Pentose phosphate pathway

* ATP is not always the most pressing need. One of the needs is pentose phosphate pathway.
* Similar to glycolysis.
* Pentose 5 carbon sugar with phosphate group creation and reorganization of phosphate group.
* Why does pentose phosphate exist? Because it provides monosaccharides and reducing agents
* 2 different phases
  + Oxidative and non oxidative phase.
  + Oxidative phase creates NADPH useful for pentose phosphate
  + Non oxidative phase provides the recycle of the products of oxidative state to produce more NADPH.
* Why wouldn’t Pythagoras eat falafel?
  + Made of fava beans will lead to favism
  + Then you develop in lysed erythrocytes (rbc)
  + Membrane has been broken down content released hemoglobin released in bloodstream → kidney failure
  + More on it later
* Pentose phosphate pathway begins with Glucose-6-phosphate
  + It can be converted into glycogen or pentose phosphate
  + You need things other than ATP
    - NADPH (reduced form of NADP+)
    - Ribonucleotides
  + Oxidative starts with G6P go through oxidation end with ribose 5 phosphate
    - Each step an electron that is lost will go to NADPH pathway.
    - If we need more DNA then the cell will push it down oxidative phase
  + Non oxidative- loopty loop
    - Need reducing agents then it wants to make more NADPH.
    - R5P will be recycled back to g6p → nonoxidative phase.
    - Can loop around to make more of this reducing agent
    - Making fatty acid oxidative process need lots of NADPH to protect the cell.
* Oxidative phase of the pentose phosphate pathway

1) aldehyde of **G6P** is oxidized to a lactone at c1 oxidation reaction

* + Performed by enzyme: **G6P dehydrogenase**
  + Electron lost will be transferred to NADP to create→ NADPH

2) Hydrolysis of lactone C1 to carboxylate group to create **6 phosphogluconate**

* + Enzyme: **lactonase**
  + Once carboxylate is formed then...

3) Decarboxylation to create **ribulose 5 phosphate**

* + lose a carbon through decarboxylation, and CO2 is released
  + oxidization at the same time to create ketone group C2 position.
  + Electrons are transferred to NADP+ generate another molecule of NADPH.
  + Enzyme: **6-phosphogluconate dehydrogenase**

