DOCTOR 2020 | JU

METABOLISM

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In the last lecture we said that the main functions For PPP pathway are :

1- Produce NADPH
2- Fighting against ROS using different anti-oxidants like Glutathione
3- Produce Pentose Sugar to synthesize Nucleotides

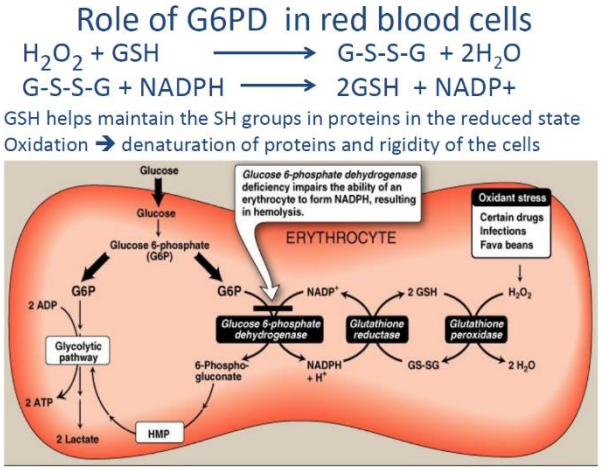
Remember that every **6** glucose molecules that get in PPP pathway one of them is lost as CO2 , that indicates how important this Pathway is ; (we lost an important resource to get into the pathway).

GLUCOSE-6-PHOSPAHTE DEHYDROGENASE DEFICIENCY

In this lecture we will start by discussing a **medical application** for PPP, which is Glucose-6-Phospahte dehydrogenase deficiency also known as التفول , because **fava beans** contain some compounds that increase oxidative stress in cells that induces this condition.

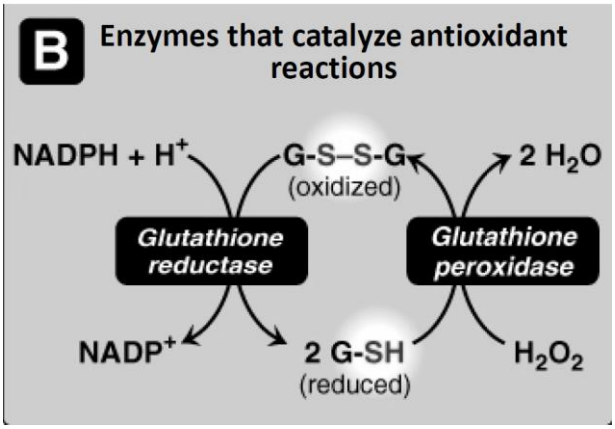
More than 400 mutation can cause G6PD deficiency and every mutation controls the severity of the condition .therefore, this disease is variable among different patients.

Let's take a look on a patient's RBC and why they develop hemolytic anemia :



In the case of G6PD deficiency NADPH amounts are decreased so when ROS are made either by infections, fava beans or drugs that will lead to the depletion of NADPH, So the ability for glutathione to fight ROS is going to be reduced **(glutathione won't return to it's reduced state " GSH " that function against ROS)** This will lead to increased oxidative stress in RBCs which will cause their hemolysis.

(this is just a single example on how G6PD deficiency affects the body)



Important Note : This disease is **X-Linked recessive** inherited and it provides resistant to falciparum **Malaria** (so is has an advantage :P).

G6PD DEFICIENCY MUTATIONS :

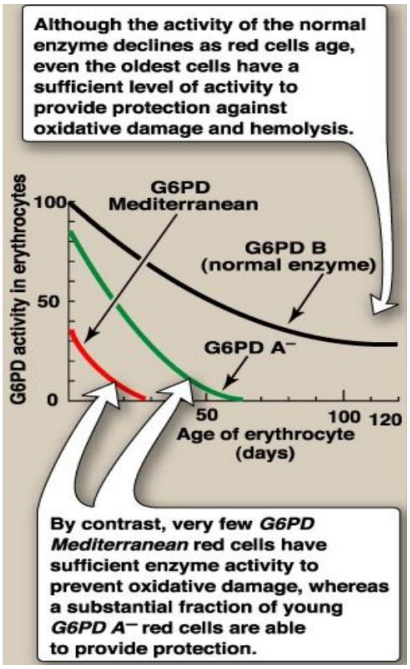
Lets talk about mutation once again, the majority of these Mutation are **Point Substitution** for a single nucleotide that causes a missense translation, and as we said there are different types and classes for this mutation :

Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	> 60%

1- **Class I** : the most severe mutation which cause the highest deficiency of the enzyme.

