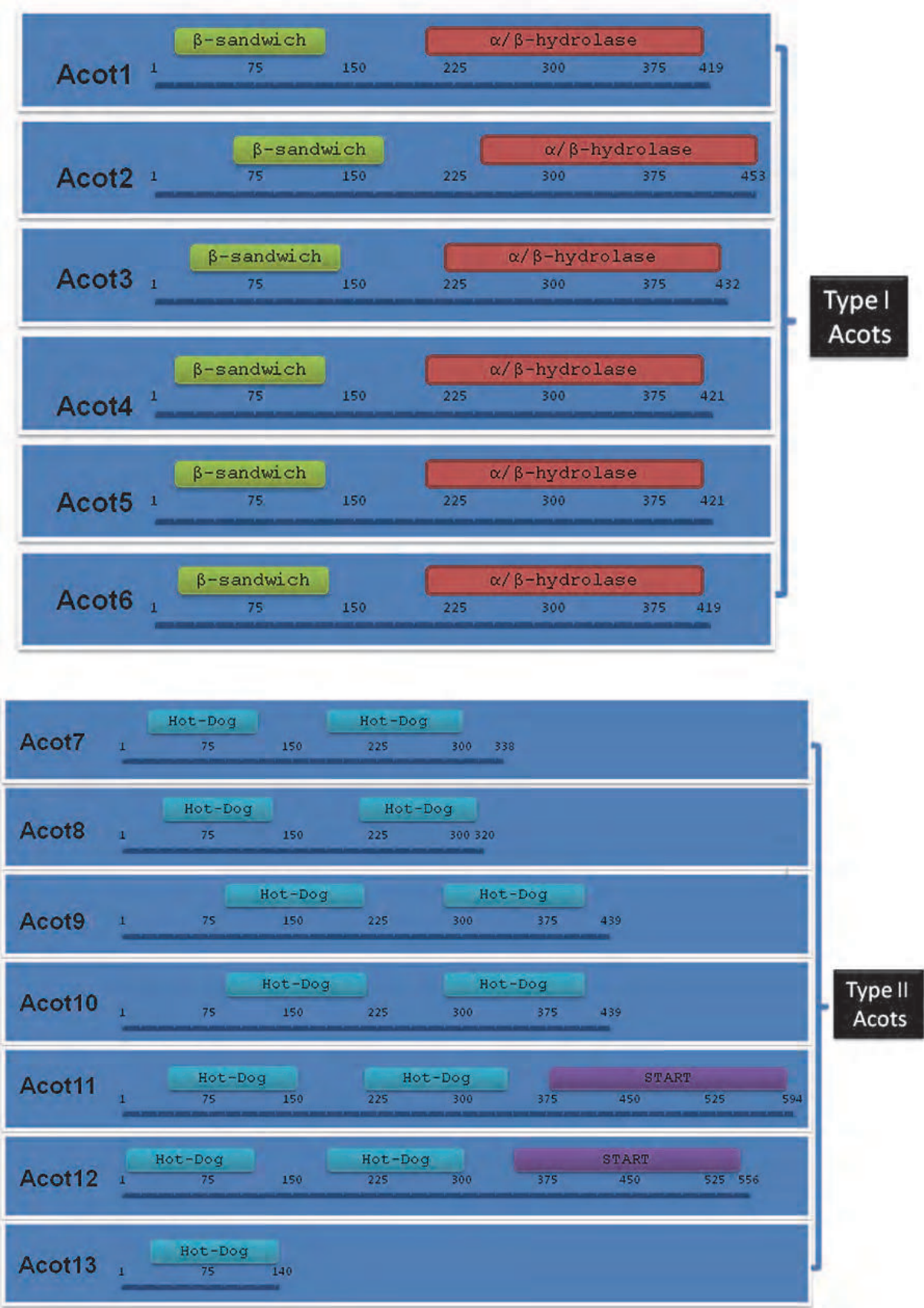


Fig. 2. Domain organisation of Acots.

