

专题报告

Acly-CoA 与ACSLs

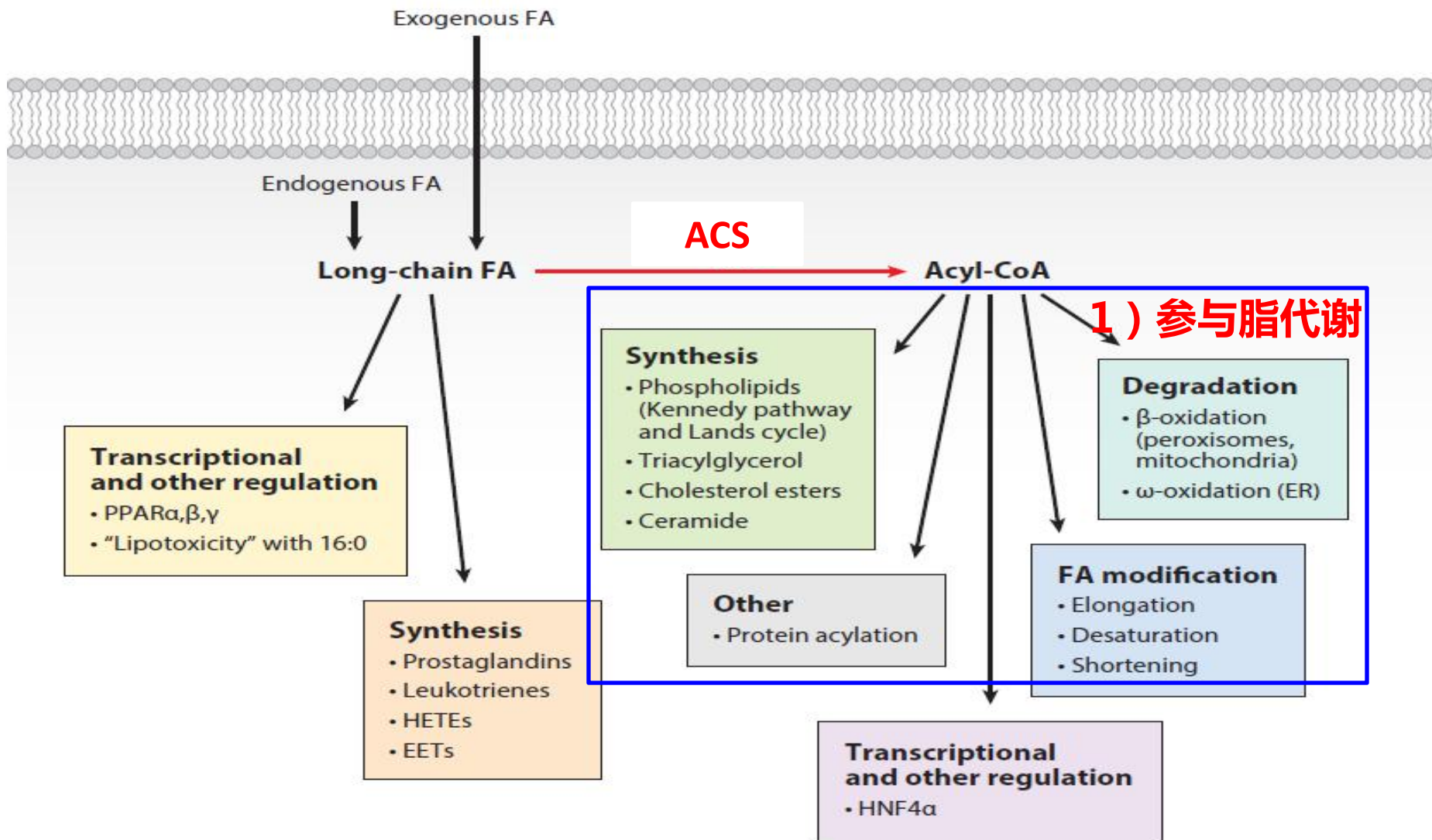
报告人：谢帝芝

2016/4/25

Acly-CoA功能

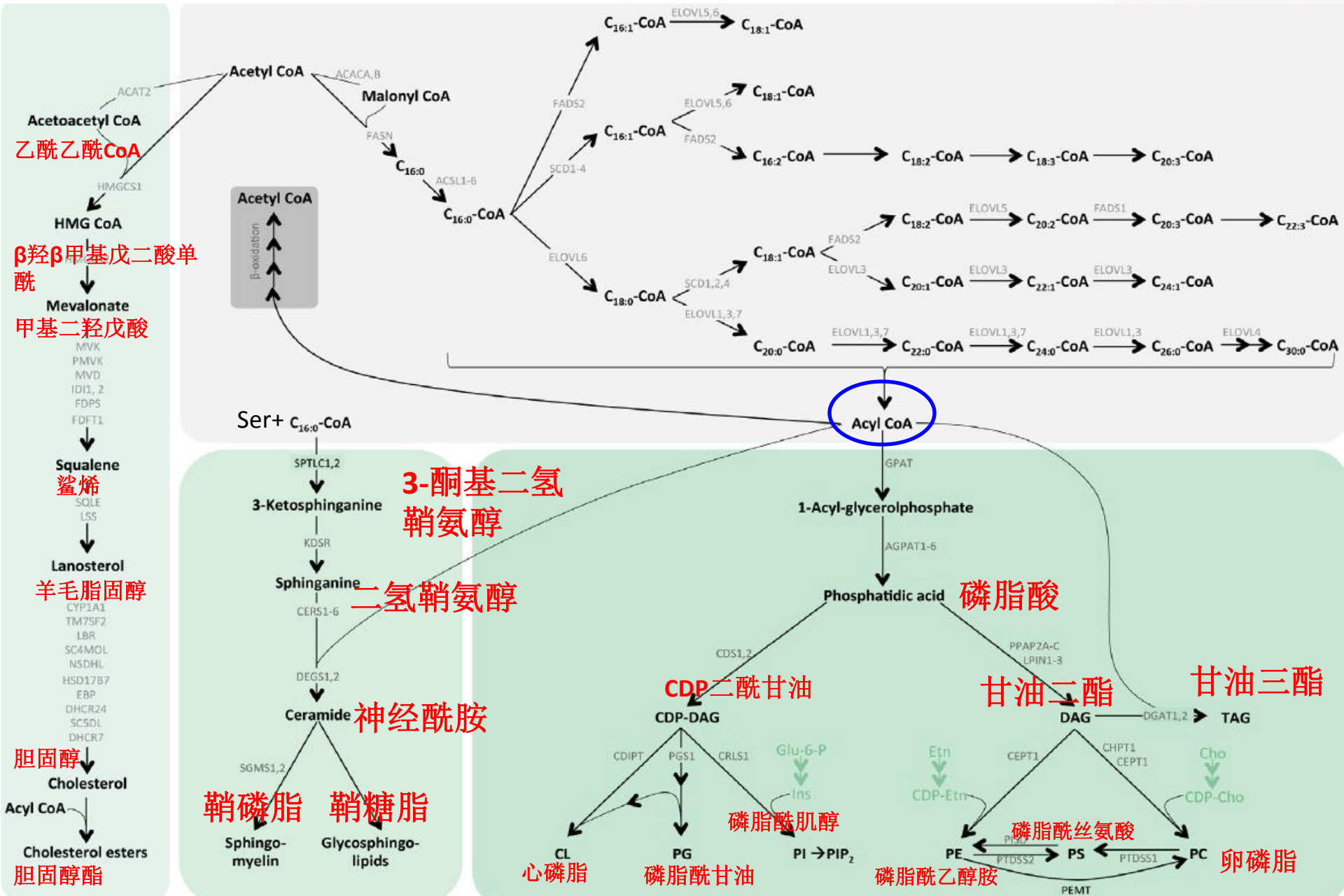
