Erythropoietin

- Known as EPO
- MW 30400Da
- Discovered by Miyake et al 1977 from urine of anaemic pts.
- LC 4 alpha helical bundle class 1 cytokine
- 193 a.a. human (192 mouse)
- When levels low e.g. in CRF, chemotherapy treatment in cancer
- Not effective when levels are high (high altitude, hypoxia due to CHD)
- Has been used in AIDS
Biological Functions

- As its name suggests, EPO stimulates growth of Erythrocytes
- It increases as a result of a negative feedback loop - low Oxygen = production of Epo.
- Produced in the Kidneys and also in the Liver (as Foetus: liver only)
- Carries oxygen in blood
Therapeutic Uses

- When Epo levels low-used in anemia resulting from chemotherapy, AIDS, CRF
- Not useful if levels already high as in cases of hypoxia, high altitude living, CHD and lung disease.
- Shown to improve QOL greatly in vast majority of cancer/AIDS pts
RHu Epo in treatment of Anaemia of Cancer

- Low levels of Epo resulting from the treatment of Cancer treated by RHuEpo
- improves Quality of life
- improves anaemia in hypo-Epo cases
Peptide Mimetics

- Enables the use of Epo in therapy for CRF and cancer without unwanted immunological effects
- Synthesised from random peptide ‘libraries’ displayed on filamentous phages (Bacterial virus)

- These bind to and activate a receptor of cytokines similarly to original cytokine.
- 14-20 a.a. In length, serve as lead compounds for development of therapeutically effective Epo, smaller, less side effects
Epo also has therapeutic **Abuses**

- Used in sports to improve endurance
- Now detected from naturally occurring EPO by protein markers appearing post-injection
Erythropoietin Receptor

- Hetero-dimer consisting of Beta sheets
- Optimum effectiveness if 120 deg. to epo
- works on JAK-stat pathway
- stimulates NF-k B
- protects against agoptosis
Regulation of Erythropoiesis

- Importance

- Factors affecting Erythropoiesis
  - Tissue Oxygenation
    - Anemia, High Altitudes, Cardiac failure, Resp Problem
    - ERYTHROPOITEN
  - Vitamins
  - Metals
  - Proteins
  - Hormones
  - Other factors/Conditions
Normal RBC Count

Importance:

- Must Not Fall
  - To supply oxygen from lungs to tissues
- Must Not Rise
  - Blood viscosity may increase
  - May impede blood flow
Factors affecting Erythropoiesis

1. Tissue Oxygenation
2. Vitamins
3. Metals
4. Proteins
5. Hormones
1. Tissue Oxygenation – Most Important Regulator of Erythropoiesis

- ANY CONDITION
  - Decrease Tissue Oxygenation
  - Increase Erythropoiesis

- Anemia
  - Immediately Increase RBCs production

- Bone marrow destruction:
  - Hyperplasia of remaining cells
- **High altitudes:**
  - Partial pressure of oxygen in air less
  - Decrease in oxygen transport to tissues
  - Tissue hypoxia
  - Result?

- **Cardiac Failure**
  - Inefficient pumping by heart
  - Decreased blood flow to peripheral vessels
  - Tissue hypoxia
  - Result?
Lung diseases:
- Failure of oxygen absorption in Lungs
- Blood carries less Oxygen
- Tissue hypoxia
- Result?

All conditions have one common problem

HYPOXIA

ERYTHROPOIETIN
Erythropoietin

- Glycoprotein
- Mol weight 34000

 Sites of production
  - Kidneys
  - Liver
  - Brain, Uterus

 If Erythropoicen production reduced
  - Effect of Hypoxia?
Stimulants of Erythropoiten production:

- **RENAL MECHANISM**
  - Anemic blood to kidney
  - Less oxygen supplied
  - Renal tubular cells - High $O_2$ consuming
  - Stimulates production of Erythropoiten

- **NON RENAL MECHANISM**
  - Hypoxia in other parts – Non renal sensor
  - Nor epinephrine, epinephrine, prostaglandins

- In Renal failure?
Formation of Erythropoiten

- **Erythrogenin** – Renal Erythropoitics factor
- **Erythropoitinogen**
  - Alpha globulin
  - Substrate for Erythropoiten
- **Stimulants of Erythrogenin**
  - Hypoxia
  - cAMP
  - NAD
  - Hemosylates
Role of **EP** in Erythropoiesis

- Formed in response to *Hypoxia* within minutes
- **RBC** production in **5 days**
- **Erythropoiten**
  - Stimulates **Proerythroblasts** formation
  - Causes cells to **pass through various stages** of Erythropoiesis **rapidly**
Recombinant Erythropoiten

- Anemia – Renal Failure
- Blood doping
  - Erythropoiten - Athletes
  - Running – Increase Oxygen demand
  - Breathlessness
  - ERYTHROPOITEN – Increase RBC’s
  - Less dyspnea
- DNA Recombinant Technique
Regulation of Erythropoiesis

- Importance
- Factors affecting Erythropoiesis
  1. Tissue Oxygenation
- Anemia, High Altitudes, Cardiac failure, Resp Problem
- ERYTHROPOITEN
  - Site of production
  - Stimulants for production
  - Mechanism of production
  - Role in Erythropoiesis
2 Vitamins
- Vit B$_{12}$ and Folic acid
- Pyridoxine
- Vitamin C
- Riboflavin and Pantothenic acid

3 Metals
- Iron, Cu, Co, Ni, Mn

4 Proteins

5 Hormones
- GH, TH, CORTISOL, TESTOSTERONE, ACTH

5 Other conditions affecting…..
If you complain about your transport system, What about them?