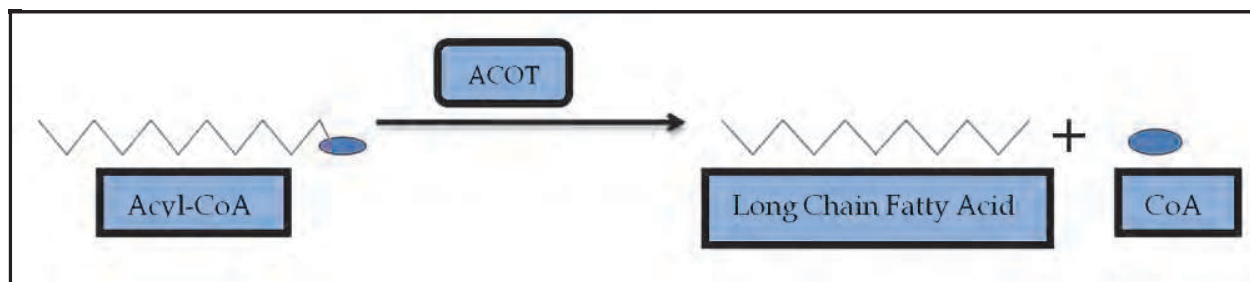


Fig. 3. ACOTs hydrolyse acyl-CoA esters to form free fatty acids and CoASH

3.1 Activity of ACOT7

It has been demonstrated that ACOT7 cleaves arachidonoyl-CoA to release CoA as CoASH and the free fatty acid arachidonic acid. Arachidonic acid is the precursor for a number of eicosanoids that enable the activation of macrophages (Kirkby, Roman, Kobe, Kellie, & Forwood, 2010), and it has been shown that ACOT7 expression is upregulated in macrophages in the presence of LPS and colony-stimulating factor 1 (CSF-1) (2007). It is from this data that the putative role of ACOT7 in inflammation was recognised. As shown in figure 4 below, ACOT7 may provide an alternative pathway for inflammation to the well characterised PLA₂-mediated pathway and a possible target for a new class of anti-inflammation therapies.

Fujita et al. (2011) found that levels of both cytosolic and mitochondrial ACOT7 within mammalian heart muscle increase in response to a high fat diet, and induce inflammation. The increased levels of ACOT7 are in response to the increasing levels of acyl-CoA imported across the mitochondrial membranes from the cytosol via the action of carnitine palmitoyltransferase (CPT). This mechanism is thought to reduce the “lipotoxic” effects of insulin resistance which leads to contractile dysfunction of the heart as the cells accumulate proinflammatory molecules such as acyl-CoA, diacylglycerol and ceramide (Fujita, et al., 2011).

ACOT7 is also known as brain acyl-CoA hydrolase (BACH) and has been purified from the brain cytosol of rats and humans and is believed to be responsible for acyl-CoA hydrolytic activity in the brain. Given the highly toxic nature of long chain acyl-CoA's, as a detergent, the activity of ACOT7 within the brain may be to reduce the levels of these within neurons (Kuramochi et al., 2002). Furthermore Takagi et al. (2006) found that ACOT7 is expressed in mouse testis and may play a role in spermatogenesis. The results of this research suggest that the regulation of ACOT7 occurs at a posttranscriptional level or that the rate of turnover in the testis is higher than in the brain. The level of ACOT7 protein was higher in the brain than the testis however the mRNA level was higher in the adult testis than the brain. The physiological significance of ACOT7 within the testis has not been determined however it is thought to scavenge cytosolic free long-chain acyl-CoA's.