ACSLs及其功能

一、Acly-CoA功能

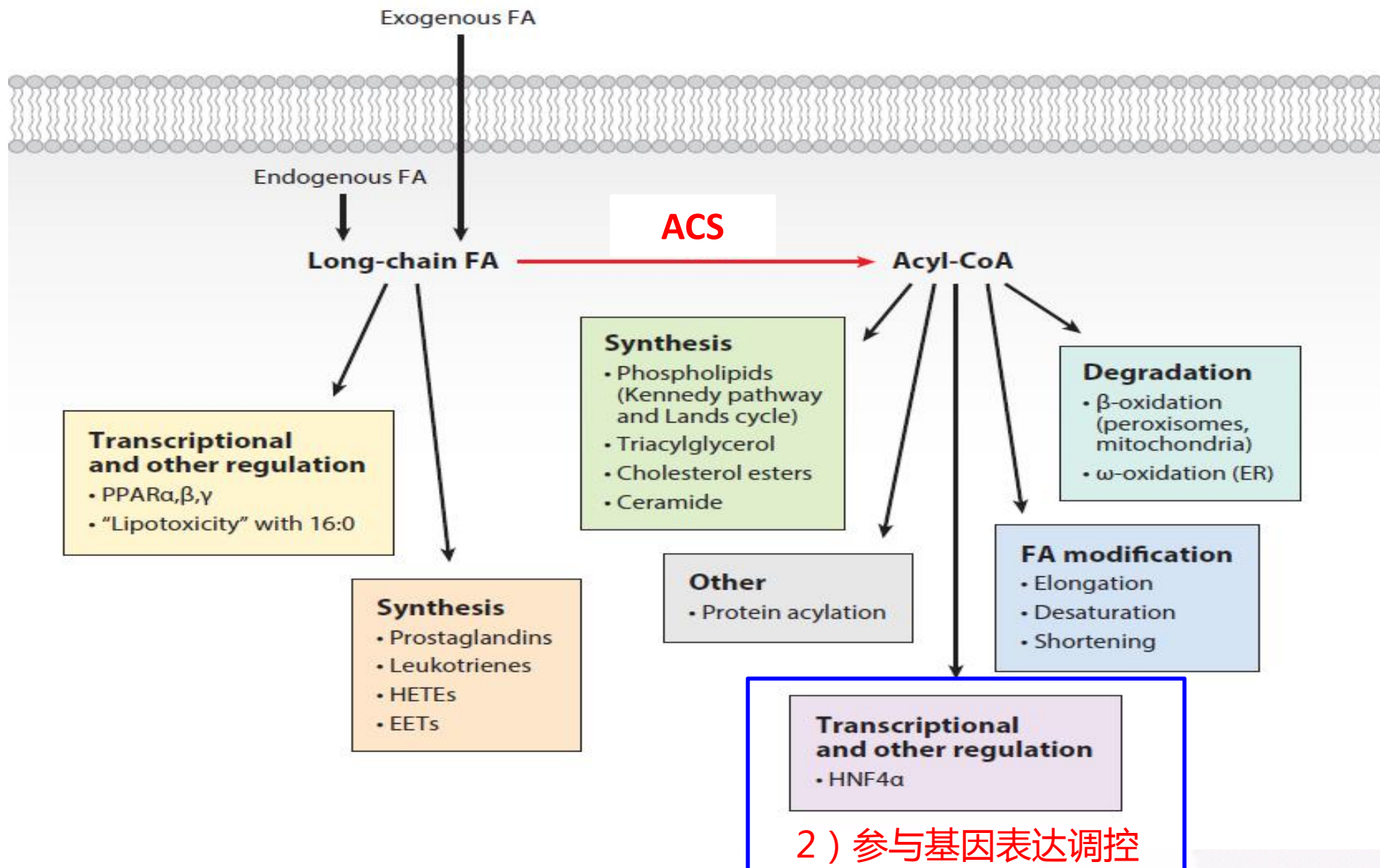


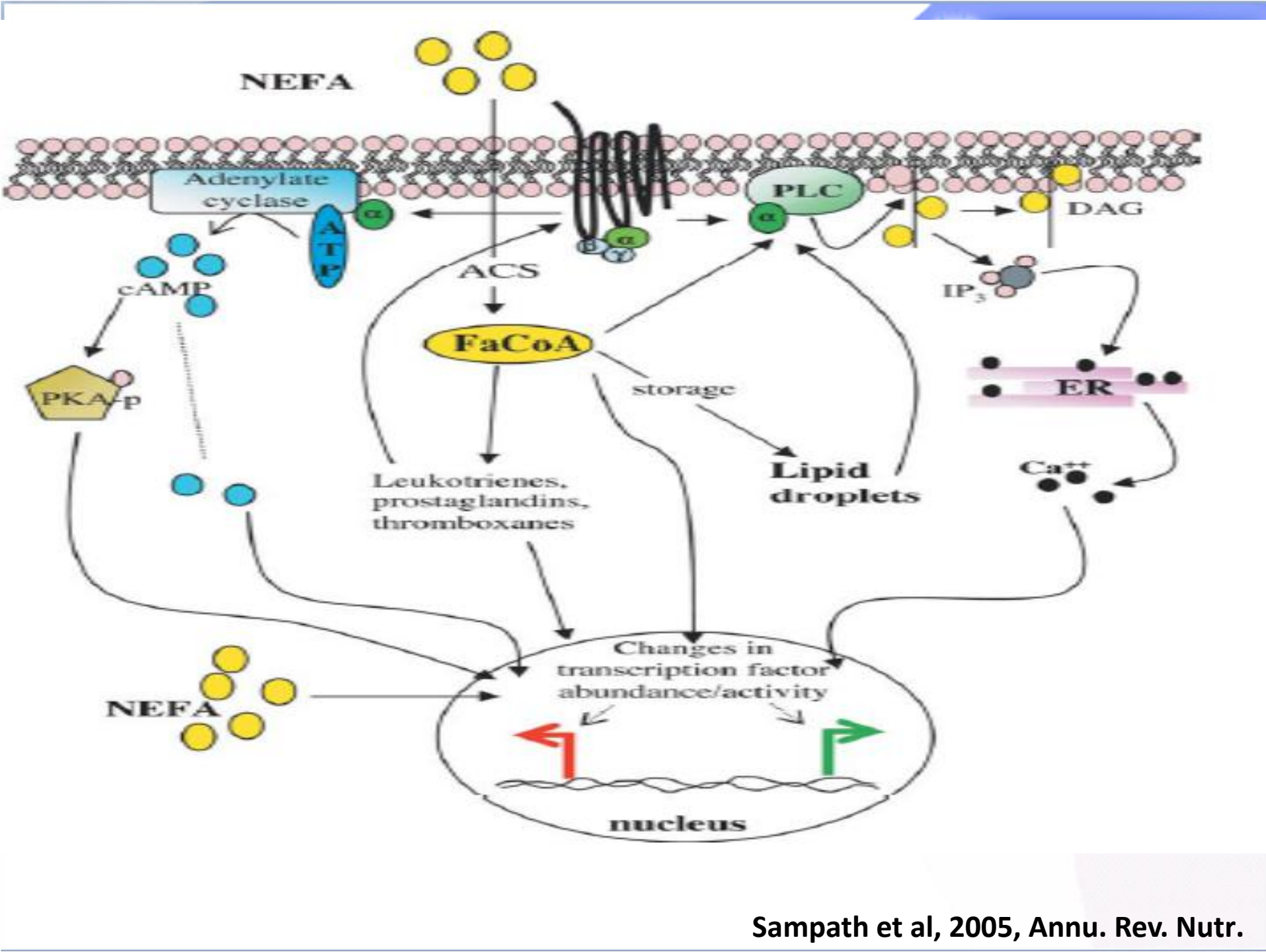
