Erythroferrone:
An Erythroid Regulator of Hepcidin and Iron Metabolism

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Iron homeostasis and regulation by hepcidin

- ~ 60% of total-body iron is contained within circulating erythrocytes
- each day the synthesis of new erythrocyte hemoglobin requires about 80% of the iron obtained from:
  - a combination of dietary sources and the recycling of senescent erythrocytes
- Iron lacks a quantitatively significant route of excretion from the body,
- therefore the absorption of new iron from the diet must be balanced with daily losses and the mobilization of stored iron to preserve systemic iron homeostasis

Iron homeostasis and regulation by hepcidin

- Ferroportin,
  - the only identified mammalian iron export protein,
  - delivers to plasma dietary iron from
    - enterocytes,
    - as well as stored iron from hepatocytes and macrophages of the RES.
- Hepcidine
  - The master regulator of ferroportin, and
  - whole-body iron homeostasis, is hepcidin,
  - a peptide hormone produced primarily by hepatocytes

Iron homeostasis and regulation by hepcidin

- Hepcidin
  - Binds to ferroportin and
  - reduces cellular iron export by 2 mechanisms:
    - induced conformational change in ferroportin its ubiquitination and degradation
    - occludes iron transport
  - decreased ferroportin activity causes
    - Decreased iron absorption and
    - reduced mobilization from stores

