Editing File

10

Major metabolic pathway of glucose

Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Foundation Block - Biochemistry Team

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MED439

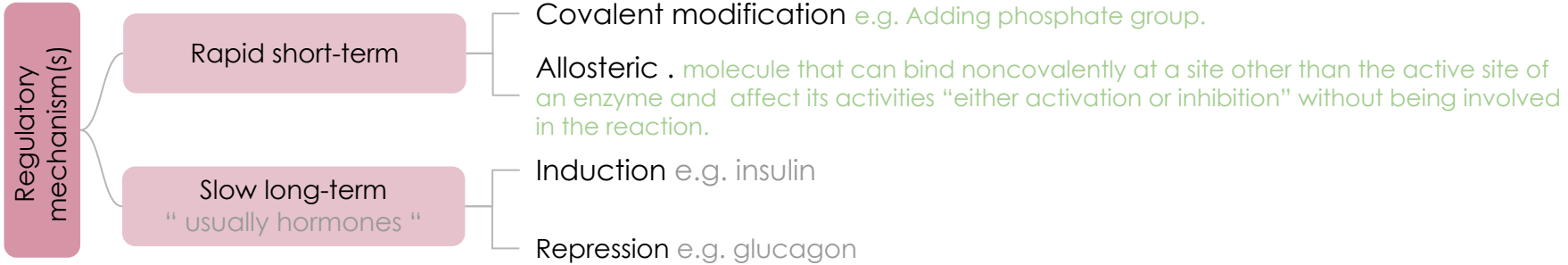
Objectives:

- Define a metabolic pathway.
- Describe the general metabolic pathways for glucose (production and utilization).
- Briefly describe the HMP.
- Recognize the mechanisms of glucose transport.

★ This slide is not that important

Metabolic pathway

- **Definition :** a sequence or a cascade of chemical reactions which results in a product that will be a substrate for other reaction. " Usually 1 to 2 pathways " .
  - Pathway : Series of chemical reactions that have one goal.



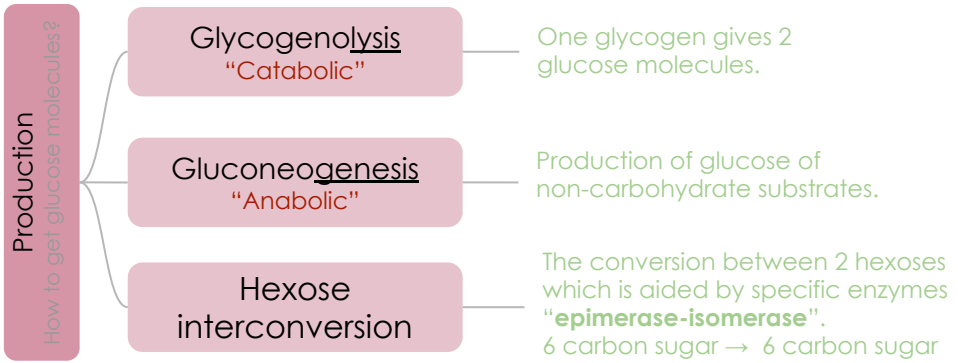
- **Site** :
  1. Cellular (Tissue): signaling between cells .
  2. Subcellular : reactions inside the cell .

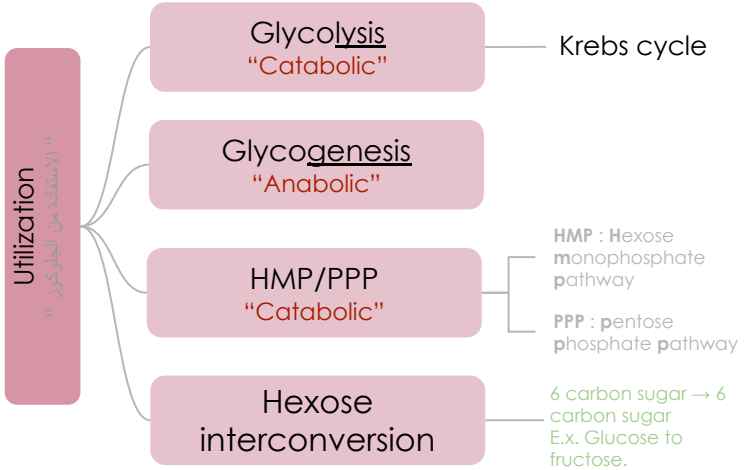
- **Reactions** : Substrate+Substrate = Product.