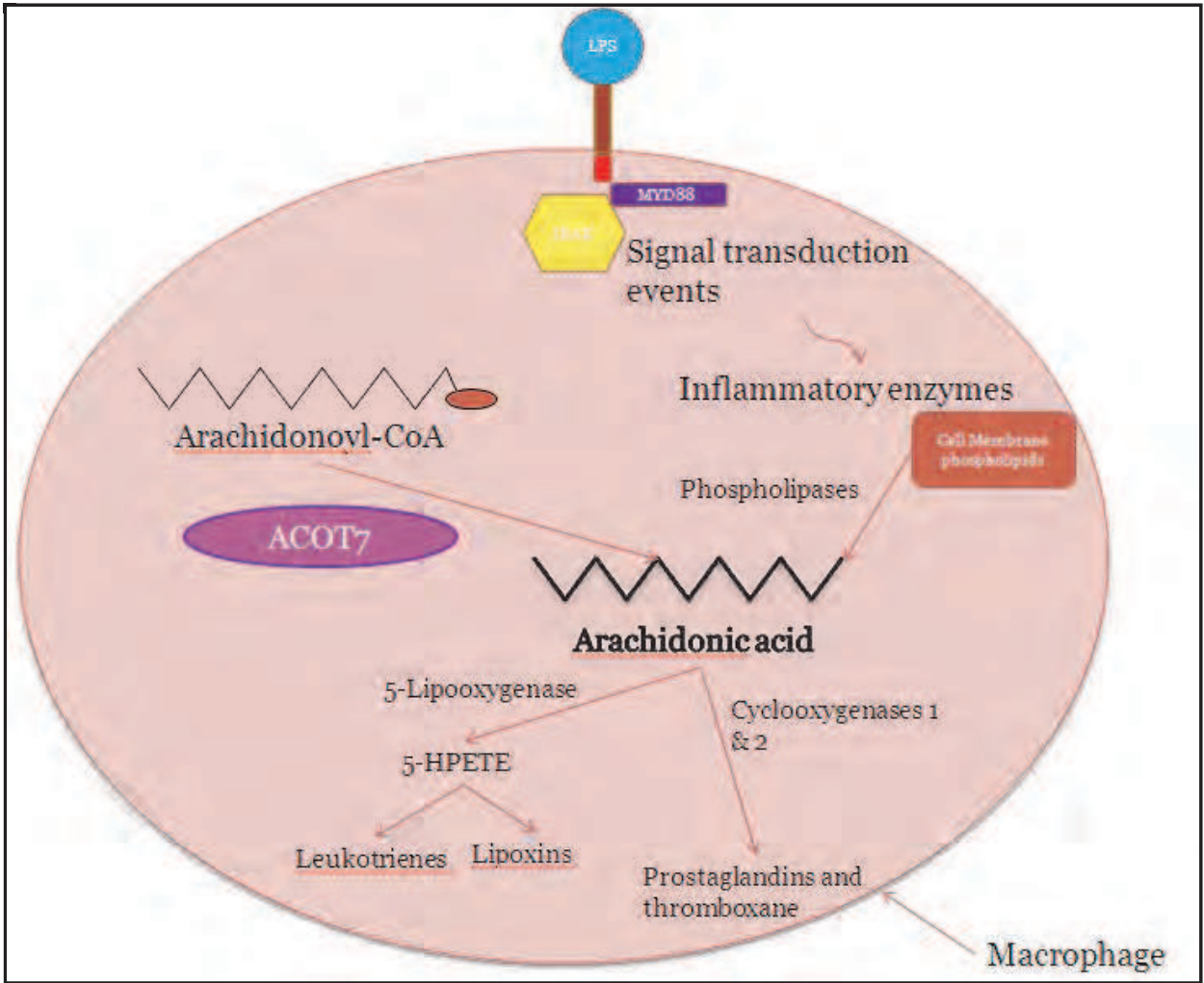


Fig. 4. Classical pathway of inflammation with role of ACOT7 in arachidonic acid production.

4. Structure of ACOT7

Structural insights into the function of ACOT7 have recently been undertaken through the cloning and high-level recombinant expression of ACOT7. Pioneering characterisation of ACOT7 was undertaken by Yamada et al. (1994) through the isolation and purification of rat liver, however high level over-expression and isolation of the enzyme required cloning of cDNA into bacterial expression vectors (Broustas, Larkins, Uhler, & Hajra, 1996; Junji Yamada et al., 1999). Serek et al. (2006) elucidated the structure of the C-terminal of the ACOT7 protein purified from *Mus musculus* by crystallising the C-terminal domain and analysing the high resolution structure using X-Ray diffraction techniques. From this data it was identified that the C-terminal domain of ACOT7 exists in a hexameric form. Forwood et al (2007) isolated and expressed both the N- and C-terminals of ACOT7. These domains were then separately crystallised and the resulting structures (in 1.8 and 2.5 Å resolution respectively) were superimposed to determine the structure of the full length ACOT7. Within the hexamer of Acot7 β-sheets from each domain form a semicontinuous antiparallel barrel with 25% of Acot7 residues involved in interdomain contacts (see Figure 5).