4) Last step take ribulose 5 phosphate convert to ribose 5 phosphate

* + Isomerization
  + Enzyme: **phosphopentose isomerase**
* Summary: 6 carbon sugar → 5 carbon sugar
  + Net gain: 2 NADPH and R5P is going to ribonucleotide synthesis.
* We can recycling pentose phosphate into glucose 6 phosphate
  + By series of carbon shuffling monosarride split and recombine to go from r5p → g6p
  + So g6p can go thru oxidative loopty loop
* Epimerization of ribulose 5 phsophate
* First step (Reverse of oxidative phase): Ribose-5p → ribulose-5p: simple isomerization aldehyde to ketone group
* Ribulose react with a molecule xylulose 5 phosphate
  + Need some xylulose
  + Epimers are 2 molecules differ at the stereocenter at one
  + R5p and x5p: Differ at C3
  + Change the stereochemistry using enzyme: **ribose S-phosphate epimerase**
  + And then we react them together...
* Transketolase uses TPP as a cofactor.
  + 1st reaction of non oxidative pathway
    - Take the (2) 5 carbon sugar (r5p and x5p)and react to create a 3 carbon and 7 carbon sugar
    - Removes a 2 carbon chain of of xy and put it on ribose 5p
      * Therefore, cleavage of carbon carbon bond.
    - Ketone group transfer it to a different sugar enzyme using enzyme **transketolase**
    - Cofactor **TPP**: (same as fermentation)
      * Reacting group C at thiazolium ring is good at stabilizing carbanion.
        + Ya know delocalization
      * If you are breaking c-c bond you need to stabilize unfavorable carbanion generated
      * Transfer this group of 2 C’s to tpp cofactor → forms a covalent bond and have resonance, now free energy decrease→ more likely for reaction to happen.
    - End products: glyceraldehyde 3-phosphate + sedoheptulose 7-phosphate (3+7)
* Transaldolase forms a schiff base to stabilize carbanion.
  + 3+7 fragment cut 3 carbon from 7 carbon sugar to the 3 carbon
  + Catalyzed by enzyme: **transaldolase**- breaks aldol sugars breaking into 2 pieces and transferring one piece to the other sugar.
  + Transaldolase requires C-C breakage→ carbanion ya know it.
  + To stabilize the carbanion, reacts with lysine (positive charged amine) will react with 3 carbons segment to produce a schiff base.
    - Stable bc electrons can be delocalized
  + End produce: Make 4 and 6 carbon (erythrose 4 phosphate and **fructose 6 phosphate**) first f6p
    - 6 carbon is done-zo
    - 4 carbon (you can’t just throw this away) make use to make some more 6 carbon
* Transketolase performs more than one reaction
* Now you have this 4 carbon thingy and you react it with another 5 xy to produce more 6 carbons. So 4 carbon + 5 carbon → 3 carbon + 6 carbon.
  + Leftover from other reactions and transketolase is performed again
  + End products: 3C (Glyceraldehyde 3-phosphate) and 6C so another **f6p** is done.
  + Same mechanism using tpp
    - Doesn’t matter if it is 4 or 5 carbon just need right reacting group
* Gluconeogeneic reactions completes the cycle
  + The g3p can be fed into the gluconeogenic pathway you will get fructose 6p
    - Mecanism recap:
    - Gly-3p → dihydroxyacetone phosphate using **triose phosphate isomerase**
    - Together (g3p+dp) will produce fructose 1,6 bisphosphate using **aldolase**
    - F1,6bp will be turned into f6p via f1,6bphatase
  + Final product take r5p can converted into 3 F6P→ will feed into last steps in gluconeogenesis and get into glucose 6 phosphate using **phosphohexose isomerase**
* Both steps are intertwined.
* Glucose 6 phosphate→ oxidative phase→ get more nadph
* Glucose 6-phosphate is partitioned between glycolysis and pentose phosphate
  + Glucose in the bloodstream can go multiple directions.
  + They are not some separate. All pathways are sharing intermediate.
  + Some control that turn on one pathway over the other bc of the needs of the cell.
    - Regulated by NADPH when there is enough it allosterically inhibit the pentose phosphate pathway. Then it is feed into glycolysis to make some ATPs.
* Why wouldn’t Pythagoras eat falafel
  + Glucose 6 phosphate dehydrogenase deficiency prevents 1st reaction of oxidative pentose → not able to perform phosphate pathway→ alter the ability to produce NADPH → favism
* Why not?
  + Because fava bean contains divicine and it will react with oxygen → produce oxide radical → converted to H2O2 (oxidizing agent)
* Conc of H2O2is increased
  + Negative results to rbc
* How to resolve?
  + Many can neutralize h2o2 using glutathione (reducing agent) to react with h2o2 into h2o
    - Present in rbc
* Ability of rbc to deal with h2o2 is depends on glutathione
  + GSH→ GSSG you can to recycle the oxidation state
  + Nadph is needed to recycle glutathione. If you have deficiency you can't perform nadph as efficiency not enough to regenerate glutathione not enough to neutralize h2o2.
  + Build up of h2o2 oxidative damage of rbc release their stuff to bloodstream.
  + NADPH is really important because it balances the oxidative species in blood cells.

