FACULDADE DE MEDICINA DE RIBEIRÃO PRETO – USP
DEPARTAMENTO DE FISIOLOGIA

RCG- 216 FISIOLOGIA II
Docente responsável: Profa Lucila L K Elias

Seminário - Paratireóide

✓Livro Texto de Fisiologia: Glândula paratireoidiana/ metabolismo osteomineral.

✓Holick MF. Vitamin D deficiency. N Engl J Med. 2007, 357(3):266-81.

✓Lieben L, Carmeliet G, Masuyama R. Calcemic actions of vitamin D: effects on the intestine, kidney and bone. Best Pract Res Clin Endocrinol Metab. 2011;25(4):561-72.

✓ Prié D, Ureña Torres P, Friedlander G. Latest findings in phosphate homeostasis. Kidney Int. 2009, 75(9):882-9.

TÓPICOS:

- ✓ *HORMÔNIOS QUE REGULAM A HOMEOSTASE DO [CA^{2+}] E FOSFATO*
- ✓*CONTROLE DA SECREÇÃO DO PTH. AÇÕES DO PTH*
- ✓*MECANISMO DE AÇÃO DO PTH NO OSSO*
- ✓*SÍNTESE DA VITAMINA D E SUAS AÇÕES CALCÊMICAS*
- ✓*PRINCIPAIS FATORES ENVOLVIDAS NO CONTROLE DA HOMEOSTASE DO FOSFATO*
- ✓*CALCITONINA: AÇÕES*
- ✓*ADAPTAÇÕES ÀS ALTERAÇÕES DO BALANÇO DE CÁLCIO*

Questões Orientadoras:

1.Discuta a participação do hormônio paratireoidiano no controle da homeostase do cálcio e fósforo.

2.Como ocorre o controle da secreção de PTH? Quais os principais mecanismos?

3.Discuta a biossíntese da forma ativa da Vitamina D.

4. Discuta as ações da vitamina D no intestino, no osso e na paratireóide. Quais os mecanismos de ação da vitamina D?.

5.Quais são as principais consequências da deficiência da vitamina D, em relação ao osso?

6.Discuta os principais fatores envolvidos no controle da homeostase do fósforo.

7.Explicar as variações do PTH e da vitamina D em uma situação de hipocalcemia e de hipofosfatemia.

8. Paciente do sexo feminino, 66 anos, com queixa de fratura vertebral, nefrolitíase apresenta os resultados abaixo. Como podemos explicar os resultados abaixo e as queixas da paciente.

		Valor de referência:
Cálcio sérico	10,9 mg/dl	8,4 – 10,4 mg/dl
Fosforo sérico	2 mg/dl	2,3 – 4,7 mg/dl
PTH sérico	90 pg/ml	15 – 65 pg/ml
Densitometria óssea – coluna lombar	T-score: – 2,8	VER CLASSIFICAÇÃO WHO (abaixo)

Postmenopausal Osteoporosis Guidelines, *Endocr Pract.* 2010;16(Suppl 3)

Table 3
World Health Organization Criteria for Classification of Osteopenia and Osteoporosis

Category	T-score
Normal	−1.0 or above
Low bone mass (osteopenia)[a]	Between −1.0 and −2.5
Osteoporosis	−2.5 or below

9. A administração de 1,25(OH)2 D3 é um dos tratamentos do hiperparatireodismo secundário à insuficiência renal crônica. Explicar os mecanismos que contribuem para o hiperparatireoidismo secundário na insuficiência renal crônica, e os efeitos do tratamento com 1,25(OH)2 D3.

Questões Orientadoras:

1.Discuta a participação do hormônio paratireoidiano no controle da homeostase do cálcio e fósforo.

2.Como ocorre o controle da secreção de PTH? Quais os principais mecanismos?

Cálcio e Fósforo

- **Cálcio e fósforo:** Principais constituintes do osso (65% do peso ósseo).

- **Cálcio ósseo:** equivale a 99% do cálcio do organismo humano

  1% cálcio ósseo: troca com cálcio extracelular não ósseo. (mineralização de cartilagens e ossos, cofator de enzimas extracelulares, principalnente de enzimas da cascata de coagulação e outros processos celulares).

- **Fósforo:** 85% do fósforo do organismo humano está presente no compartimento mineral do osso. 15%: compartimentos intracelulares e extracelulares. (constituinte de ácido nucléico, fosfolípides, carbohidratos complexos, fosfoproteínas estruturais, enzimáticas e de sinalização, cofatores de enzimas e proteína G, ATP, difosfoglicerol → estoque de energia química)

PRINCIPAIS FATORES ENVOLVIDOS NO CONTROLE DO METABOLISMO DE CÁLCIO E FÓSFORO

- PTH
- 1,25-DIHIDROXIVITAMINA D (1,25(OH)2D)
- FOSFATONINAS
- CALCITONINA

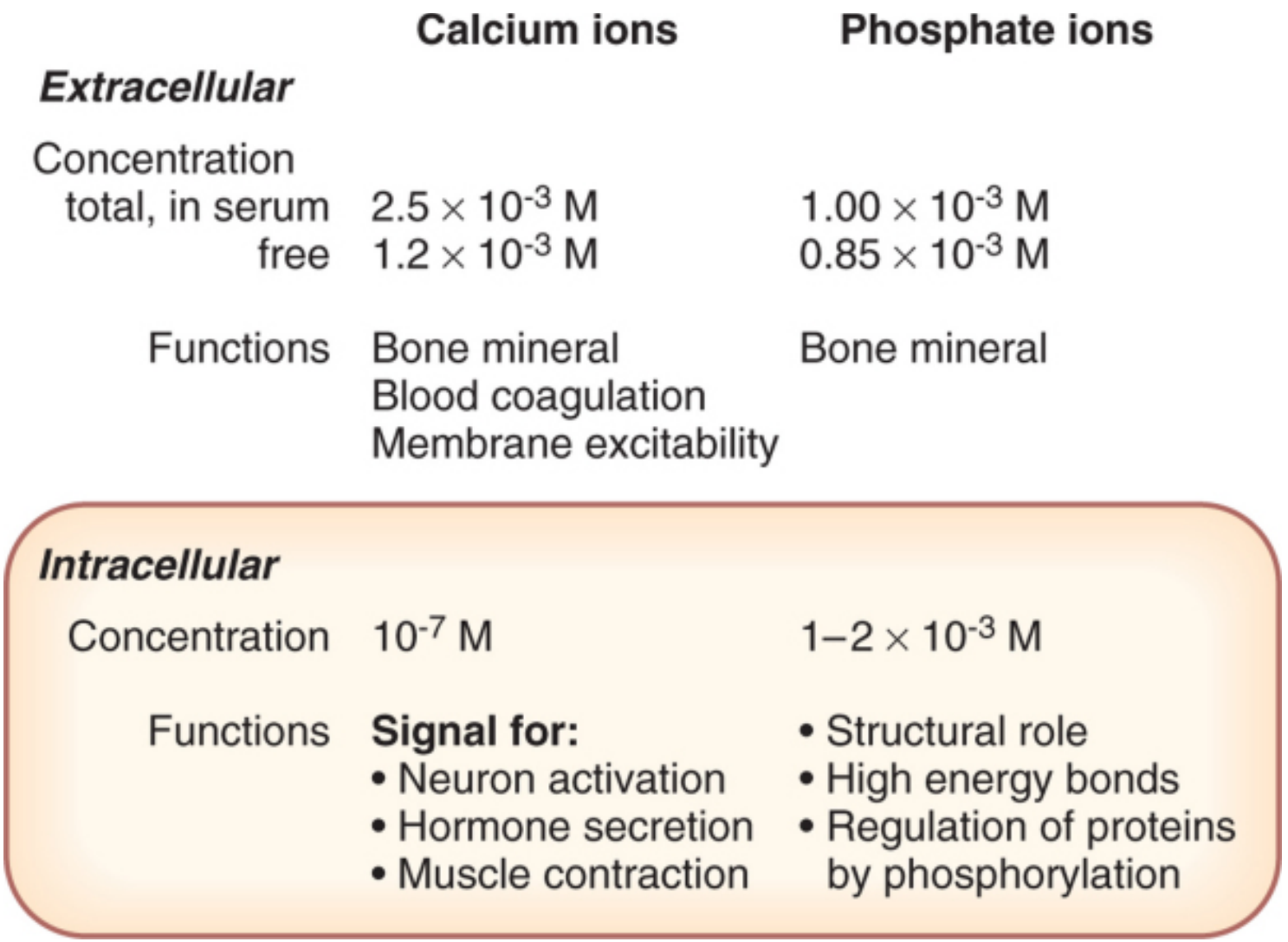
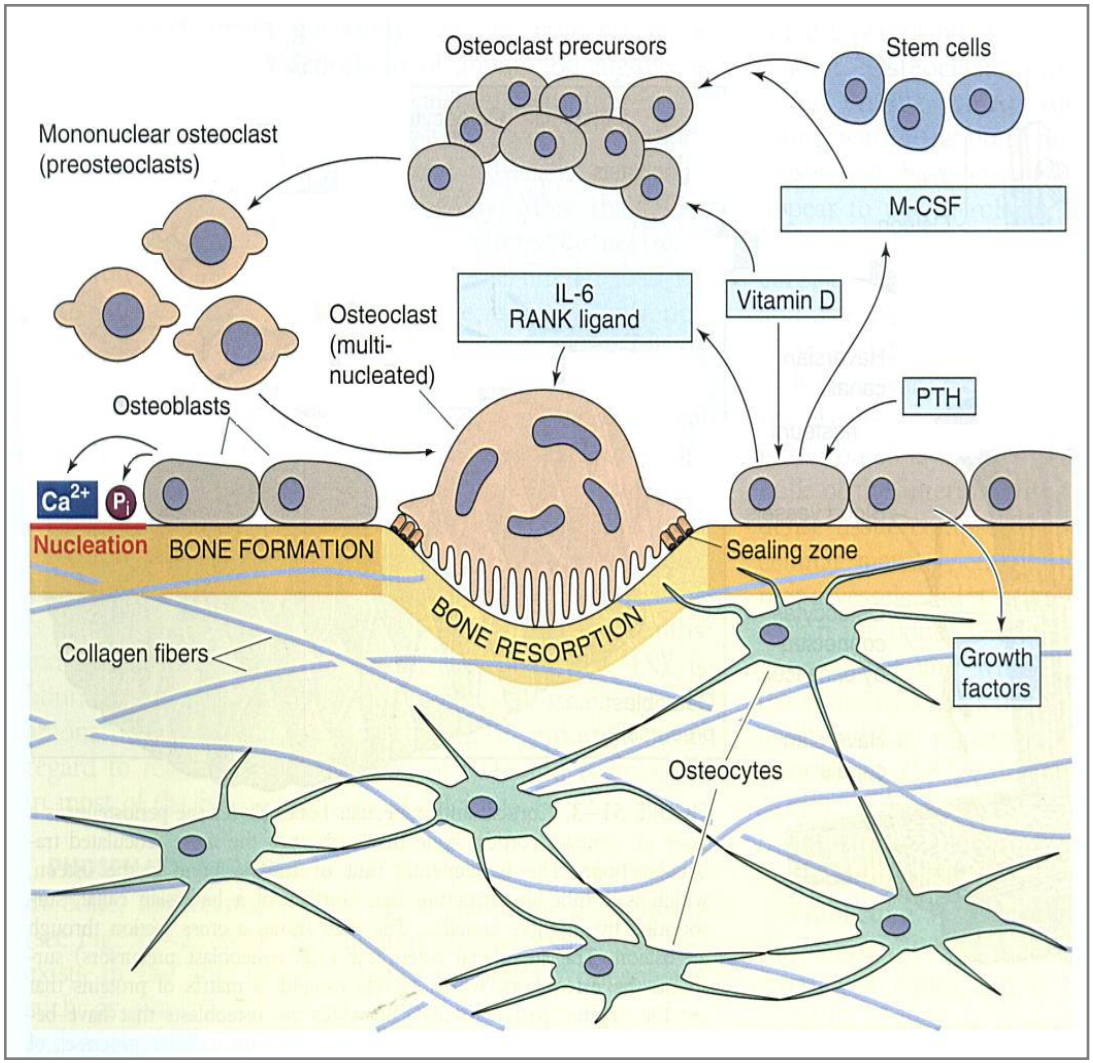


Figure 27-1 Distribution and function of calcium and phosphate. Note the dramatic differences between intracellular and extracellular concentrations of calcium ion and the dramatically different functions of calcium and phosphate inside cells.

Formação e Ressorção Óssea



M-CSF: macrophage colony stimulating factor

RANK : Receptor for activation of nuclear factor-kB

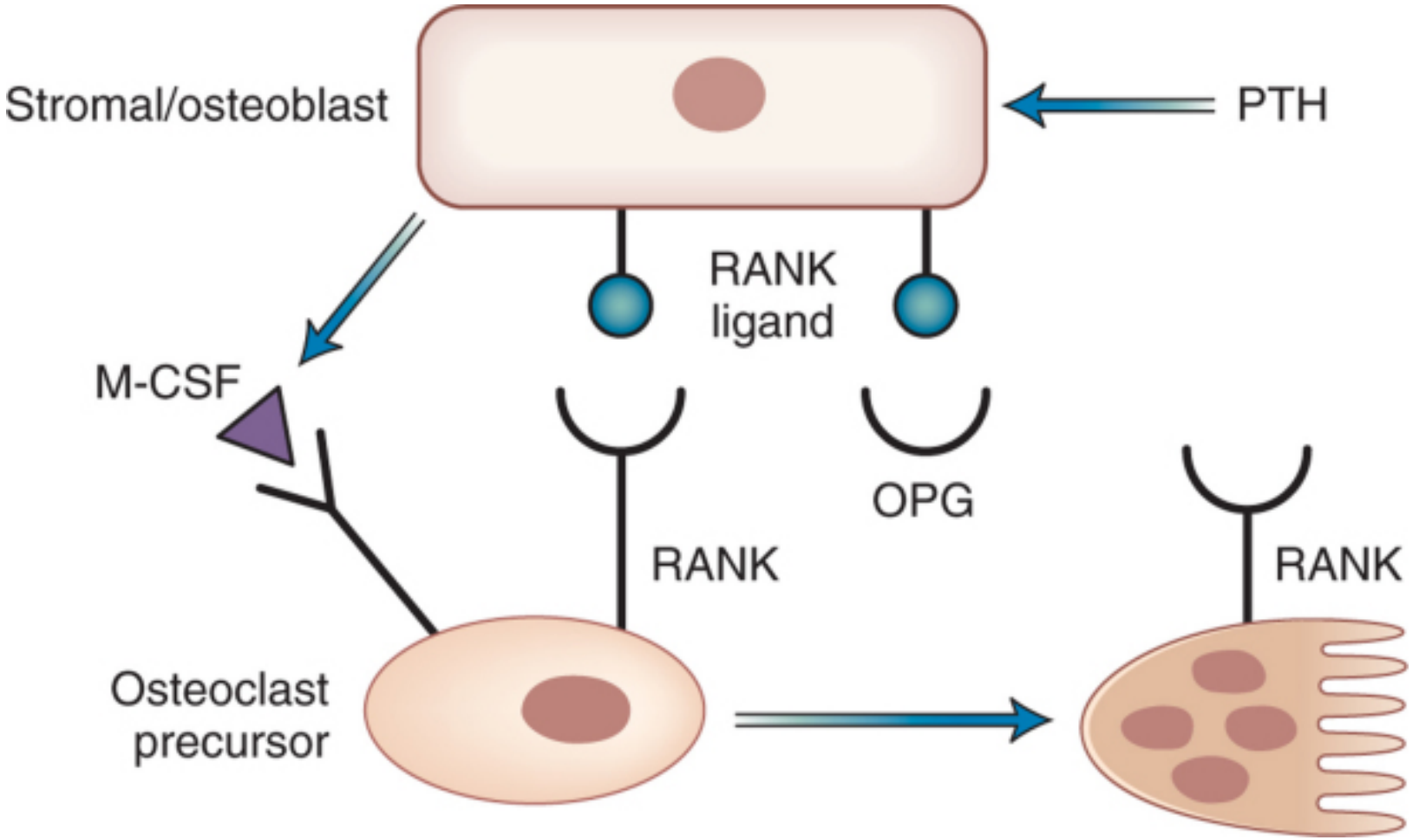
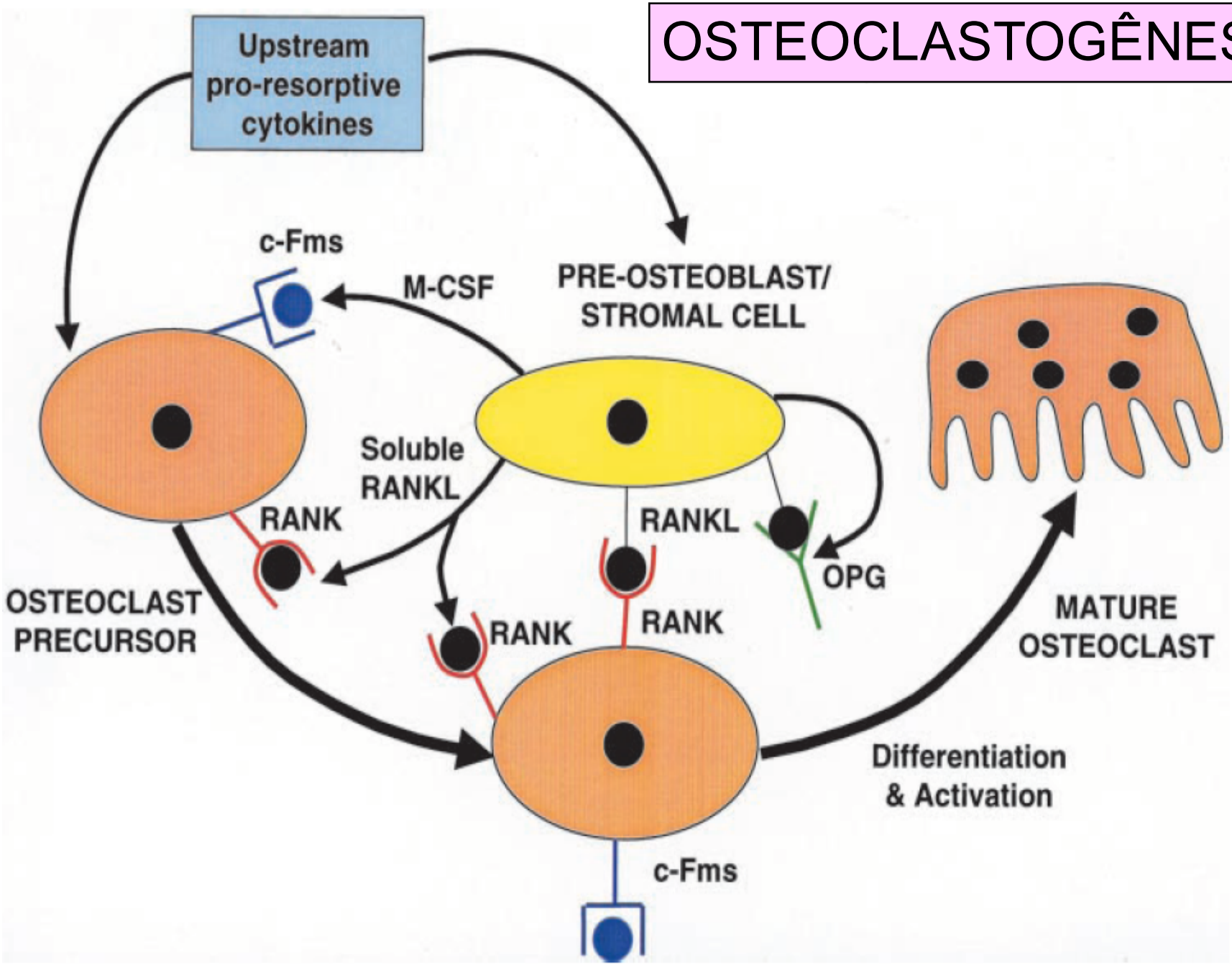
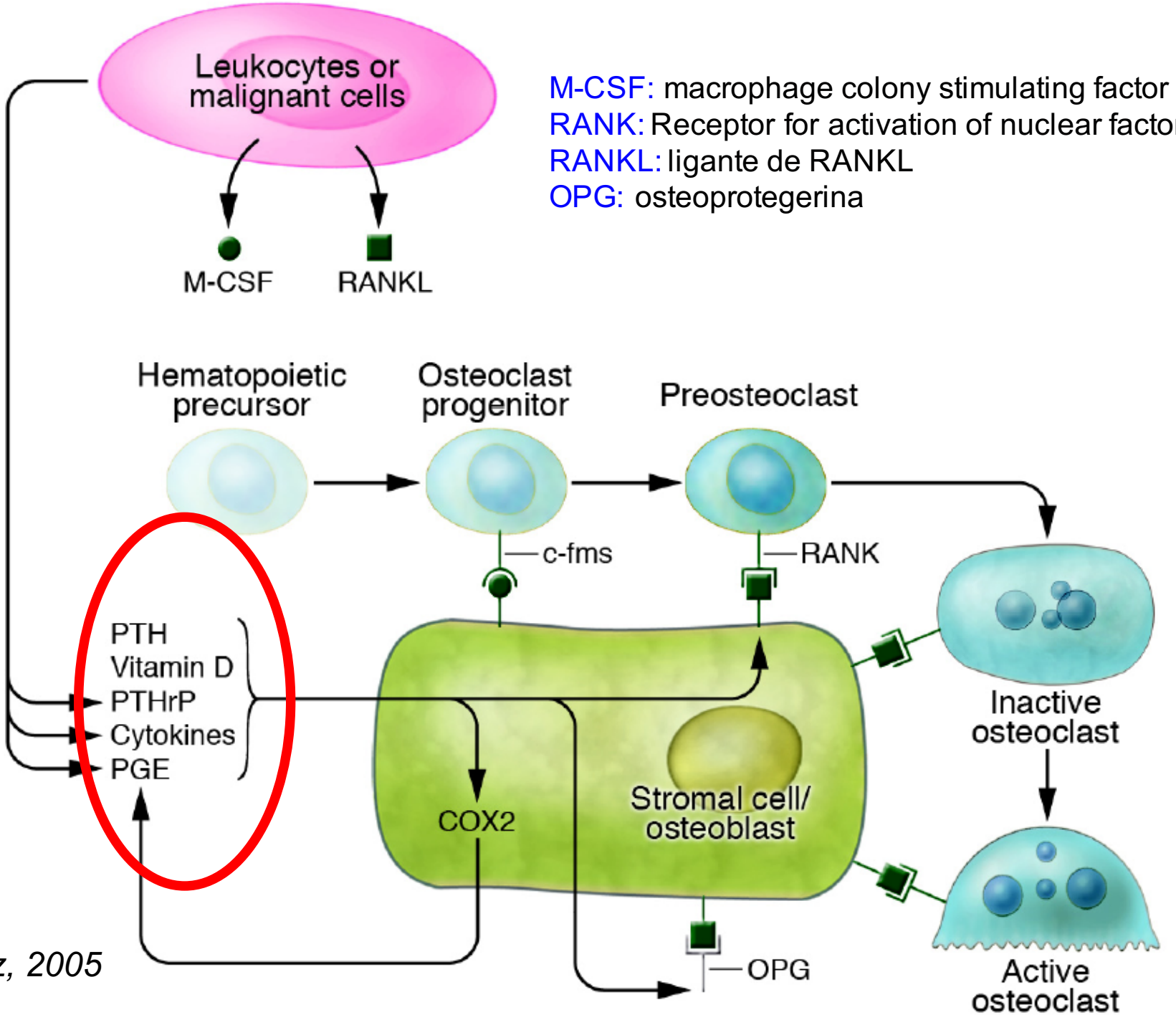


Figure 27-9 Stromal cell control of osteoclastogenesis and osteoclast activity. Parathyroid hormone (PTH) acts on PTH/PTH-related protein (PTHrP) receptors on precursors of osteoblasts to increase the production of macrophage colony–stimulating factor (M-CSF) and RANK (receptor activator of nuclear factor κB) ligand and to decrease the production of osteoprotegerin (OPG). M-CSF and RANK ligand stimulate the production of osteoclasts and increase the activity of mature osteoclasts by binding to the receptor RANK. OPG blocks the interaction of RANK ligand and RANK.