Long-chain acyl-CoA at the center stage of lipid metabolism

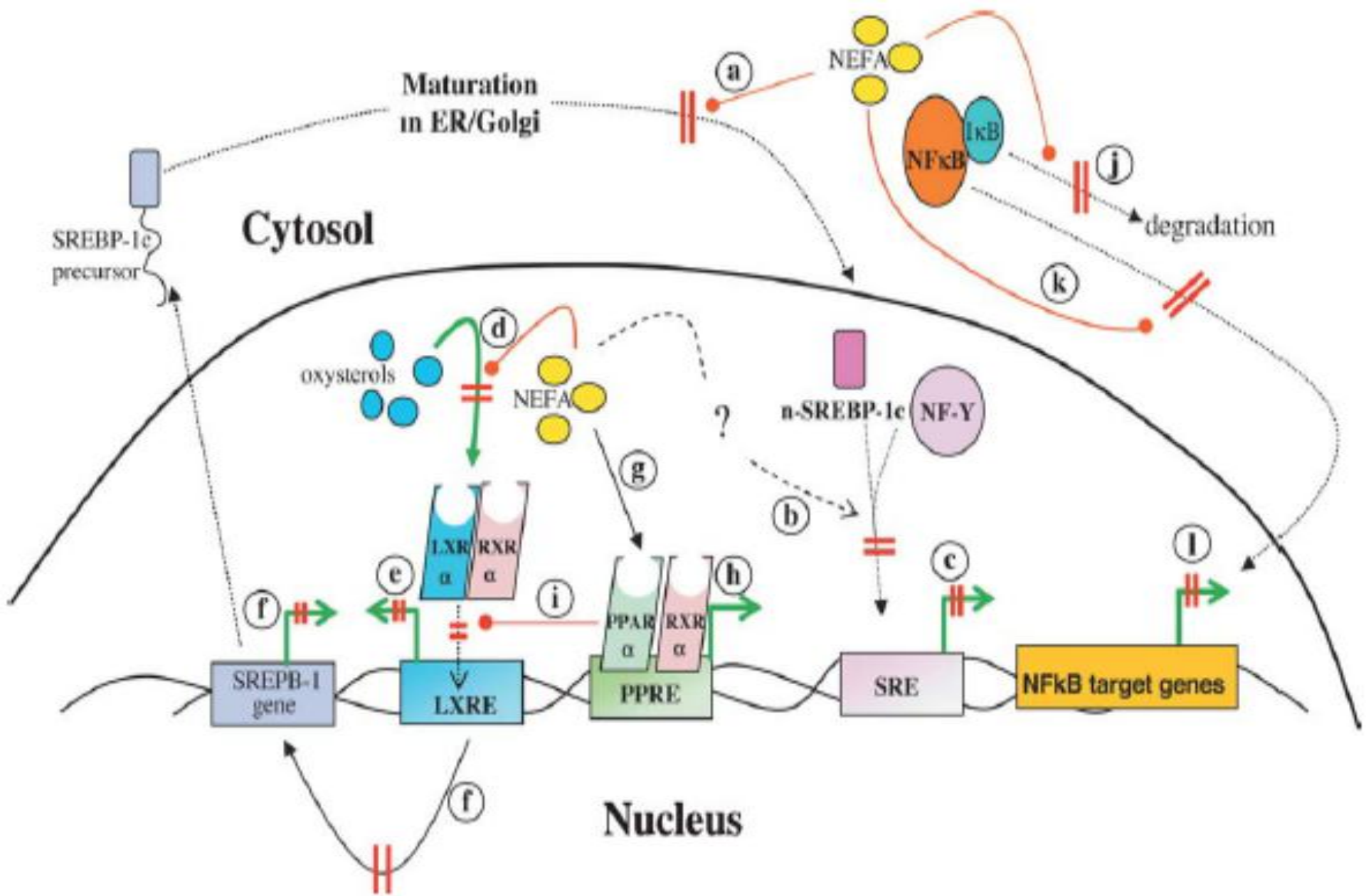
(Neess et al, 2015, Progress in Lipid Research)