Glycogen Metabolism

* Under starving ATP→ gluconeogenesis
* Slow pathway, you need to turn on the transcription factor for them to be activated
* When blood glucose level is low, there is storage of glycogen extra glucose.
* Physical activity haven’t eat
* Glycogen metabolism
* Glycogen can be synthesis and broken down.
* Highly regulated pathways both allosterically and hormonally.
* Repeating glucose residues and glucagon highly branch.
* Storage form of
* 10% of the weight of liver
* Source of glucose readily available in a limited period of time.
* Glycogen granules form beta particles.
* Will deplete if you don’t eat
* Excess glucose→ glycogenesis
* Lack → glycogenolysis
* Glycogenolysis begins with glycogen phosphorylase activity
* Key enzyme: glycogen phosphorylase
* Made up of alpha 1→ 4 along linear chain branch point alpha 1→ 6 linkage.
* At one end non reducing end.
* Extremities of all are formed at nonreducing ends.
  + Outside are all nonreducing.
* Glycogen phosphorylase recognizes the glycogen polymer and it remove a single glucose residue from NE one at the time. It converts into glucose 1 phosphate.
* GP chew back the glucagen polysaccharide liberated form of glucose 1-phosphate
* Inorganic phosphate attack glycosidic bond 1→ 4 break and leaves phosphate and glucose residue at 1. Polysaccharide one shorter.
  + Slowly chew back.
* **Glycogen phosphorylase**- Important only chew back along linear chain when in branched point it stops. **4 residues** of branch point. Stops.
* Glycogen phosphorylase is highly regulated (Skeletal muscle cell)
* Isozyme: Different protein catalyzing the same protein.
  + Skeletal Muscle cells: pp dimeric first phosphorylase to be discovered.
  + Exist in A (active) and B (inactive)
  + Same enzyme: only modification
  + Active capable to break glycosidic bonds and b no
  + Switch is the phosphorylation of serine chains (they are present in the surface of the enzyme)
  + They are two serines so you need 2 ATPs for pp to be active.
  + Kinase and phosphatase balance the concentration of both things.
  + Adrenaline upregulates phosphorylates pp1 converts it to active form so you can chop more glucose.
  + Both PBK and PP1 is regulated by hormonal control.
* Glycogen phosphorylase is highly regulated: liver cells.
  + Additional regulatory sites.
  + Similar structure same serine. Now additional allosteric sites.
  + Same serine to be phosphorylated
  + Different allosteric site.
* Serine is first case is active
  + Serine is phosp active breaking the bonds and everything
  + but phosphate group are hidden
* Logic: If glucose levels are high they can bind to the allosteric site in glucose phosphorylase and binding causes a conformational change→ reorganize position of phospho serine and make it more accessible for pp1 to remove the phosphoryl group.
* Glycogen p activity is high→ liberating glucose
  + You don’t want it to deplete so as glucose increases it is a negative feedback loop to stop the gp activity.
* Glycogen branches are cleared by **debranching enzyme**
* Second enzyme that comes along to debranching.
* 2 activities: branch transfer and glucosidase (glucose removal)
  + Lots of glucose is liberated and debranching is removing 3 closest to branch point
  + Transfer them to the end of the nearest polysaccharide chain.
  + Left with single polysaccharide chain.
  + 2nd activity Then it removes the glucose at the branch point (1,6) yielding a molecule of glucose. To participate in glycolysis.
* **Phosphoglucomutase** converts G1-P→ G6P
  + G1p is the end product of the glycogenolysis
  + You want g6p for glycolysis
  + Enzyme: phosphoglucomutase
    - Change position that is present in sugar
    - Bind a mole of g1p and perform a switch take phosphate in 1 to 6
    - First handed to the sugar and
    - Serine sidechain is phosphorylated and will donate it to c6 g16bp
    - Available hydroxyl of serine react with C1 and remove the phosphate and regenerate the serine phosphatase. C1 gets a becomes a hydroxyl.
  + G6p will enter ER and encounter g6pase feeds into the final step of gluconeogenesis generate glucose large pool of glucose. Then it will be available to all your tissue.
* Glycogen synthesis requires sugar nucleotide.
