rahaf romei <3

RBC metabolism

components: in → 35% solids, hemoglobin

mb ال يعني out → proteins + lipids + oligo. sac

⊗ mitochondria → ⊗ ATP by ox. ph. → aneorobic glycolysis instead

↳ produces LESS ATP than aer.

⊗ nucleus → ⊗ DNA / RNA syn.

⊗ replace damaged lip/prot →

whats the primary function of RBC?

gas exchange, a box to carry O_2 & metabolic functions

- ATP
- NADPH
- NADH

for:
1. osmotic balance
2. electroneutrality
3. fighting ox. stress

2 imp shunts

① rapoport shunt

by diphosphoglycerate → 2,3-bis

② pentose phosphate shunt

! redox, 2 moles of NADPH

What type of energy production happens in Erythrocytes?
Anaerobic (WHY?) Because there is no mitochondria in Erythrocytes so there is no ETC, no TCA, no Ketolysis etc. (since those pathways need oxygen)

- Zn++
is a co-factor for at least 10 enzymes very active in erythrocytes including the most important 3 enzymes which are:
Carbonic Anhydrase (CA) — acid- base balance
Copper/Zinc (Cu/Zn) Superoxide Dismutase (SOD)
Lactate Dehydrogenase (LDH) — energy production

- Mg++ is a co-factor for Kinases in the Glycolytic pathway (Phosphoglycerate Kinase, Pyruvate Kinase). Those 2 enzymes are what produce energy in erythrocytes under Substrate Level Phosphorylation. ATP

- K+ maintains the volume of Erythrocytes so it keeps them in shape. Therefore, high concentration of K+ intracellularly and Na+ outside will change the shape of erythrocytes from Biconcave to Spherical form (Spherocytes) which cannot pass through the blood capillaries.

imp!

Glucose enter erythrocyte by GLUT1 (insulin independent) into the glycolytic pathway by 2 reactions (Phosphoglycerate Kinase, Pyruvate Kinase) so each one makes 2 ATP (total 4 ATP), 2 moles will be removed by activation reactions catalyzed by Hexokinase and PhosphoFructoKinase 1 (at the end, total 2 ATP) and it result at the end to make Lactic Acid and Pyruvate. (Zn++ plays a role in this pathway since it's a cofactor for Lactate Dehydrogenase) then lactate passing outside to the liver by Cori cycle (liver convert lactate coming from organs like erythrocytes and skeletal muscles which have anaerobic glycolysis to glucose) then the cycle continues.

so it doesn't accumilate — since ⊗ mitochondria

Pyruvate is converted to lactate which needs NADH (NADH comes from glyceraldehyde-3-phosphate dehydrogenase 6 (, but pyruvate have much more molecules than NADH (WHY?) cause some NADH will react with methemoglobin reductase (when hemoglobin is converted to methemoglobin, it will be reduced to hemoglobin using NADH)

↳ NADH converts meth → Hgb

↑ problematic

free radicals exposure:

Hgb autooxidize → $O_2^{\cdot -}$ → ROS يعني

↓

toxic change to structure of cyto. → RBC becomes fragile

↓

catalytic ions leakage

[! tiny capillaries >] [G6DP deficiency]

energy requirments for:

Q. energy from newly produced adenine ? NO

↳ 1) salvage pathway

2) protect against ox. stress by pentose phosphate pathway NADPH

3) maintain ↑ K^+_i ↓ Na^+ & Ca^{++} → if opposite? concave → spherical

4) prevent met. Hgb accumilation ferric بدل ferrous

5) modulate oxy. Hgb 2,3- bis

6) keep sulfhydryl groups, Hb, mbs in ! active reduced form oxidized form → precipitation = RBC break

2,3 - bisphosphate ?