2- **Class II (B- variant)**: **cytosine is replaced with thymine** on position 563 on the gene and this type is the most common type in **Mediterranean** countries , this contain intermediate deficiency of G6PD.

3- **Class III (A- Variant)**: more predominant in **African** population , their enzyme activity is really close to normal, made up from 2 point mutations.



Notice how affected erythrocytes have much lower life span that normal ones (check the graph -->):

30 days for class 2 RBCs

60 days for class 3 RBCs

PPP AND ROS RELATION :

we have previously mentioned glutathione and how it reacts with ROS , now we will discuss some other molecules and enzymes that does the same function such as :

1- Super Oxide Dismutase **(SOD)**, acts on super oxide ion and convert it into Hydrogen peroxide (H_2O_2) , Hydrogen peroxide can be degraded by **catalase** enzyme into water and oxygen.

2- Other anti-oxidant chemicals like Vitamin E,C and carotenoids (mainly Vitamin A)

Side note : carrots are named like that because they contain **β carotene** which is the compound that gives carrots it's orange color , and which happen to contain **Vitamin A that enhances the vision.**

SOURCES OF ROS :

1- Reactions by Oxidases (usually **produce H_2O_2**)

2- Reaction by Oxygenases (confined to sites equipped with protective enzymes) like :
   a- **Mono** oxygenase (carry out hydroxylases)
   b- **Di**oxygenases which is important in the synthetic pathway of **eicosanoids** Arachidonic acid products , like prostaglandins, thromboxane and leukotrienes.

3- Coenzyme Q in ETC can be a source for **super oxide** ion " O_2^- ".

4- Respiratory Burst: it's the condition where **super oxide ion** is produced in high concentrations in the phagolysosome during the destruction of an invading microorganism
   Note : It starts with super oxide ,then other ROS may be produced such as NO, H_2O_2, HOCL and $OH^{\cdot}$ **.** also Nitrogen Oxygen RS , and in this case they are produced **on purpose** to fight microorganisms.

5- Ionizing Radiation (over exposure produce $OH^{\cdot}$) : like lab technicians and Radiologists, those people will be continuously tested for the amount of radiation they have. because overtime, ROS can develop cancer .

CYTOCHROME P450 MONOOXYGENASE SYSTEM :

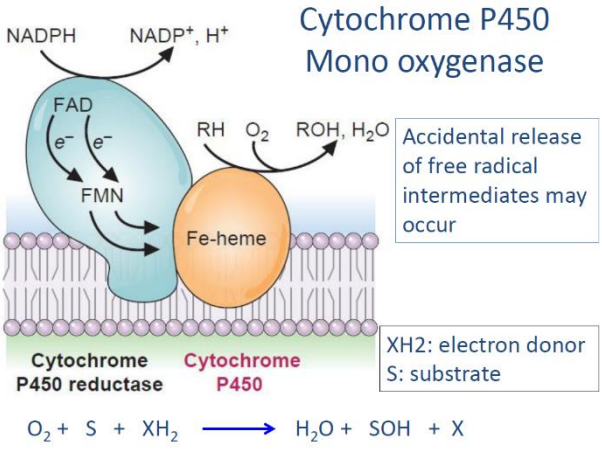
ITS RELATION TO FORMATION AND DESTRUCTION OF ROS

A) It takes an O_2 molecule and use one atome to form an OH group , and another one will interact with H^+ to form water, the source of H^+ will be by NADPH oxidation.

$$R\text{-}H + \mathbf{O_2} + NADPH + H^+ \longrightarrow R\text{-}\mathbf{O}H + H_2\mathbf{O} + NADP^+$$

B) P450 system is mostly in hepatocytes, and it is present in multiple places within the cell , like the **mitochondria** (that is mainly concerned with hydroxylation Reactions which happens during **steroids**, **bile acid and vitamin D** synthesis.
Note: The active from of Vitamin D contain multiple hydroxyl groups, and remember that vitamin D was originally a cholesterol molecule.

