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 CO_2 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