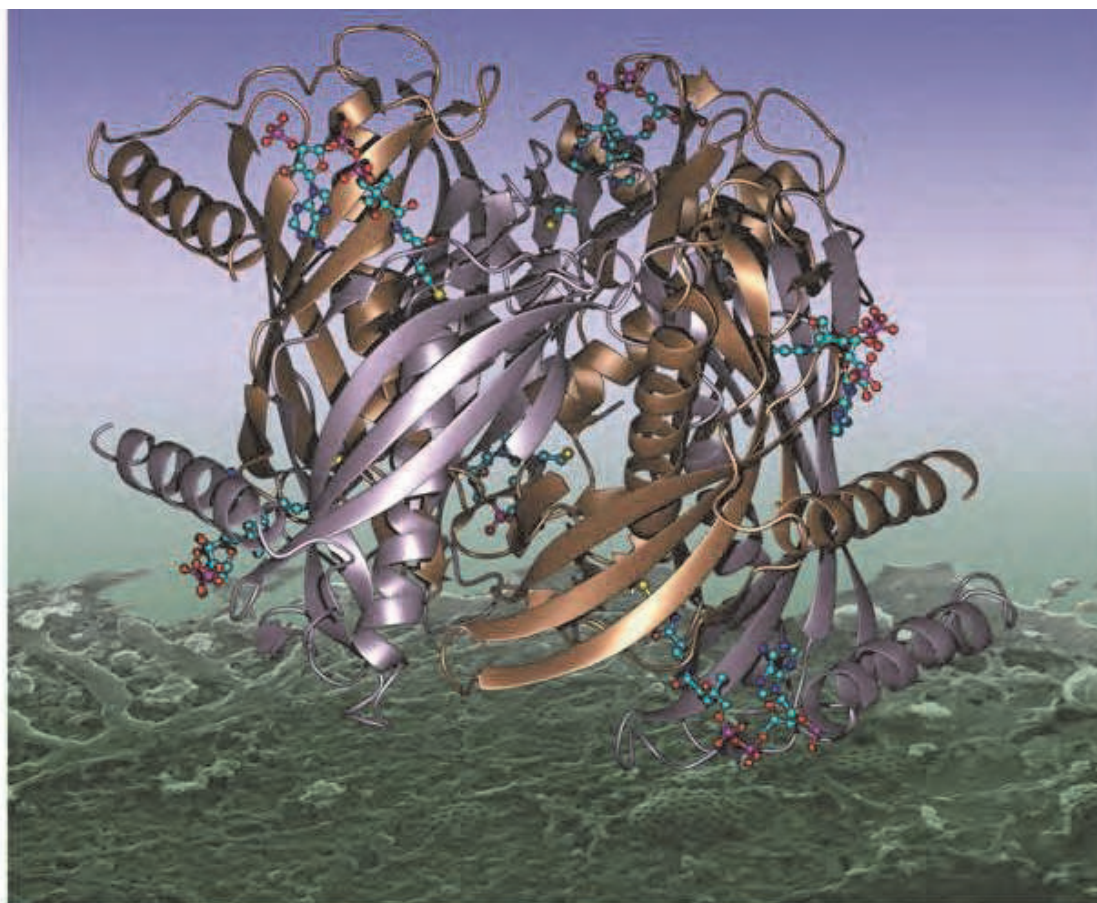


Fig. 5. Structure of full-length Acot7 showing monomer and trimer arrangement.

Wedge between the two monomers that make up the protomer are six CoA molecules, making contacts with residues from each domain. Opposite this binding site is a large hydrophobic tunnel, conserved within thioesterases that may be involved in the fatty-acid recognition and release. The individual domains are inactive when in homomeric complexes however when combined the activity can be restored to half that of the wild type enzyme. The arrangement of the N- and C-domains within ACOT7 and the positioning of the CoA molecules within the N-domain suggest that the full molecule contains three copies each of two distinct active sites in ACOT7. There are two potential active sites within ACOT7 (sites I and II, see Figure 6); these were determined via sequence analysis of mammalian ACOT7s. To assess the role that each of these active sites play in catalysis each residue was mutated to Ala and the recombinant mutant enzymes were isolated and the activity of the mutant residues determined. The mutations in site I resulted in dramatic reductions in catalytic activity, whereas the analogous mutations in site II did not affect activity. These findings demonstrated that site II were not directly involved in catalysis. Furthermore the introduction of the key catalytic residues from site I into site II resulted in a four-fold increase in catalytic activity when compared with the wild-type Acot7. Thus, Acot7 (structures of each domain presented in figure 7) is believed to contain a “half-of-sites” activity, which may regulate the enzyme by placing an upper limit on enzyme efficiency and allows the cell to regulate the cellular concentrations of AA-CoA and arachidonic acid.

5. Genetic regulation of ACOTs

The acyl-CoA thioesterase gene (*ACOT*) family encodes for two specific types of enzyme, acyl-CoA thioesterase type I and type II, which are determined by differences in structure and sequence. These two types catalyse similar reactions but share no similarity in structure or function, demonstrating that they are analogous and not homologous. They are an example of convergent evolution, whereby two molecules have evolved to fill the same need within the cell. Type I ACOT proteins are members of the α/β hydrolase fold enzyme superfamily. This superfamily also includes a number of esterase-activity-inhibiting enzymes such as carboxyl-esterase's and lipases. This group is comprised of only four genes; *ACOT1*, *ACOT2*, *ACOT4* and *ACOT6*. These proteins share a high degree of sequence homology, all forming an 80 kilobase gene cluster on chromosome 14q24.3, demonstrating that they have arisen as a result of gene duplication. Within the mouse and rat orthologues there is a similar phenomenon; *Acot1*, *Acot2*, *Acot3*, *Acot4*, *Acot5* and *Acot6* are clustered on chromosomes 12 D3 within the mouse and 6q31 within the rat. This can be seen in figure 8 below which also demonstrates the cellular compartments in which each is expressed (Brocker, Carpenter, Nebert, & Vasiliou, 2010).