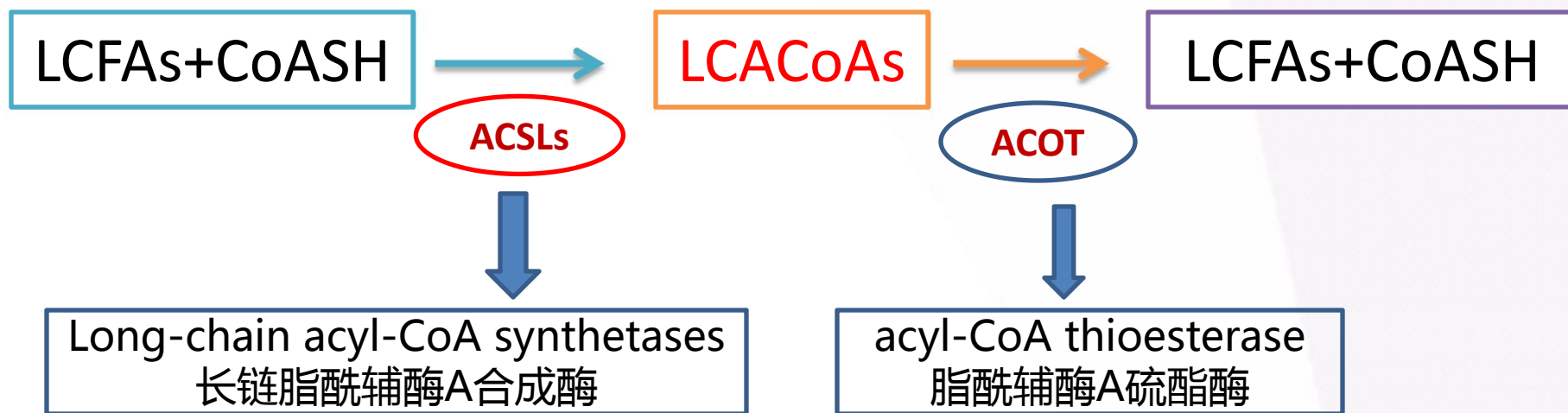
一、Acly-CoA功能







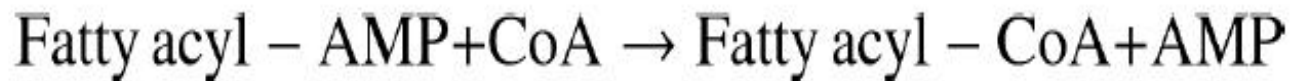
Long-chain fatty acids (LCFAs) — de novo synthesis, dietary sources, or degradation of TAG, PL, and Chol.



二、ACSLs及其功能

长链脂酰辅酶A合成酶(ACSL), 隶属于脂酰辅酶A合成酶ACS体系 [ACSS、ACSM、**ACSL**、ACSVL (FATP)] (Jia et al. 2007 ; Lopes-Marques et al. 2013) 。

基本步骤：



二、ACSLs及其功能

1. ACSs两保守区

2. ACSs的功能

3. ACSL亚型及其剪切体

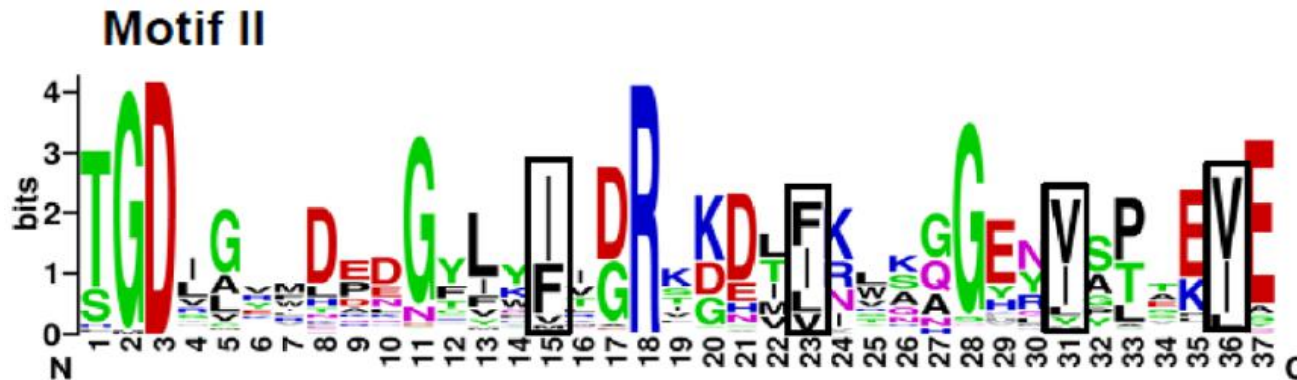
4. ACSLs组织分布及亚细胞定位

5. ACSLs 底物偏好性

1、ACSs两保守区



ATP-binding domain



Four hydrophobic residues

2. ACS的功能

ACSS

activate FA of less than 4 carbons

ACSM

activate FA of 4 to 12 carbons

ACSL

activate FA of 12 to 22 carbons

5种

ACSBG

activate FA of 14 to 26 carbons

2种

ACSVL

activate FA of 18 to 26 carbons

6种

2. ACS的功能(续)

Table 1 Evidence for partitioning from loss-of-function studies

Gene	Tissue	FA partitioning information	Phenotype
<i>Acs11</i> KO	Liver-specific	Decreased FA incorporation into TAG and oxidation	None
	Adipose-specific	Decreased FA oxidation	Increased adipose mass; defective thermogenesis
	Multi-tissue- heart	Decreased FA oxidation	None
	Heart-specific	Decreased FA oxidation	None
	Macrophage-specific	Altered 20:4 metabolism and PGE ₂ production	Protects macrophages against diabetes-mediated inflammation
	Endothelial cell-specific	No information	None
<i>Acs13</i> KD	Rat hepatocytes	Glycerolipid synthesis on lipid droplets? Regulation of transcription factors	—
<i>Acs14</i> KD	Cultured cells, various	Altered eicosanoid metabolism	Human X-linked mental retardation