- Rate-limiting enzymes " Enzymes can slow down the reaction or activate them and They are found only in irreversible pathways "

Metabolic pathway of glucose " Production and Utilization "

- For a better understanding :
- Perfix :
  1. Glyco = glucose "Glycolysis".
  2. Glycogeno = Glycogen " except in synthesis of glycogen we say Glycogenesis instead of saying glycogeno-genesis
     " To differentiate : the synthesis of glucose is gluco**neo**genesis .
- Suffix :
  1. Genesis = process of producing " synthesis " .
  2. Lysis = breaking down .





Metabolic pathway of glucose "Catabolic and Anabolic"

Catabolic cycles	Anabolic cycles
• Glycolysis. (Mainly) • Krebs cycle. (Mainly) • Glycogenolysis. • HMP.	• Gluconeogenesis. • Glycogenesis.

Glycolysis

- Oxidation (breakdown) of glucose to provide energy.

	Anaerobic glycolysis "Anaerobic = without oxygen"	Aerobic glycolysis "Aerobic = with oxygen"
Occurs when ?	In absence of oxygen and in cells that lack mitochondria	In adequate supply of oxygen and in cells with mitochondria
End product	The end product is lactate	The end product is Pyruvate

Glycogenesis and Glycogenolysis

	Glycogenesis	Glycogenolysis
Definition	Synthesis of glycogen from glucose .	Degradation (breakdown) of glycogen into glucose .
Occurs when ?	Occurs when glucose and ATP are present in relatively high amounts . (This process is: storage). يعني اذا زاد الـ glucose في الجسم وكانت الطاقة موجودة " ATP " يتم تخزين الـ glucose على شكل glycogen عشان يحرقه ويستخدمه بعدين . "More details in MSK block"	Occurs in response to hormonal and neural signals. اذا احتاج الجسم راح يرسل اشارات " هرمونات " لتكسير الـ glycogen وتحويله لـ glucose .
Location	Mainly liver, muscles, and cytosol	

Gluconeogenesis

- Synthesis of glucose from non-carbohydrate precursors .
- Precursor : is a chemical that is transformed into another compound.
- The precursors could be lactate (anaerobic), pyruvate (aerobic), glycerol and alpha-keto acids.
  - Glycerol: is a part of the triacylglycerol molecule which is the main constituent of body fat.
  - Keto acids: are organic compounds that contain a carboxylic acid group and a ketone group. The alpha-keto acids are especially important in biology as they are involved in the Krebs citric acid cycle and in glycolysis.
- It requires mitochondria and cytosolic enzymes " cytosolic enzymes = present in cytosol " .
- Occurs in Liver (mainly) and kidney.

Hexose monophosphate pathway shunt (HMP) / Pentose phosphate pathway (PPP)

- HMP shunt is an alternative (another) pathway of glucose oxidation " The major pathway is glycolysis " .
- Oxidation of glucose, also known as glycolysis, is the process which releases energy stored in glucose by combining it with oxygen.
- It has the same regulatory mechanism(s) as glucose (rapid short-term and slow long-term).
- it is not involved in the generation of energy unlike glycolysis .
- Around 10% of glucose (that all the body makes) is entered in this pathway.
- In liver and kidney → this percentage is up to 30% .
- Occurs in many places such as the cytosol of the liver, adipose tissue (to produce fatty acids from glucose).

- **Biomedical importance " it has two main functions "** :

1 Provide NADPH which is required for :
   - Synthesis of fatty acid, steroids, and amino acids.
   - Detoxification of drugs, cytochrome P450. Cytochrome P450: enzymes also function to metabolize potentially toxic compounds, including drugs and products of endogenous metabolism such as bilirubin.

2 Provide pentoses " The most important pentose is ribose " :
   - Pentose and its derivatives are useful in the synthesis of:
     1. Nucleic acids (DNA and RNA).
     2. Nucleotides (ATP, NAD, FAD, CoA).