Type II ACOTs are members of the 'hot dog' fold enzyme superfamily. The type II ACOTs are far less related than the type I ACOTs. There is only one type II ACOT that does not contain a double 'hot dog' domain suggesting that they may have evolved as a gene duplication event, allowing for the accommodation of bulky substrates. Type II ACOTs show highly divergent sequences making evolutionary comparisons difficult without three-dimensional structures, as structural interaction conservation does not directly correspond with residue conservation. Within the mouse genome there is an additional type II ACOT, known as *Acot10*, which shares 95% mRNA identity with *ACOT9*. The other seven type II ACOT genes are highly conserved among human, mouse and rat indicating that they were all present in the ancestor preceding mammalian radiation (Brocker, et al., 2010; M. C. Hunt & Alexson, 2008; Kirkby, et al., 2010).

5.1 Expression and regulation of ACOT7

The ACOT7 enzyme is highly conserved, exhibiting greater than 95% sequence homology at the amino acid level between human, mice and rats (Kuramochi et al., 2002). Transcription start sites for ACOT7 were characterised by Takagi et al. in 2004 and shown to encode a 43kDa subunit, located in the cytosol; and six isoforms comprised of 50kDa subunits, expressed at trace levels and located in the mitochondria. Independent studies have confirmed that the ACOT7 gene can generate up to seven different protein isoforms as can be seen below in figure 6 (J. Yamada, 2005). The human ACOT7 gene consists of 13 exons, with the first four of these able to be used as first exons. The most well characterised of the ACOT7 isoforms, ACOT7a, is derived from the sequence corresponding to transcription initiation at exon 2 (M. Hunt et al., 2007; Kirkby, et al., 2010).

Expression of ACOT7 has been detected in the developing mouse embryo brain as early as embryonic 11.5 days although in very low concentrations and increases until day seven following birth. Thereafter the level declined until day 28 following birth when it reached a steady state which was about 70% of its highest expression (on day 7) and identical to