2. ACS的功能(续)

<i>Acs15</i> KD	Primary hepatocytes	Decreased FA incorporation into glycerolipids and cholesterol esters	Decreased lipid droplet formation
<i>Acs15</i> KO	Total KO	No information	None
<i>Acs16</i> KD	Neuroblastoma cells	22:6 ω 3 metabolism?	Inhibited neurite outgrowth
<i>Fatp1/Acs14</i> KO	Skeletal muscle, BAT, L6E9 cells Retina	Decreased FA oxidation Decreased FA oxidation?	Defective thermogenesis Accelerated retinal aging
<i>Fatp2/Acs11</i> KO	Total KO	Decreased oxidation of 24:0?	None
<i>Fatp3/Acs13</i> KD	Glioma	No information	Decreased anchorage-dependent growth
<i>Fatp4/Acs15</i> KO	Human mutation Keratinocytes	Decreased type II diester wax in the sebum Decreased long-chain ceramides	Ichthyosis prematurity syndrome Postnatal restrictive skin
<i>Fatp5/Acs16</i> KO	Gallbladder bile	Decreased conjugated bile acids	Low weight gain on a high-fat diet
<i>Fatp6/Acs12</i>	—	No information	—
<i>AcsBg1</i> KD	Neuro2a cells	Decreased β -oxidation	—
<i>AcsBg1</i> KO	Various tissues	Increased amounts of some long-chain FAs	None
<i>AcsBg2</i>	—	No information	—

3. ACSL亚型及其剪切体

Table 1. The Mammalian ACSLs^a

Gene	Characteristics			Spliced transcript variant			
	Alternative elements	Isoforms	Length (aa)	Human	Mouse	Rat	
<i>ACSL1</i>	F,Y-exon	Y-exon	698	v1	DQ083029		
		F-exon	698/699 ^b	v2	NM_001995.2	NM_007981.3	NM_012820.1
		no F,Y-exon	672	v3	DQ083028		
<i>ACSL3</i>	5'-UTRs		720	v1	NM_004457.3	v1	NM_028817.2
			720	v2	NM_203372.1	v2	NM_001033606.1
<i>ACSL4</i>	5'-UTRs / AUGs	AUG2	670	v1	NM_004458.1	v3	NM_001033600.1
			670			v2	NM_019477.3
		AUG1	711	v2	NM_022977.1	v1	NM_207625.2
<i>ACSL5</i>	5'-UTRs / AUGs	AUG1	739	v1	NM_016234.3		
		AUG2	683	v2	NM_203379.1		
			683	v3	NM_203380.1	NM_027976.2	NM_053607.1
<i>ACSL6</i>	5'-UTRs / AUGs / exon8 / F,Y-exon	AUG1 / Y-exon	722	v1	NM_015256.2	v2	NM_001033597.1
		AUG1 / F-exon	722	v2	NM_001009185.1	v1	NM_144823.4
		AUG2 / Y-exon	697			v4	NM_001033599.1
		AUG2 / F-exon	697			v3	NM_001033598.1
		AUG2 / no F,Y-exon	622	v3	BC047453.1		
		AUG? / ΔF-exon	^d	v4	DQ083030		
	AUG2 / Ex.8 / F-exon	712	v5	DQ083031			

3. ACSL亚型及其剪切体 (续)

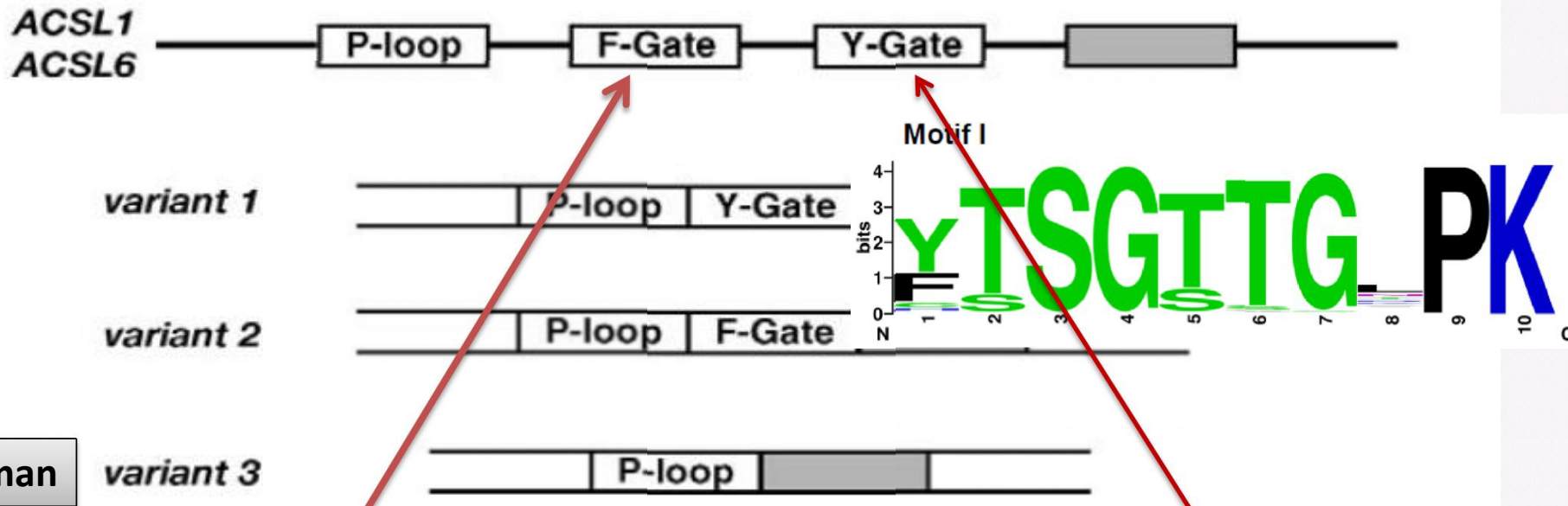


Fig1. Representation of the spliced events affecting the fatty acid Gate domains.

