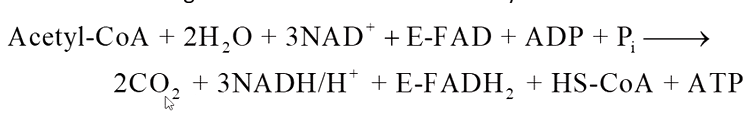
* 2 hormones that regulate glycolysis – insulin and glucagon
* Citric acid cycle and glyolalate
* Visualise CAC and why is it important
* Regulate CAC
* Glyoxalase – plants and bacteria- not human
* Pathway that generates pyruvate – glycolysis – in cytoplasm
* Today – 3 stages – coloured in different colours
* Metabolic oxidation that happens in the cell – cellular respiration – oxidises glucose for example – ATP is produced – use oxygen to oxidise glucose – that’s why cellular respiration
* Happen in mitochondria
* Stage 1 – pyruvate to acetyl-CoA – then famous CAC
* Stage 2 – CAC – it is a cycle – oxaloacetate is regenerated – aCoA has 2 C – lost one from pyruvate as CO2 – 2C in aCoA are lost in the CAC through CO2 – e- means electron – also generate ATP – reduced species such as NADH that are electron carriers
* Stage 3 – Electron carriers will go into electron transport chain – produce ATP – transfer electron pumps proton that is used by ATP synthase
* Acetyl-CoA – coming from pyruvate, amino acid, fatty acids – very central
* Pyruvate to aCoA uses enzyme called phyruvate dehydrogenase – multicomplex – 3 enzymes – E1 E2 E3
* E1 – TPP produce CO2 from pyruvate
* E2 – LD – forming acoa – free SH
* E3 – SH is reduced – form NADH
* 
* Stage 2 – CAC
  + Acoa produced by pyruvate
  + Acoa reacts with oxaloacetate
  + Acoa has 3 C
  + Oxaloacetate has 4C
  + From citrate – citrate is acid – citric acid – 6C
  + 3 – generate NADH and CO2 – lose 1C – same in 4
  + 6 – FADH becomes FADH2
  + 8 – generate another NADH
  + When 1 acoa enters CAC – 3 NADH and 1 FADH2 and 1 ATP produced – oxaloacetate is regenerated
  + Important as we can see that we start with acoa – form CO2 and generate energy in the form of reducing equivalent
  + 2C of acoa coloured differently in the image
  + 2C lost as CO2 are from oxaloacetate not acoa
  + Some reactions are very important
* Reaction 1 – catalysed by citrate synthase
  + Synthesise citrate
  + Exergonic – favourable
  + Acoa + oxaloacetate to citrate
* Reaction 2 – aconitase
  + Delta G more than 0 but quite close – equilibrium reaction
* Reaction 3 – isocitrate dehydrogenase
  + OH to carbonyl group
  + Isocitrate to alpha-ketoglutarate
  + C been oxidised
  + NAD+ is reduced – take the electron – become NADH
  + Lose first carbon as CO2
* Reaction 4 – alpha-ketoglutarate dehydrogenase complex
  + Very similar to reaction 1
  + Losing another carbon
  + 5 to 1 C
  + Oxidation – form CO2 – NAD+ become NADH
  + Exergonic – very favourable
* Reaction 5 – succinyl-CoA synthetase
  + SCoA to succinate
  + SCoA is a thioester – nest bond between CoA and succinyl group – easily hydrolysed – can couple with ADP to form ATP when hydrolyse this bond
  + Substrate level phosphorylation – phosphorylate ADP to make ATP
  + ATP is good because energy for cell
* Reaction 6 – succinate dehydrogenase
  + Up until now are in mitochondria – soluble enzymes
  + Succinate dehydrogenase – bound to inner mitochondria – membrane-bound – part of electron transport chain
  + Take succinate and transform to fumarate
  + Take FAD and reduce to FADH2
  + FADH2 will transform electron to CoQ in e- transport chain
  + Deliver enzyme directly to CoQ
  + Enzyme is inhibited by malonate – 3C but very similar to succinate
  + Malonate will bind to the enzyme so succinate cannot bind to suc dehydrogenase
* Reaction 7 – fumarase
  + Take fumarate and add water and produce malate
  + Almost equilibrium – delta G is slight negative – close to 0
  + Hydration reaction – add water
  + Not hydrolysis – hydrolysis is when we cleave water eg. trypsin – cleave enzyme to small protein or aa