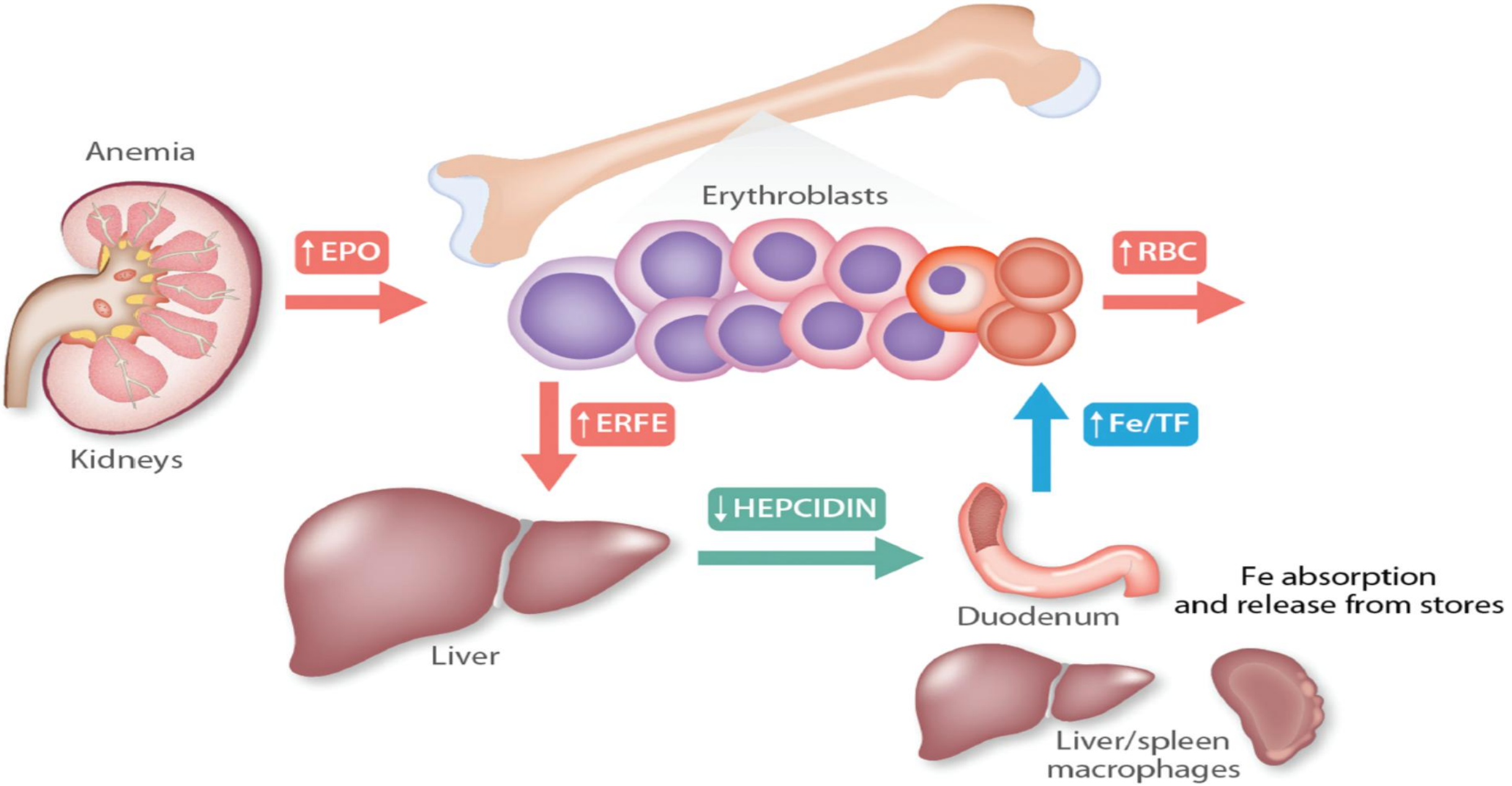
Hepcidin regulators

- Hepcidin expression is regulated by
  - iron status,
    - increasing with elevated serum iron concentrations and liver iron stores and
    - decreasing in response to iron deficiency
- Mutations
  - in genes involved in the regulation of hepcidin expression,
  - in the gene encoding hepcidin itself,
    - inappropriately low hepcidin levels,
      - excessive iron accumulation and tissue damage in iron-accumulating tissue