1. NADH : in the electron transport chain as energy molecule .
2. NADPH : cofactor in the glutathione system

Tissue distribution

Location of HMP in the Cytosol of the following locations:

01 Liver.

02 Lactating mammary gland.

03 Adrenal cortex.
- The adrenal cortex: the outer part of the adrenal gland.

04 Gonads.
- Gonads: an organ that produces gametes; a testis or ovary.

05 Adipose tissue.

06 Erythrocytes to reduce glutathione.
- Glutathione: antioxidant capable of preventing damage caused by reactive oxygen species. (Free Radicals)

07 Lens and cornea.
- Cornea: the transparent layer forming the front of the eye.

Phases of HMP shunt

It has two phases:

1 Oxidative phase.
- Produce NADPH and it's irreversible.

2 Non-oxidative phase.
- Produce pentose and it's reversible .

$$\text{Glucose} + NAD^{+} \xrightarrow{\text{Oxygenation}} NADPH$$

original pic

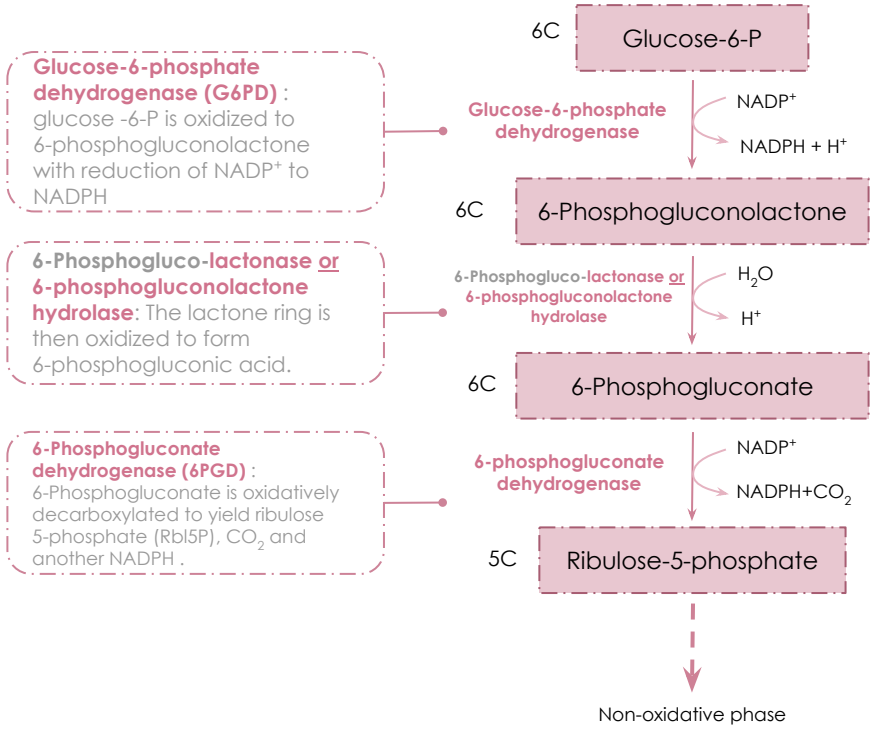
Phase 1:Oxidative phase " Irreversible"

A helpful video

1. We start with glucose-6-phosphate which will be oxidized " loss of electron " to 6-Phosphogluconolactone with the help of **Glucose-6-phosphate dehydrogenase (G6PD)** enzyme and the electron that being lost will be added to $NADP^+$ to produce NADPH .

2. Now we have 6-Phosphogluconolactone and it has a ring structure so we have to open this ring by hydrolysis reaction that catalyzed by **lactonase** enzyme or you can say 6-phosphogluconolactone **hydrolase** that will produce 6-Phosphogluconate and we release H^+ .

3. We have 6-Phosphogluconate which doesn't have a ring structure and ready to undergo decarboxylation and oxidation reaction that catalyzed by **6-phosphogluconate dehydrogenase** enzyme which means we will remove a carbon and oxidize it " loss of electron " to Ribulose-5-phosphate which will release CO_2 and add an elctron to $NADP^+$ to produce NADPH .