OSTEOCLASTOGÊNESE





M-CSF: macrophage colony stimulating factor
RANK: Receptor for activation of nuclear factor-kB
RANKL: ligante de RANKL
OPG: osteoprotegerina

Raiz, 2005

PTH: Mechanims of action

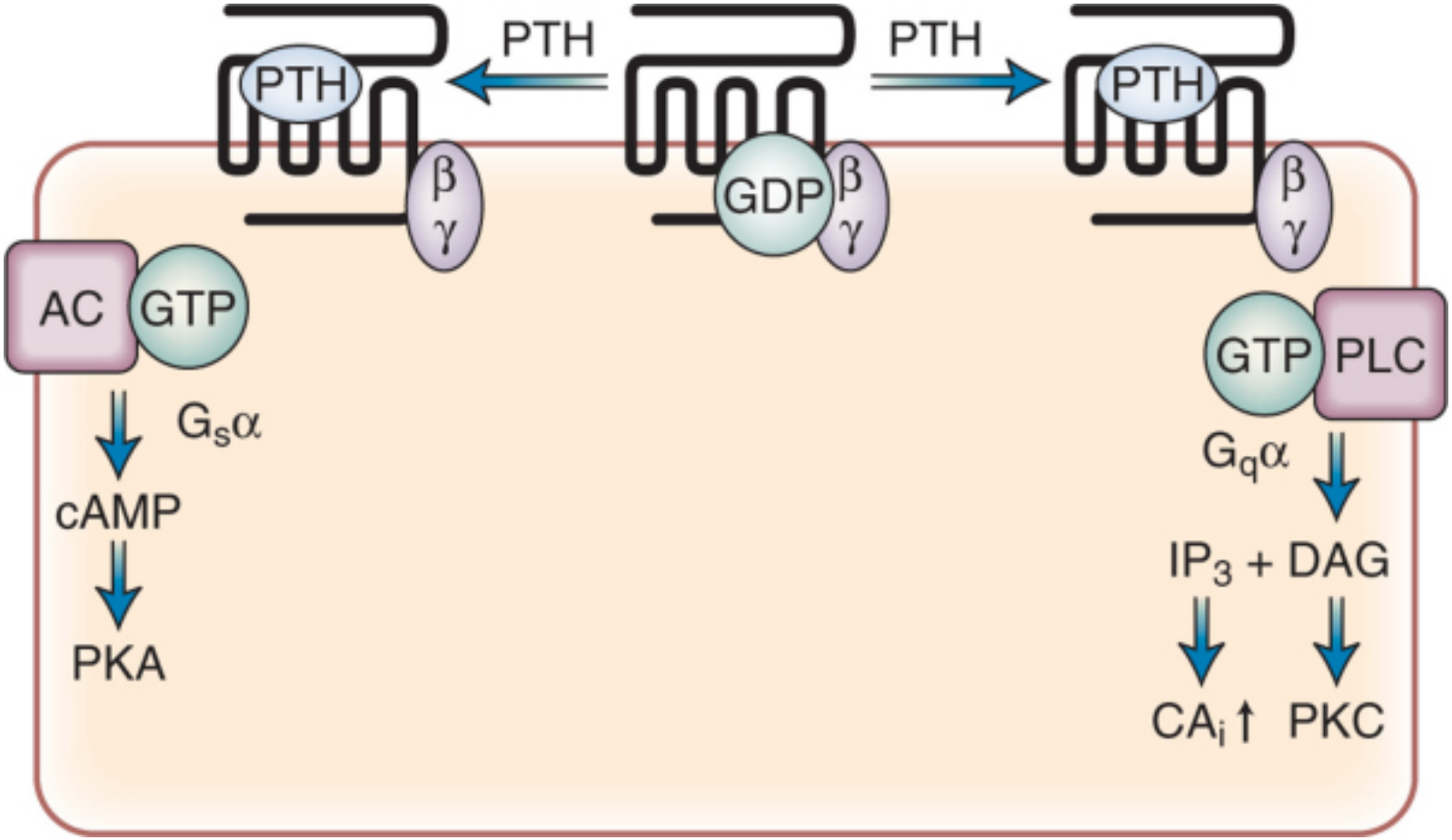


Figure 27-10 Parathyroid hormone (PTH)/PTH-related protein (PTHrP) receptors act as nucleotide exchangers. PTH binding to the receptor leads to exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) bound to Ga subunits. Ga subunits bound to GTP are released from the receptor and from the βγ subunits and then activate effectors. $G_s\alpha$ activates adenylate cyclase (AC), leading to the formation of cyclic adenosine monophosphate (cAMP), which then activates protein kinase A (PKA). $G_q\alpha$ and related a subunits activate phospholipase C (PLC). PLC hydrolyzes phosphotidyl inositol (1,4,5)tris-phosphate to generate diacyl glycerol (DAG) and inositol (1,4,5)tris-phosphate (IP_3). The DAG then activates protein kinase C (PKC), and the IP_3 activates a receptor on microsomal vesicles that directs the movement of calcium from microsomal vesicles into the cytosol. CA_i, intracellular calcium.

Secreção de PTH

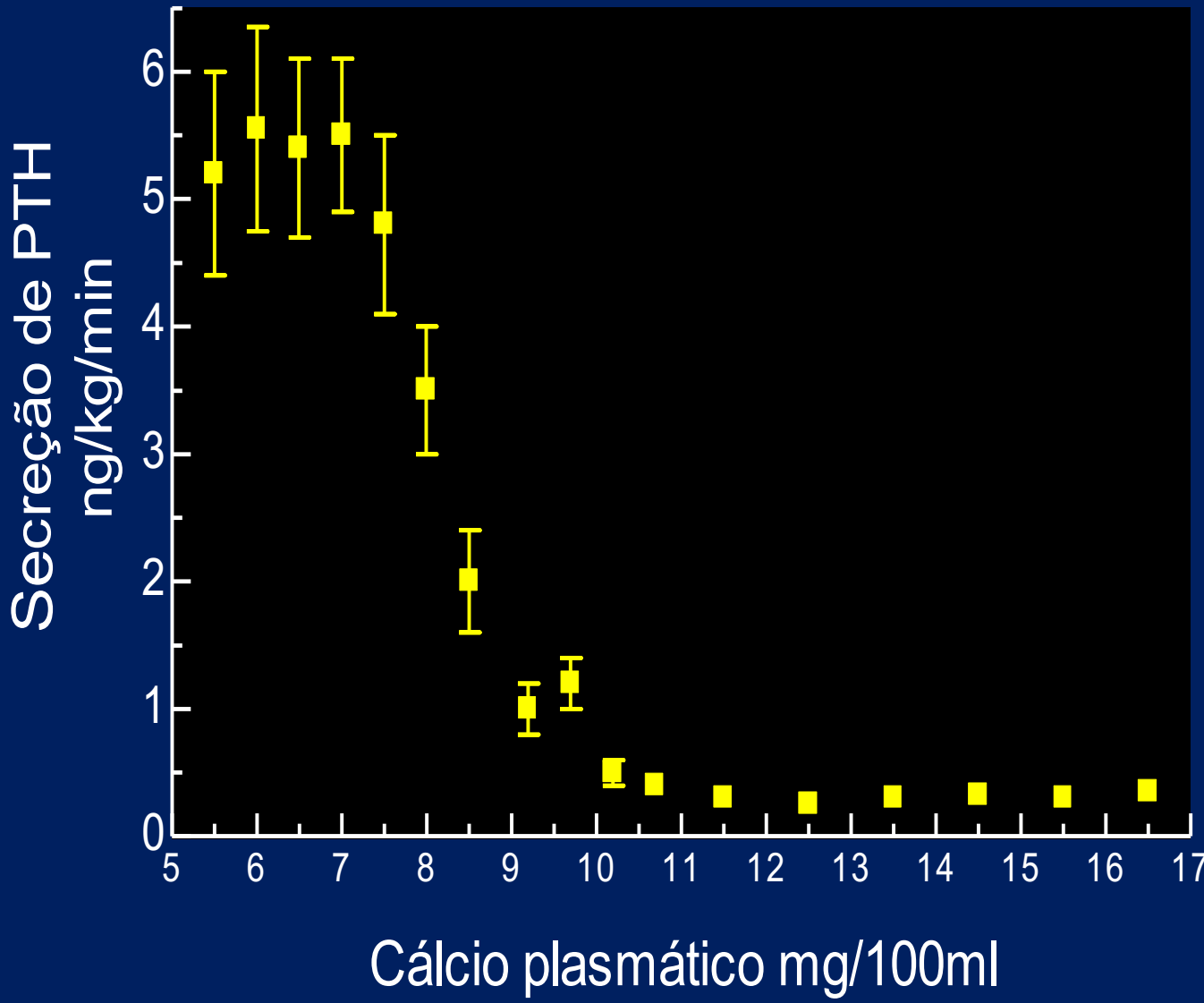
- Receptor de cálcio extracelular (**sensor de cálcio**) na glândula paratireóide (GPCR)

- Ligação do cálcio a esse receptor causa:

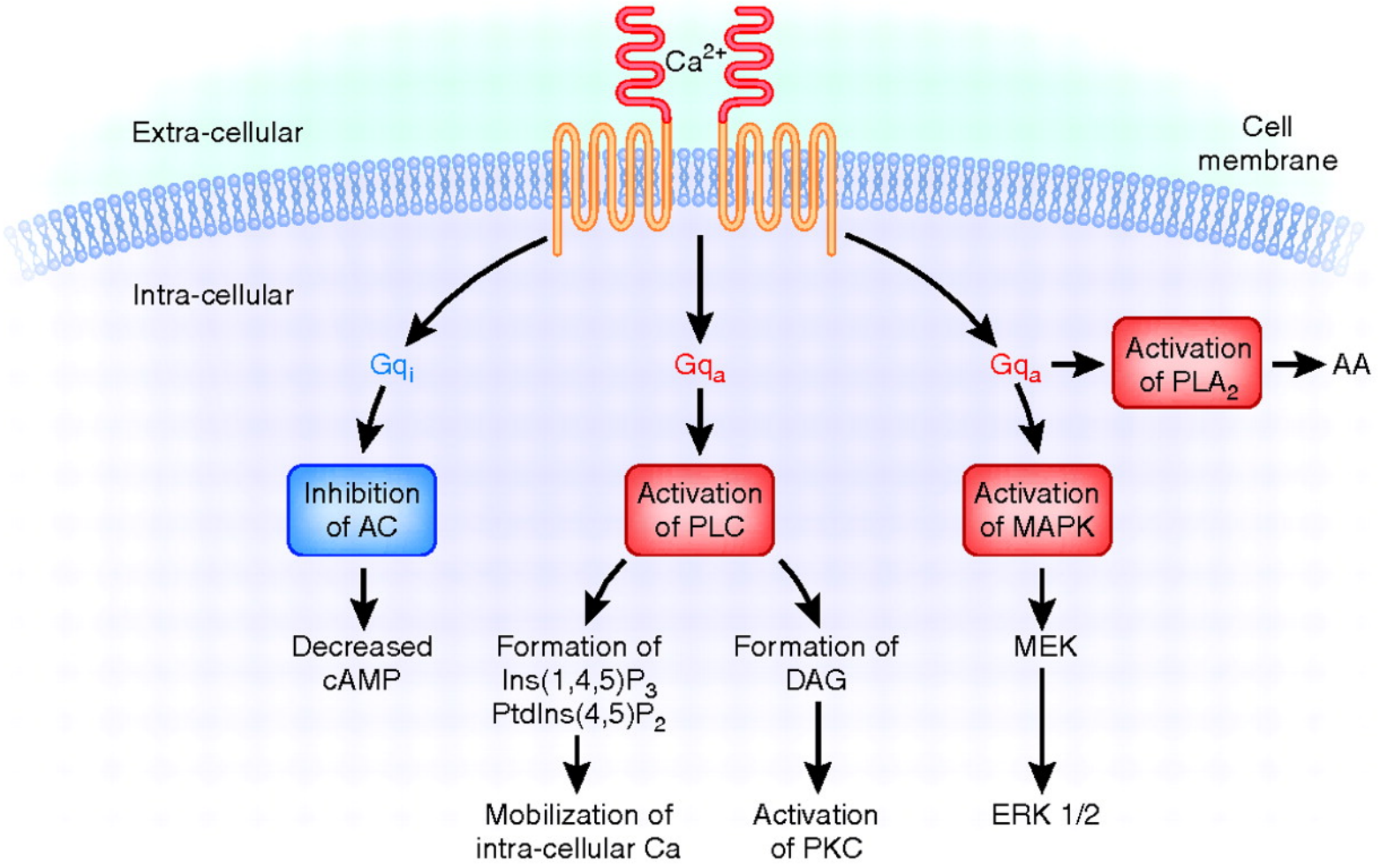
  - ativação da fospolipase C (↑ DAG e IP3) e aumento de cálcio intracelular
  - Iinibição da adenil ciclase (↓ AMPc)
  - aumenta a concentração de Ca+ intracelular que resulta em diminuição de secreção de PTH (Inibição da transcrição do gene do PTH)
  - Diminui a síntese e secreção de PTH

- **Hipercalcemia hipocalciúrica familial**: mutação inativadora do gene do sensor de cálcio (Cálcio alto com PTH inapropriadamente alto)

Resposta do PTH às alterações nas concentrações plasmáticas de cálcio



Pathways by which the CaSR homodimer signals in cells after binding of Ca2+ to the extracellular domains (red line) of the CaSR molecules in the homodimeric pair.



Kumar R , Thompson J R JASN 2011;22:216-224

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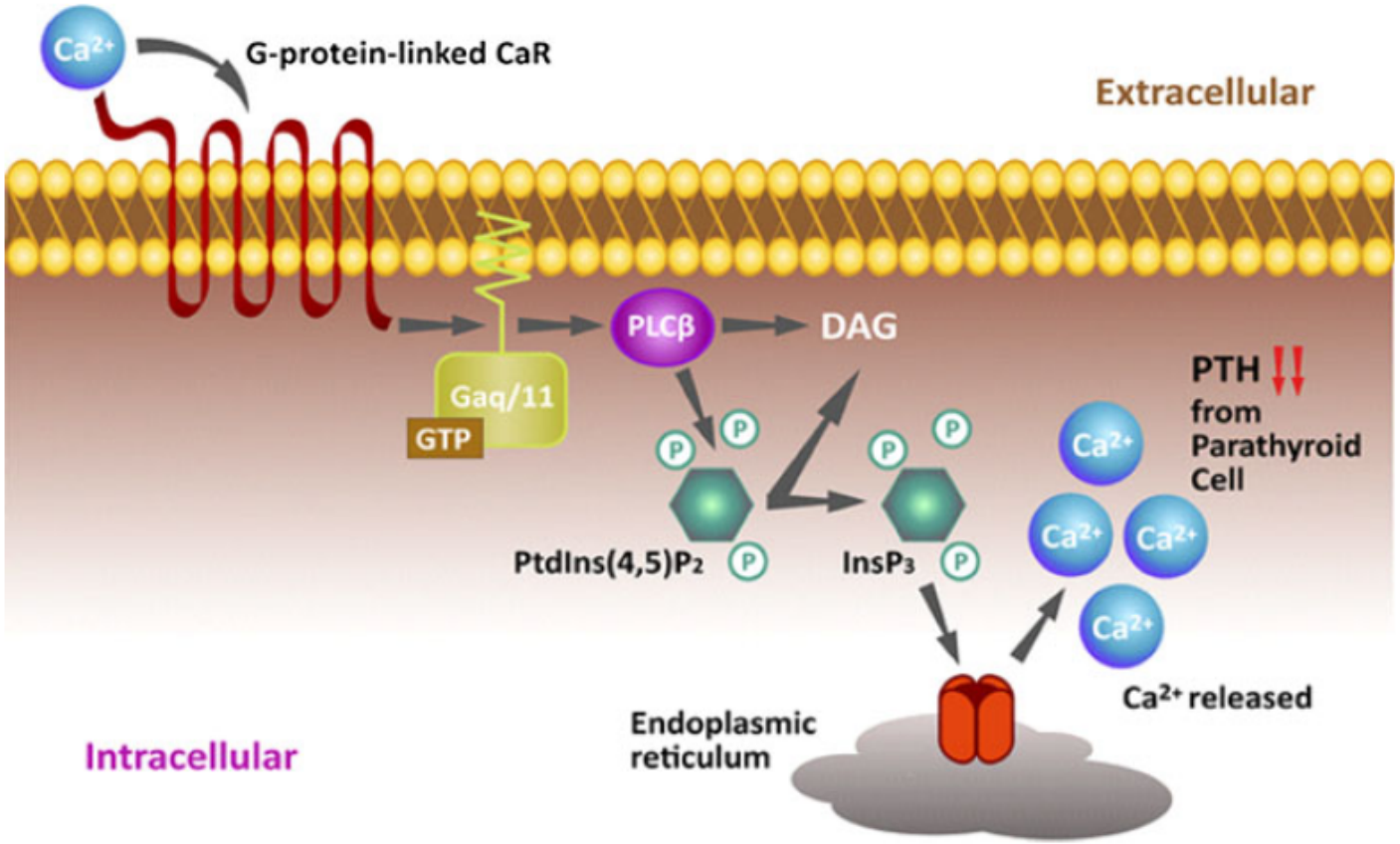
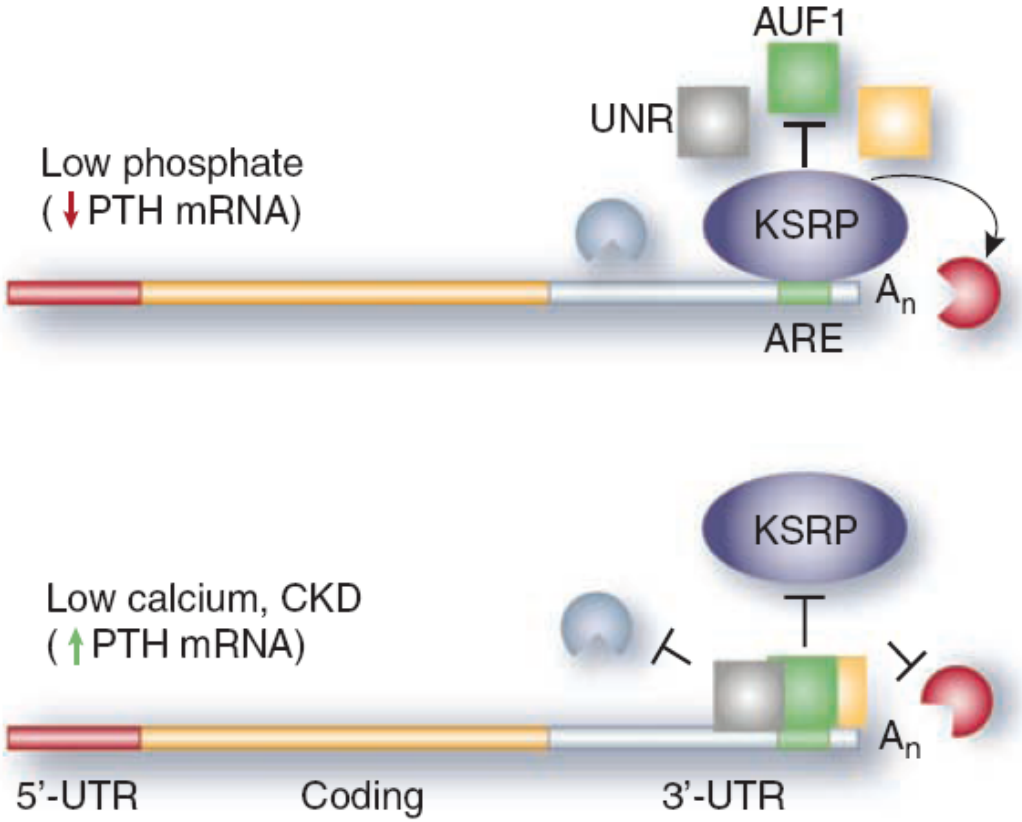
Calcium-sensing receptor



Leonidas H. Duntas • Nikolaos Stathatos 2011

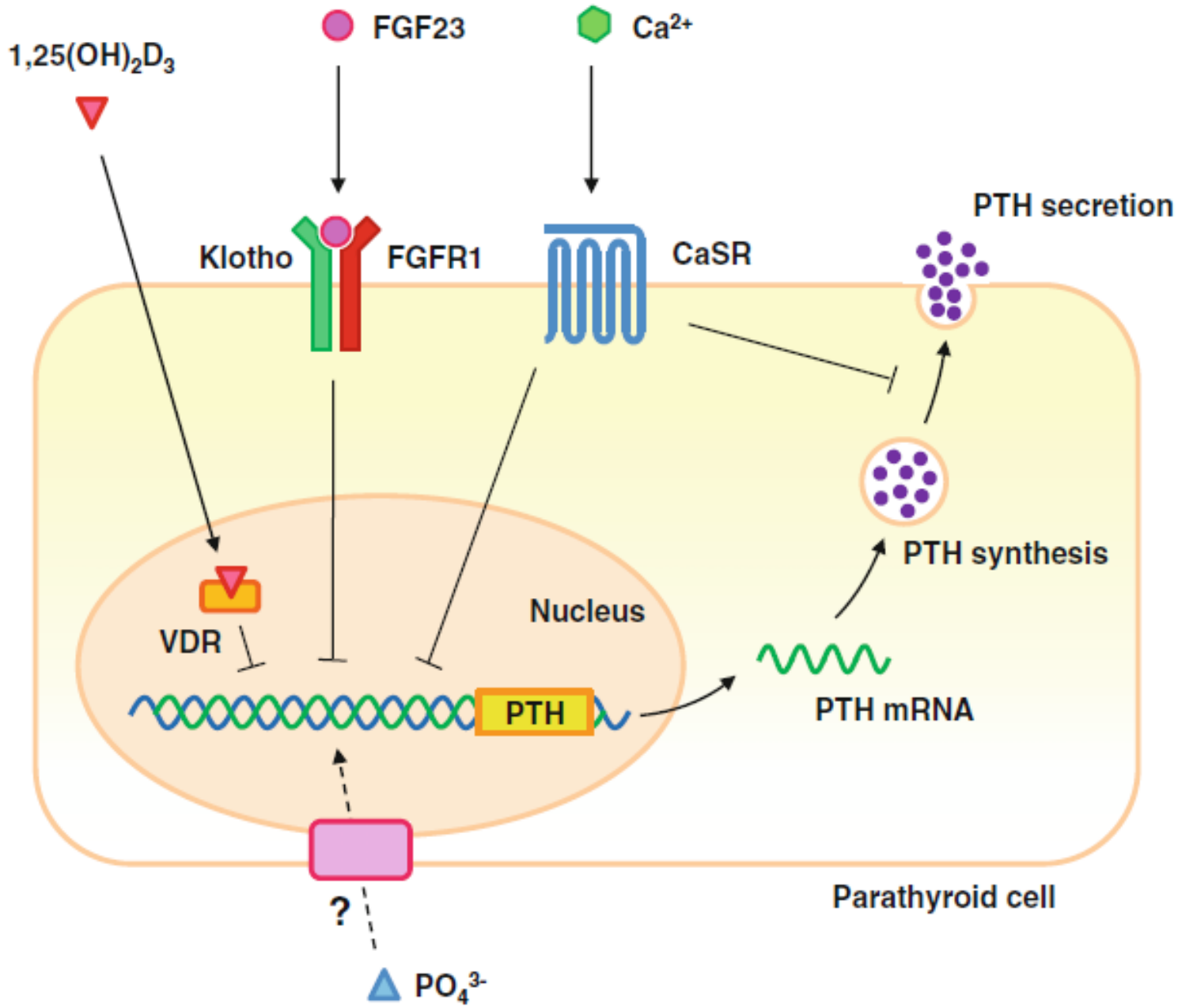
Cálcio e Fósforo no controle da expressão de RNAm de PTH



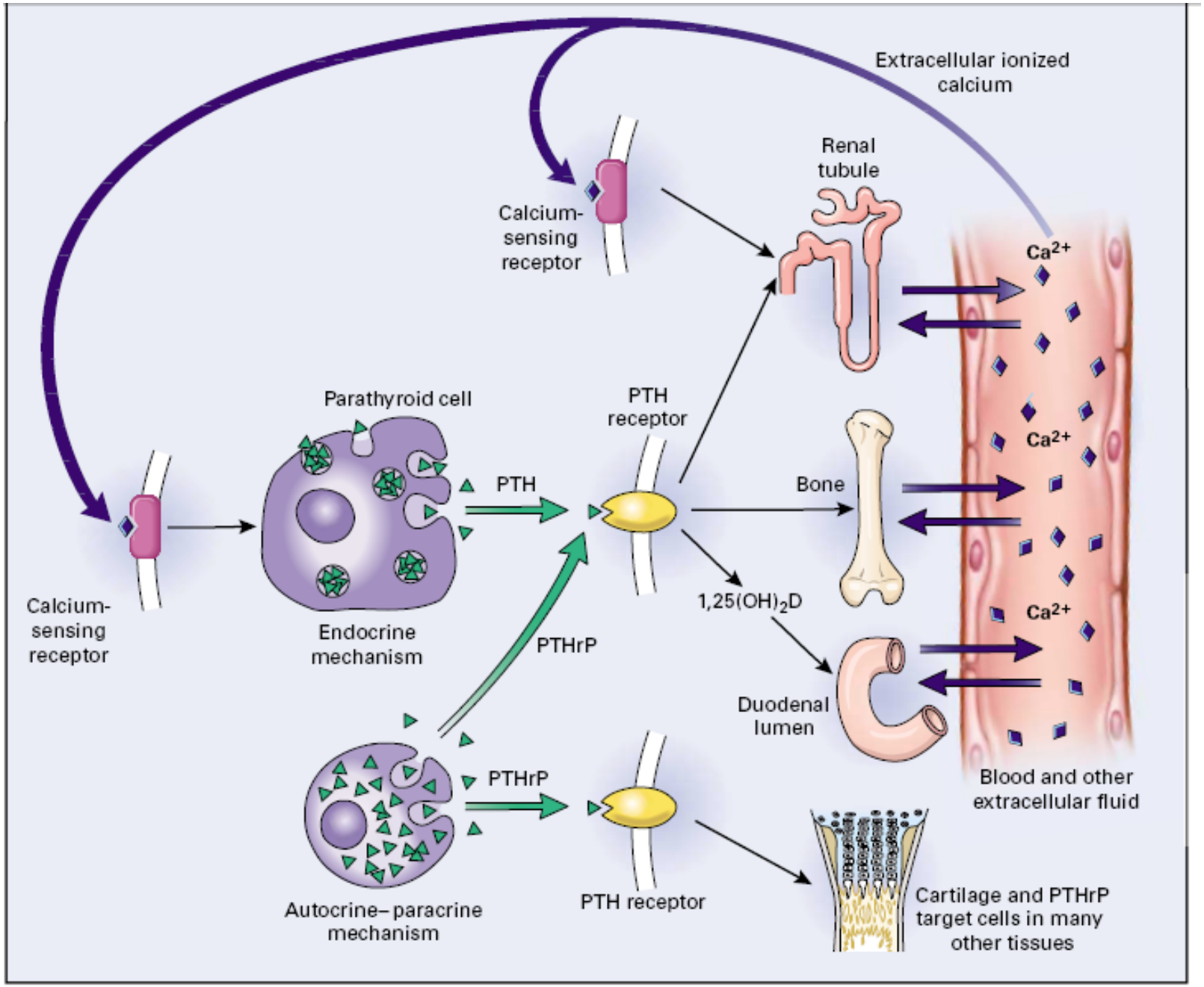
Justin Silver1 and Tally Naveh-Many, 2009.