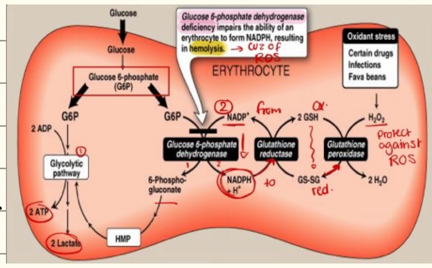
-ve allosteric of O_2 affinity to Hgb = ↑ O_2 release

[O_2 affinity in Hgb alone >> than whole RBC]

↑ ⊗ 2,3- bis

! HbF Less sensitive than HbA to 2,3-bis.

glutathione? [catalase & glutathione peroxidase] → against ROS



→ خلاصة الفكرة

membrane proteins [very imp for shape] → defect ? =

- spectrin: α, β — head to head tetramer
- ankyrin: w/ spectrin → attaches spectrin to mb.
- band 3: w/ ankyrin + spectrin → anion exchange → Cl^- for HCO_3^- [acid- base balance]
- actin: w/ spectrin + protein 4.1
- glycophorins: w/ integral proteins — اي هم ال gly. p

⬭ → heridetary spherocytosis

⬯ → elliptocytosis

glycosylated $HgbA_{1c}$

↑ glucose stick to Hgb w/o enzymes

ex? :

uncontrolled DM > 6.5

normal value 5%

L1

deficiencies:

1) G6DP [X - linked]

- non- immune mediated
- bean (fava)
- ↑ ROS production why? ⊗ NADPH to fight ROS → H_2O_2 accumilation

G6DP ⊗ = ⊗ ↓ pyr, ⊗ → PPP

- severe w/ chronic hemolytic anemia
- severe w/ intermittent H. AN
- mild def hem. w/ stress only
- non. def ⊗ clinical features
- ↑ enzymatic activity

in: young, africa (egypt), w/ Jaundice] case Q.

most → assymptomatic

يس مرض X-linked بيصيب بالرجال والنساء بتكون carrier

طيب في إستثناء؟ ✓

F, w/ unfavorable lyonization → random X inactivation

if BOTH X → F as sensitive as M

treatment?

- acute → blood transfusion
- splenoectomy
- folic acid
- anti- ox → vit E / selenium

tests show:

- ! heinz body
- ↑ lactate deny.
- liver enzymes
- coomb's -ve

2) pyruvate kinase

[Chronic hemolytic anemia]

⊗! → ✓

⊗ pyr = ↑ 2,3- bis "compensation"

most mutations → missense

nonsense c.721G → T (Glu241 stop) → مابعرف tbh

3) triose phosphate isomerase

الطبيعي dihydroxyacetone ph. ⊗→ G3P → ! metabolic pathways

↑ in TPI def

↑↑ = minute ATP decrease

hemolytic anemia + neuro. dysfunction

4) phosphoglucose isomerase

G6P ⇄ F6P الطبيعي

when start to show effect? below very low critical residual activity

↑ G6P = feedback inhibition of hexokinase → مو ال isomerase

↓ glycolysis ↑ PPP → ⊗ ATP, D23PG, GSH → hemolytic anemia

F6P "compensate" glycolysis lack (team)

1-6 كلهم deficiency بالانزيمات بالجلايكوليسيس!

5) diphosphoglycerate mutase

! for synthesis & dephos. of D23PD → energy pathway

↓↓ DPM = shift to ph.gly. kinase & pyr. kinase to make energy instead

↑ ATP, FDP, triose ph., P3G, P2G, PEP

↓ ADP, D23PG, F6P, G6P

6) phosphoglycerate kinase

! key of ATP production

1,3-DPG → 3PG [bypassing rapoport-lew shunt]

↓ ATP, ↓ glucose consuption, ↑ D23GP (alt. pathway)