Soupeine *et al.* *BMC Biochemistry* 2010, **11**:18
<http://www.biomedcentral.com/1471-2091/11/18>

Activity of the acyl-CoA synthetase ACSL6 isoforms: role of the fatty acid Gate-domains

3. ACSL亚型及其剪切体 (续)

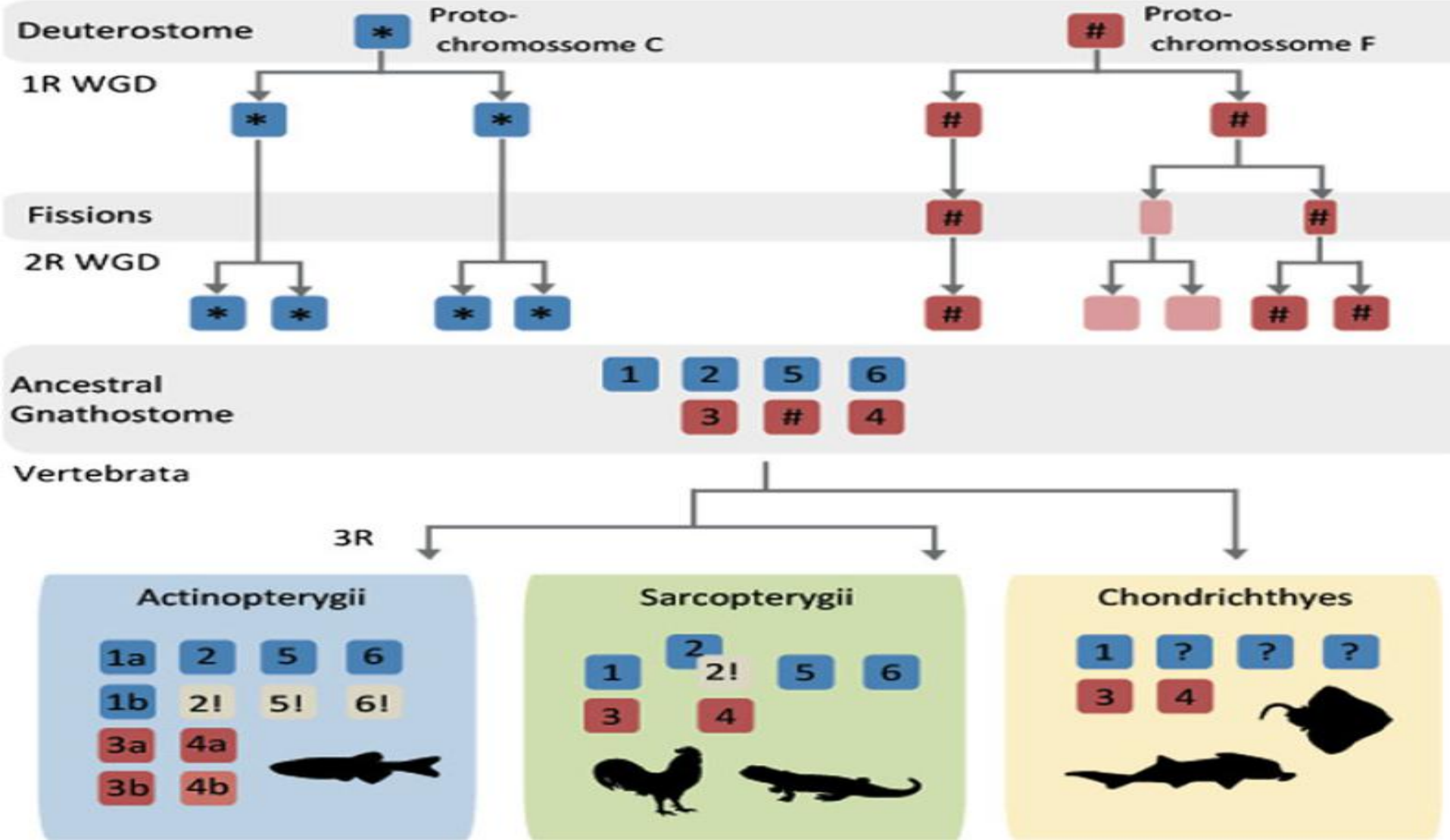
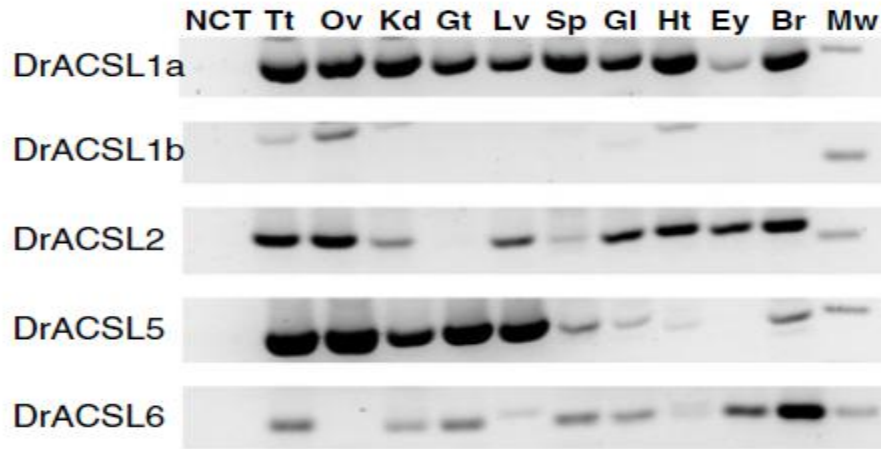