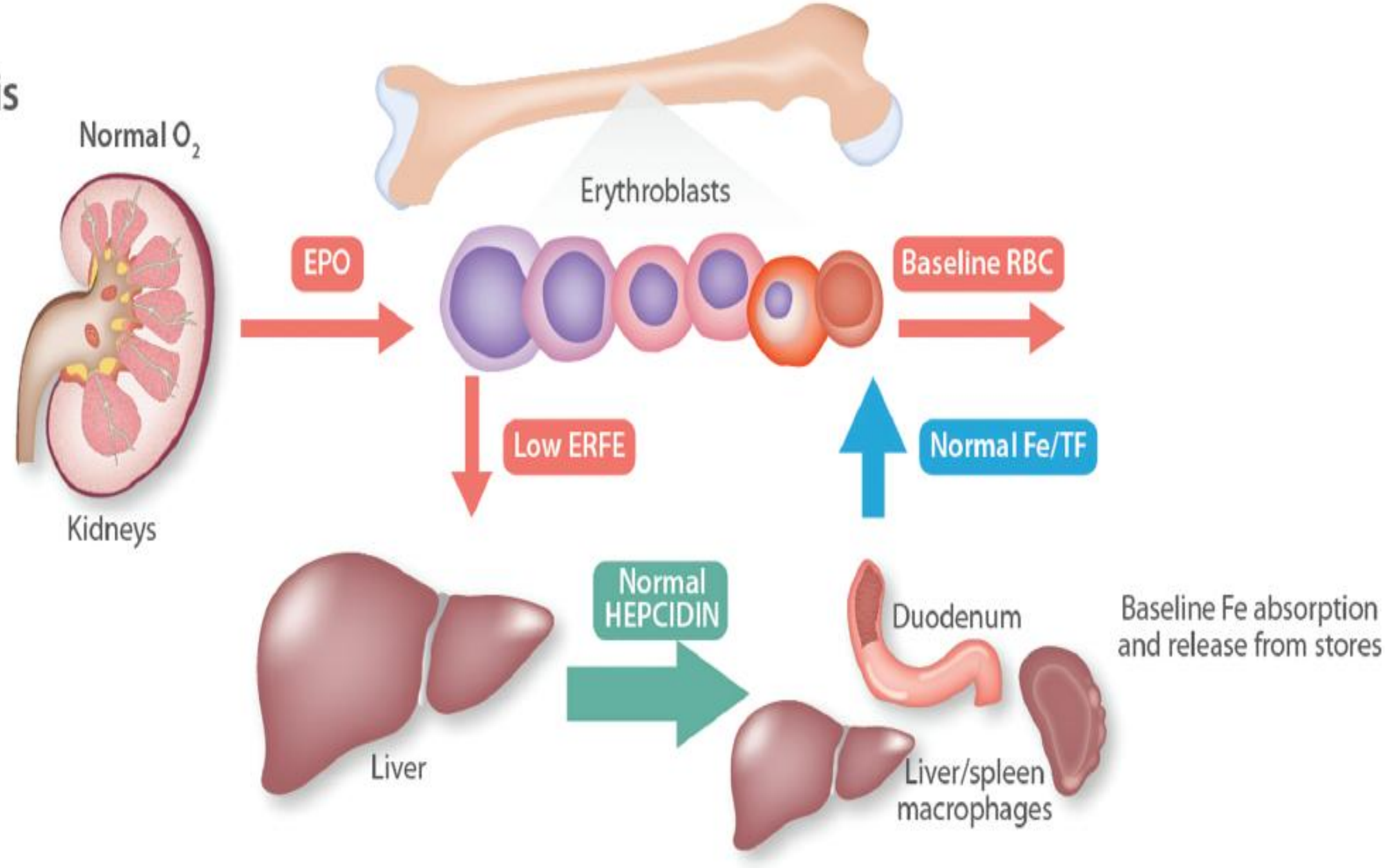
Hepcidin mutation effects

- Decreased Hepcidin Iron overload
  - Depending on the timing, severity, and extent of iron loading,
    - iron-induced tissue injuries include
      - Hepatic fibrosis and cirrhosis
      - endocrinopathies such as diabetes
      - cardiomyopathy.
- inappropriately elevated hepcidin concentrations,
  - iron-deficiency anemia that does not improve in response to iron supplementation,
  - referred to as iron-refractory iron-deficiency anemia (IRIDA)