Model for the regulation of PTH mRNA stability by changes in calcium and Pi levels and experimental chronic kidney disease, the role of PTH mRNA-interacting proteins. **Low serum Pi** increases the association of PTH mRNA with KSRP through the PTH mRNA 30-UTR ARE (green box). KSRP may then recruit the **exosome** to PTH mRNA leading to decreased PTH mRNA stability and levels. A **calcium-restricted diet** induces the binding of a stabilizing complex consisting of AUF1 and Unr to the PTH mRNA ARE. This complex competes for the binding of KSRP to PTH mRNA and thereby inhibits PTH mRNA degradation leading to increased PTH mRNA stability and levels. Similar to calcium depletion, kidney failure increases PTH gene expression and this is associated with decreased PTH mRNA–KSRP interaction compared with control rats.

***ARE**, Adenosine uridine rich element; **KSRP**, KH type-splicing regulatory protein; **PTH**, parathyroid hormone, **UTR** unstranslated region, **UNR** upstream of N-ras, **AUF1**: adenosine uridine-rich binding factor 1*


1,25(OH)2D3
FGF23
Ca2+
Klotho
FGFR1
CaSR
PTH secretion
PTH synthesis
VDR
Nucleus
PTH
PTH mRNA
?
PO4 3-
Parathyroid cell

Komaba, 2011



TEPHEN, 2000; NEJM

FUNÇÕES OSTEOBLÁSTICAS REGULADAS PELO PTH

Proliferação

Metabolismo celular
- Transporte de Gli e aa
- Síntese de glicogênio, oxidação gli
- Síntese de RNA, Proteína, lípides

Transporte de íons
- Transporte de Ca, fosfato, ions H+
- NaK ATPase

Estrutura de Membrana e citoesqueleto
- Actina, tubulina, vimentina

Responsividade hormonal
- Expressão de receptor de PTH/ PTHRP
- Expressão de receptor de EGF
- Expressão do receptor da vitam D

Síntese e secreção de prot. Matrix
- Colágeno
- Osteonectina
- Osteopontina

Síntese e secreção de enzimas
- FA
- Colagenase
- Inibidor da metaloproteinase

Liberação de fatores de crescimento

Parácrinos, citocinas
- IGF-I, IGF-II, IGF-BP
- TGF-beta
- M-CSF
- Prostaglanidina E2
- IL-6
- RANKL, osteoprotegerina

PTH RECOMBINANTE HUMANO NA OSTEOPOROSE

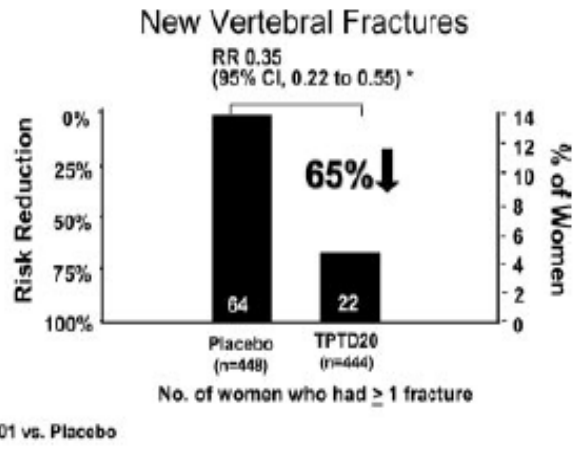


FIG. 2. Reduction in the risk of new morphometric vertebral fractures in postmenopausal women with severe osteoporosis after teriparatide, 20 μg/d, over a median treatment period of 19 months, compared with placebo. [Derived from Ref. 50.]

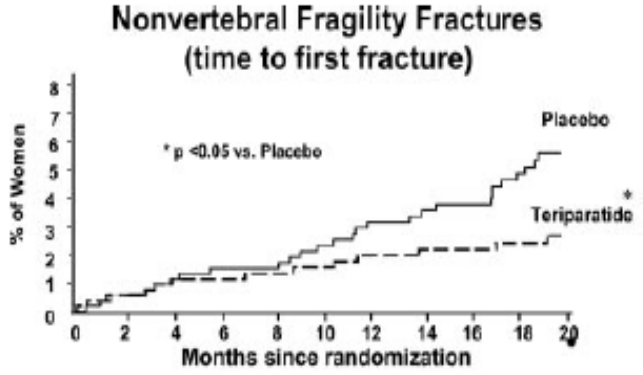
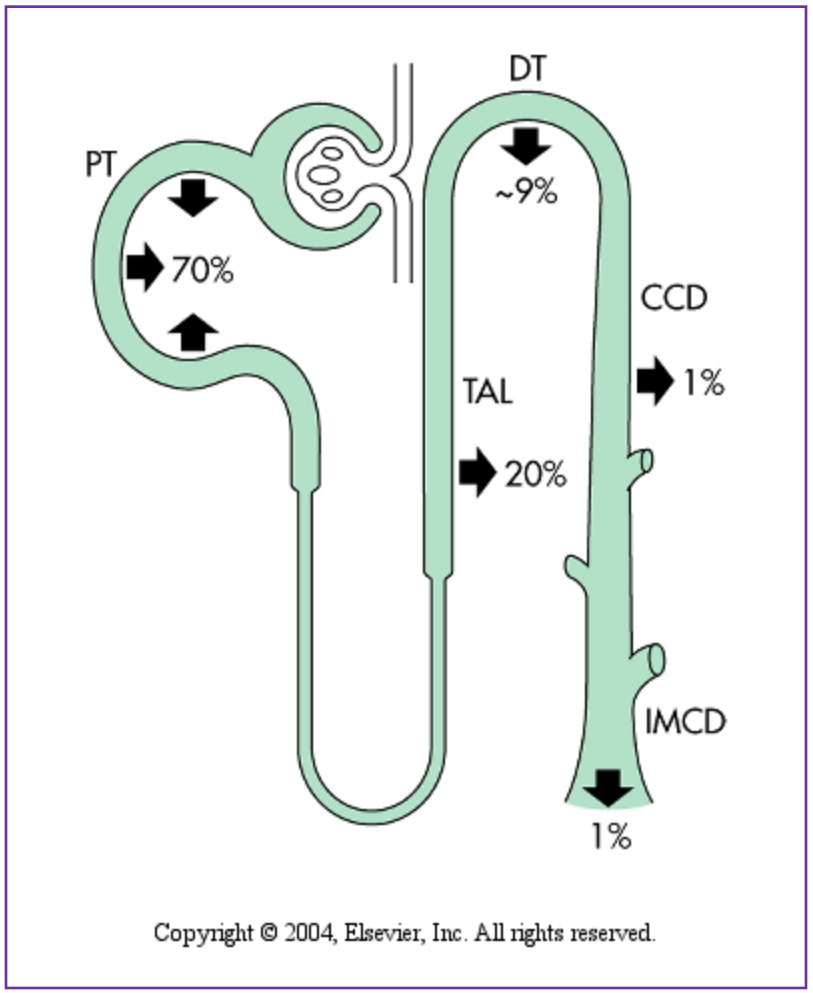
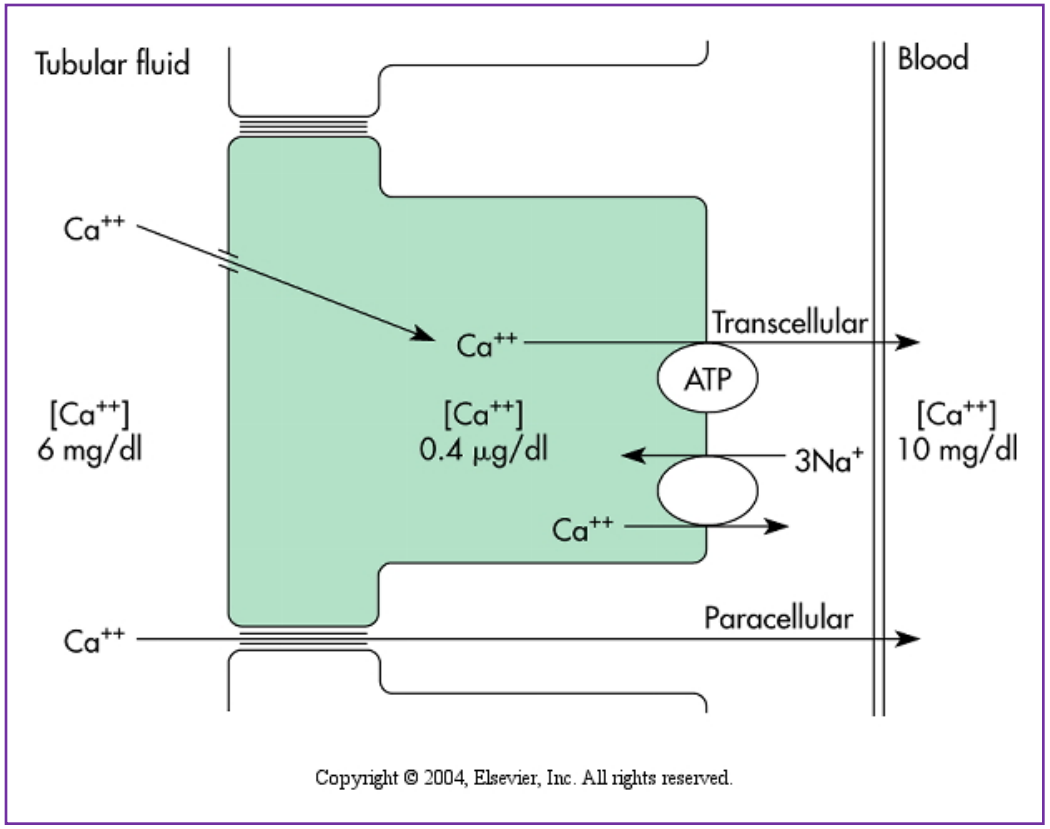


FIG. 3. Cumulative incidence of new nonvertebral fractures, occurring with minimal trauma, in postmenopausal women after teriparatide therapy, 20 μg/d, over a median treatment period of 19 months: relative risk, 0.47 (confidence interval, 0.22–0.88) compared with placebo (Eli Lilly, Canada, Forteo Product Mongraph). [Derived from Ref. 50.]

Transporte tubular de Cálcio

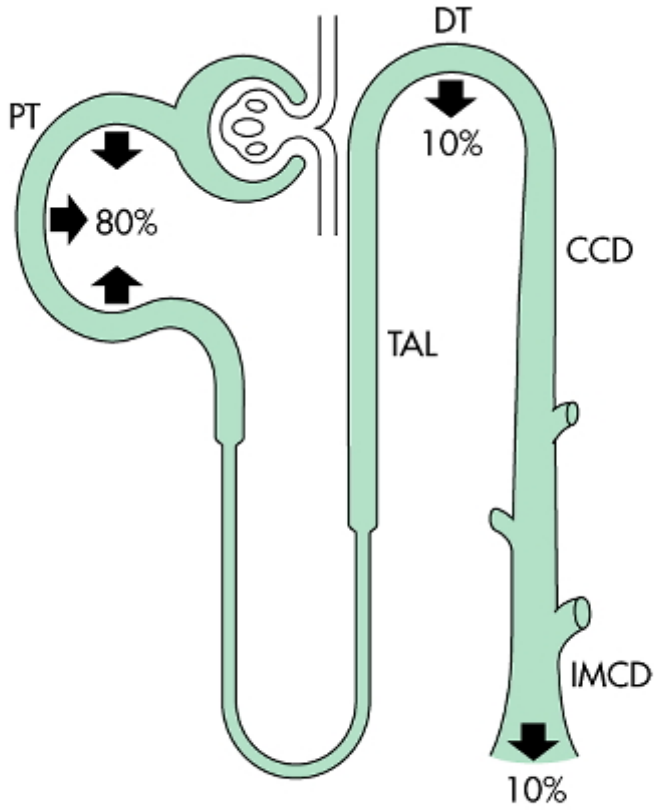




TP: transcelular e paracelular. TAL ramo ascendente grosso: Paracelular.

PTH estimula a reabsorção de cálcio no no túbulo distal: estimula a translocação de canais de Ca para a membrana apical e aumenta a atividade do trocador Na/Ca na membrana basolateral.

Transporte tubular de Fosfato



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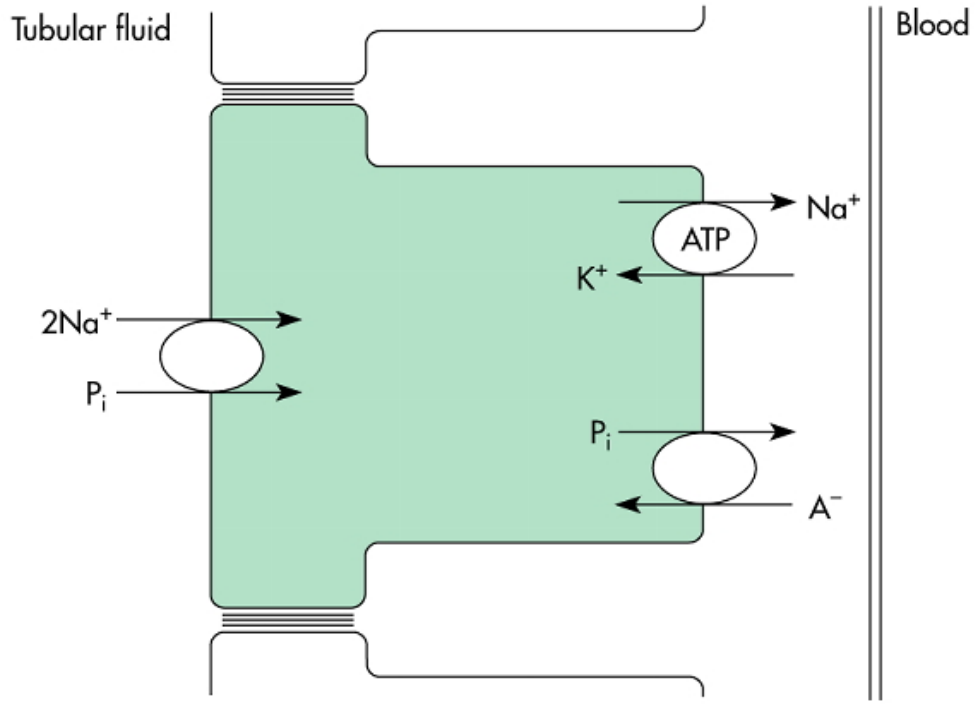

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PTH aumenta a excreção renal de fosfato no TP, induzindo a internalização e degradação lisossomal do co-transportador sódio-fosfato (NPT2).

Questões Orientadoras:

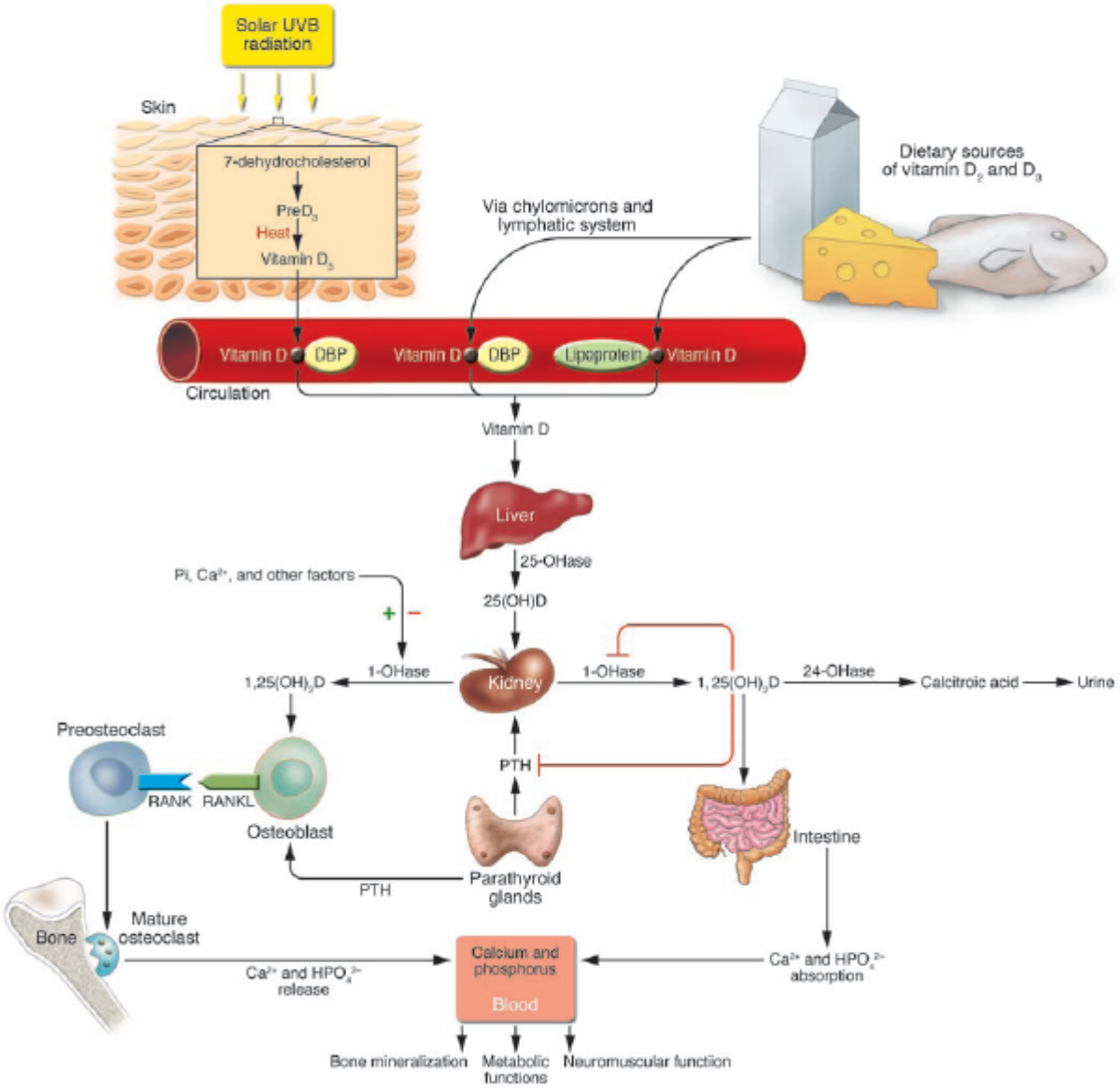
3. Discuta a biossíntese da forma ativa da Vitamina D.

4. Discuta as ações da vitamina D no intestino, no osso e na paratireóide. Quais os mecanismos de ação da vitamina D?.

5. Quais são as principais consequências da deficiência da vitamina D, em relação ao osso?

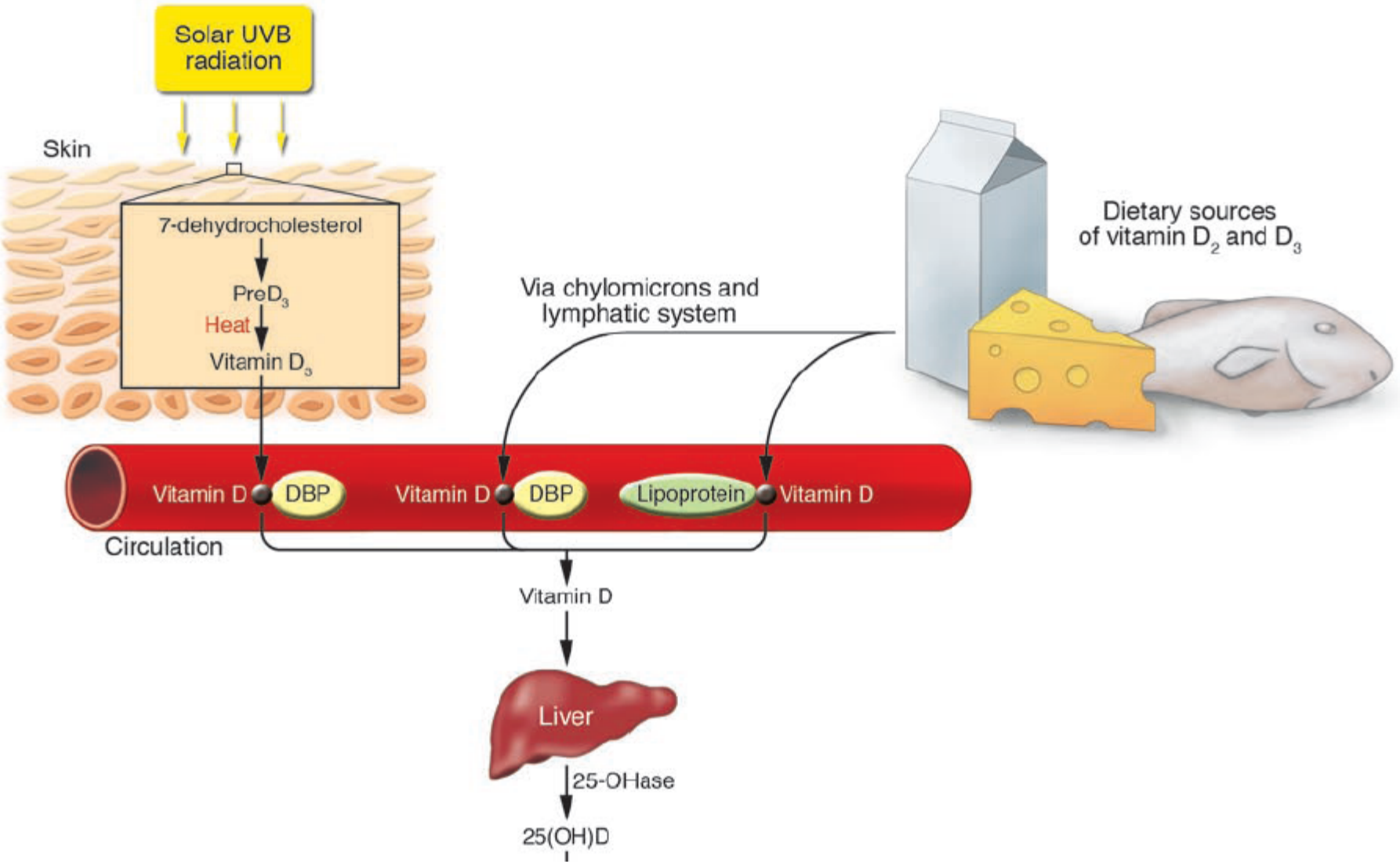
SEMINÁRIO - Paratireóide

3 - Biossíntese da forma ativa da Vitamina D.