⊗ 1,3DPG to 2,3-DPG — أنسى بالـ RBC

Hgb synthesis

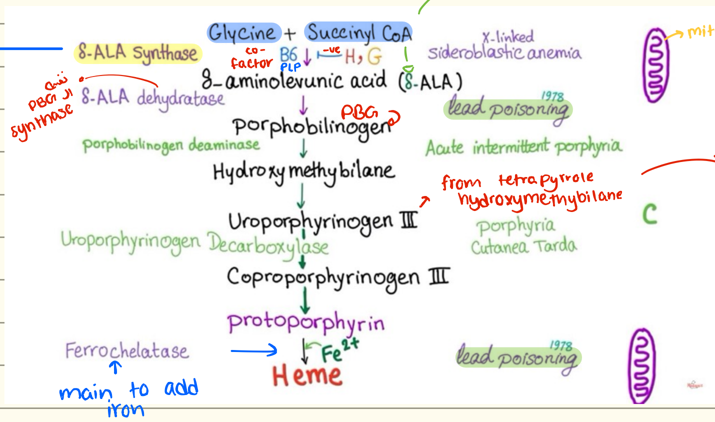
how is it regulated?

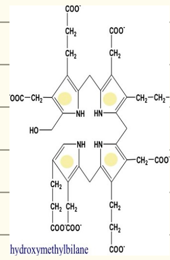
1. gene expression
2. feedback inh. by heme
3. iron availability

ALAS1	ALAS2
ch.3	X-ch.
house-keeping	heme production

rate-limiting step → δ-ALA Synthase

CoA-SH lost by consendation + CO2 by decarboxylation





L3

طيب شو فايدة الـ uro؟

1. ring closure & flip = assymetrical
! (assymetrical ليش الـ Hgb لا)
2. ⊕ uro 3, precursor B12, chlorophyll, heme

Q. which enzyme is blocked by lead poisoning? ALA dehydrogenase

PBG .. (احكي شوي عنها :))

Zn^{++} "binding site" بس co-factor نعوض بالرصاص

إذا صار ⊗ PBG syn. / ALA dehy. how?? → by lead (Pb^{++}) poisoning

= 1. blood ALA
2. depression of ALA synthase gene]! بس هو بيأثر ع الـ ALA dehydr.
3. impaired heme synthesis (هيك صح؟ إذا فهمتوا)

→ clinical presentation:

- sideroblastic anemia
- neuro. manifestation → but why?? → 2 reasons:
  1) ALA similar to GABA
  2) accumilation = ↑ ROS
- foot / wrist drop
- arthritis (joints)

types of heme

- b → in RBC
- c → cytochromes [covalent bonding here only!]
- a → chlorophyll of green plants

regulation of enzymes:

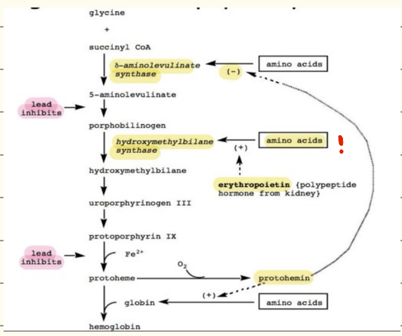
erythrocytes → always need to produce

other tissues → depending on need

regulation of ALA synthase / heme:

- Fe^{3+} oxidation → hemin
  - → -ve feedback
  - → ⊗ ALA cyto → mito
  - → ⊗ enzyme synthesis

كلهم بسبب الـ hemin



! avoid calcium w/ iron supplements

can iron be excreted? not specifically.. then how?

① duodenal shedding
② excess bleeding / menstrution

note: مشان الـ خريطة

transferritin → iron transport / delivary

transferritin receptor → iron uptake by endocytosis

ferroportin → iron release / exit door

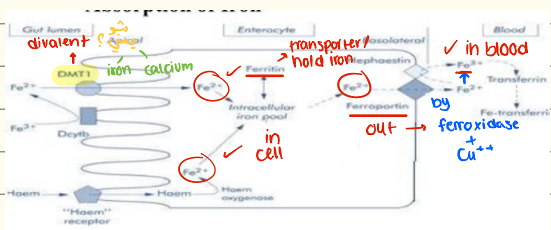
hepcidin ?!