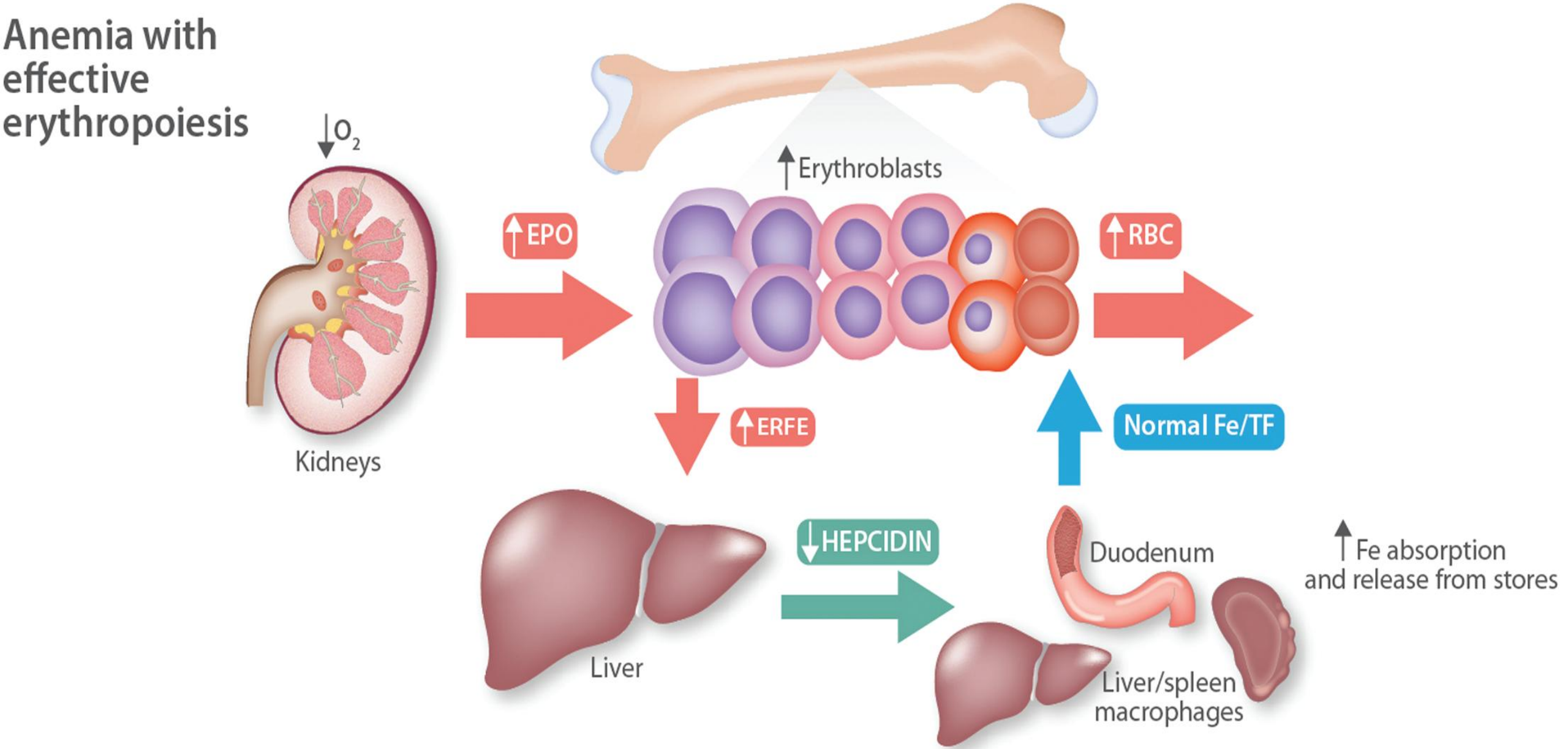
Erythroferrone in systemic iron homeostasis