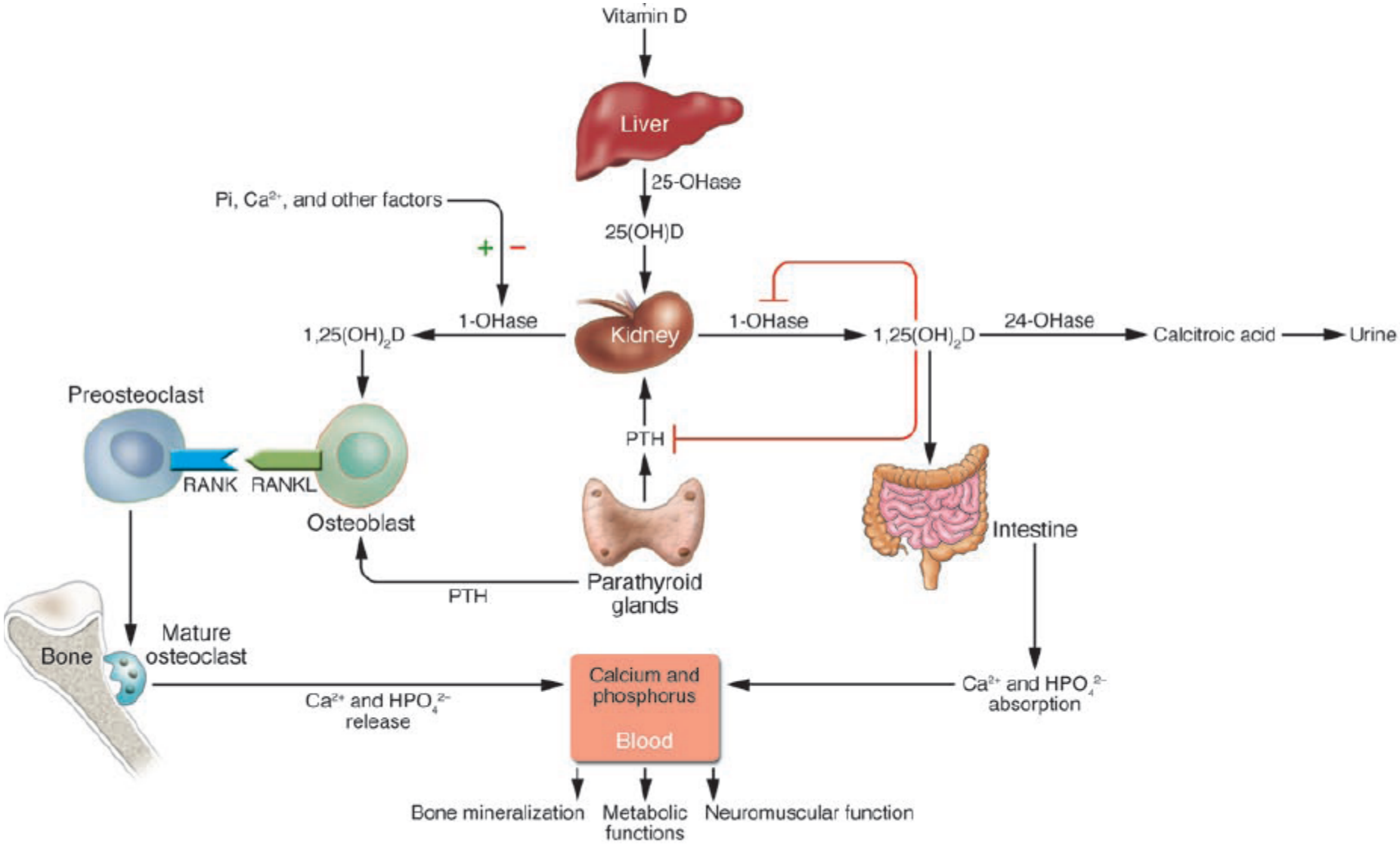
SEMINÁRIO - Paratireóide

3 - Biossíntese da forma ativa da Vitamina D.

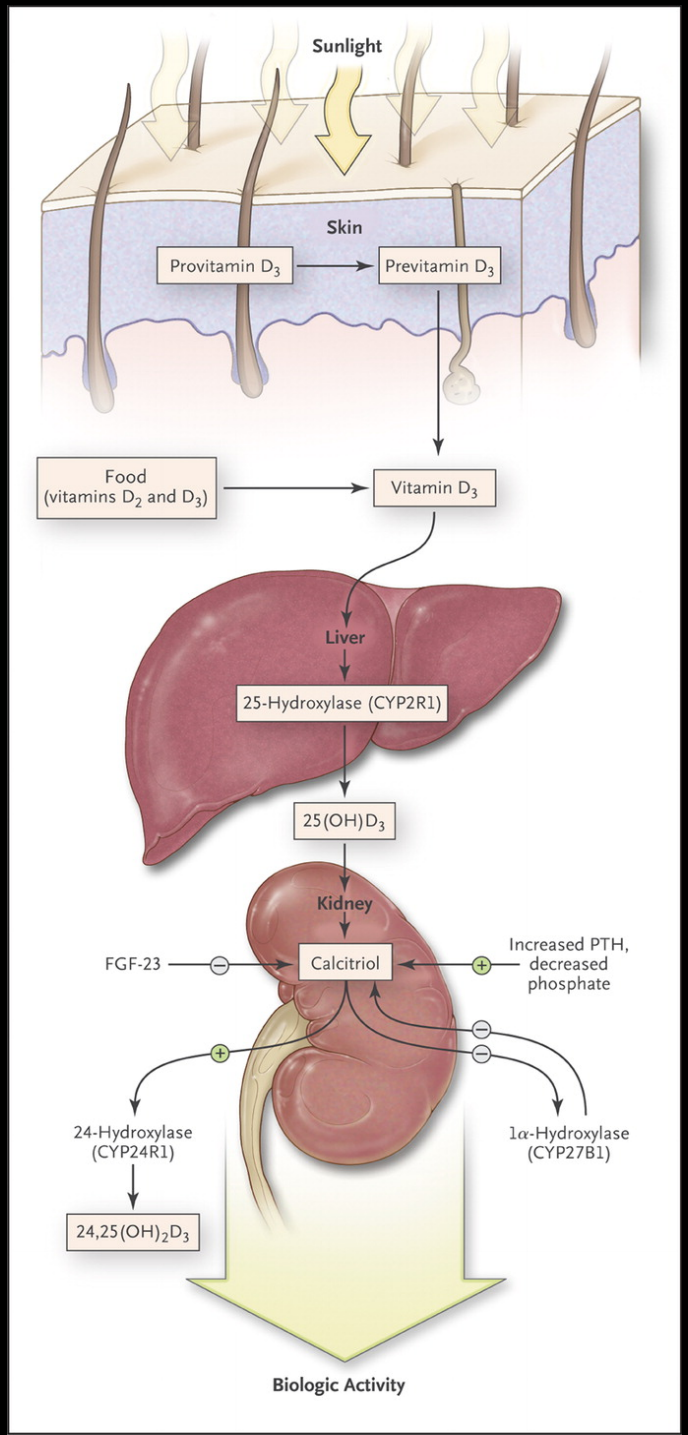


SEMINÁRIO - Paratireóide

3 - Biossíntese da forma ativa da Vitamina D.



Synthesis and Metabolism of Vitamin D.



Vitamin D is initially generated in the **skin** from the nonenzymatic conversion of provitamin D_3 to previtamin D_3. Dietary intake of vitamin D is usually relatively limited, since few foods, with the exception of certain kinds of fish, contain sizable amounts; supplements are commonly used.

Vitamin D is either stored in adipose tissue or converted in the **liver** by the enzyme 25-hydroxylase to **25-hydroxyvitamin D_3 (25[OH]D_3)**, the form that circulates in the highest concentration and reflects solar and dietary exposure.

It is converted to the active metabolite, **1,25-dihydroxyvitamin D (1,25$[OH]_2D$), or calcitriol**, in the **kidney**, although other tissues have 1α-hydroxylase enzymatic activity.

The synthesis of calcitriol is **enhanced** (+) by increasing levels of parathyroid hormone (**PTH**), which rise in response to lower levels of serum calcium. Reduced levels of serum phosphate can also increase (+) the production of calcitriol.

Its synthesis is **suppressed** (–) by the production of fibroblast growth factor 23 (**FGF-23**), which is secreted by osteocytes in the bone matrix.

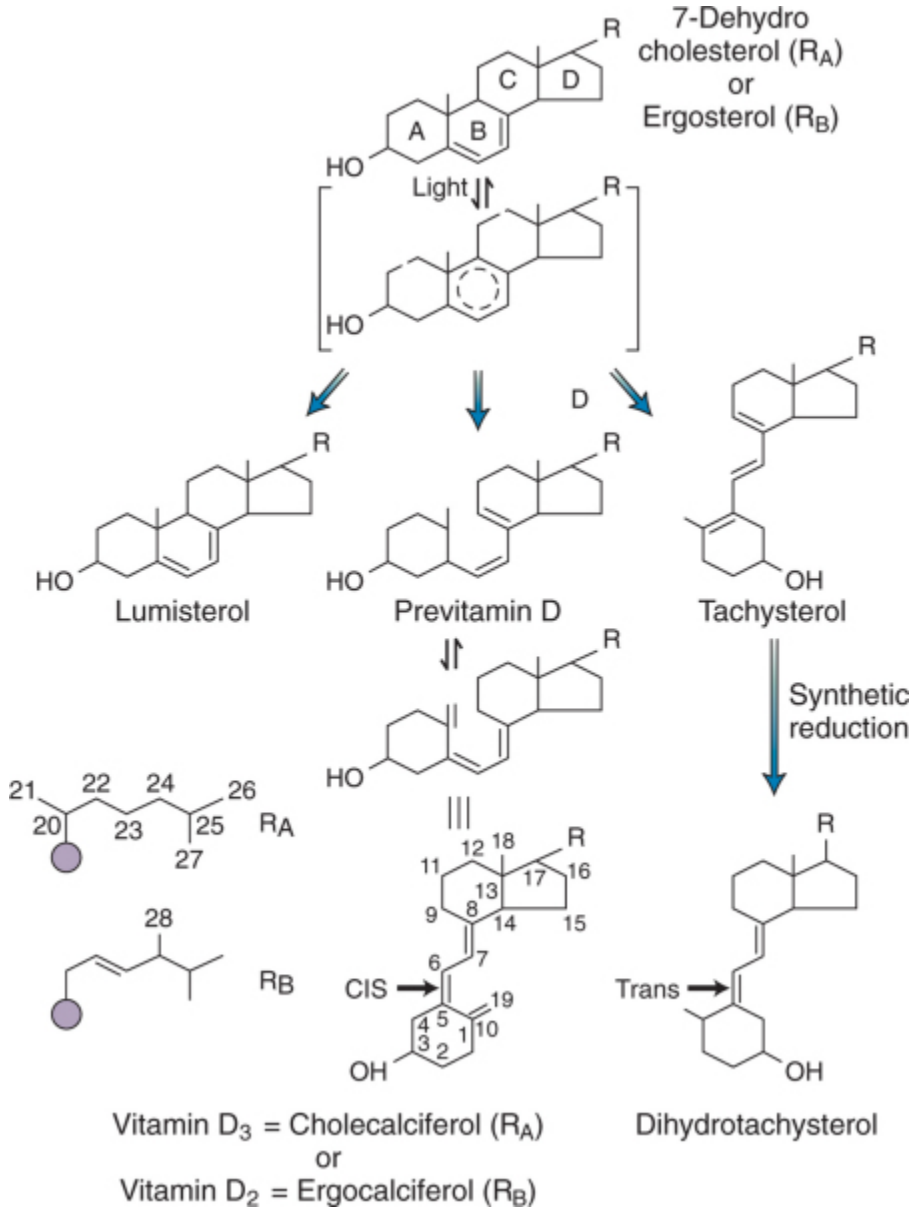
Calcitriol inhibits the activity of **1α-hydroxylase** (CYP27B1) and stimulates the activity of 24-hydroxylase (CYP24R1), an enzyme that promotes production of 24,25$(OH)_2D_3$, a vitamin D product that is not biologically active. In CYP2R1, CYP27B1, and CYP24R1, CYP denotes cytochrome P.

Rosen CJ. NEJM 2011;364:248-254.

The NEW ENGLAND JOURNAL of MEDICINE

SEMINÁRIO - Paratireóide

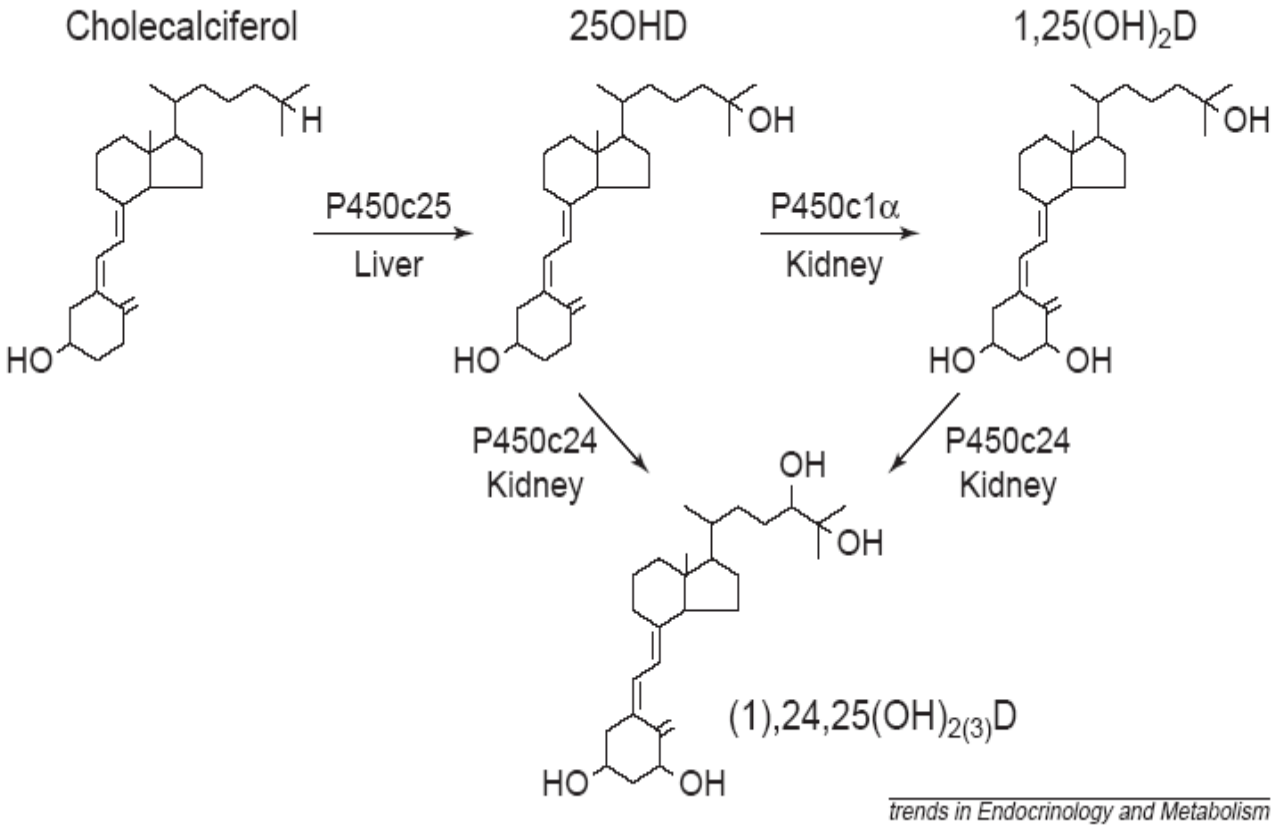
3 - Biossíntese da forma ativa da Vitamina D.

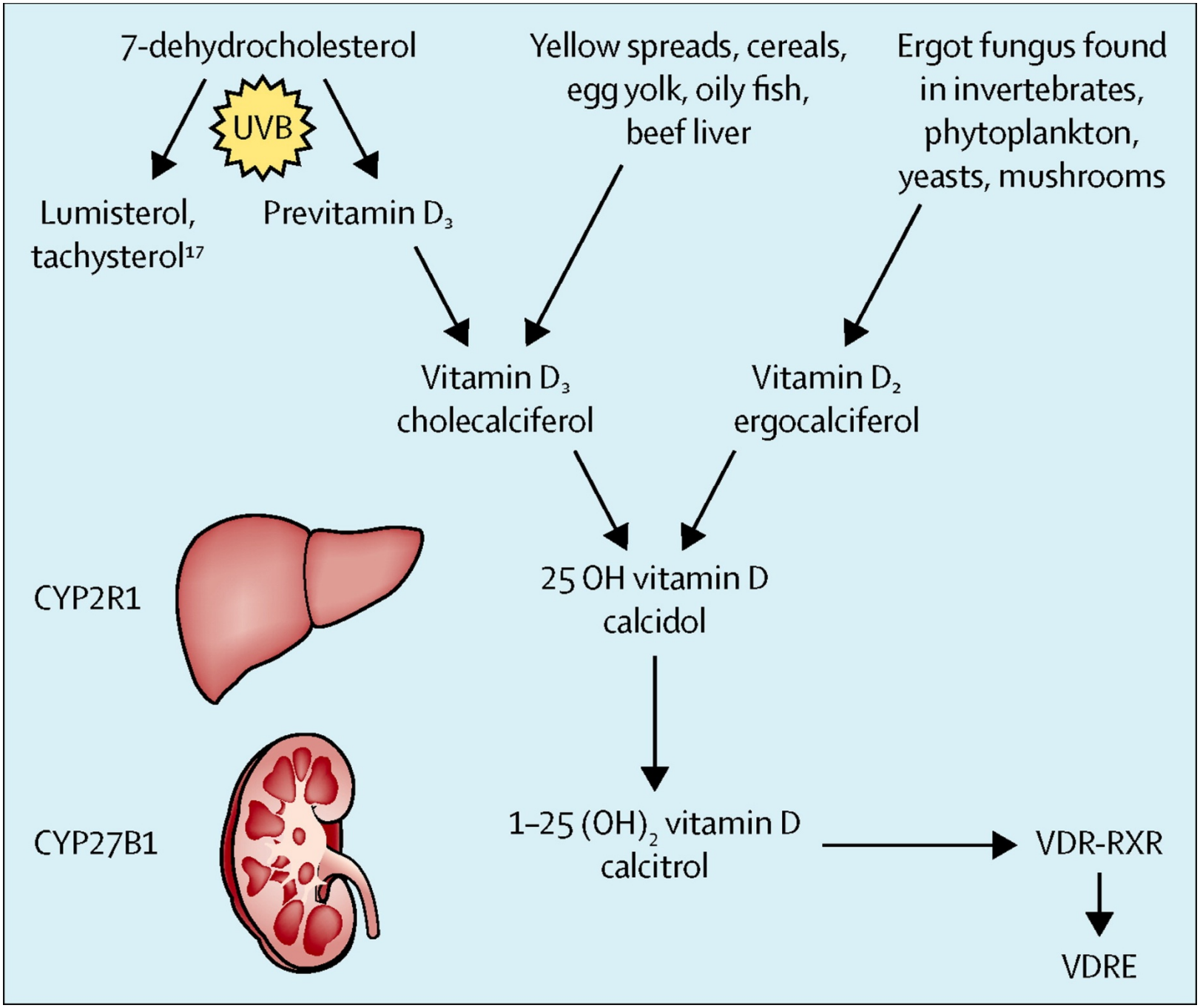


SEMINÁRIO - Paratireóide

3 - Biossíntese da forma ativa da Vitamina D.

Síntese de 1,25-dihidroxivitamina D [1,25(OH)2D




7-dehydrocholesterol
UVB
Lumisterol, tachysterol[17]
Previtamin D_3
Yellow spreads, cereals, egg yolk, oily fish, beef liver
Ergot fungus found in invertebrates, phytoplankton, yeasts, mushrooms
Vitamin D_3 cholecalciferol
Vitamin D_2 ergocalciferol
CYP2R1
25 OH vitamin D calcidol
CYP27B1
1–25 $(OH)_2$ vitamin D calcitrol
VDR-RXR
VDRE

Annu. Rev. Genom. Human Genet. 2001.2:299-341. Downloaded from arjournals.annualreviews.org
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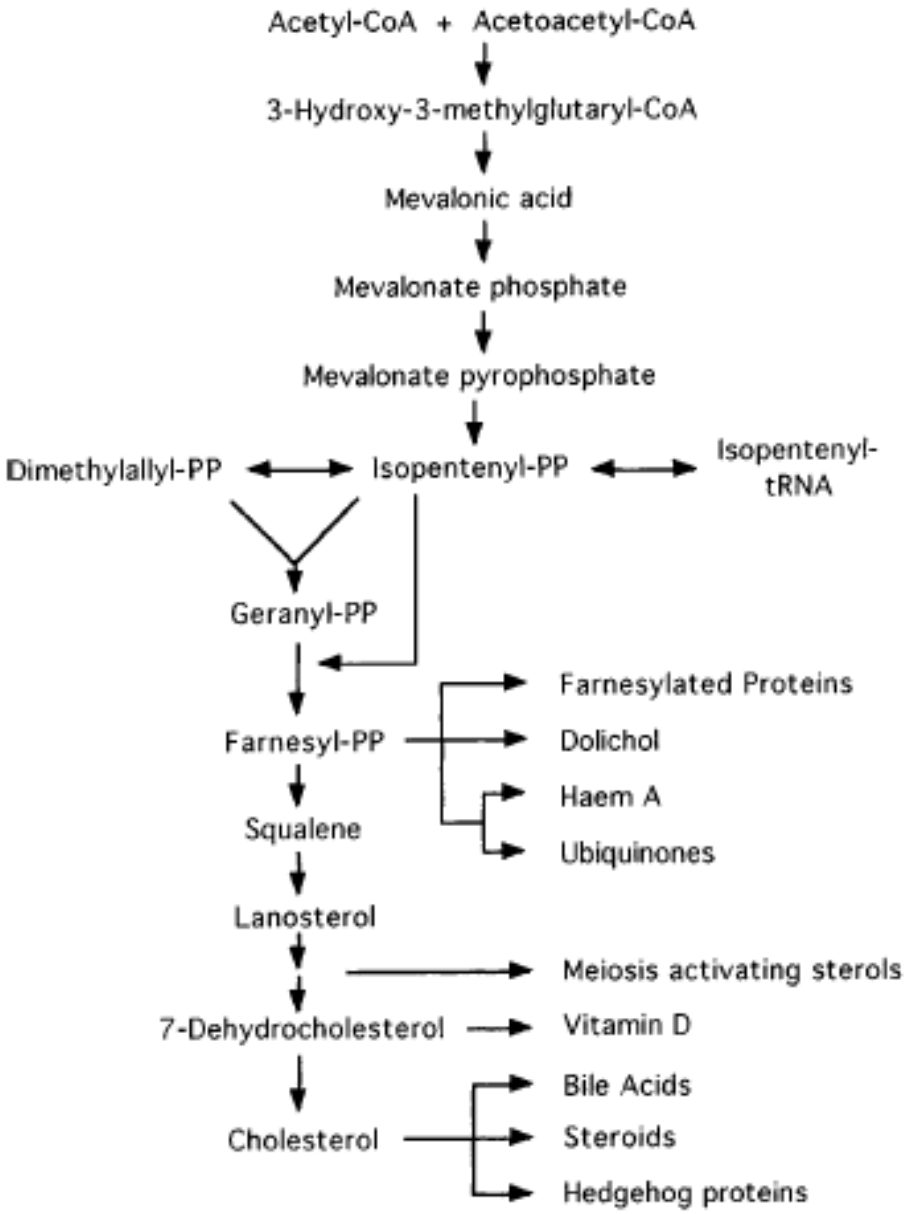


Figure 1 Outline of the pathway for the synthesis of sterols, nonsterol isoprenoids, and their derivatives.