1) -ve to iron abs.
2) antimicrobial
3) induces degradation of ferroportin = ↓ serum iron

NOTE: الجدول إلي تحت:

Ch. 11 → beta, gamma, delta, epsilon

Ch. 16 → alpha, zeta



pathology:

① hereditary hemochromatosis

excessive iron abs / transport / storage

by mutations in:

transferritin R, HFE, hemojuvelin, ⊗ hepcidin

in: liver, heart, joints, pit. gland

② genetic polymorphism

single nucleotide polymorphism, SNP

! iron deficiency anemia

- matriptase 2
- transferrin gene
- HFE

change of gene function

Type of Hb	Type of Globin Gene	Region	Time
Hb Gawer1 ($\zeta\varepsilon)_2$	ζ & ε	Yolk Sac	3 weeks of Gestation
Hb Portland($\zeta\gamma)_2$	ζ &γ	Yolk Sac	5 weeks of Gestation
Hb Gawer II ($\alpha\varepsilon)_2$	α & ε		
Hb F ($\alpha\gamma)_2$	α & γ	Liver & spleen	6-30 weeks of Gestation
Hb A_2 ($\alpha\delta)_2$	α & δ	Liver	30 weeks of Gestation
HbA($\alpha\beta)_2$	α & β	Bone marrow	At Birth

	Hb A	Hb A_2	Hb F
Structure	$a_2\beta_2$	$a_2\delta_2$	$a_2\gamma_2$
Normal %	96-98 %	1.5-3.2 %	0.5-0.8 %
	~ 95%	< 3.5%	< 1 %

if more ?? thalassemia

---

heme degredation

how about "intravascular" → could cause renal failure

RBC → Hgb → globin → amino acid pool
- Hgb → Fe^{+2} → iron pool
- Hgb → heme → bilirubin !

↳ "extravascular"

- haptoglobin: hemoglobin-haptoglobin complex [prevent loss of iron / precipitation]
- hemopexin: bind to free heme
- methemalbumin: complex of ox. heme & albumin

bilirubin

RBC → biliverdin → bilirubin
↑ free, hydrophobic, unconj. bil

its transport:
- w/ albumin 2:1
- > 2.1 by, anions -ve charge OR low/ acidic PH [comp. inh.]
  - ↳ ↑ UCB [Free bil ↑ = BAD]

① uptake
- hepatic uptake,
- UCB ~ alb. complex
- ↓ w/ cirrhosis

② conjugation
- UCB → ER → CB
- UDPGT !
- lipid soluble / hydrophobic
- water soluble / hydrophilic

③ biliary excretion
- CB → bile canaliculis
- ↓ hepatic ducts
- ↓ major papillea in and
- part of duodenum

heme → biliverdin → bilirubin] normal adult daily = 250-300 mg of bilirubin
- ↳ plasma conc: < 1 mg/dL

L2 pt. 1

NADPH: $CO + Fe^{3+} + NADP^+$; NADPH: $NADP^+$

conjugation:

1. glucoronic acid 2. xylose 3. ribose
- by UDP glucuronyl transferase

conjugated → direct 3.4 μmol/L , < 0.2 mg / 100 ml
unconjugated → indirect 13.6 μmol / L, < 0.8 mg / 100 ml
total: 17 μmol/L

in Gut:
! converted to :
- stercobilinogen (by GI bacteria [colorless]), oxidized → colored [brown in feces]
- urobilinogen, re-absorbed [entero-hepatic circulation] liver / kidney [yellow urine]

bilirubin physio:

neonate, ⊗ UDPGT → unconj, so ↑↑ free bil in blood [dangerous]
- ↳ treatment: sun, phototherapy [physiological jaundice]

enterohepatic circulation:

conj is unstable & can become unconj to reabsorp & become uro..
1. non enzymatic → duo. & jeju
2. enzymatic → β-glucuronidase [↑ can in new borns / human milk]