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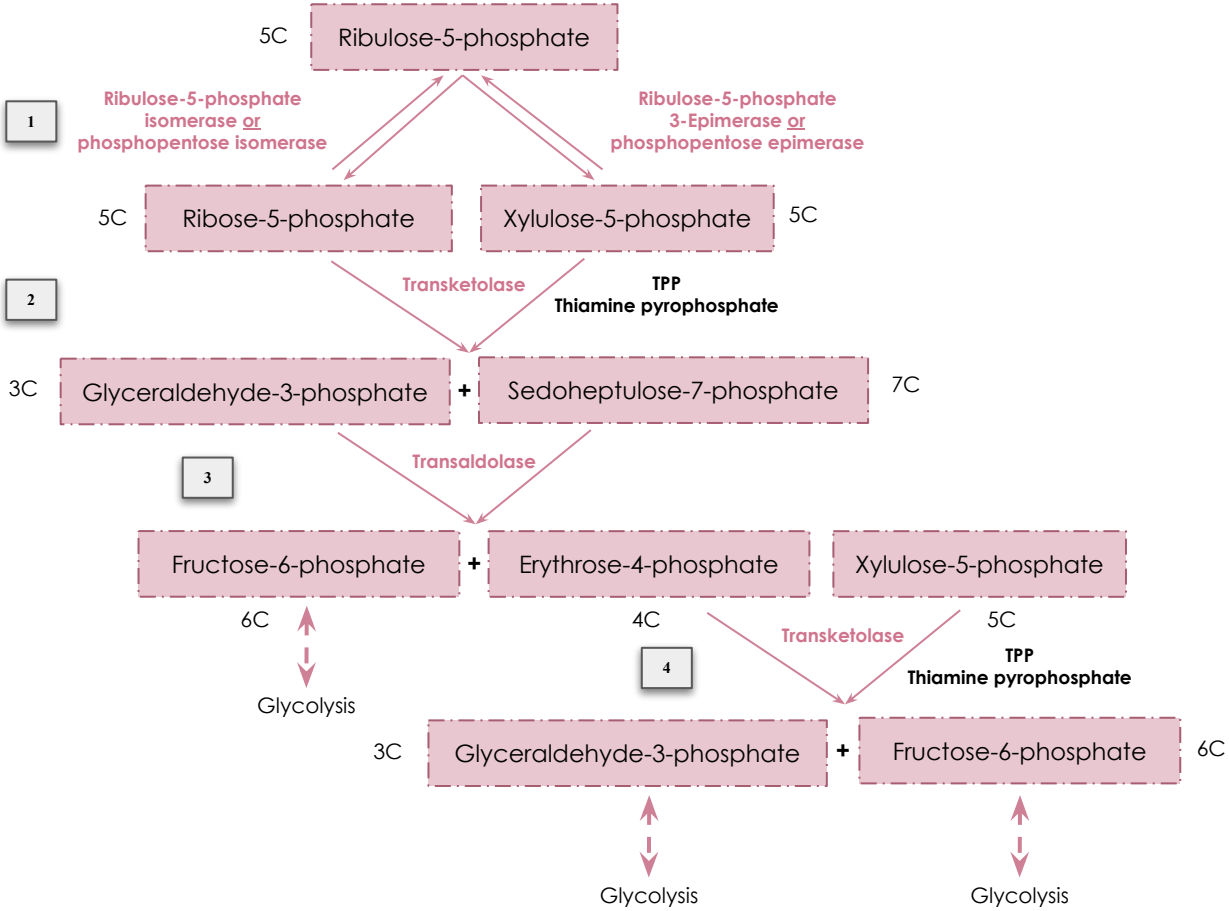
Phase 2: Non-oxidative phase "Reversible"



A helpful video

Phase 2: Non-oxidative phase "Reversible"

★ Extra explanation

1. We will take Ribulose-5-phosphate and convert it to Ribose-5-phosphate by Ribulose-5-phosphate isomerase or you can say **phosphopentose isomerase** " نسوي هالخطوة مرتين عشان يصير الناتج اثنين مو واحد " and also we will reverse the reaction from 2 Ribose-5-phosphate to 2 Ribulose-5-phosphate by Ribulose-5-phosphate isomerase or **phosphopentose isomerase** فهمتوا لفة جحا ؟ كل ذا عشان نوصل لناتج اخر

   Now we have 2 Ribulose-5-phosphate will be converted to 2 Xylulose-5-phosphate by Ribulose-5-phosphate 3-Epimerase or you can say **phosphopentose epimerase** .