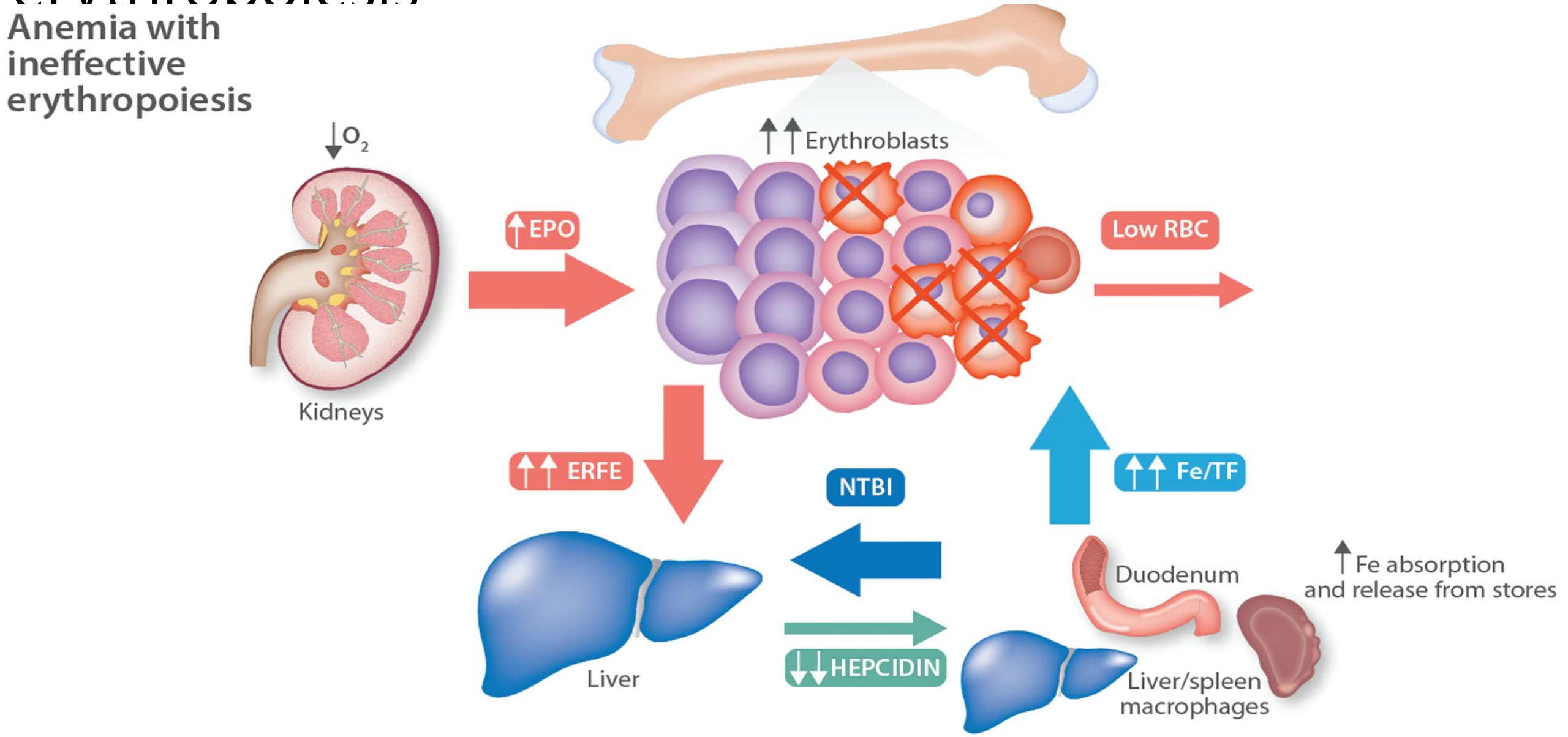
Normal erythropoiesis



Erythroferrone in anemias with effective erythropoiesis



Erythroferrone in anemias with ineffective erythropoiesis



Clinical concepts

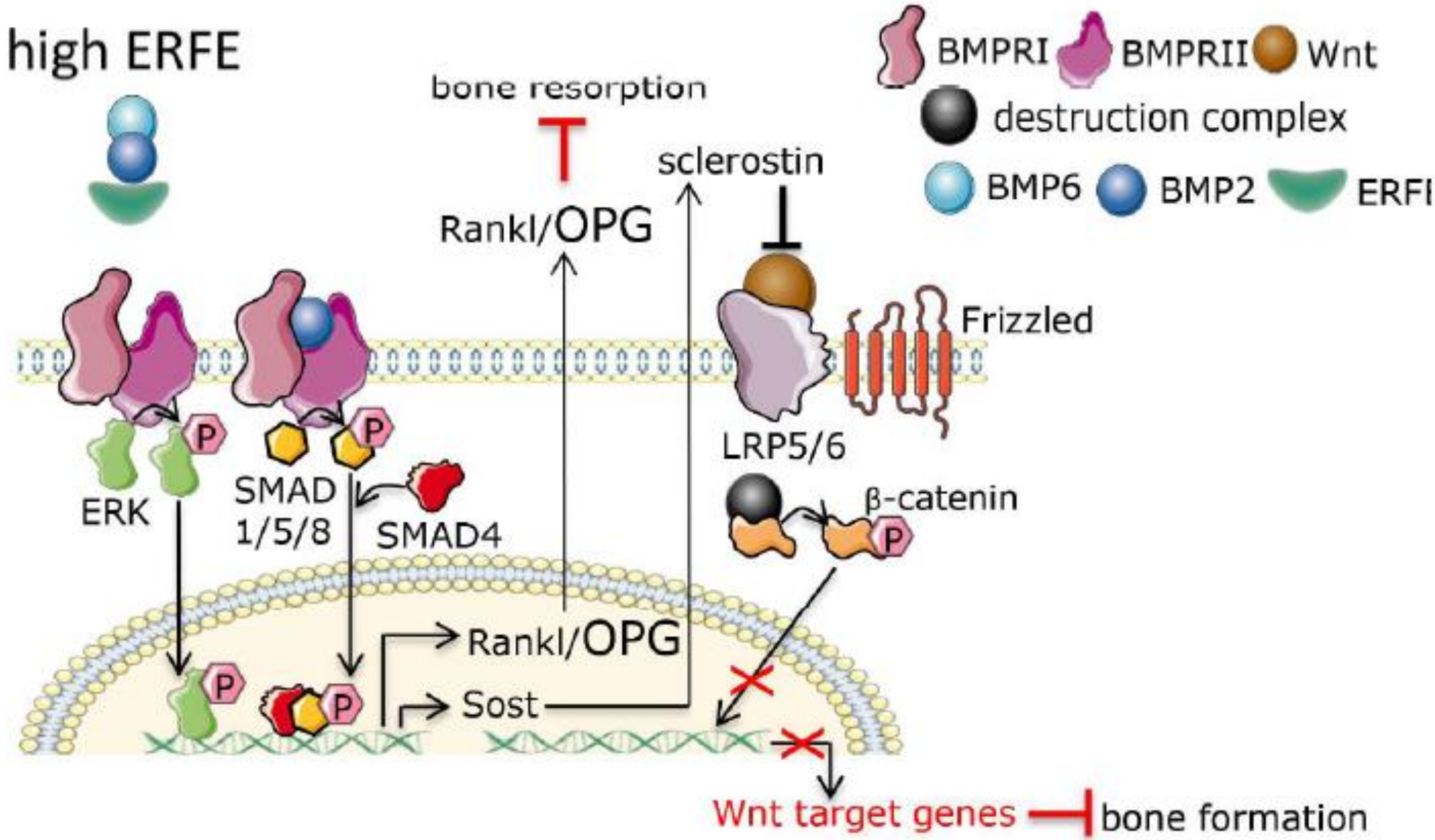
- In human b-thalassemia,
  - serum ERFE concentrations are greatly increased,
  - are transiently suppressed after erythrocyte transfusions,
  - and inversely correlate with serum hepcidin concentrations,
  - suggesting that ERFE contributes to the pathogenesis of iron overload.