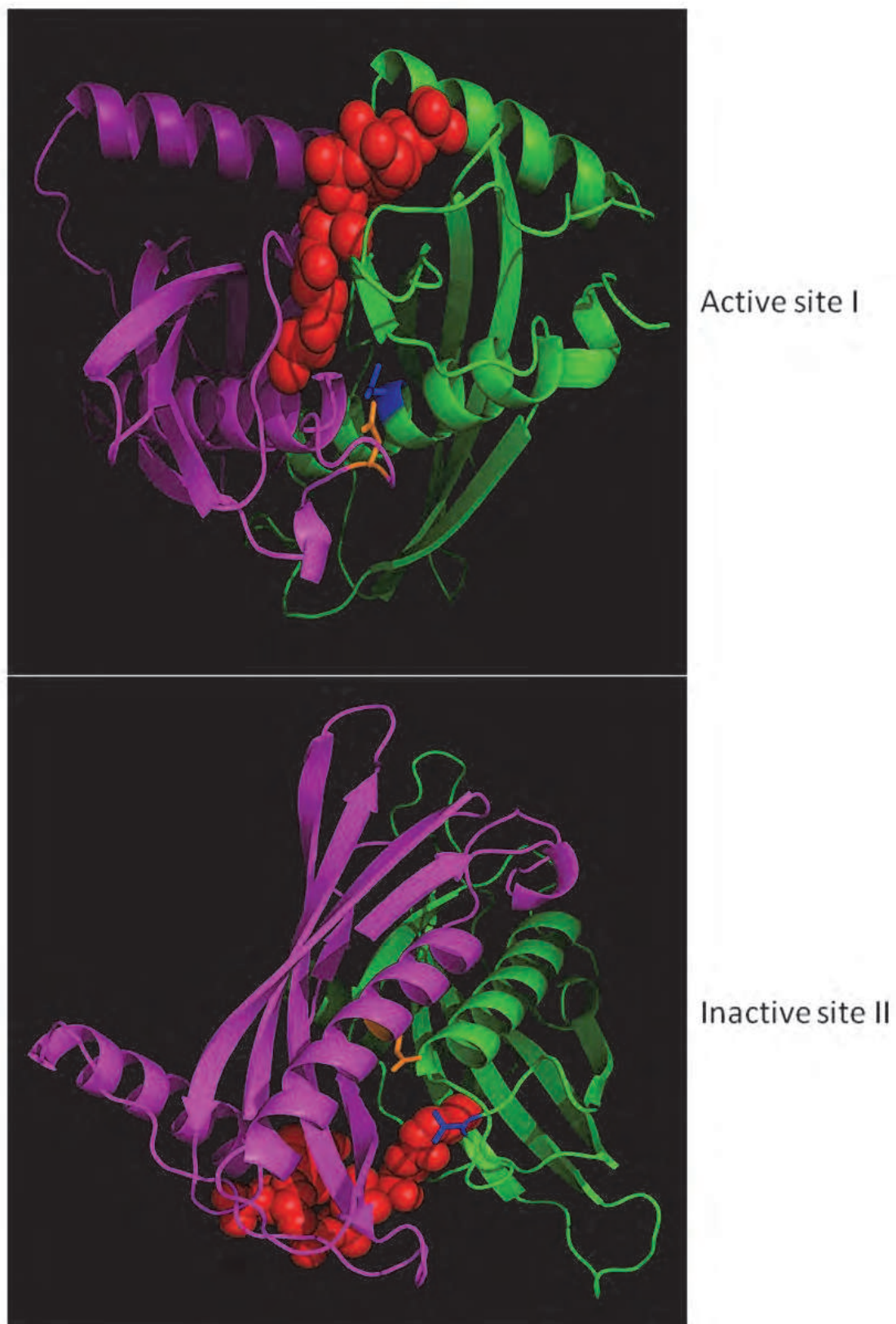


Fig. 6. Active sites of Acot7: Active site I is comprised of Asn24 from the N-domain and Asp213 from the C-domain; the analogous site (later determined to be inactive) is comprised of Glu39 from the N-domain and Thr198 from the C-domain

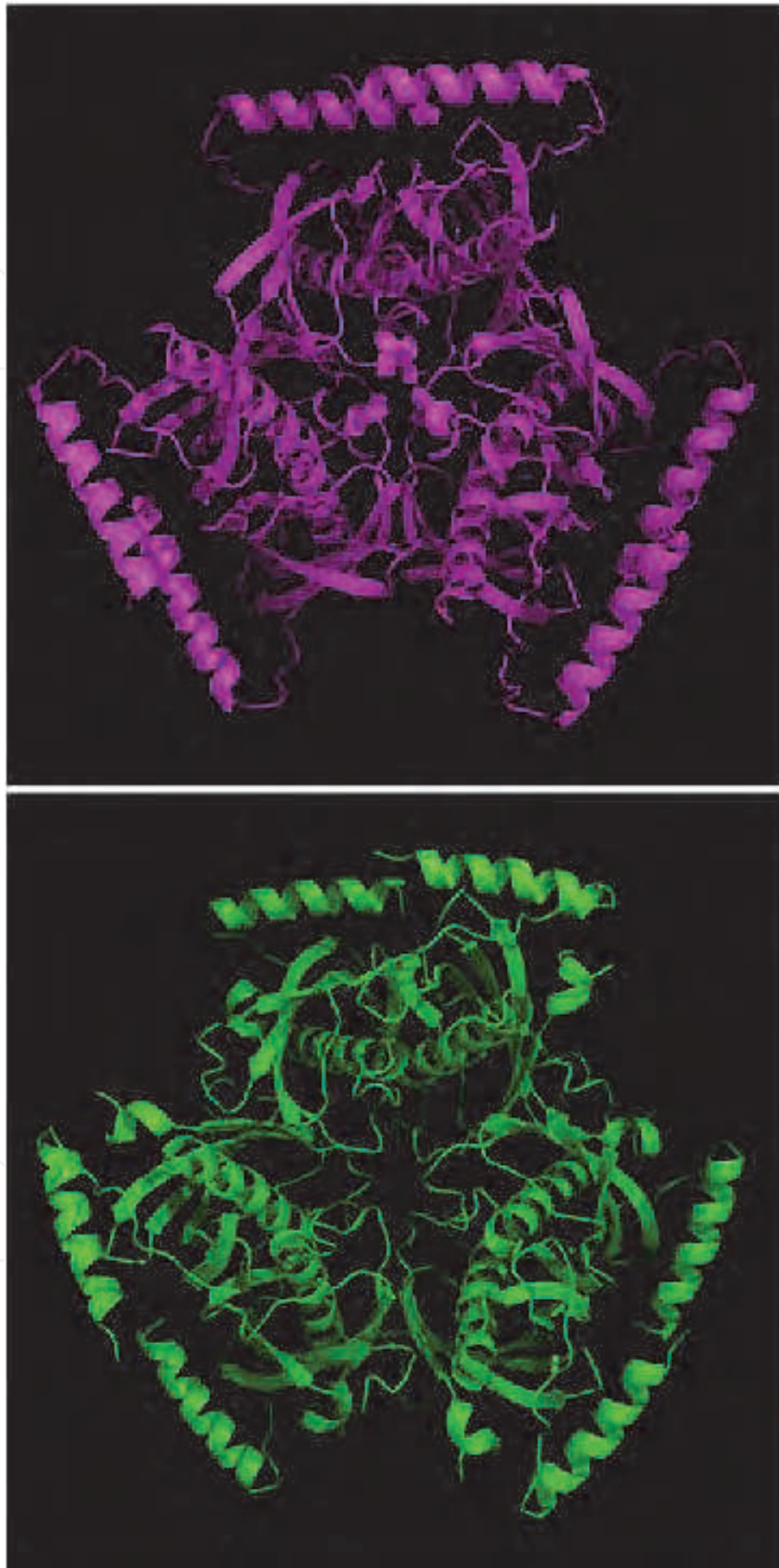


Fig. 7. (A) (B) Quaternary structure of Acot7 (N terminus) and C terminus respectively