* Reaction 8 – malate dehydrogenase
  + Also very important
  + From malate to oxaloacetate
  + OH becomes carbonyl – oxidised
  + NAD+ is reduced – form NADH
  + Delta G is very high – but oxaloacetate is also the substrate of the first reaction which has very low delta G so it carries this reaction
  + As soon as oxaloacetate is produced – it will react with acoa – no oxa to go back to malate
* Summary of one turn of CAC
  + For each cycle, start with acoa
  + Produce one ATP or GTP
  + Produce 3 NADH, 1 FADH2 – equivalent to 8 e- because 1 NADH and 1 FADH can each transfer 2 e-
  + The energy will go to e- transport chain and generate more ATP
  + 
  + Take pyruvate – convert to acoa – and then convert to reduced molecule like NAHD and FADH2
* Regulation of CAC
  + Green – molecules that activate the reactions
  + Red – inhibit
  + Acoa is the inhibitor of pyruvate dehydrogenase because too much products – no need to convert
  + Insulin – when we have high glucose – want to degrade or store – so use pyruvate to send to CAC
  + Allosteric activation/inhibition
* Regulation of PDH complex
  + Pyruvate dehydrogenase
  + E1 phosphorylated by kinase – inactive
  + Dephosphorylated – activated
  + Regulation by phosphorylation
* Summary
  + Regulation – don’t want to produce too much energy
  + Substrate availability, product inhibition,…
* CAC in all 3 domains of life
  + Found in bacteria, archaea, eukaryotes
  + Very ancient
  + Anaerobic – do not need oxygen – eg. use glucose oxidation – still find some enzymes like in CAC – but it is not cyclic
* Effects of defects in CAC enzymes
  + If humans have mutation in those enzymes – can be very lethal
  + The person will not have energy for basic functions
  + Some mutations associated to some enzymes in CAC – related to neurodegenerative diseases and tumors
* CAC is key to metabolism
  + Degrade molecule is catabolic pathway
  + Citrate can produce fatty acids – the intermediates can be used to synthesise other molecules – can be anabolic too
  + Amphibolic – both catabolic and anabolic
  + Pink arrow eg. pyruvate to oxaloacetate – take molecule from another pathway and synthesis intermediate of another cycle – eg. low oxaloacetate can use asparate to produce oxaloacetate – anapletrotic pathways – can put in intermediates from another reaction
  + The pathways are connected – can synthesise new molecules from the intermediates – do not stand alone
  + How cells decide if citrate should go to fatty acid or continue in CAC – depend on the need of the cell
* Other pathways use CAC intermediates
* Reactions
  + From pyruvate to oxaloacetate – glucogenesis needs this step to go from pyruvate to PEP
  + Can produce malate directly from pyruvate
  + Can produce aa through transamination – eg. take glutamate can give away amino group and form alpha-ketoglutarate
* Glyoxylate cycle – plants can do it but not humans – convert acoa into glucose via gluconeogenesis without losing C atoms
  + In plants and bacteria – not vertebrates
  + Consist of 3 enzymes of CAC – citrate synthase – aconitase – malate dehydrogenase
  + 2 new reactions – isocitratelyase – form glyoxylate and succinate from isocitrate
  + Fatty acids to acetyl-CoA and to glucose
  + Lose C in reaction 3 and 4 in CAC – plants bypass those reactions – all Cs in acoa are still present after the reaction ends
  + Seed in plants full of lipid – when plants need to germinate – need sugars for cellulose – use glyoxylate pathway
  + Happens in glyoxysomes – organelles inside plants – where the glyoxylate pathway happens – very close to lipid body and mitochondria