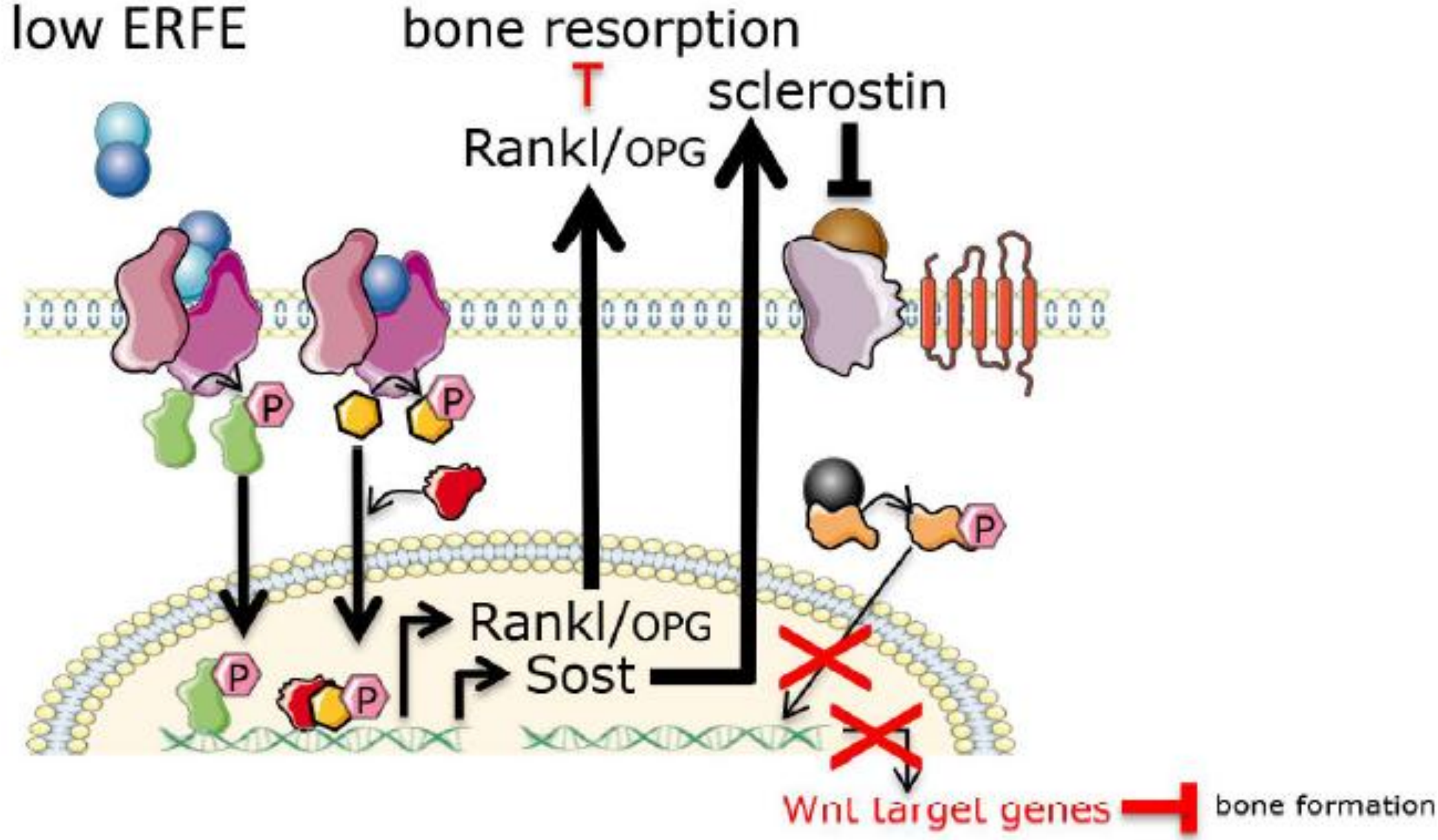
Clinical concepts (continue)

- Erythroferrone (ERFE),
  - the erythroid regulator of iron metabolism,
  - inhibits hepcidin to increase iron availability for erythropoiesis.
  - plays a pathological role during ineffective erythropoiesis as occurs in
    - X-linked sideroblastic anemia (XLSA)
    - β-thalassemia.
- supraphysiological amounts of ERFE may be required to
  - lower inappropriately high hepcidin in
    - anemia of inflammation
    - iron-refractory iron deficiency anemia

The hepcidin regulator erythroferrone is a new member of the erythropoiesis-iron-bone circuitry

- ERFE exerts an
  - osteoprotective effect by
    - modulating BMP signaling in osteoblasts,
    - decreasing RANKL production to limit osteoclastogenesis,
  - prevents excessive bone loss during expanded erythropoiesis in β–thalassemia.


high ERFE
BMPRI
BMPRII
Wnt
destruction complex
BMP6
BMP2
ERFI
bone resorption
Rankl/OPG
sclerostin
Frizzled
LRP5/6
β-catenin
P
ERK
SMAD
1/5/8
SMAD4
Rankl/OPG
Sost
Wnt target genes
bone formation