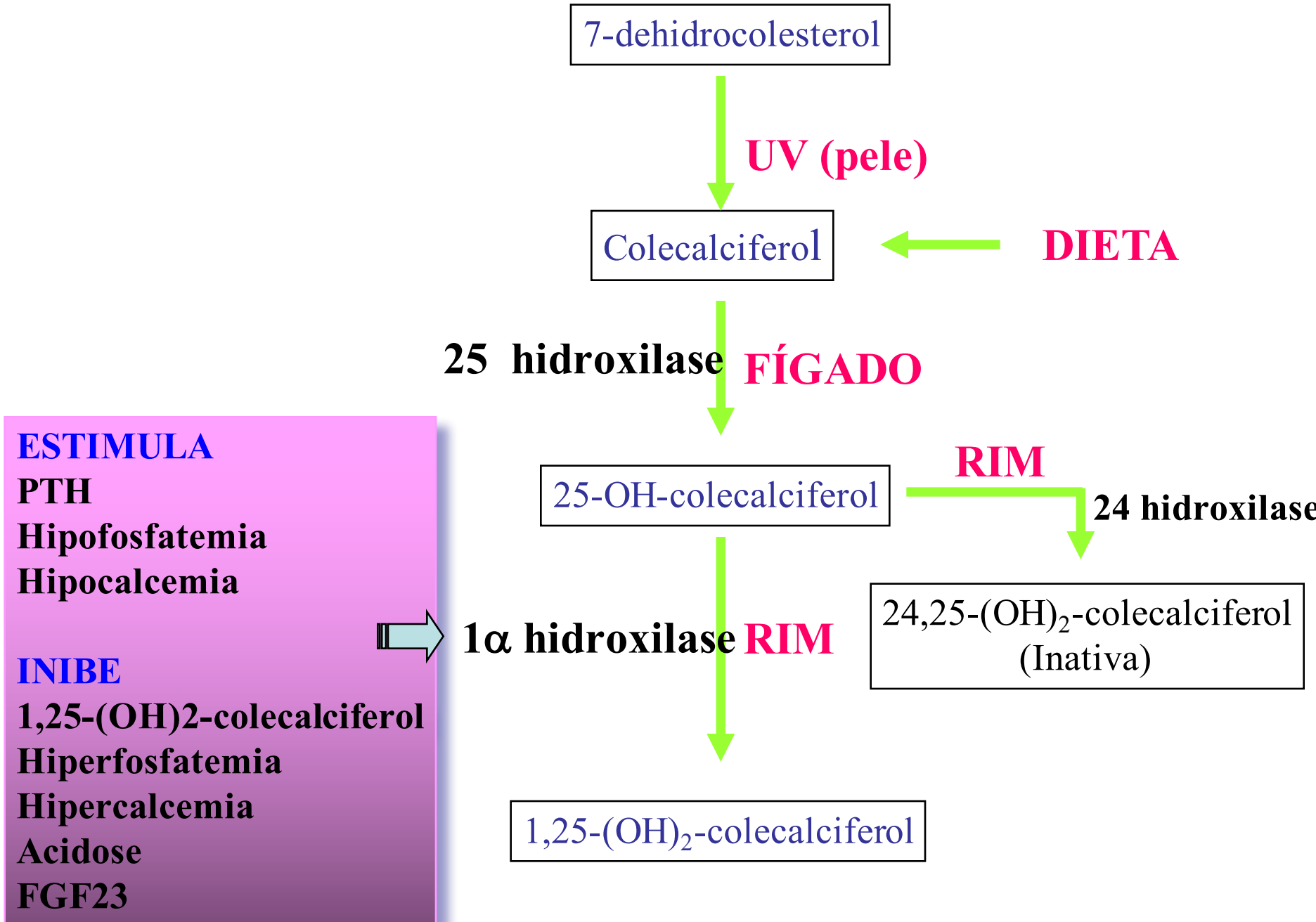
REGULAÇÃO DA PRODUÇÃO DE VITAMINA D

- Etapa mais importante: **1 α hidroxilase** (hidroxilação do carbono 1 no rim). Regulação pelo PTH.

- Contra-regulação exercida pela própria 1,25(OH)D que inibe a hidroxilação no carbono 1 no rim e carbono 25 no fígado.

- Hipofosfatemia aumenta a atividade da 1 α hidroxilase e reduz atividade da 24-hidroxilase.

- FGF23 inibe 1 α hidroxilase


7-dehidrocolesterol
UV (pele)
Colecalciferol
DIETA
25 hidroxilase
FÍGADO
25-OH-colecalciferol
RIM
24 hidroxilase
24,25-(OH)2-colecalciferol
(Inativa)
1α hidroxilase
RIM
1,25-(OH)2-colecalciferol
ESTIMULA
PTH
Hipofosfatemia
Hipocalcemia
INIBE
1,25-(OH)2-colecalciferol
Hiperfosfatemia
Hipercalcemia
Acidose
FGF23

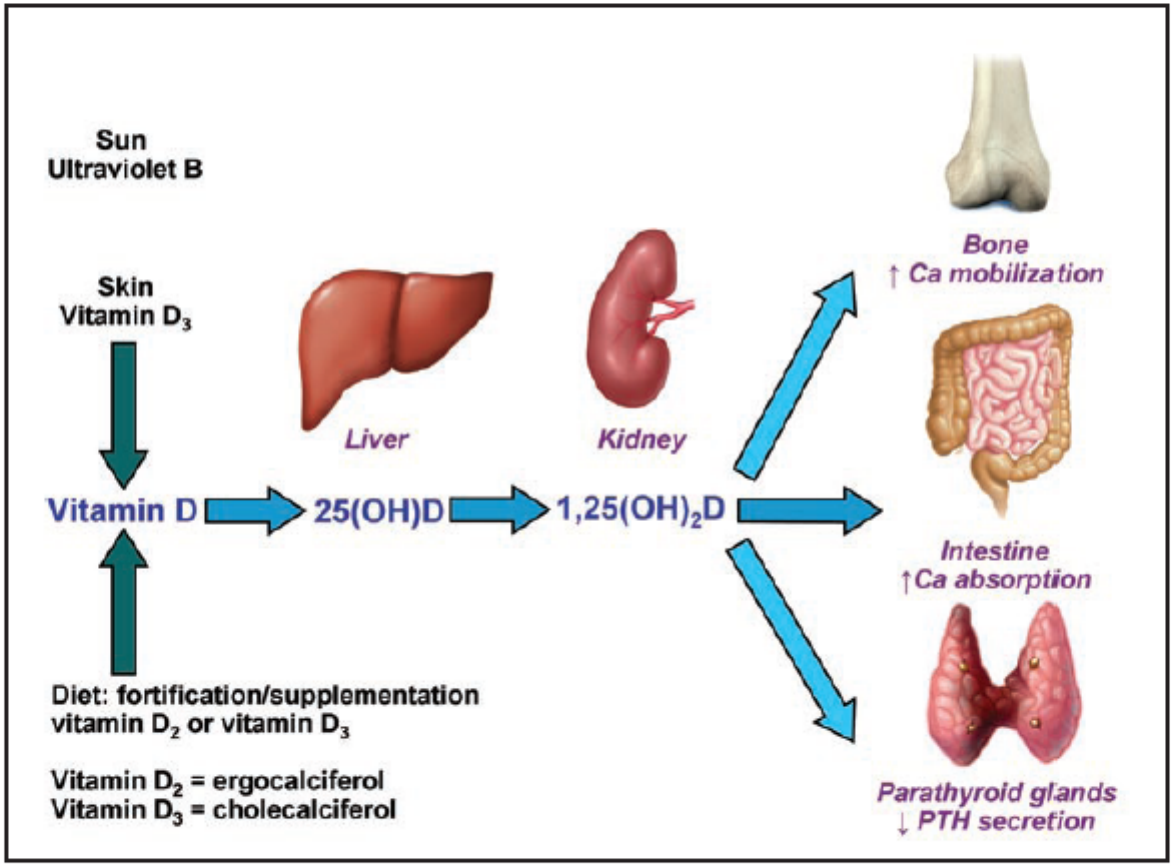
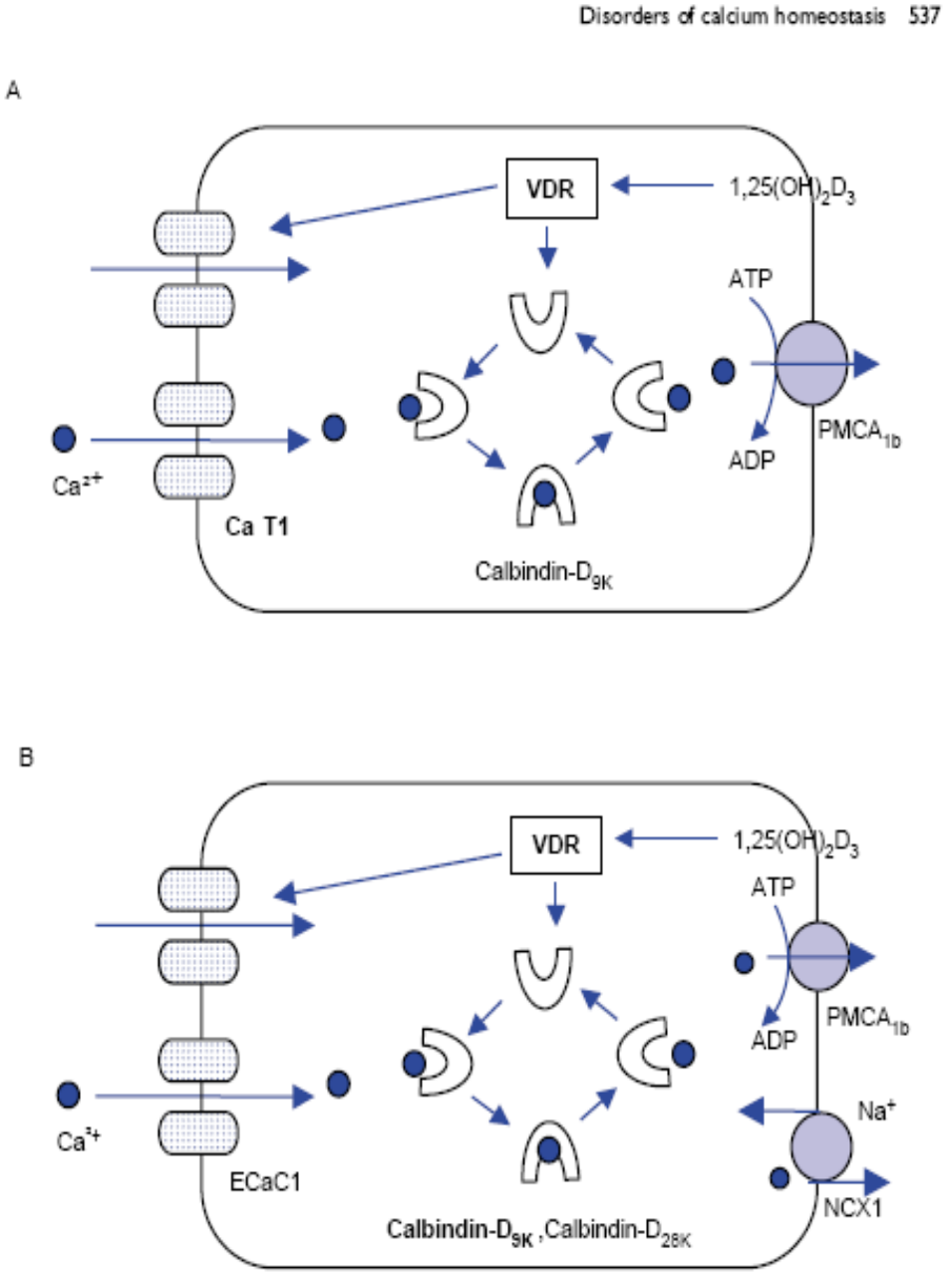


FIGURE. Vitamin D metabolism. Ca = calcium; 1,25(OH)2D = 1,25-dihydroxyvitamin D; 5(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone.

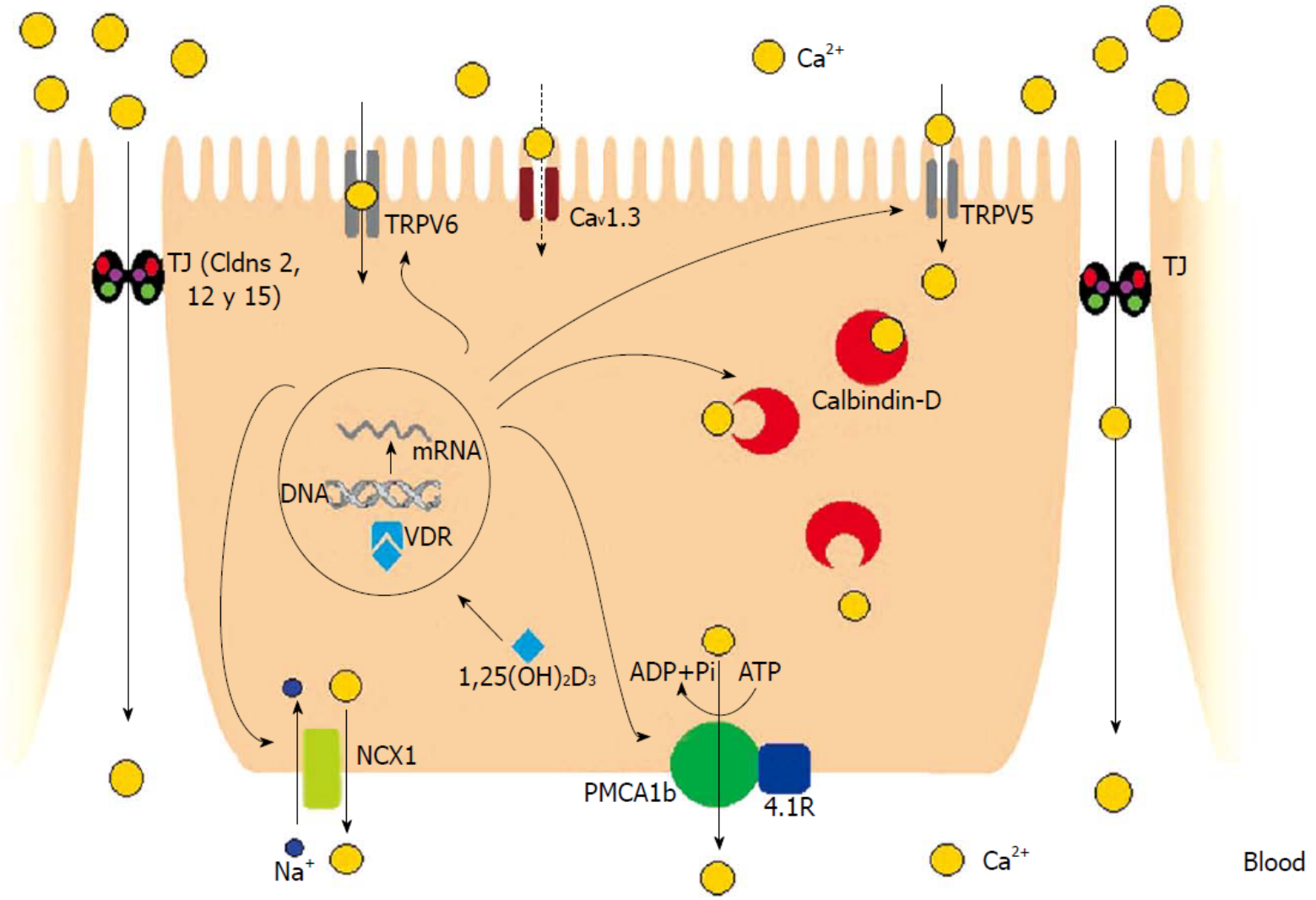
Vitamin D Insufficiency
Tom D. Thacher, MD, and Bart L. Clarke, 2011



Gene targets of 1,25(OH)2D action in the enterocyte (A) and renal tubular cell (B).

Carmeliet 2003

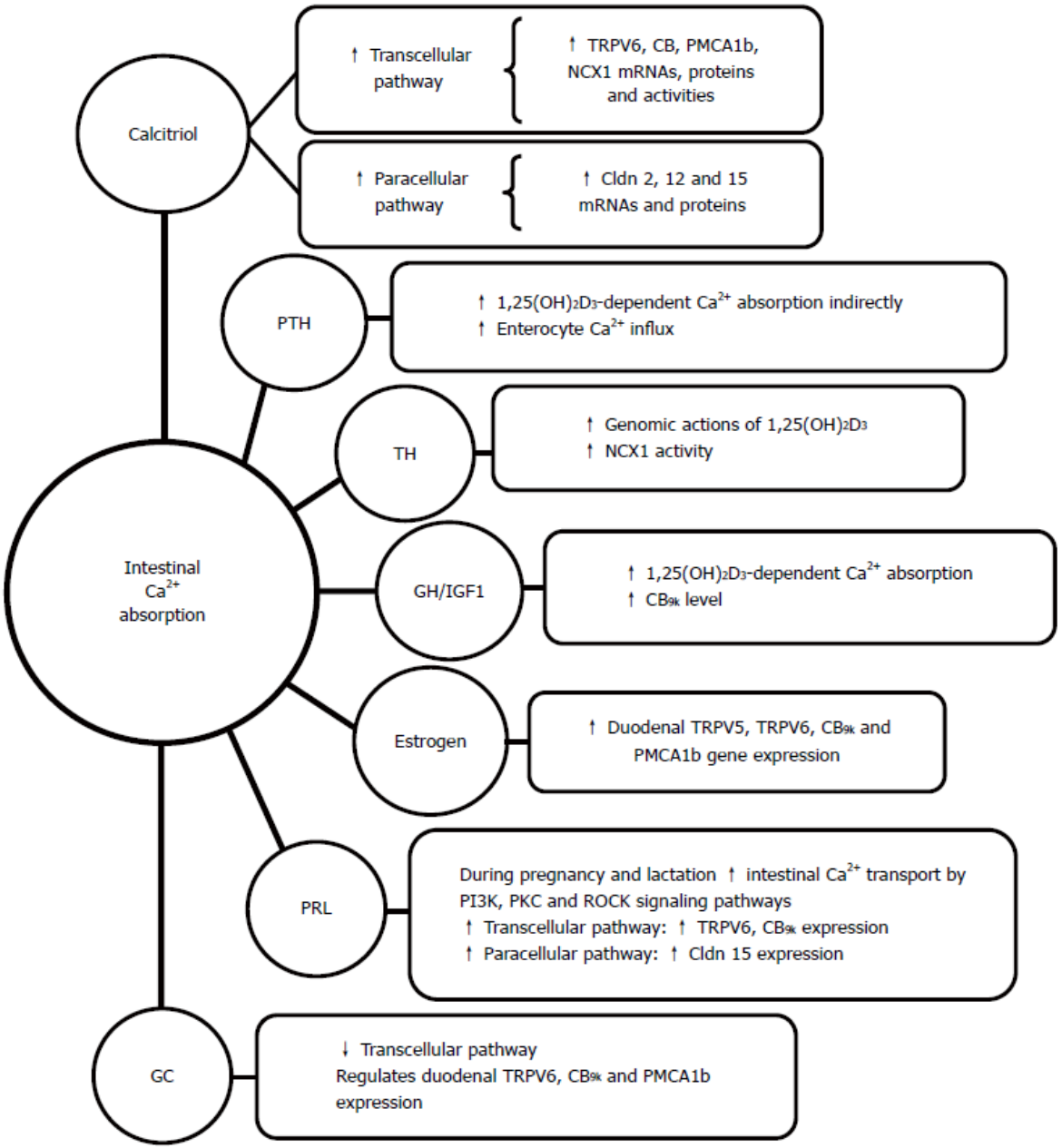
Diaz de Barboza G *et al*. Intestinal Ca^{2+} absorption



***ADP**: Adenosine monophosphate; **ATP**: Adenosine triphosphate; **Cldns**: Claudins; **NCX1**: Intestinal Na+/Ca2+ exchanger; **PMCA1b**: Plasma membrane Ca2+- ATPase 1b; **TJ**: Tight junctions; **TrpV6**: Transient receptor potential vanilloid 6; **TRPV5**: Transient receptor potential vanilloid 5; **VDR**: Vitamin D receptor; **1,25(OH)2D3**: Calcitriol.*

Hormonal regulation of intestinal calcium absorption.

Diaz de Barboza G *et al*. Intestinal Ca^{2+} absorption



CB: Calbindin;

Cldn: Claudin;

GC: Glucocorticoids;

GH: Growth hormone;

IGF1: Insulin-like

growth factor 1;

NCX1: Intestinal Na+/Ca2+ exchanger;

PI3K: Phosphoinositide 3-kinase C;

PKC: Protein kinase C; PMCA1b:

Plasma membrane Ca2+- ATPase 1b;

PRL: Prolactin;

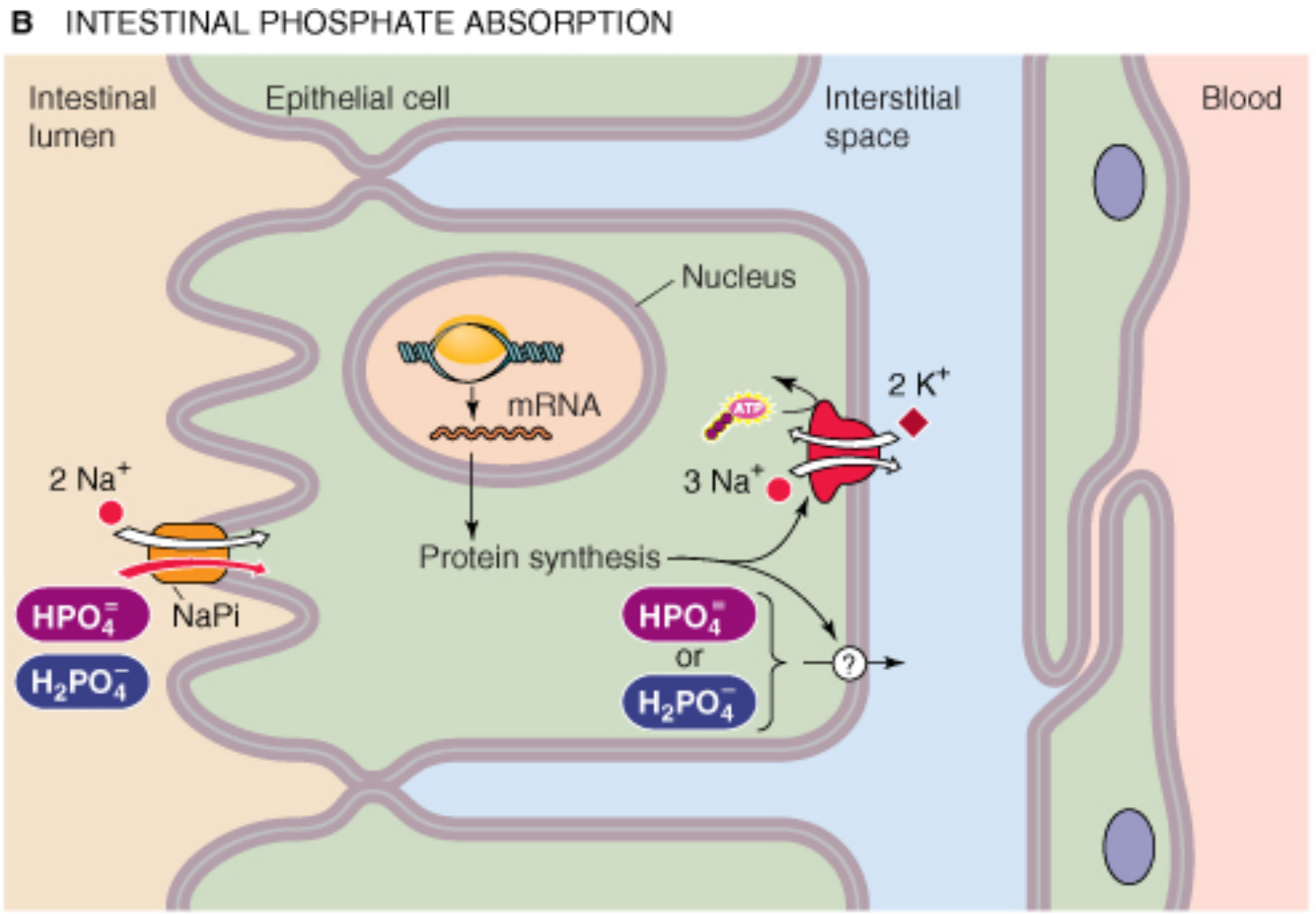
PTH: Parathyroid hormone;

ROCK: RhoA-associated coiled-coil-forming kinase;

TH: Thyroid hormones;

TrpV6: Transient receptor potential vanilloid 6.