C) **Microsomal system** which is present in the **ER** , it's main function is detoxification of drugs and xenobiotics, sometimes this system activates the drug.
The main purpose of this degradation is to produce **excretable** (mainly in Urine) form of the drug (convert it from lipid soluble to water soluble)
Note : Monooxygenase is present in both Mitochondria and ER but in each site **it has a different function**

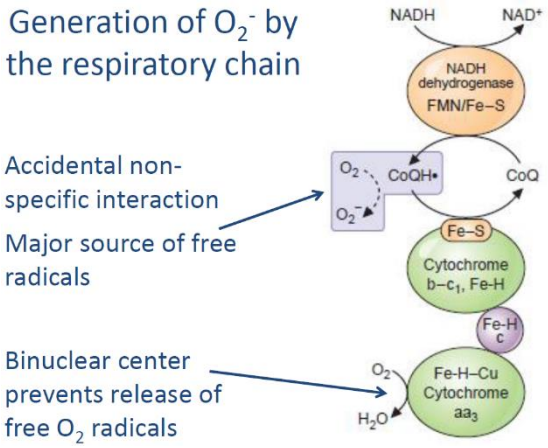


D) Also FAD and FMN can aid in getting rid of ROS by reacting with the heme group which will make the **Fe** in the heme group to **sway between ferrous and ferric states**, but sometimes accidental release of free radicals may occur.
Notice that p450 can fight and also produce ROS.

GENERATION OF O2- BY ETC :

Co- enzyme Q receive electrons from complex 1 and 2, these electrons can be added to oxygen to form **O_2^-** as a side product.

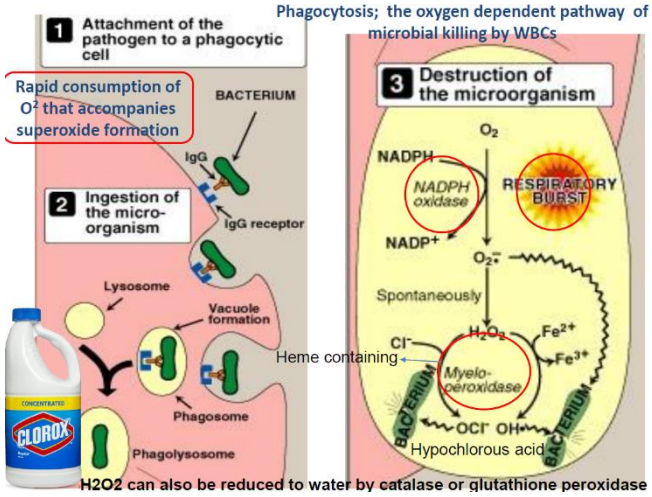
Note : ROS amount produced by this method is Low due to the fact that the main function of O_2 in ETC is to be the last electron acceptor.



RESPIRATORY BURST :

Associated with **immune responses and phagocytosis** of microorganism

When IgG and IgG receptors interact the production of ROS will be activated.



Inside the phagolysosome, oxygen is going to be converted to O_2^- , this reduction reaction is catalyzed by **NADPH oxidase** , O_2^- can act directly on bacteria or it can be converted to H_2O_2 through SOD which can be converted to $OH^\cdot$ Or OCl^- with the involvement of Cl- and Fe^{2+} .

Note : OCl^- is used in disinfectants like Clorox because it's a **very strong microorganism killer** (more potent that alcohol) .