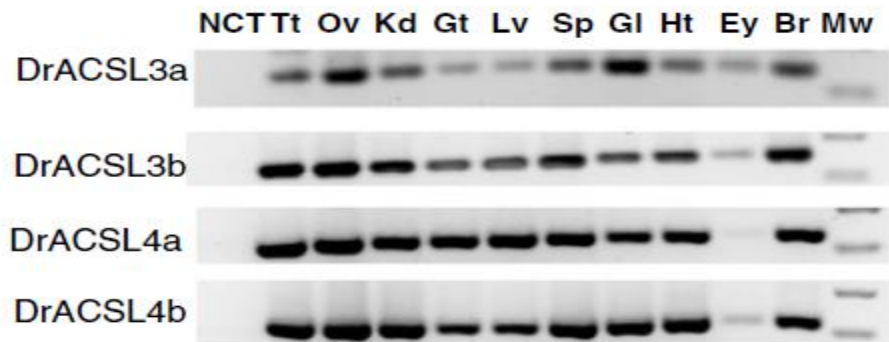
Figure 7 Proposed evolutionary history and duplication timing of the *AcsI* gene family in vertebrates. Questions marks indicates unknown data, and exclamation signals gene loss.
(Lopes-Marques et al. 2013, BMC)

4. ACSLs组织分布及亚细胞定位

A

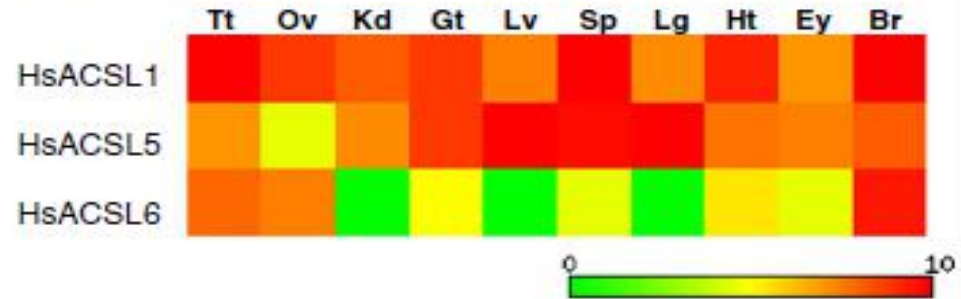


B



斑马鱼ACSLs组织表达分布
(Lopes-Marques et al. 2013)

C

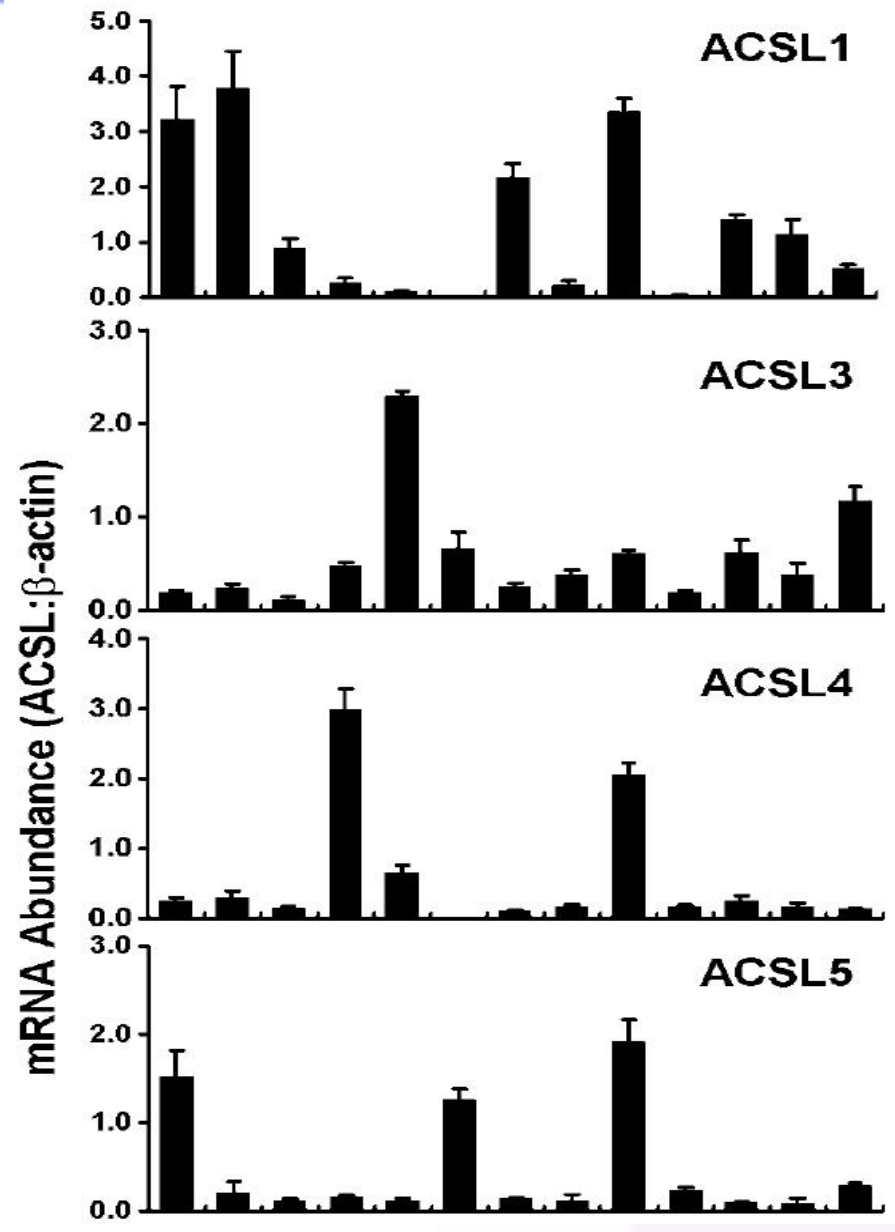
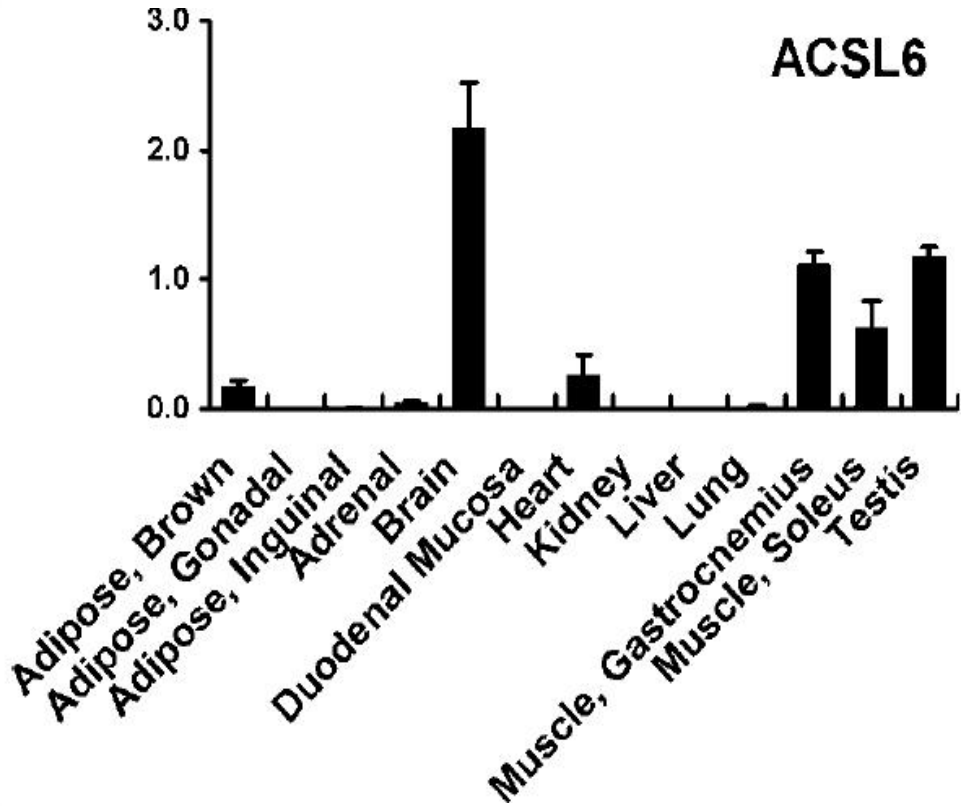