Vitamina D: Aumenta a absorção de **Fosfato** no **INTESTINO**



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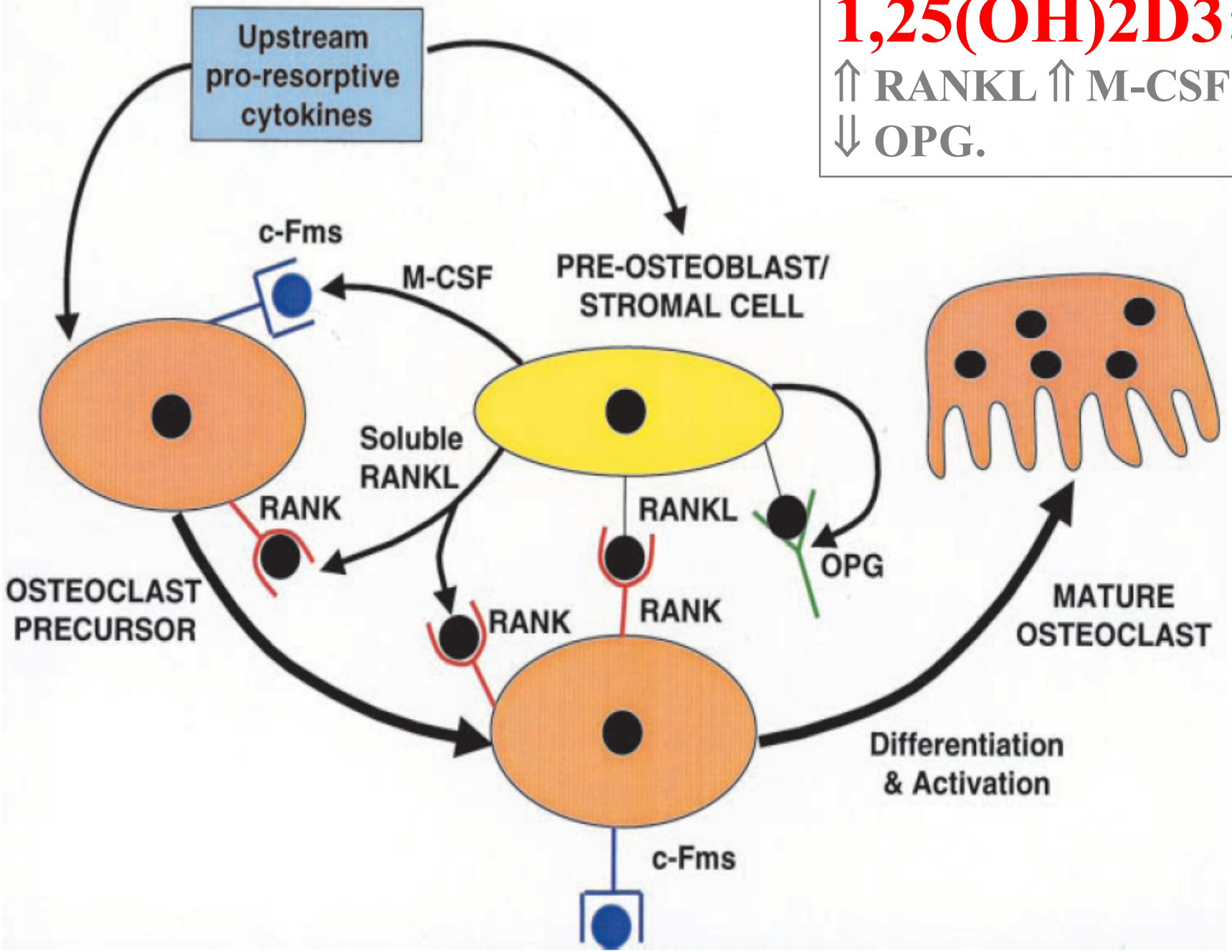
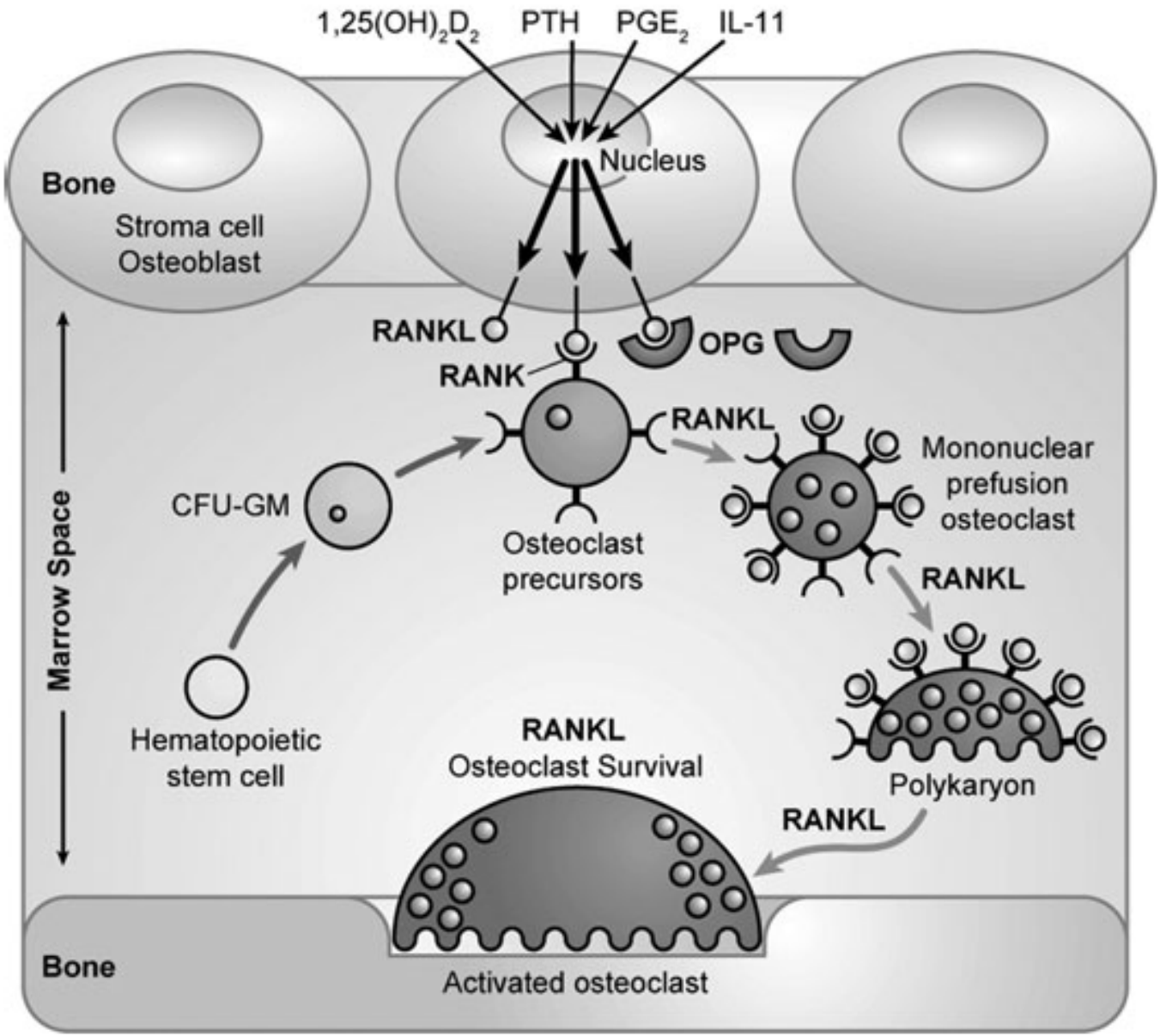
1,25(OH)2D3:
⇑ RANKL ⇑ M-CSF
⇓ OPG.





Osteoclast formation and activation in response to the vitamin D hormone, parathyroid hormone, PGE2, and IL-11.

Evolution of our understanding of vitamin D. *Hector F DeLuca, 2008*

S2- Paratireóide

4- Descrever as ações da vitamina D no intestino, osso e na paratireóide.

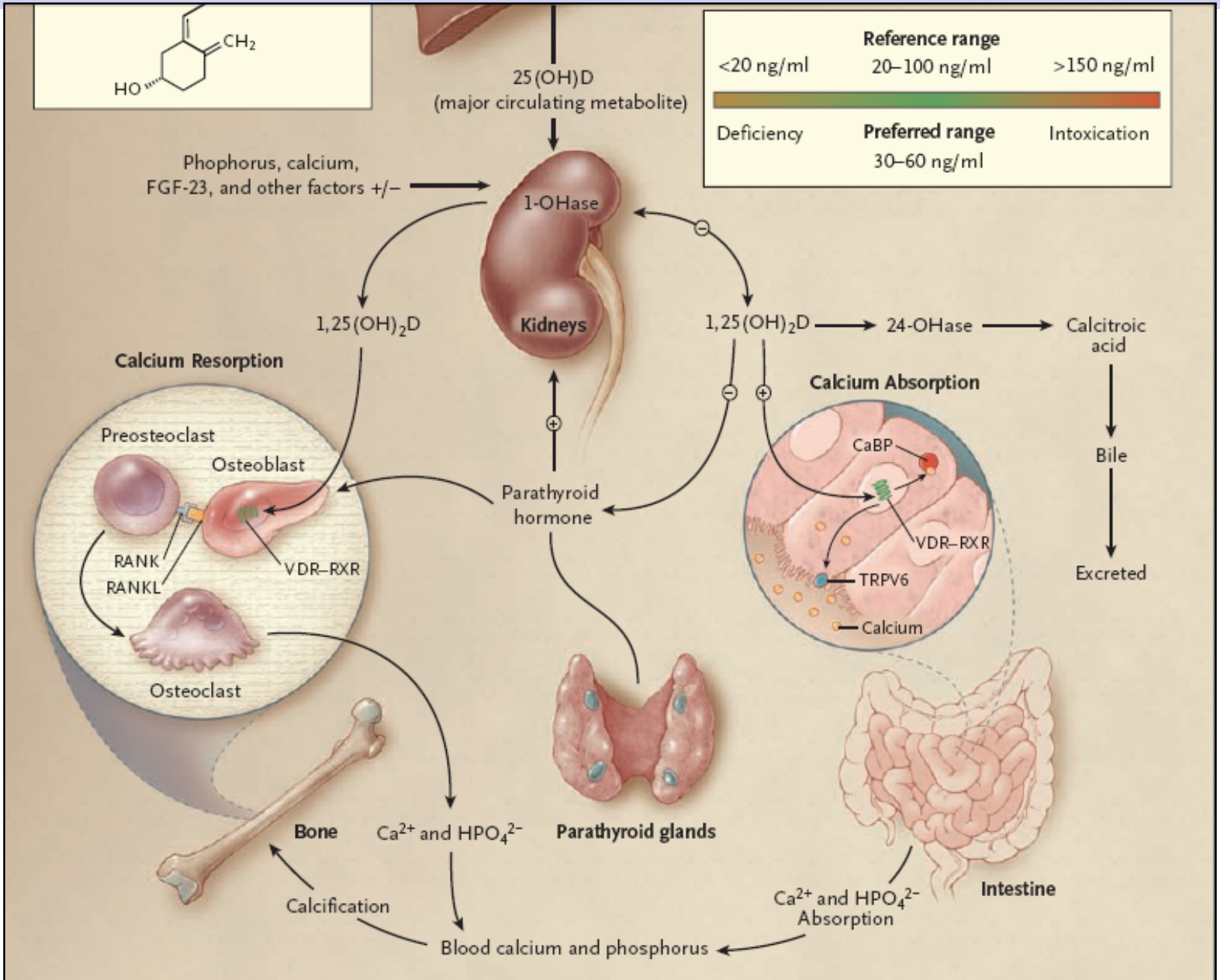
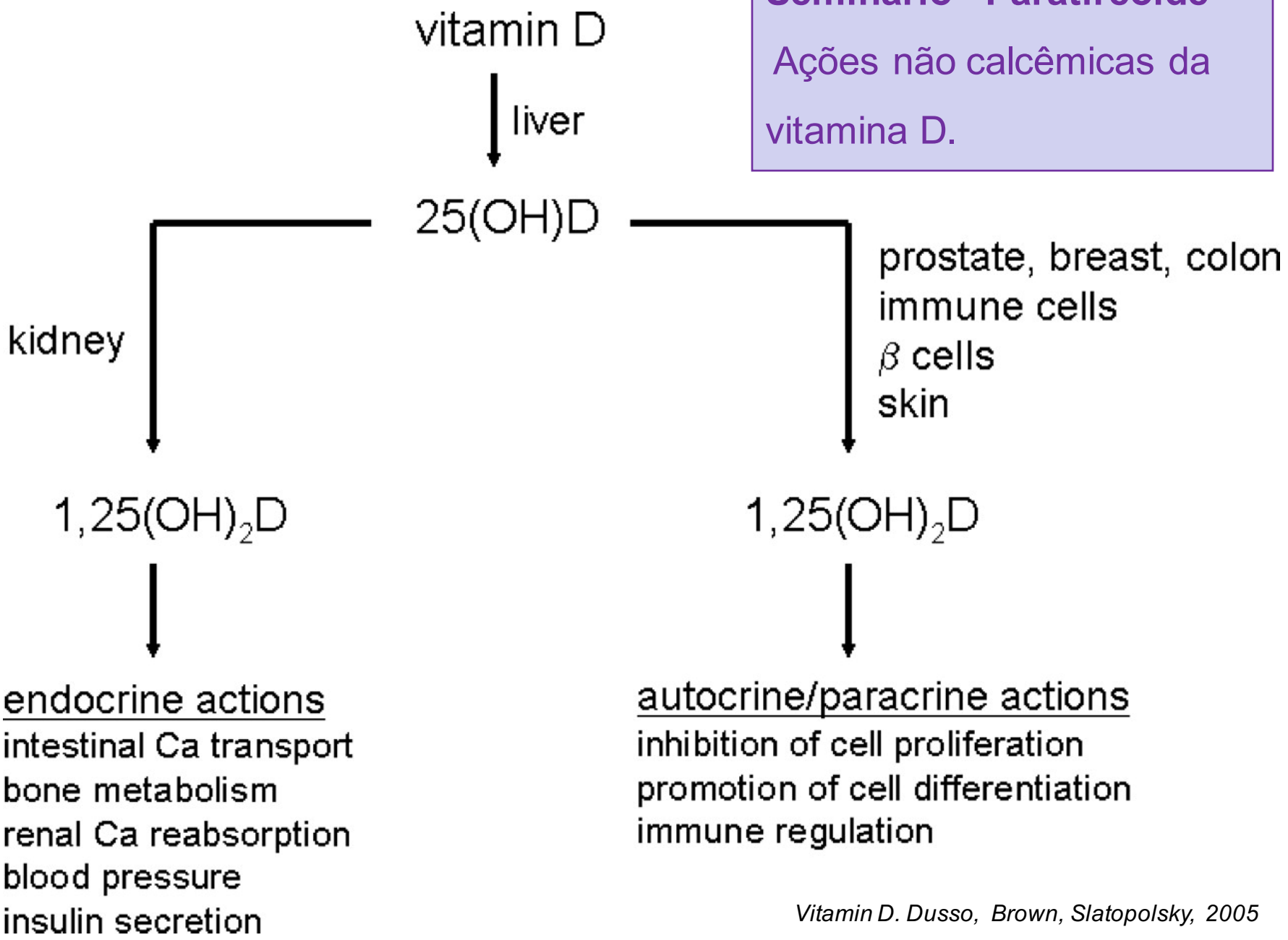


Table 1. Regulation of RANKL and OPG by systemic hormones

	RANKL	OPG
Stimulation	Dexamethasone $1\alpha,25\text{-}(OH)_2D_3$ PTH PGE_2	17β-Estradiol
Inhibition	17β–Estradiol	Hydrocortisone Dexamethasone $1\alpha,25\text{-}(OH)_2D_3$ PTH PGE_2

Seminário - Paratireóide

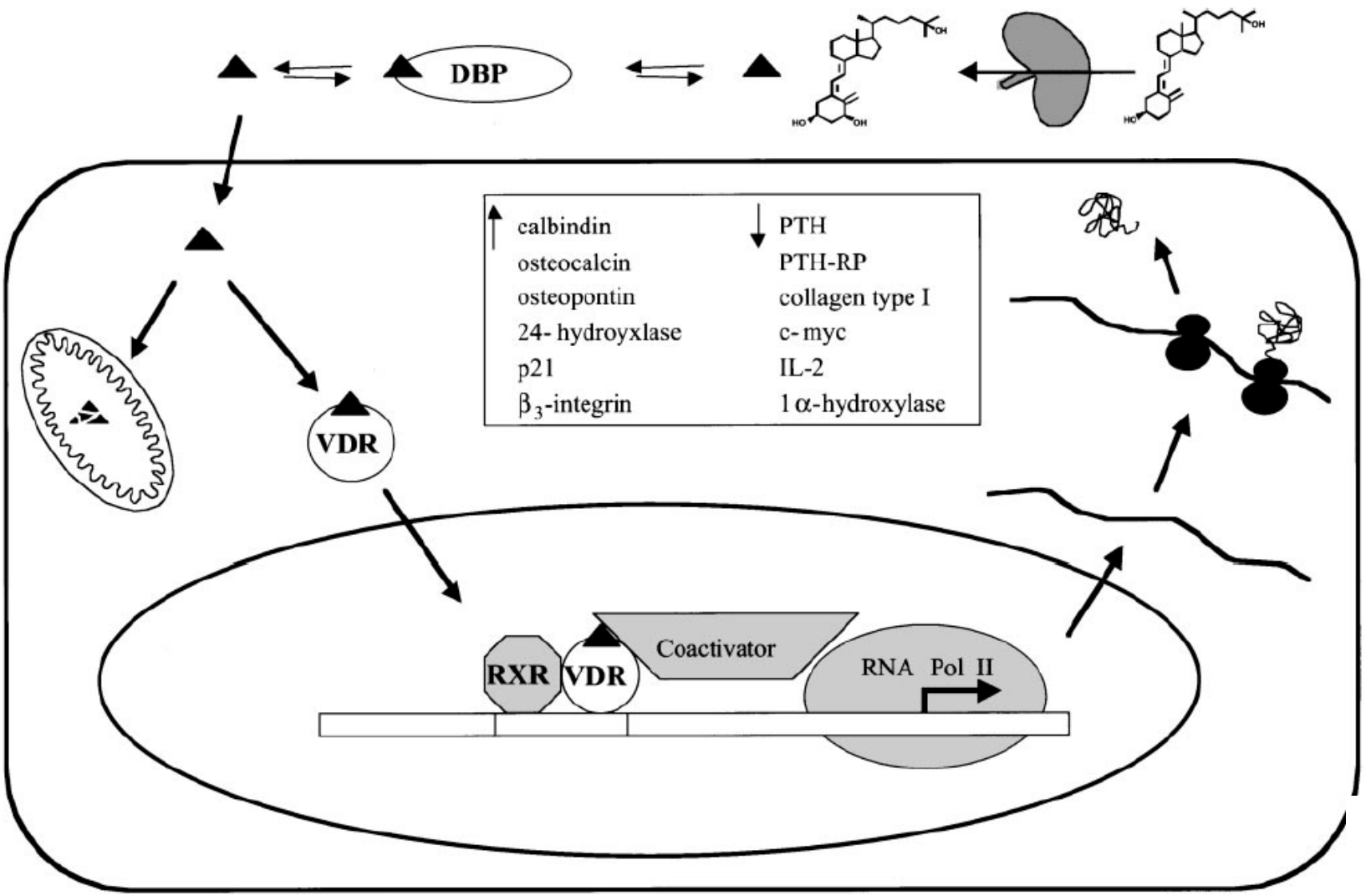
Ações não calcêmicas da vitamina D.



Vitamin D. Dusso, Brown, Slatopolsky, 2005

Seminário- Paratireóide

5- Descrever os mecanismos de ação da vitamina D.



BROWN et al.

