Compartmentalised28(3-hydroybutyryl-CoA,)-260.2(2-hydroyisob

acyl transfer in thermodynamically unfavourable reactions [5]. Acyl-CoA metabolites are conserved throughout biological kingdoms and across evolution [6], and thioesters are proposed as a biochemical basis for primordial metabolism [7,8]. Although the acyl-groups in acyl-CoAs are commonly derived from short-chain mono- or di-carboxylic acids, they can also include longer chain hydrophilic acyl-chains and xenobiotic compounds [9

indicating the presence of succinyl-CoA in the cytosol and nucleus [28—3]. Indeed, effective export of succinyl-CoA precursors from the mitochondria is supported by studies in SDH-deficient cells, which exhibit elevated cellular succinate and succinyl-CoA levels, asas increased succinylation inmultiple compartments, including the cytosol and nucleus [31]. Through what mechanisms is succinyl-CoA generated outside of mitochondria? A direct transport mechanism for acyl-CoAs across themitochondrialmembranes is notknown to exist, indicating that succinyl-CoA is likely generated extra-mitochondrially. A large number of the 26-memberfamily of acyl-

to form (S)-methylmalonyl-CoA catalysed by propionyl-CoA carboxylase (PCC), conversion of (S)- to (R)-methylmalonyl-CoA by methylmalonyl-CoA epimerase and subsequent conversion of (R)-

4. CROTONOYL-COA

4.1. Crotonoyl-CoA generation: metabolic pathways and compartmentalisation

Crotonoyl-CoA is of low abundance compared to other acyl-CoA spe-

could plausibly participate in the pathogenesis of such diseases. Specific regulation of butyryl-CoA metabolism in the nucleus has not yet been defined, and elucidating its nuclear abundance and regulation compared to acetyl-CoA and other acyl-CoAs will aid in understanding the role of butyryl-CoA in communicating nutritional cues to chromatin.

6. OTHER ACYL-COAS THAT MODIFY HISTONES

6.1. Malonyl-CoA

Malonyl-CoA is a three-carbon product of acetyl-CoA carboxylation by acetyl-CoA carboxylase (ACC) in the cytosol and a major substrate for fatty acid synthesis [149]. Malonyl-CoA is also an inhibitor of carnitine palmitoyltransferase 1 (CPT1). CPT1 is located on the outer mitochondrial membrane and catalyses the initial step in the mitochondrial import of long-chain fatty acids for β-oxidation. Thus, malonyl-CoA plays a critical role in preventing fatty acid synthesis and oxidation from occurring simultaneously in a futile cycle [15]. In the mitochondria, malonyl-CoA is an intermediate in the less well-recognised process of mitochondrial fatty acid synthesis [151], and mitochondrial malonyl-CoA can be generated from malonate by Acyl-CoA synthetase family member 3 (ACSF3) [152]. Decarboxylation of malonyl-CoA to acetyl-CoA by malonyl CoA decarboxylase (MCD) may also occur in the mitochondrial and cytosolic compartments [153].

Lysine malonylation occurs predominantly non-enzymatically and is removed by SIRT5 [64,67,75,154,155]. Functional studies highlight malonyl-CoA as a reactive thioester metabolite that can modify and inhibit glycolytic enzyme activity [64], although examination of hypermalonylation in isolated mitochondria from SIRT5 and MCD

onyl-CoA is16-CoAKhisgoh-304.87bl97niyn67/F4 1 Tf 456 0 T00 [(nad.)-213.7(and)-221 c2 -4/F4 9 307.3honRTinhib deletion models show543.2(my18.m(SIRT5)-537.2(and)-543.9(MT7ls)-s3unc9(MT3(.6(show57(fatty)-424.3(ac5. 9estspl4.38ryrom)-438(occurring)-4ies)-42)-3
(50Tj 24 1-i2romlonfo82 Tf 4. 0 TD (151)Tj 0 0 0 rg 1.4i7(19 TD [(].)6223(Functional)-425.82)]TJ Ch.2ghromat86deriSf 4.9101 duousd3

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