---

jaundice → icterus

yellow discoloration, serum bilirubin @ 27-35 μmol/L or 1.5-2 mg

classification

	presentation	reason	cause	laboratory findings
prehepatic	hemolytic ↑ unconj.	excess production of bilirubin	. extra / intra vasc. hemolysis . impaired conjugation (gilbert, crigler, hyperthyroidism) . impaired uptake . ineffective erythropoiesis . pyr kinase & G6D def.	⊗ bilirubinurea U [bilirubin → ⊗ absent in urine urobilinogen [urine] → ↑ or normal F [stercobilinogen [feces] → normal cases ↓ ↓↓ !! → overwhelming amount of bil but still normal ⊗ gut / liver problems

intrahepatic - congenital / aquired - impaired uptake, conj, secretion (↑ unconj / ↑ conj)

hepatocellular injury - generalized liver dysfunction

[hyperbilirubinemia]

- impaired conjugation – gilbert – crigler
- hepatocellular necrosis
- hepatitis, cirrhosis

liver حرفياً أي اشي

- liver function test → AST ↑ ALT ↑
- CB & UCB → both ↑
- bilirubinuria [↑ CB → blood cuz water soluble → kidney]
- urobilingen [urine] → ↓ or normal → ⊗ secretions to GI or anything (GI empty, blood full)
- stercobilingen [feces] → ↓ or normal

postnepatic obstructive

bile duct obs.

⊗ to gut pale → stool

dark → urine

↑ CB w/o converting to uro

ال uro هو اللي بيسوي pale بالعكس

- ✓ liver
- ✓ conjugation
- ✓ bil. production

] use UCB ↑ CB

✗ bile secretion to gut (CB back to blood = ↑ in serum)

intrahepatic:

- block bile canaliculi
- dubin-johnson

extrahepatic:

- obstruction by tumor
- pancreatitis
- parasitic inf.

- serum bil ↑ why? total of normal UCB & ↑ CB
- urobilingen [urine] → ↓, absent in complete obstruction
- stercobilingen [feces] → ↓
- bilirubinuria [↑ CB → blood cuz water soluble → kidney]

	Pre-hepatic	Hepatic	Post-hepatic
Urine	No Bilirubin Urobilinogen ↑ (overwhelming amount)	There is bilirubin Normal urobilinogen	There is bilirubin Urobilinogen is absent
Faeces	Dark	Pale	Pale
Blood	↑Reticulocyte count (hemolytic) ↑ Unconjugated bilirubin (up to 100µmol/L) Normal ALP and γ GT Normal AST and ALT PT Normal	Normal reticulocyte count ↑ Bilirubin – mixed conjugated & unconjugated ↑ ALP and γ GT ↑ AST and ALT ↑ PT – not correctable with Vit K (↑ liver damage / failure)	Normal reticulocyte count ↑ Bilirubin (up to 1000µmol/L) – conjugated ↑ ALP and γ GT Normal AST and ALT ↑ PT – correctable with Vit K (↑ fat malabsorption)

→ case Q's

neonatal jaundice

physiological why? immaturity of conjugation enzymes

pathological if: could cause kernicterus pass BBB

started → first 24h

lasts → > 10 D

treatment:

phototherapy w/ UV light / sun

blood transfusion

phenobarbital

Gilbert's syndrome

hereditary bilirubin increase ↑ UCB in serum

↓ glucoronyl transferase

70-80% reduction of glucoronidation of enzyme UDP-glucuronosyltransferase 1A1

1/2 patients inherited it

> male

teen, early 20

treatment: phenobarbital بيحفز الانزيمات

ال conjugation عن الاخر

Dubin-Johnson & Rotor's syndrome

impaired biliary secretions of CB

conjugated hyperbilirubinemia mild

crigler-najjar syndrom, type 1

serum bilirubin ABOVE 345 µmol/l

autosomal recessive

COMPLETE absence of UGT1A1

recessive يعني w/ kids

these children, died of kernicterus OR survive w/ clear neurological impairment

→ treatment

1) exchange transfusion
2) 12h/D phototherapy
3) heme ox. inhibitors
4) oral calcium phosphate & carbonate
5) liver transplant

↓

type 2

BELOW 345 µmol/l

bile is pigmented [pale in 1]

UGT1A1 present but reduced [complete ⊗ in 1]

✓ phenobarbital

! go back to slides for numbers