D



人ACSLs组织表达
(Lopes-Marques et al. 2013)

4. ACSLs组织分布及亚细胞定位(续)



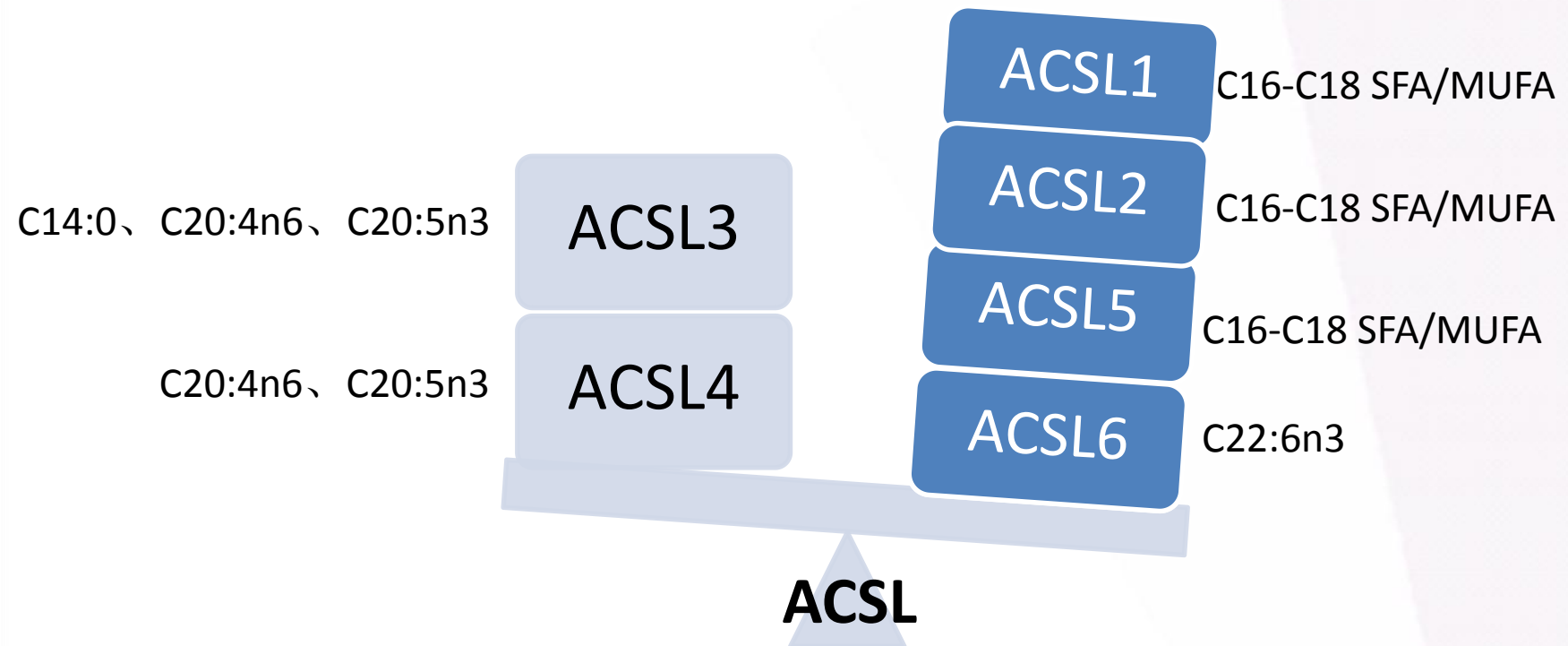
大鼠ACSLs组织表达分布
(Douglas et al. 2006, JLR)

4. ACSLs组织分布及亚细胞定位（续）

Subcellular Localization (Detection by Antibody and by MS)

ACSL Isoforms	Subcellular Localization
ACSL1	Plasma and mitochondria membrane, ER, Lipid droplet
ACSL3	Lipid droplet, ER
ACSL4	Lipid droplet, peroxisome and microsomal membranes
ACSL5	Plasma and mitochondria membrane
ACSL6	Plasma membrane

5. ACSLs 底物偏好性



ACSL分类及其底物特异性

(Lopes-Marques et al. 2013; Fujino et al. 1996; Kang et al. 1997; Marszalek et al. 2005)

Thanks for your attention