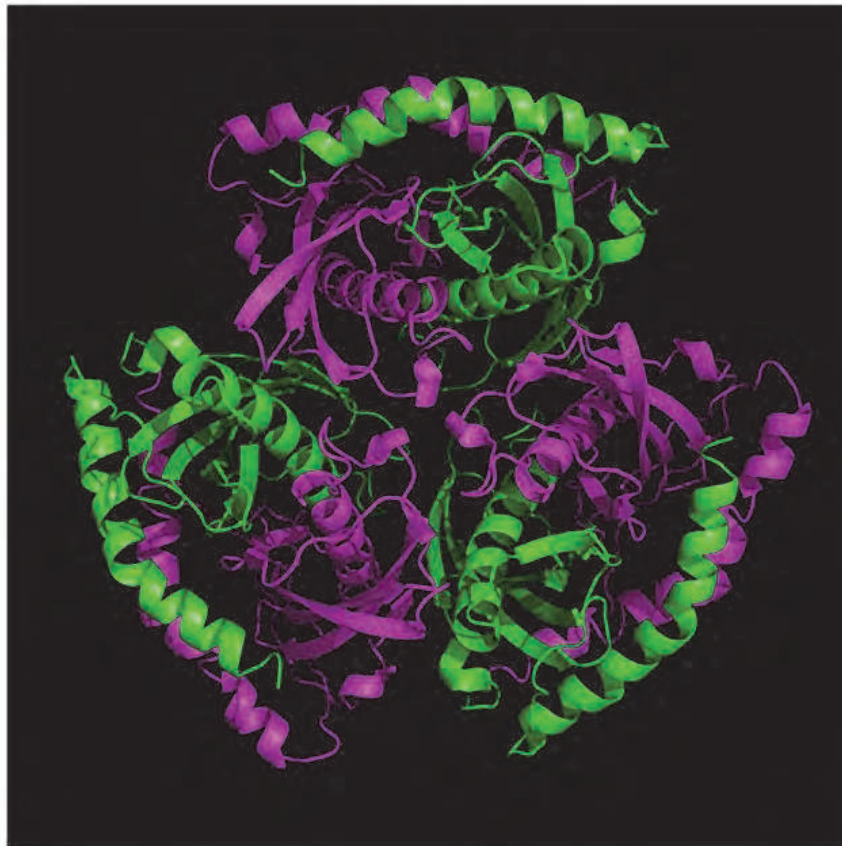


Fig. 8. Full length Acot7 demonstrating the N terminus domain (in green) and C terminus domain (in purple)

levels recorded at birth. The expression of *ACOT7* was located only in cells committed to neuronal lineage, and continues to be expressed in these cells resulting in the high expression of *ACOT7* in the adult brain (Junji Yamada, Kuramochi, Takagi, & Suga, 2004).

Research by Takagi, Suto, Suga & Yamada (2005) showed that *ACOT7* gene expression is regulated by Sterol Regulatory Element-Binding Proteins (SREBPs). SREBPs form a few transcription factors which play a critical role in the regulation of cholesterol and fatty acids. Within the cell SREBPs are located in the membrane, to enter the nucleus they undergo proteolytic cleavage and their N-terminals are released as nSREBPs. Within the nucleus SREBPs bind to the sterol regulatory element (SRE) of target genes. The *BACH* gene promoter region contains two SRE motifs providing a binding partner for nSREBPs stimulating the production of cDNA of *Acot7* (Takagi, et al., 2005).