   يعني بكل بساطة راح نستخدم الـ Ribulose-5-phosphate ونحوله لـ Ribose-5-phosphate واعيد الرياكشن مره ثانيه عشان يصير عندي الناتج اثنين من الـ Ribose-5-phosphate حلو ؟ الحين راح نعكس الرياكشن عشان نوصل لناتج اخر فراح نعكسه ويكوّن عندنا اثنين من الـ Ribulose-5-phosphat وهالناتج راح يكون مُتفاعل لتفاعل ثاني وراح نحوّله ويعطينا اثنين من Xylulose-5-phosphate ليش كل هاللفة ؟ لان بالكميستري الـ Ribulose اقرب كشكل ويتحول بسرعه لـ Xylulose وليش عندنا الحين اثنين من الـ Xylulose ؟ لان واحد بنستعمله الحين وواحد بنستعمله بعدين فالفكره نبي نكوّن اثنين من الـ Xylulose يفيدونا بالتفاعل

2. **Transketolation:** Now we will take Xylulose-5-phosphate and another Ribose-5-phosphate with the help of **Transketolase** enzyme .

   يعني اخذنا واحد من الـ Xylulose-5-phosphate اللي طلع عندنا من الخطوة اللي راحت ونجيب Ribose-5-phosphate جديده من رياكشن الـ oxidative phase اللي مافهم يشوف الفيديو .

   Transketolase enzyme requires a cofactor which is Thiamine pyrophosphate (TPP) to be activated, now this enzyme will take 2 carbons from Xylulose-5-phosphate and put them on Ribose-5-phosphate to form Sedoheptulose-7-phosphate and the rest 3 carbons from Xylulose-5-phosphate will form Glyceraldehyde-3-phosphate .

3. **Transaldolation:** Here we will take Glyceraldehyde-3-phosphate and Sedoheptulose-7-phosphate with the help of **Transaldolase** enzyme, now this enzyme will take 3 carbons from Sedoheptulose-7-phosphate and put them on one carbon from Glyceraldehyde-3-phosphate to form Erythrose-4-phosphate and also it will take the rest 4 carbons from Sedoheptulose-7-phosphate and put them on the rest 2 carbons from Glyceraldehyde-3-phosphate to form Fructose-6-phosphate .

4. Remember Xylulose-5-phosphate in step 1 ? We used one of them in the previous reaction and the other one we will use it here so **Transketolation:** we will take Xylulose-5-phosphate and Erythrose-4-phosphate with the help of **Transketolase** enzyme requires a cofactor which is Thiamine pyrophosphate (TPP) to be activated,Now this enzyme will take 2 carbons from Xylulose-5-phosphate and put them on Erythrose-4-phosphate to form Fructose-6-phosphate and the 3 carbons from Xylulose-5-phosphate will form Glyceraldehyde-3-phosphate " both Glyceraldehyde and fructose are intermediates of glycolysis ".

To summarize

HMP shunt		
Phases	Oxidative $NADP^+ \rightarrow NADPH$ 1 glucose → 2 NADPH	Non-Oxidative
Mains outcomes	1. NADPH 2. Ribose (for DNA , NAD^+ ..etc)	
Main enzymes	1. Glucose-6-phosphate **dehydrogenase**. 2. 6-Phosphogluco-**lactonase** or 6-phosphogluconolactone **hydrolase.** 3. 6-phosphogluconate **dehydrogenase**.	1. Ribulose-5-phosphate **isomerase** or phosphopentose **isomerase** . 2. Ribulose-5-phosphate 3-**Epimerase** or phosphopentose **epimerase** . 3. **Transketolase** " Transfers 2 carbons " . 4. **Transaldolase** " transfers 3 carbons " .

Clinical correlation
“ G6PD deficiency “

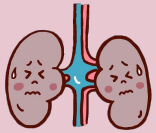
- Deficiency in **Glucose-6-phosphate dehydrogenase** enzyme results in :
  - The condition is characterized by abnormally low levels of glucose-6- phosphate dehydrogenase, an enzyme involved in the pentose phosphate pathway that is especially important in the red blood cell. G6PD deficiency is the most common human enzyme defect.

1

Neonatal jaundice

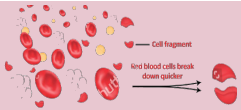
Neonatal : relating to newborn children

2



Kidney failure

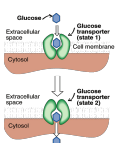
3



Hemolytic anemia

Hemolytic anemia: relating to or involving the rupture or destruction of red blood cells.