low ERFE
bone resorption
T
sclerostin
Rankl/OPG
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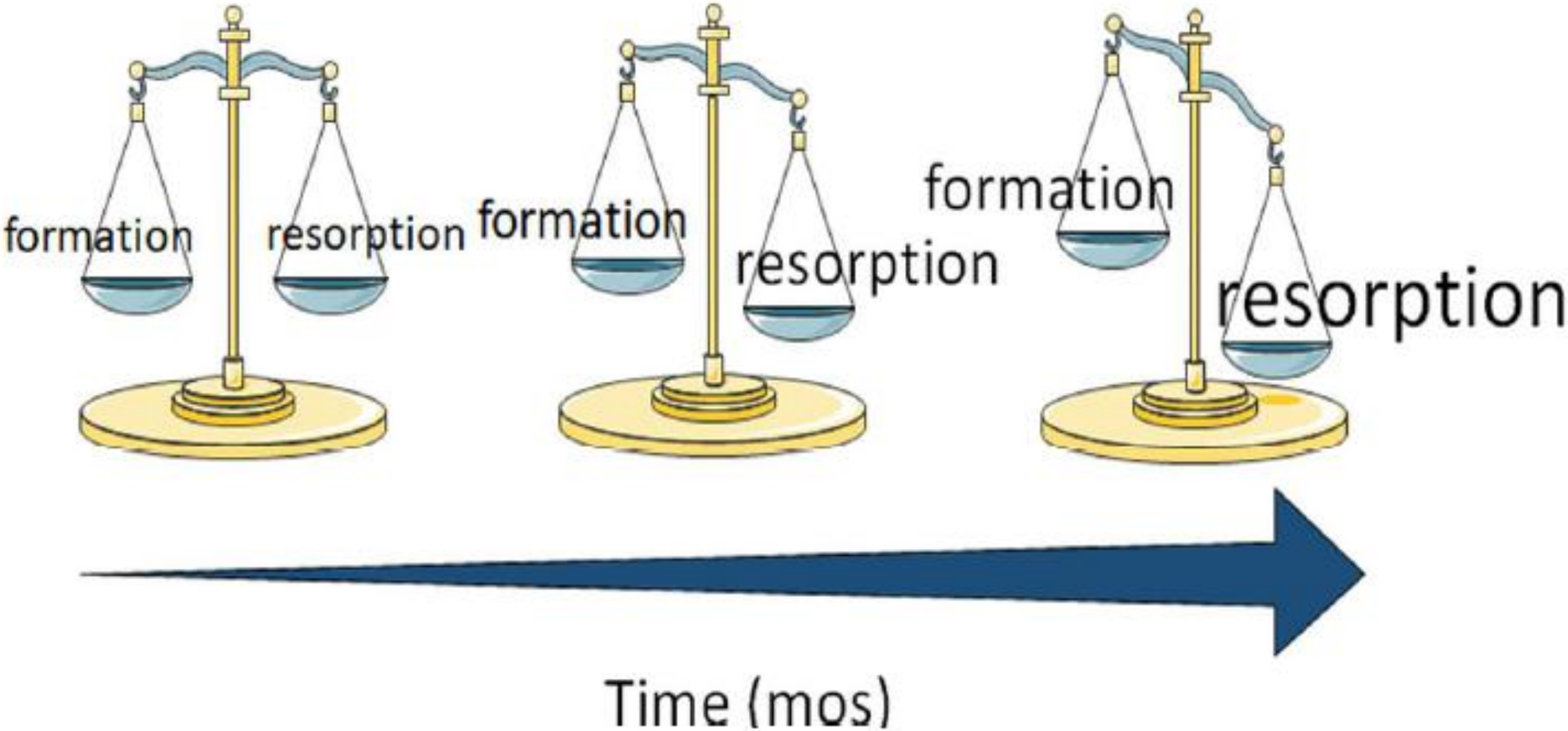
Rankl/OPG
Sost
Wnt target genes
bone formation


formation
resorption
formation
resorption
formation
resorption
Time (mos)

Conclusion

- Erythroferrone now considered is one of potential clinical biomarkers for assessing erythropoiesis activity in patients with blood disorders regarding to iron imbalance.
- Thus, future therapeutic intervention:
  - inhibiting the action of ERFE
  - beneficial for preventing iron overload in b-thalassemia and other anemias with I.E.

Thank you for your attention