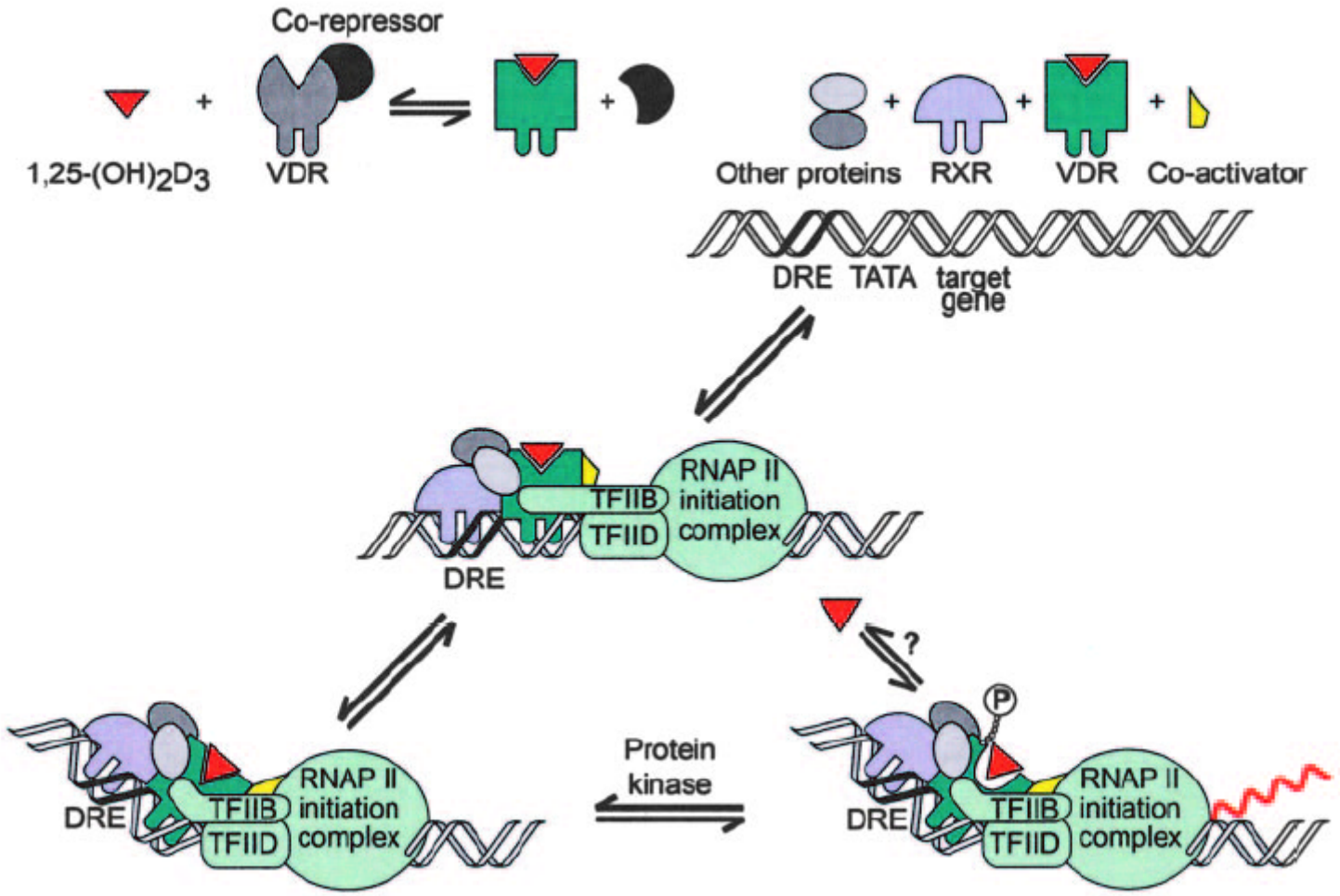
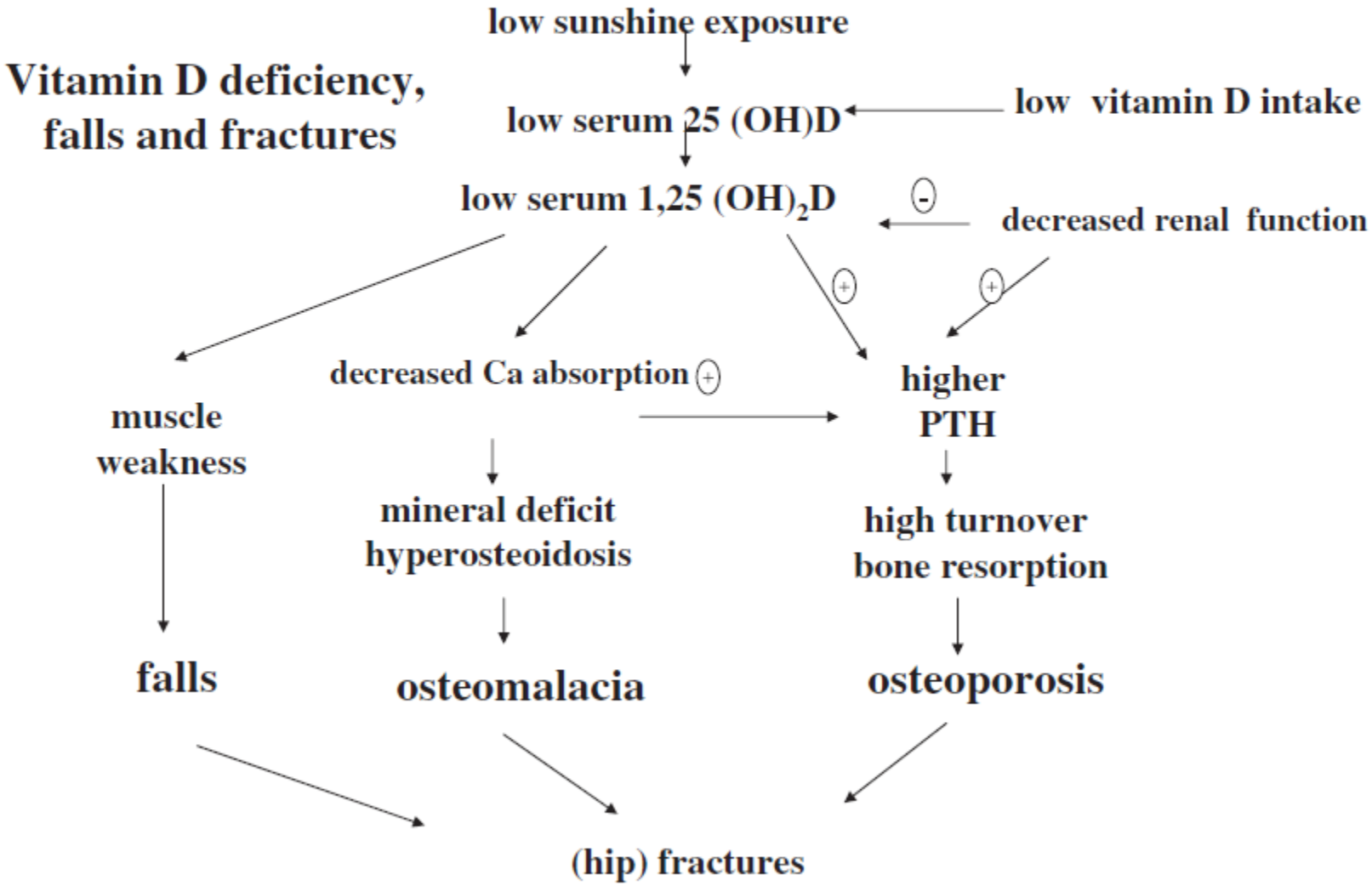
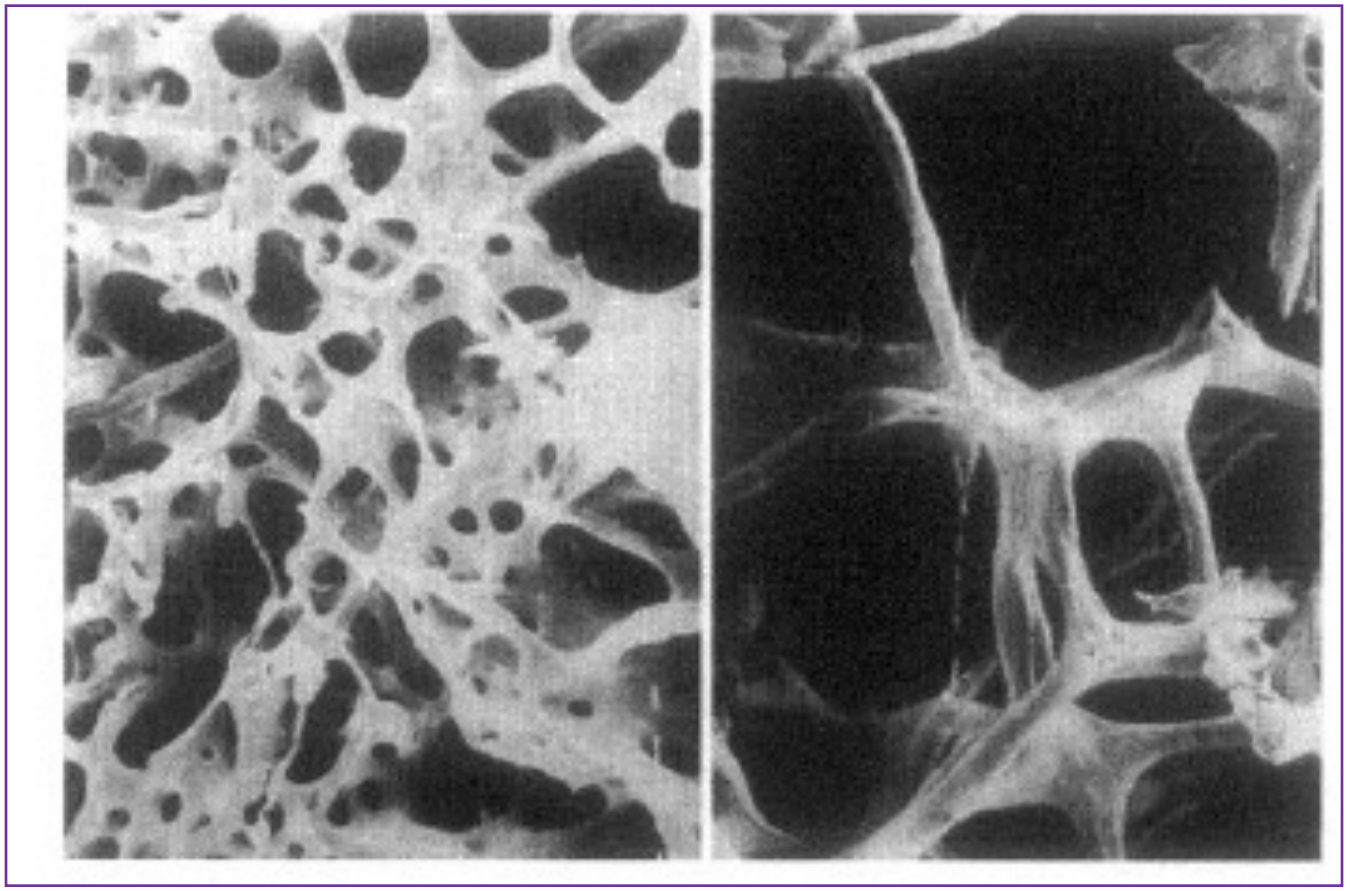


FIGURE 6. Diagrammatic representation of the known molecular events in the regulation of gene expression by the vitamin D hormone, 1,25(OH)2D3, acting through its receptor, VDR. The result of regulation may be either suppression or activation. RXR, retinoidXreceptor; DRE,VDRE(see Figure 5); TFIIB, transcription factor IIB; TFIID, transcription factor IID; RNAP, RNA polymerase.

S2- Paratireóide

6- Citar as conseqüências da deficiência da vitamina D para o osso.


Vitamin D deficiency, falls and fractures
low sunshine exposure
low serum 25 (OH)D
low vitamin D intake
low serum 1,25 (OH)2D
decreased renal function
decreased Ca absorption
higher PTH
muscle weakness
mineral deficit hyperosteoidosis
high turnover bone resorption
falls
osteomalacia
osteoporosis
(hip) fractures



Scanning electron micrograph of normal (left) and osteoporotic (right) vertebral trabecular bone. Note transformation of trabecular plates to rods and trabecular perforations (photograph by Dr. Jon Kosek, reproduced with permission). *Marcus, 1996*

Table 2 World Health Organization (WHO) definition of osteoporosis

Diagnostic Category	T-score	Bone Mineral Density
Normal	>−1	Within 1 SD of a young normal adult
Low bone mass	−1 to −2.5	Between 1 and 2.5 SD below that of a young normal adult
Osteoporosis	<−2.5	>2.5 SD below that of a young normal adult
Severe osteoporosis	<−2.5 and ≥1 fragility fracture	>2.5 SD below that of a young normal adult

Adapted from WHO Technical Report Series.[10]

FATORES DE RISCO PARA OSTEOPOROSE

- Sexo feminino
- Menopausa
- Genética/história familiar
- Dieta (deficiência em cálcio, excesso de fósforo)
- Tabagismo
- Ingestão de bebida alcoólica
- Inatividade física, Peso corporal baixo
- Uso de medicamentos: glicocorticóides
- Doenças que se associam à osteoporose: Síndrome de Cushing, Hipogonadismo, hipertireoidismo.

RAQUITISMO

FIGURE 4 Child with rickets.

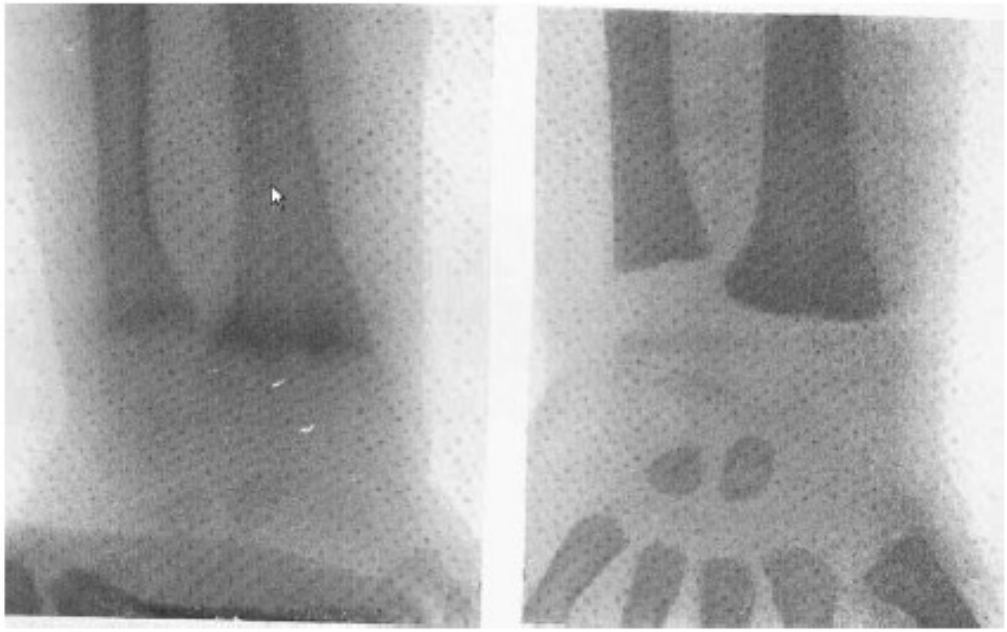
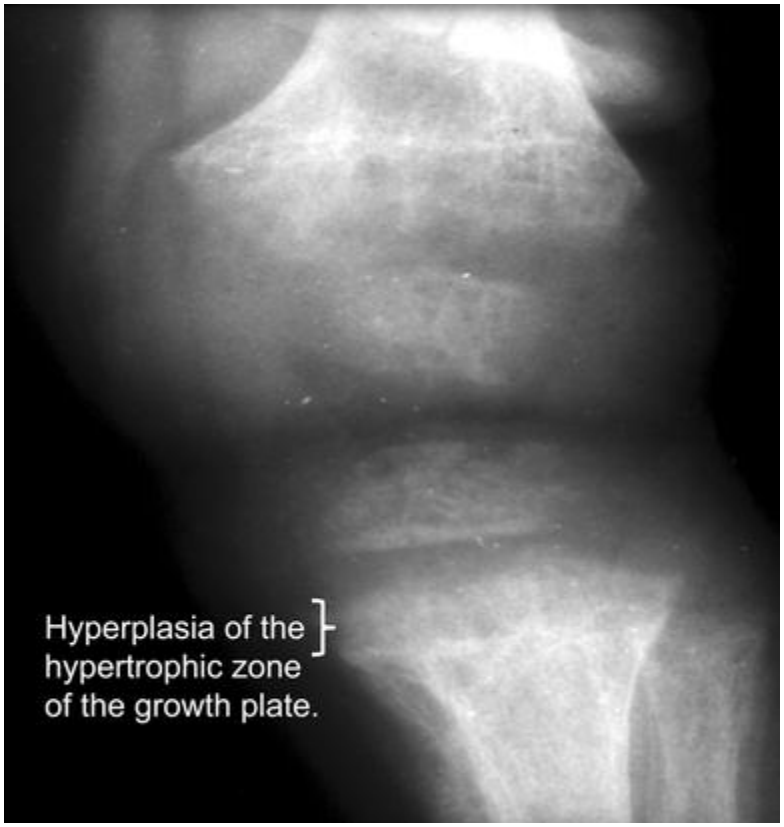


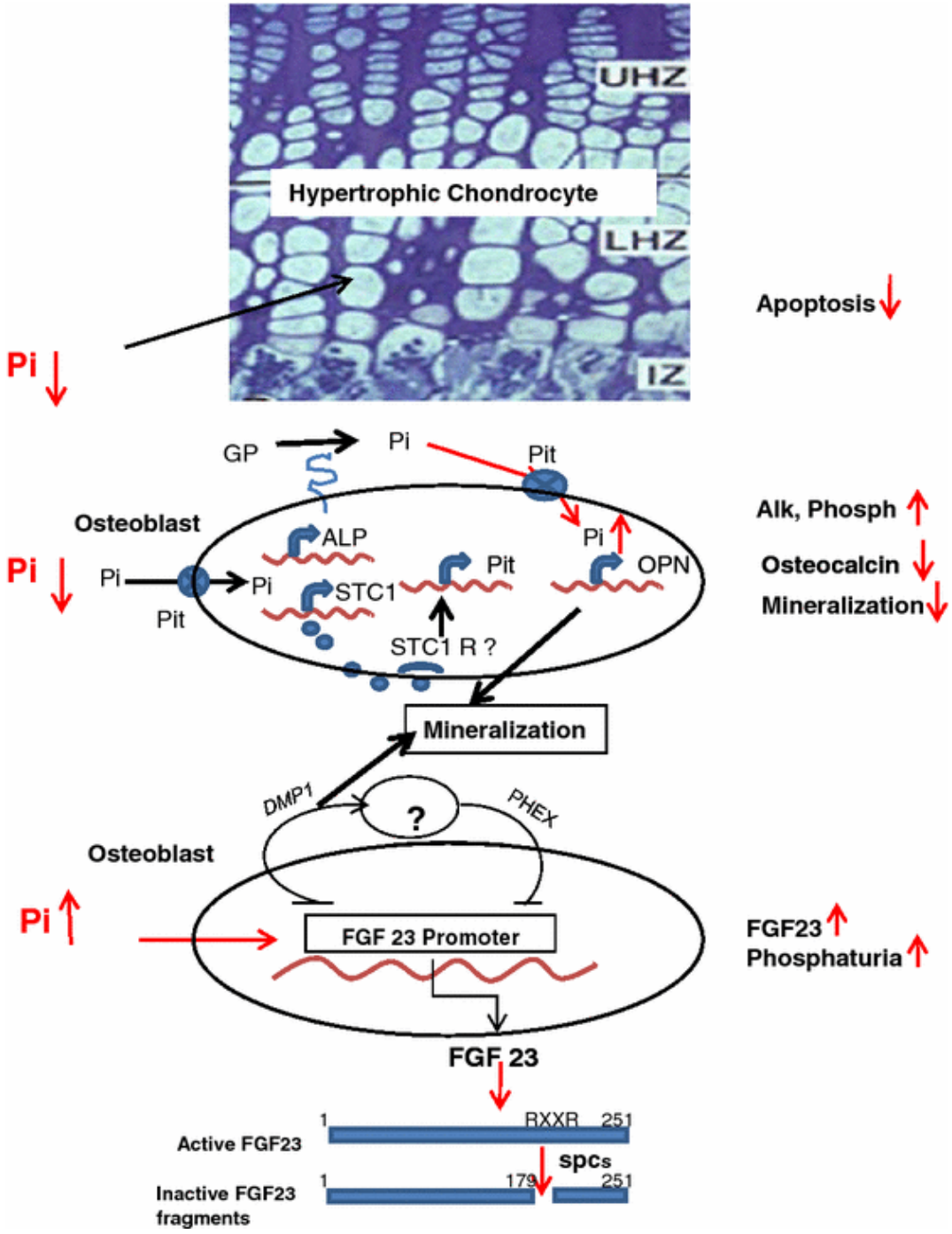
FIGURE 5 Florid rickets of severe degree. Radiograms taken before (*left panel*) and after treatment with 1 h UVR 2 times/wk for 8 wk. Note mineralization of the carpal bones and epiphyseal plates (*right panel*) [in the public domain].

Holick 2005



ALP: alkaline phosphatase
OPN: osteopontin
STC1: stanniocalcin 1
GP: glycerol phosphate

Hypophosphatemia: the common denominator of all rickets . Tiosano and Hochberg, 2009



45 years old, female

Low sun exposure

Ca: 8.4 mg/dl per (ref: 8.0 - 10.4 mg/dl)

Phosphate: 1.5 mg/dl (ref: 2.5 - 4.5 mg/dl)

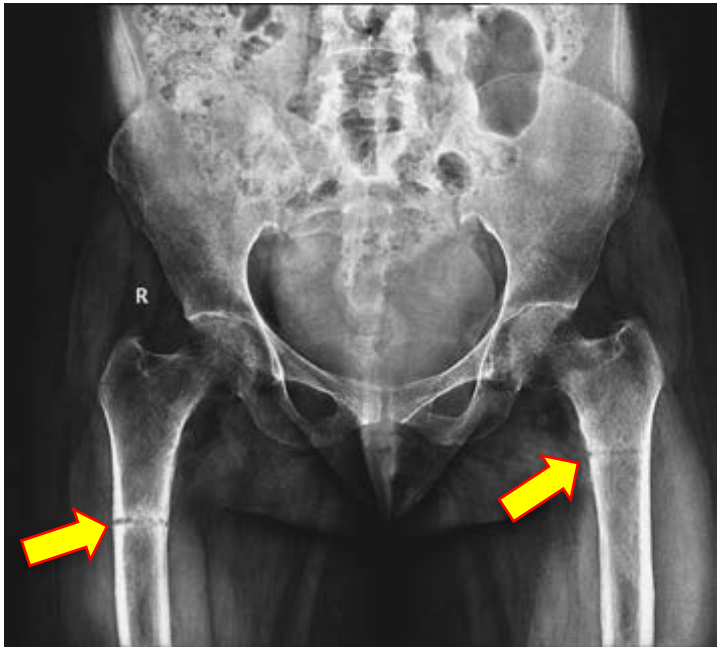
Alkaline phosphatase: 916 U/l (ref: 30 - 120 U/i)

25-hydroxyvitamin D: 9 nmol/l (ref: 18 - 100 nmol/l)

OSTEOMALACIA

Phpsphate: 3.0 mg/dl

Alkaline phosphatase: 418 U/l



Looser zones or pseudofractures

Calcium and vitamin D

Munagala, NEJM , 2014

PRINCIPAIS FATORES ENVOLVIDOS NA REMODELAÇÃO ÓSSEA

FORMAÇÃO ÓSSEA

Estímulo

GH
IGF
Insulina
Estrógeno
Andrógeno
Vitamina D
TGF beta
Fator de crescimento derivado do osso
PTH

Inibição

Glicocorticóides

RESSORÇÃO ÓSSEA

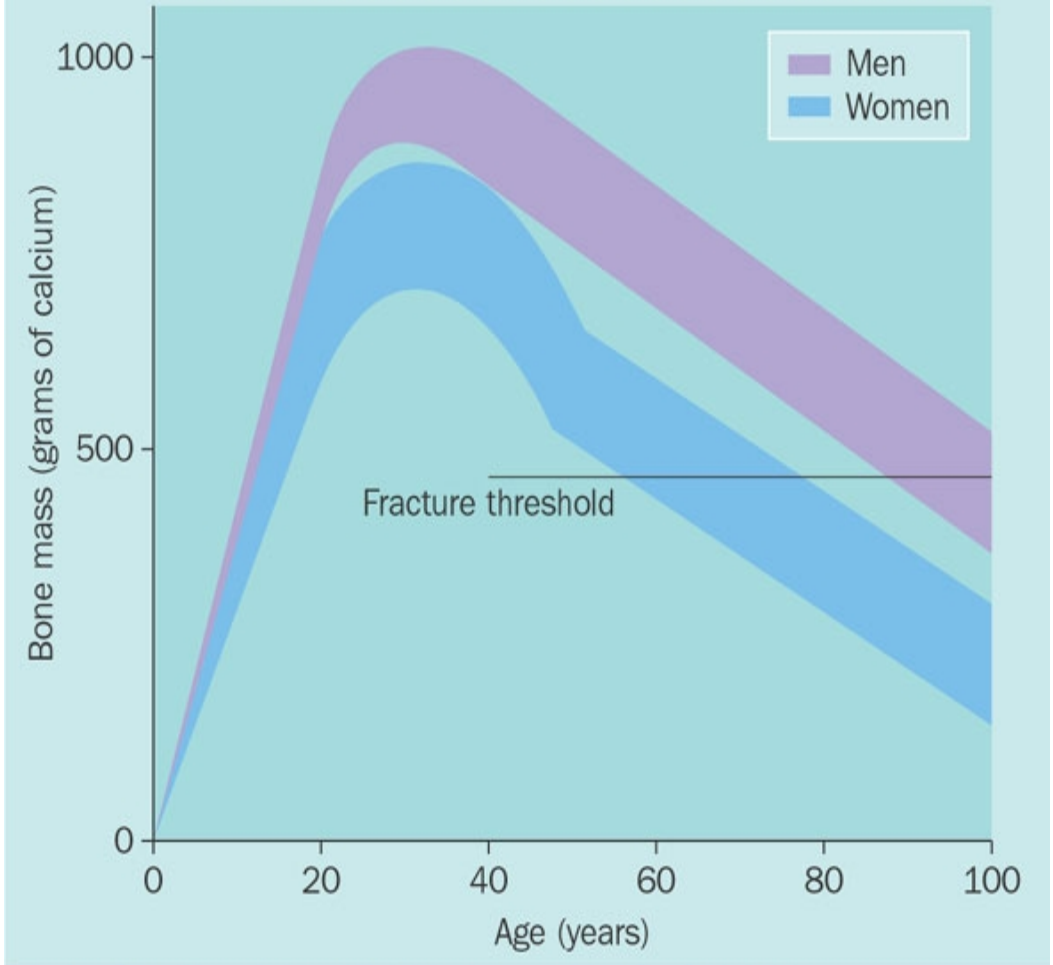
Estímulo

PTH
Vitamina D
Glicocorticóide
Prostaglandinas
IL-1
IL-6
TNF

Inibição

Estrógeno
Andrógeno
Calcitonina
TGF beta
Gama interfon

Changes in bone mass with age



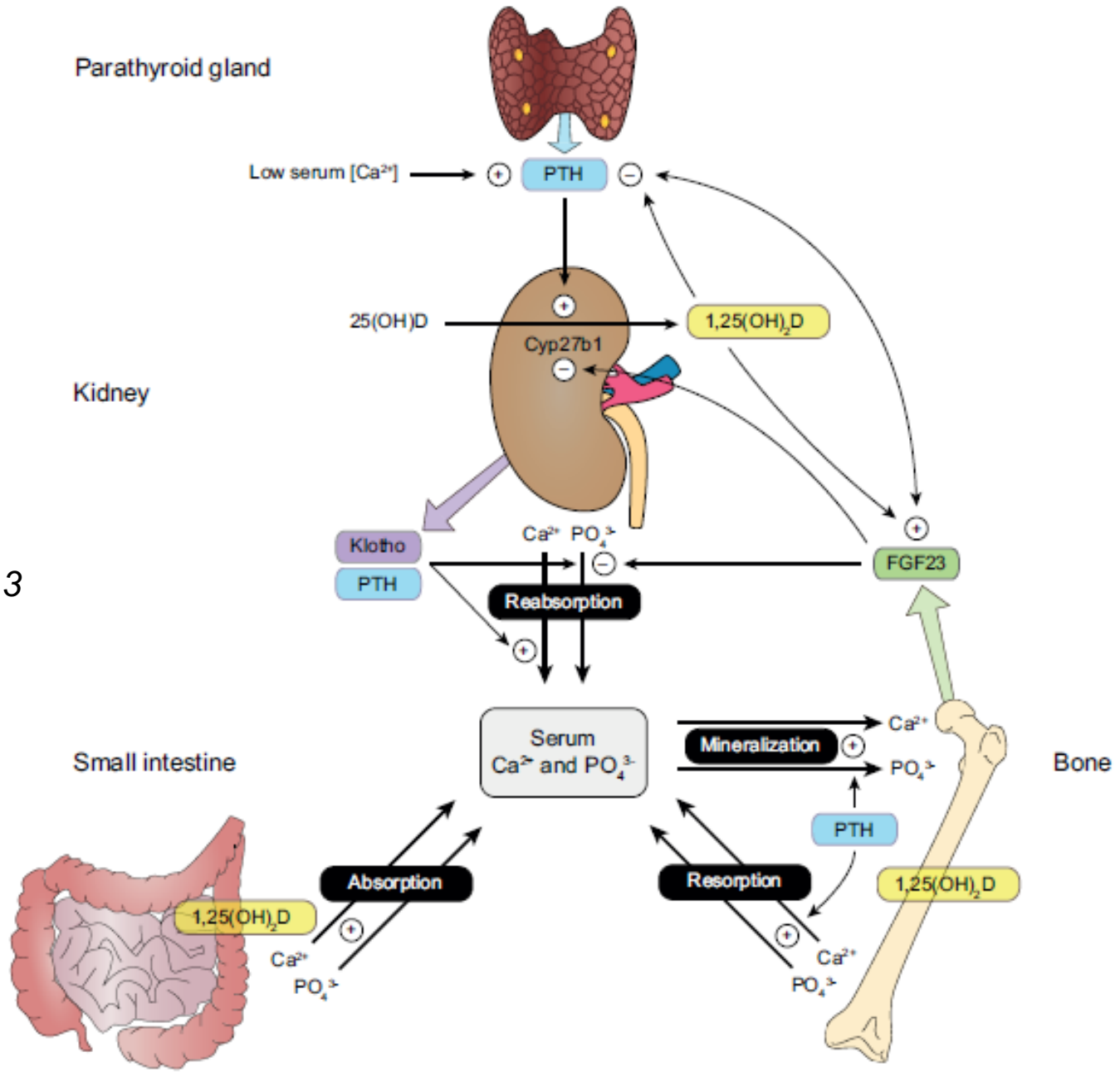
Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd

NECESSIDADE DIÁRIA DE CÁLCIO (elementar)

- 1 – 3 anos: 500mg/dia
- 4 – 8 anos: 800mg/dia
- 9 – 18 anos: 1300mg/dia
- 19 – 50 anos: 1000mg/dia
- Acima de 50 anos: 1200mg/dia
- Gravidez/lactação:1000 a 1300mg/dia

Endocrine regulation of calcium (Ca2+) and phosphate metabolism.