Glucoses transport

	Na+ Monosaccharide Co-transporter	Na+ - Independent Facilitated diffusion
About	Glucose is hydrophobic molecule that's why it cannot pass easily inside the cell so it needs another way to go inside the cell either by Co-transporter which will take Na+ and glucose together to go inside the cell or by Facilitated diffusion which mean it has a specific carrier to it as you see in the right pic 	
Movement of glucose	Against concentration gradient " From low concentration to high concentration "	Down the concentration gradient " From high concentration to low concentration "
Energy need	Energy dependent "requires energy"	Energy Independent "doesn't require energy"
-	It's Carrier-mediated and Coupled to Na+ transport	Glucose Transporters (GLUT 1-14)
Location	-	Small intestine, renal tubules and choroid plexus

"Na+ - Independent Facilitated diffusion "Glucose transporters"

BBB kids lips are pink mother father " mnemonic "
بالنسبة لـ function نحفظ المتشابه عشان تسهل علينا

	Transporter	Location	Function
BBB	GLUT-1	**B**lood (RBCs), **B**rain and (**b**aby = fetus)	Glucose uptake from blood
Kids **L**ips	GLUT-2 (Gluconeogenesis for maintain Homeostasis)	**L**iver , **K**idney and **P**ancreas	Blood and cells (either direction)
Pink	GLUT-3	**N**eurons , **P**lacenta and **k**idney	Glucose uptake from blood
Mother **F**ather	GLUT-4 (Insulin dependent)	Adipose tissues (**F**at) and skeletal **m**uscles	Glucose uptake from blood
	GLUT-5	Small intestine and testes	Fructose transport
	GLUT-7	Liver (ER – membrane)	-

Take home messages

- There are multiple pathways for glucose that can be grouped in to catabolic (utilizing glucose) or anabolic (producing glucose).
- Glycolysis is the major metabolic pathway of glucose breakdown to provide energy .
- Alternative pathway for glucose oxidation but not meant for producing energy .
- Has two phases- oxidative and non-oxidative .
- During oxidative phase, glucose-6-P is oxidized with generation of 2 moles of NADPH, and one mole of pentose phosphate, with liberation of CO_2.
- During non-oxidative phase, pentose phosphate is converted to intermediates of glycolysis .

For extra MCQs and SAQs, Click Here

Quiz

Q1 : The metabolic pathway of HMP shunt is :			
A) Catabolic	B) Glycogenesis	C) Gluconeogenesis	D) Anabolic
Q2 : The end product of aerobic glycolysis is :			
A) Glycerol	B) Glucose-6-phosphate	C) Pyruvate	D) Lactate
Q3 : The conversion of ribulose-5-phosphate into ribose-5-phosphate is aided by :			
A) Ribose-5-phosphate dehydrogenase	B) Glucose-6-phosphate dehydrogenase	C) Transketolose	D) Isomerase
Q4 : The end product of the oxidative phase of HMP pathway is :			
A) Glyceraldehyde-3-phosphate	B) Ribulose-5-phosphate	C) Xylulose-5-phosphate	D) Glucose
Q5 : GLUT-2 is found in:			
A) RBCs	B) liver	C) Neurons	D) Adipose tissues
Q6 : Which of the following enzymes is found in the oxidative phase ?			
A) G6PD	B) Isomerase	C) Epimerase	D) Transketolose

SAQs :

Q1: enumerate which molecule responsible for Fructose transportation and in what organ is it located ? ?

Q2: What is the final product of the oxidative phase of HMP shunt ?

★ **MCQs Answer key:**

1) A 2) C 3) D 4) B 5) B 6) A

★ **SAQs Answer key:**

1) GULT-5 & it's in small intestine and testes
2) Ribulose-5-phosphate

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Shaden Alobaid
Noura Alsalem
Lama Alahmadi
Sadem Alhazmi
Somow Abdulrahman
Budoor Almubarak
Samar Almohammedi
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Abdullaziz alomar
Abdulaziz alrabiah
Saud alrasheed
Abdullah almazro
Hamad almousa
Ahmad alkhayat

We can either walk towards Growth, or stand in Safety.

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