* **Sugar nucleotide-** monosaccharide covalent bound to nucleotide group.
* Important for
  + Why?
  + Formation has large negative negative G to make pathway irreversible
    - Once we started it it will continue
  + Handle for enzyme to bind to for downstream enzyme.
  + UMP (nucleotidyl group) is good LG
  + Can tag a glucose to be available for glycogen synthesis and not glycolysis.
* Conversion of glucose to glucose 1-phosphate
  + Reverse last steps: take glucose+ATP→ glucose 6 phosphate using hexokinase
  + **G6p ⇌ glucose 1-phosphate using phosphoglucomutase**
* Formation of UDP-glucose (mechanism)
* Take g1p and react with nucleotide uridine triphosphate
  + Negative charge of phosphate will bind to the positive charge of the alpha phosphate of utp
  + Yield **sugar nucleotide (ntp sugar)** leave a product of pyrophosphate
  + Broken down 2 inorganic phosphate.
* It is the breakdown of 2 inorganic phosphate → Big burst of energy bc of the resonance.
* Take udp glucose transfer it to glycogen chain.
* Just like breakdown you take polysaccharide chain and grow slowly.
* React UDP-glucose with the nonreducing end on a linear section of the polysaccharide
* Enzyme: Glycogen synthase → add glucose to non-reducing ends.
  + Formation of glycosidic bond. Extend it by 1 residue.
* Extremity always has a nonreducing end. Outside surface all nonreducing end
  + all available for glycogen phosphorylase when we want to perform breakdown of glycogen storage.
* Glycogen synthase only add residue of a polysaccharide chain when there is at least 4 residues of a branch point.
* Glycogen synthase is highly regulated
  + Regulated allosterically and hormonally.
  + Glycogen synthase is present in 2 forms A (active) B (inactive)
    - Is determined by the phosphorylation state of enzyme
  + Direction of switch is reversed.
    - Phosphorylation of serine takes it from active→ inactive form
  + Has multiple serine sidechain at the C terminus of enzyme
  + All phosphorylated when converted from active to inactive B
  + Phosphorylation performed primarily by GSK3 take active → inactive under control of insulin
    - Requires prior phosphorylation by CK2 comes along phosphoryl glycogen synthesis and GSK can phosphorylate the serine sidechain
  + Dephosphorylation (inactive to active) performed by phosphorylase a phosphatase (PP1)
    - Same enzyme doing same different consequence
    - Turn on glycogen synthesis then turn off glycogen breakdown
    - Same enzyme do same time→ control so one is turned on and the other is turned off.
* Glycogen synthase must be primed for GSK3 activity
  + The serine residue downstream 4 away (+4)
  + CK2 add a phosphate group to this serine.
* GSK3 binding site lined with positive side chains so it can bind bind to negative phosphate holds gsk in place.
  + One the phosphate group is in place in the pocket, it is able to catalyze phosphorylation in the 0 position (active site)
  + Once we phosphates the 0 phosphate group fill in binding site.
  + Skip over fill it in the -4 position.
* Branches are formed by glycogen→ branching enzyme.
  + Glycogen synthase that adds it one at the time incapable of forming the branches
  + Another enzyme that performs this
  + **Glycogen branching enzyme** cleaves glycosidic bonds picks up 11 residues breaks it on adds it glucose 1,6 branches. Every 11 or so cut of piece creates a branch. Two reducing ends so glycogen. **Increase branching increasing soluble**. Additional non reducing more for glycogen synthase to work on more efficient process.
* **Glycogenin** primes the initial sugar residues in glycogen.
  + Acts as the seed C glycogenin emerge. Dimeric and bind of UDP glucose.
  + 2 Tyrosine residues. Reacts with anomeric carbon from molecule UDP-glucose form a covalent bond.
* First part of glycogen synthase→ formation of covalent tyrosine and UDP glucose Linkage of first glucose to the end of tyrosine sidechain.
  + Then it catalyze a 2nd addition up until 6 different glucose added to tyrosine sidechain long enough for glycogen synthase comes in
  + until chain is long enough for it to add UDP s
* Glycogenin remains attached to the first glycogen (primer).
  + Center of each there is a glycogenin