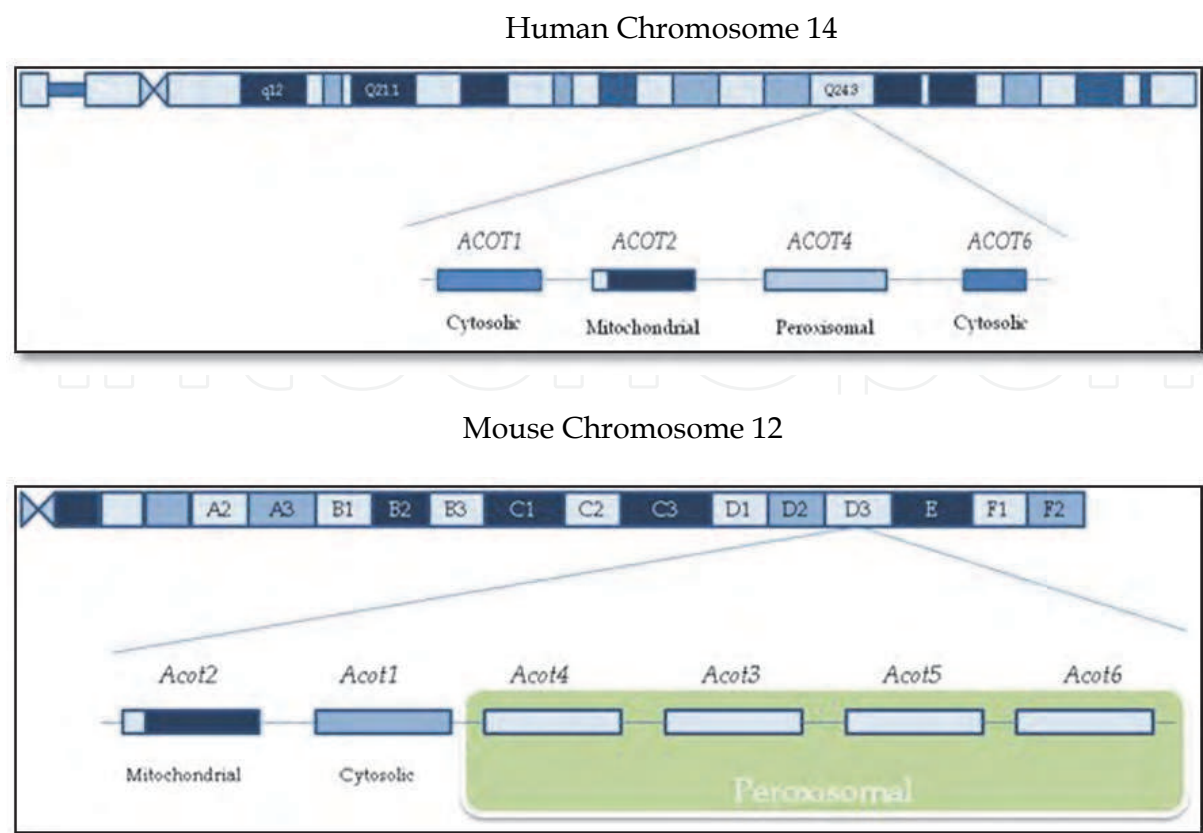


Fig. 9. The type I acyl-CoA thioesterase gene cluster is found on chromosome 14q24.3 in the human genome and chromosome 12 D3 in the mouse genome, adapted from Hunt & Alexson (2008)

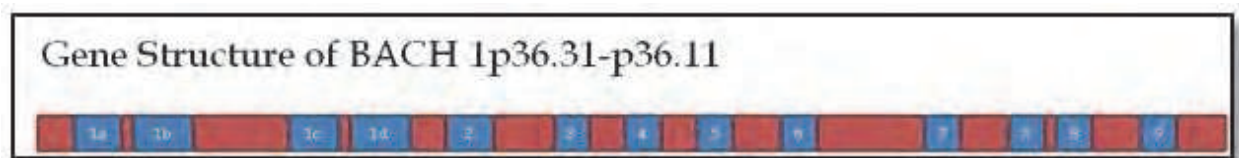


Fig. 10. Structural organisation of the human BACH gene, exons are designated by blue boxes and introns by red segments, adapted from Yamada et al. (2005)

6. Conclusion

Inflammation is a complex immune response that involves the production of eicosanoids via AA. The cellular role of ACOT7 has been extended to include the cleavage of arachidonoyl:CoA to yield arachidonic acid, and therefore may provide a mechanism for the supply of arachidonic acid from intracellular arachidonoyl-CoA. This is supported by a number of lines of evidence: ACOT7 is highly expressed in macrophages and upregulated by proinflammatory stimuli; the preferred substrate of ACOT7 is arachidonoyl-CoA and the reaction product is the central precursor for lipid inflammatory mediators; and finally, over-expression of ACOT7 in activated macrophages increases prostaglandin production. Thus, ACOT7 is able to complement the well-characterised PLA₂ AA-producing pathway, and

may play a role in inflammation by producing sufficient levels of AA for eicosanoid production.

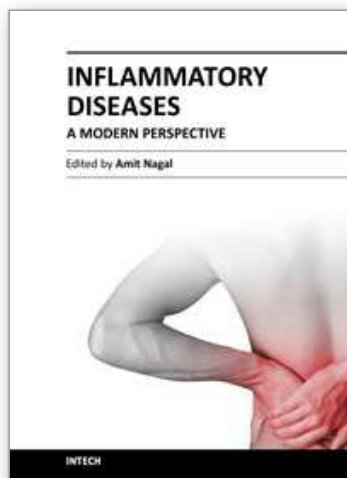
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