NITRIC OXIDE (NO):

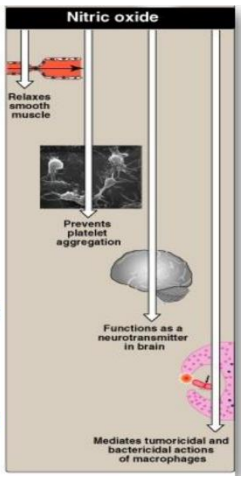
NO; is a signaling molecule that is produced in the cell and is also considered as an ROS. It's a small gaseous molecule so it's diffused very easily. Therefore, it's effect is really wide and it may cause toxicity in higher amounts.

The effects of NO:

1- Vasodilation
2- Neurotransmitter in the **Brain**
3- Reduce platelet aggregation
4- Can react with ROS producing **RNOS**

NO and Reactive Nitrogen Oxygen Species (RNOS)

- Diffuses readily
- Essential for life and toxic
- Neurotransmitter , vasodilator
- ↓Platelet aggregation
- At high concentration combines with $O_2\bullet^-$ or O_2 to form **RNOS**
- **RNOS** are involved in neurodegenerative diseases and inflammatory diseases

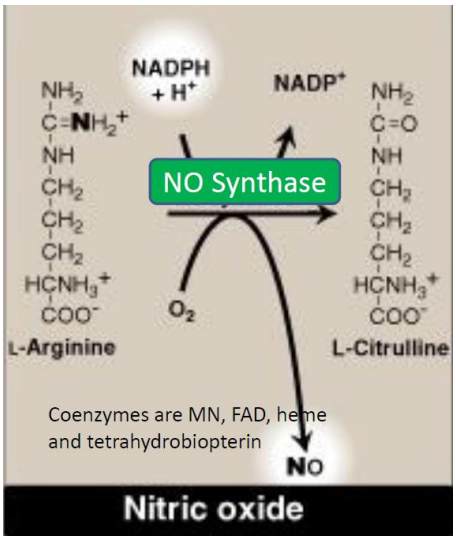


How NO is produced ?

It's produced from **arginine** amino acid (because it contains a plenty of Nitrogen atoms) and that's through **NO synthase** with the interference of NADPH as indicated in the slide.

NO synthase has different isoforms

1- nNOS "neural"
2- eNOS "endothelial"
3- iNOS (inducible Ca^{2+} independent) which is activated under certain conditions, one of these conditions is the process of fighting of an infection (kill a microorganism) which will induce the **production of RNOS to kill invading bacteria.**



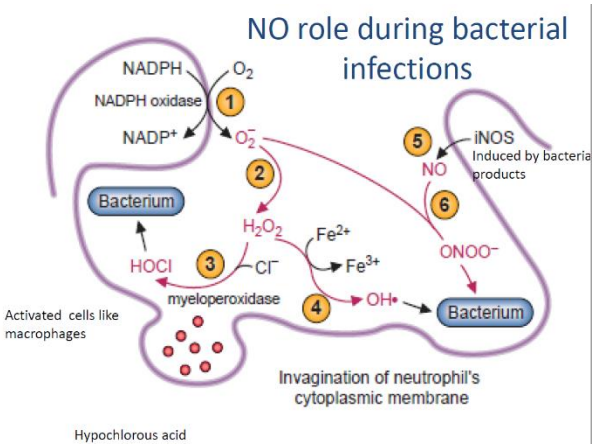
Note : nNOS & eNOS have **constitutive actions** , which means that they don't need a certain stimulus to induce their action

how NO act as a vasodilator ?

1- it's going to activate **Guanylyl cyclase** that converts GTP to cGMP
2- which leads to the activation of **protein kinase G**
3- phosphorylate **Ca^{2+} channels**
4- causes entry of Ca^{2+} into SER and cause **muscle relaxation**
5- which **decreases** the blood pressure

Role of NO in hydrolyzing microorganism:

iNOS is induced by bacterial products, NO combines with O_2^- producing **ONOO-** which hydrolyze bacteria.



دعوة من قلبك

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