Hannes Olauson, 2013

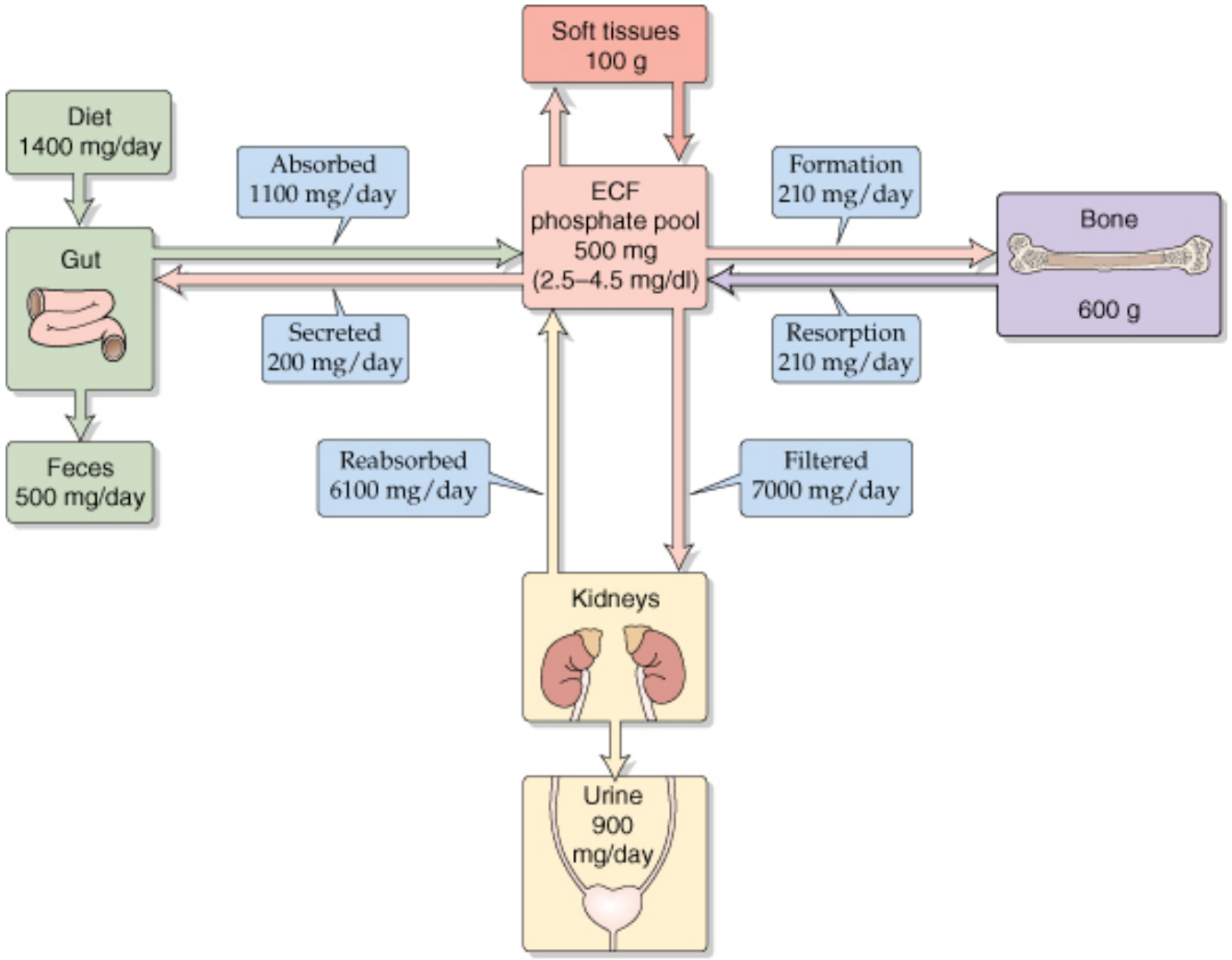


Questões Orientadoras:

6. Discuta os principais fatores envolvidos no controle da homeostase do fósforo.

Seminário - Paratireóide

8. Principais fatores envolvidos no controle da homeostase do fósforo.



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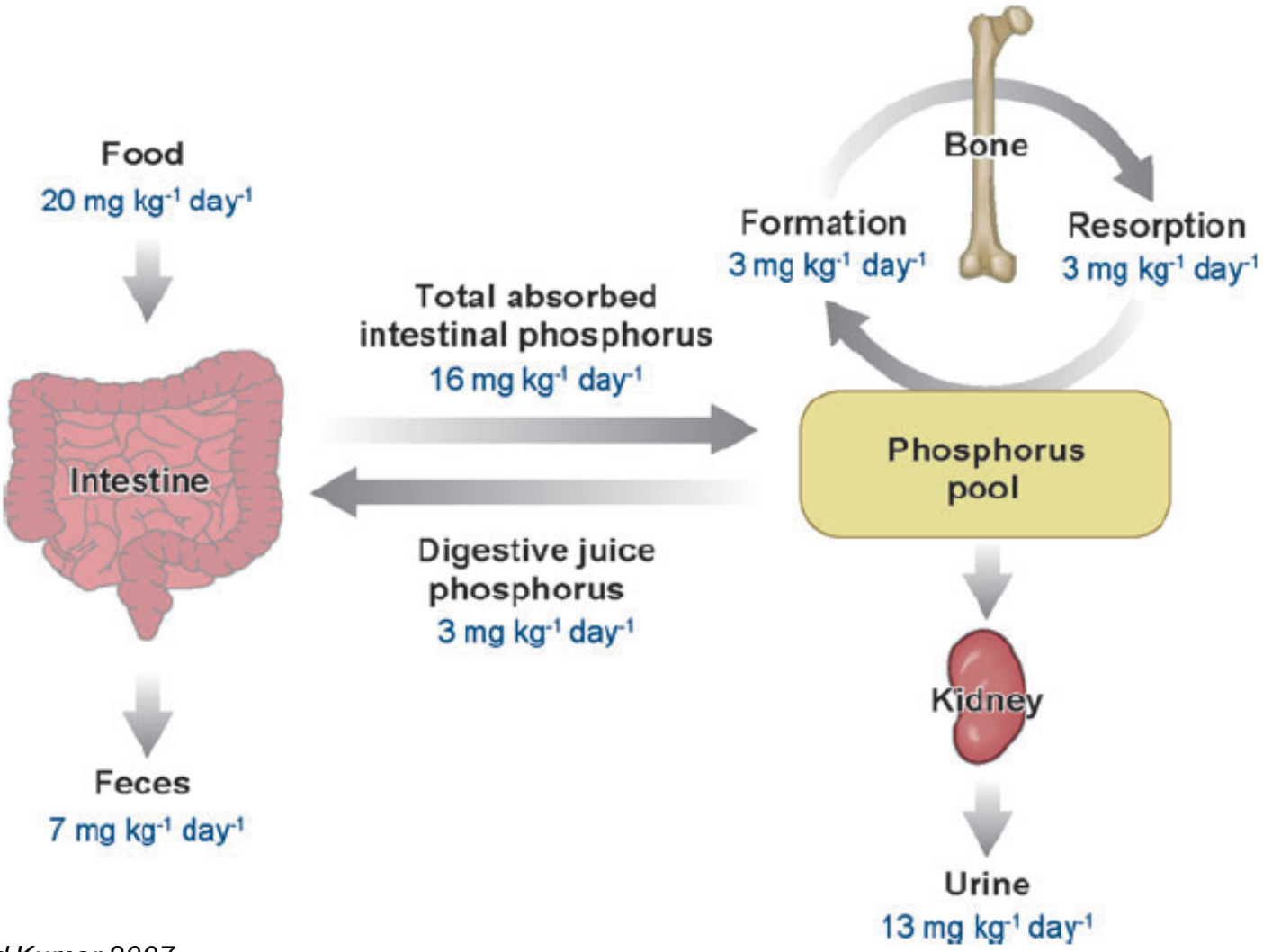
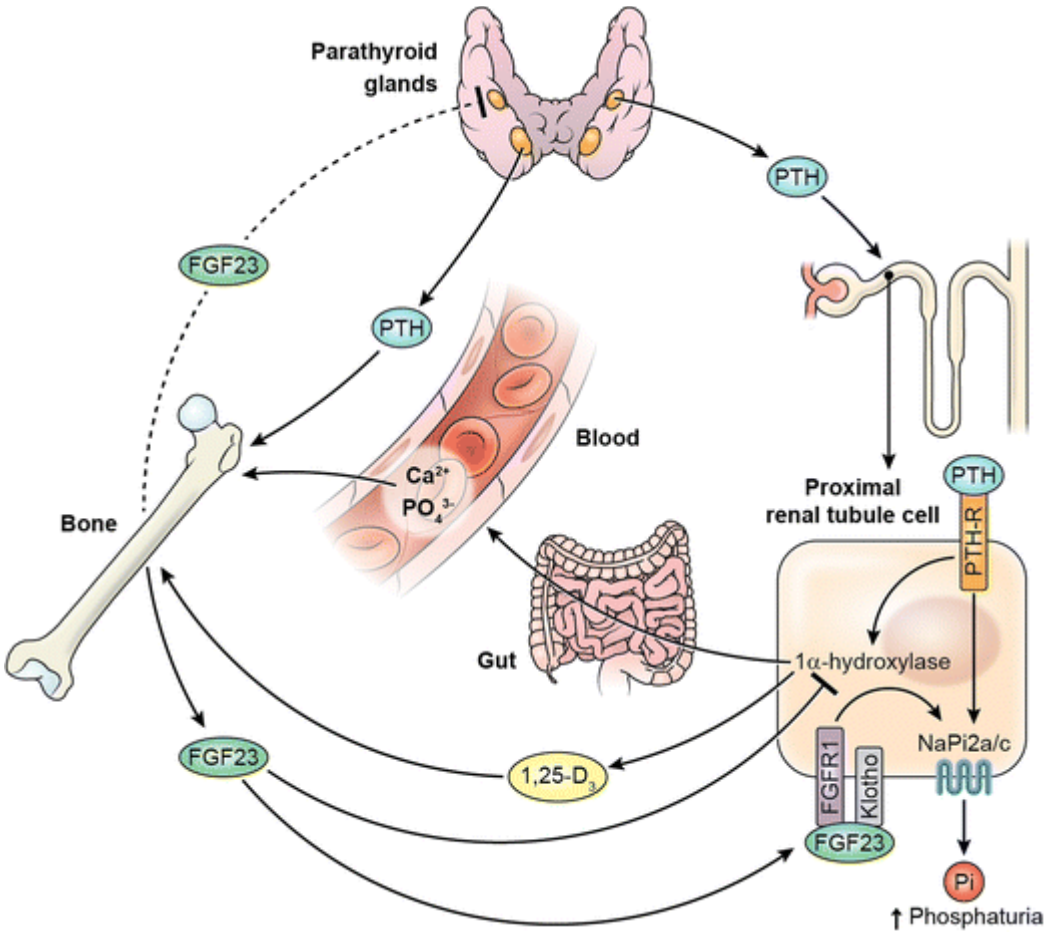
Phosphorus homeostasis in humans.



Berndt and Kumar 2007

PTH -Vitamin D - FGF23 axis



Blau& Collins, 2015

FGF23:

Phosphaturia via NaPi 2a /c co-transportes, similar to PTH

Supression of 1α hydroxylase activity.

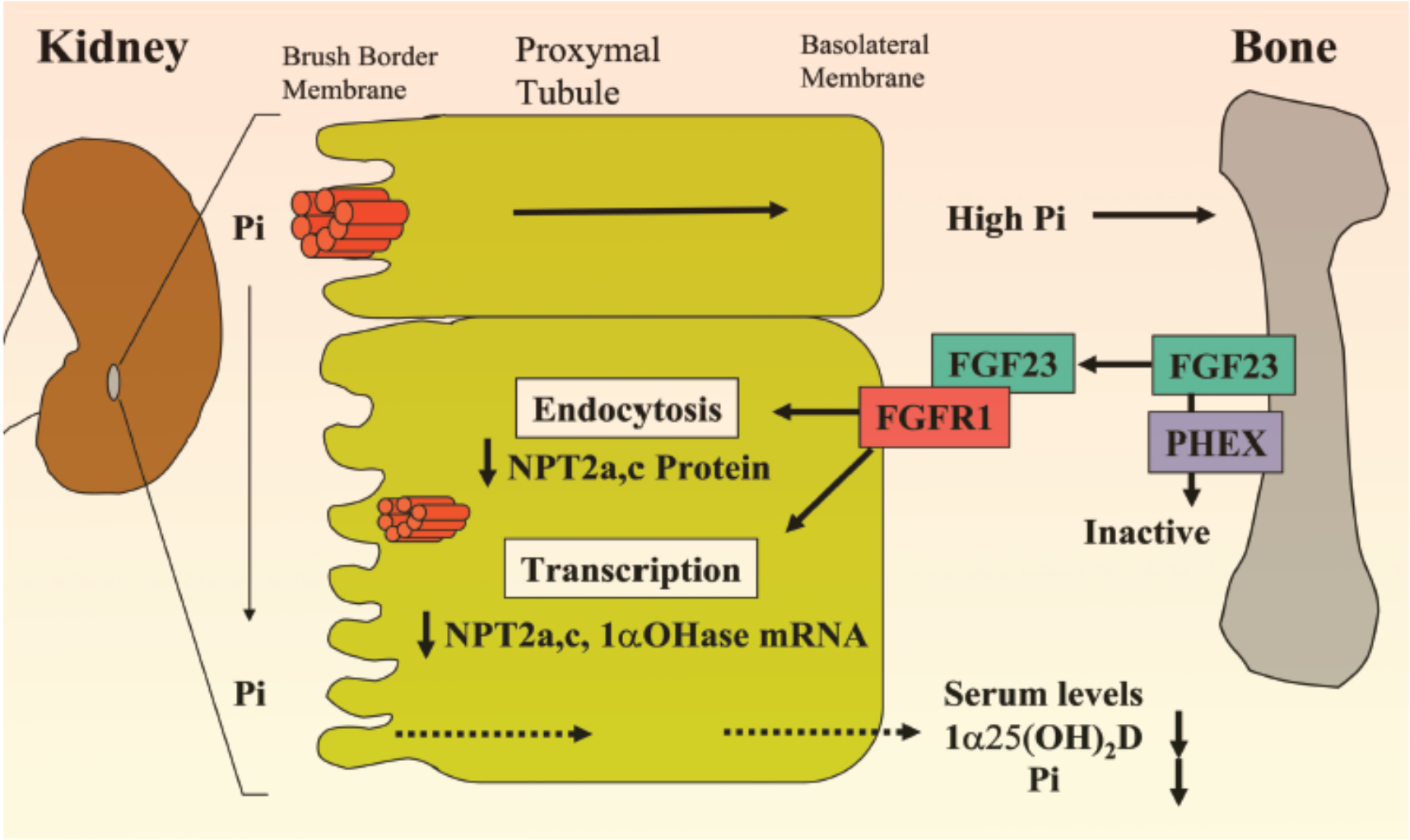
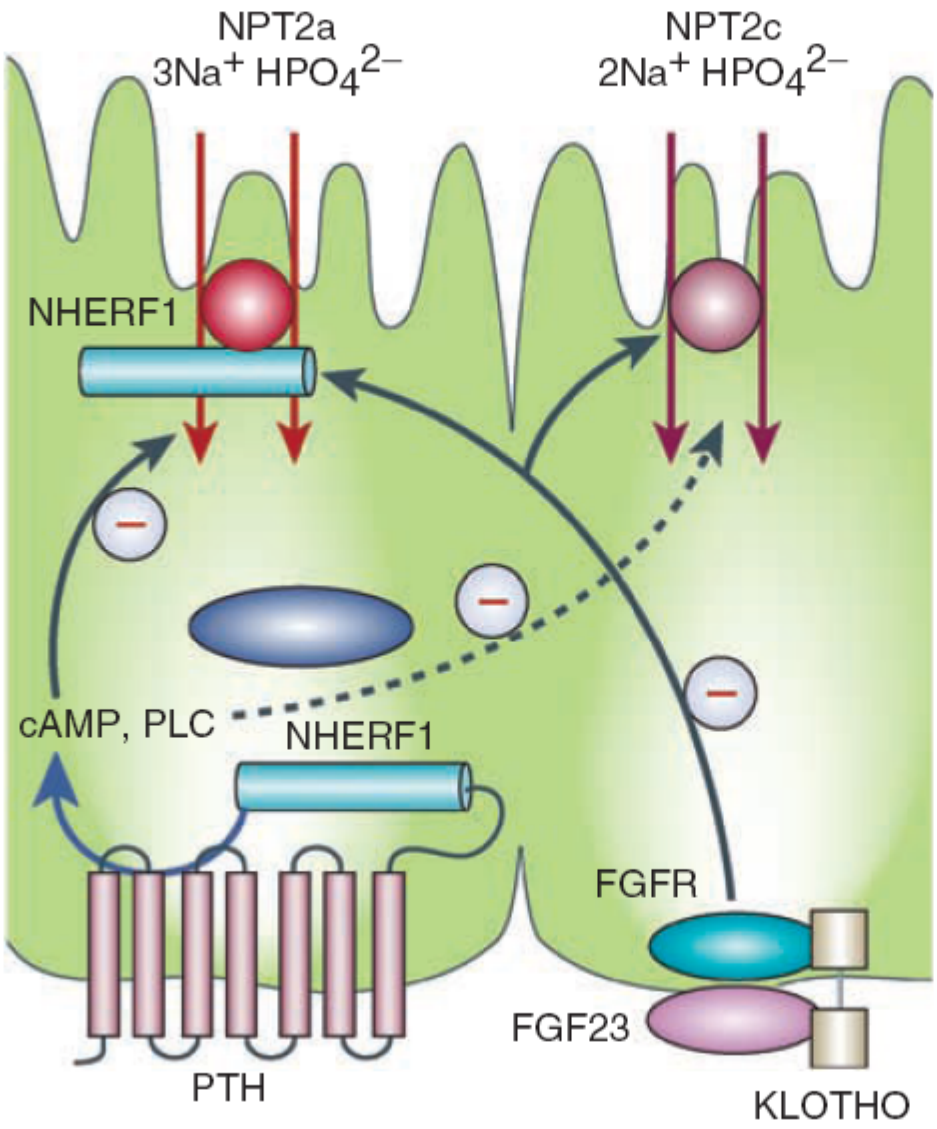


Fig. 1 Phosphate homeostasis regulated by FGF23.

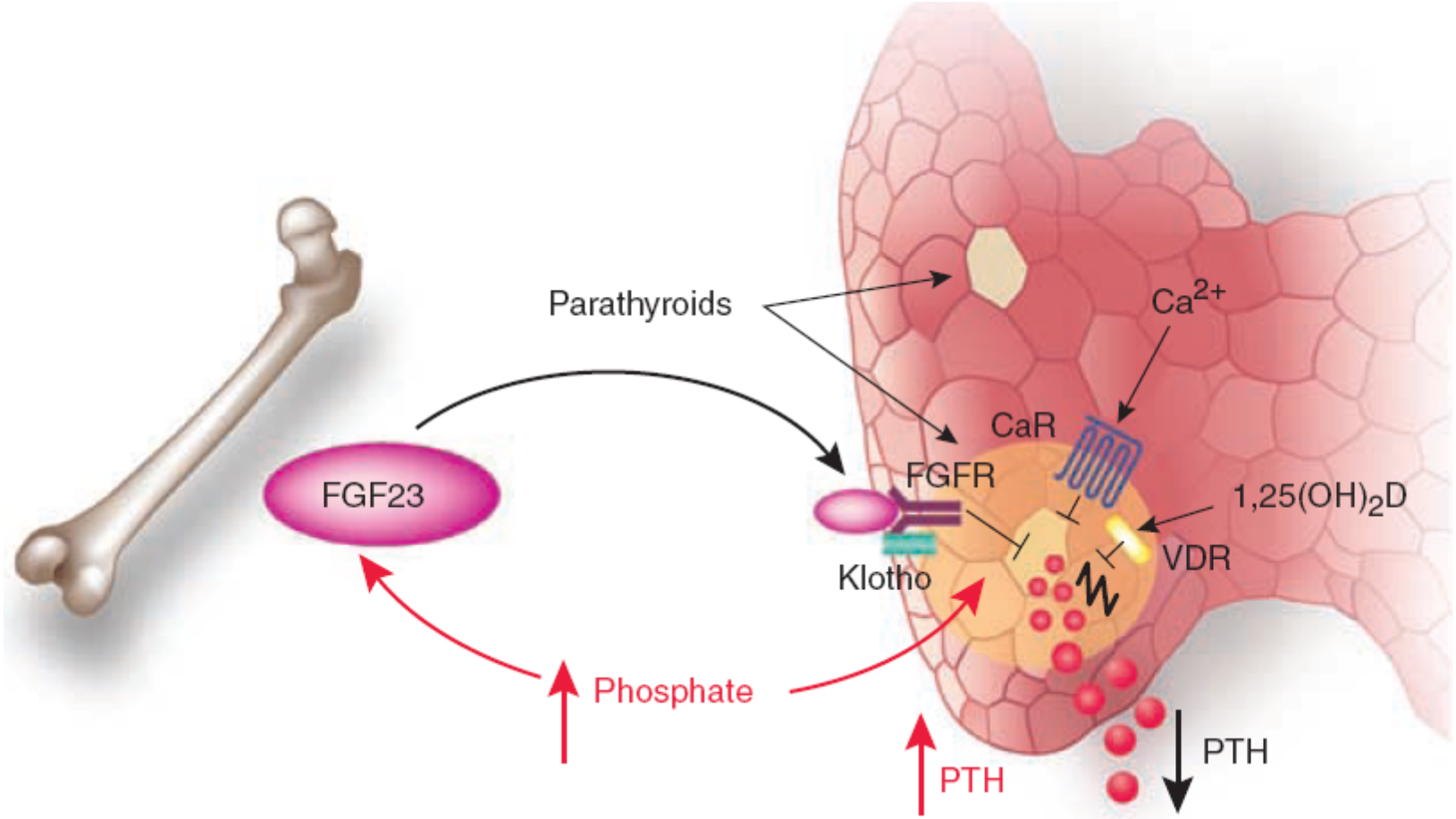
Inorganic phosphate homeostasis and the role of dietary phosphorus. Eiji Takeda *, Hironori Yamamoto, Kunitaka Nashiki, Tadatoshi Sato, Hidekazu Arai, Yutaka Taketani, 2004

Transporte tubular de Fosfato



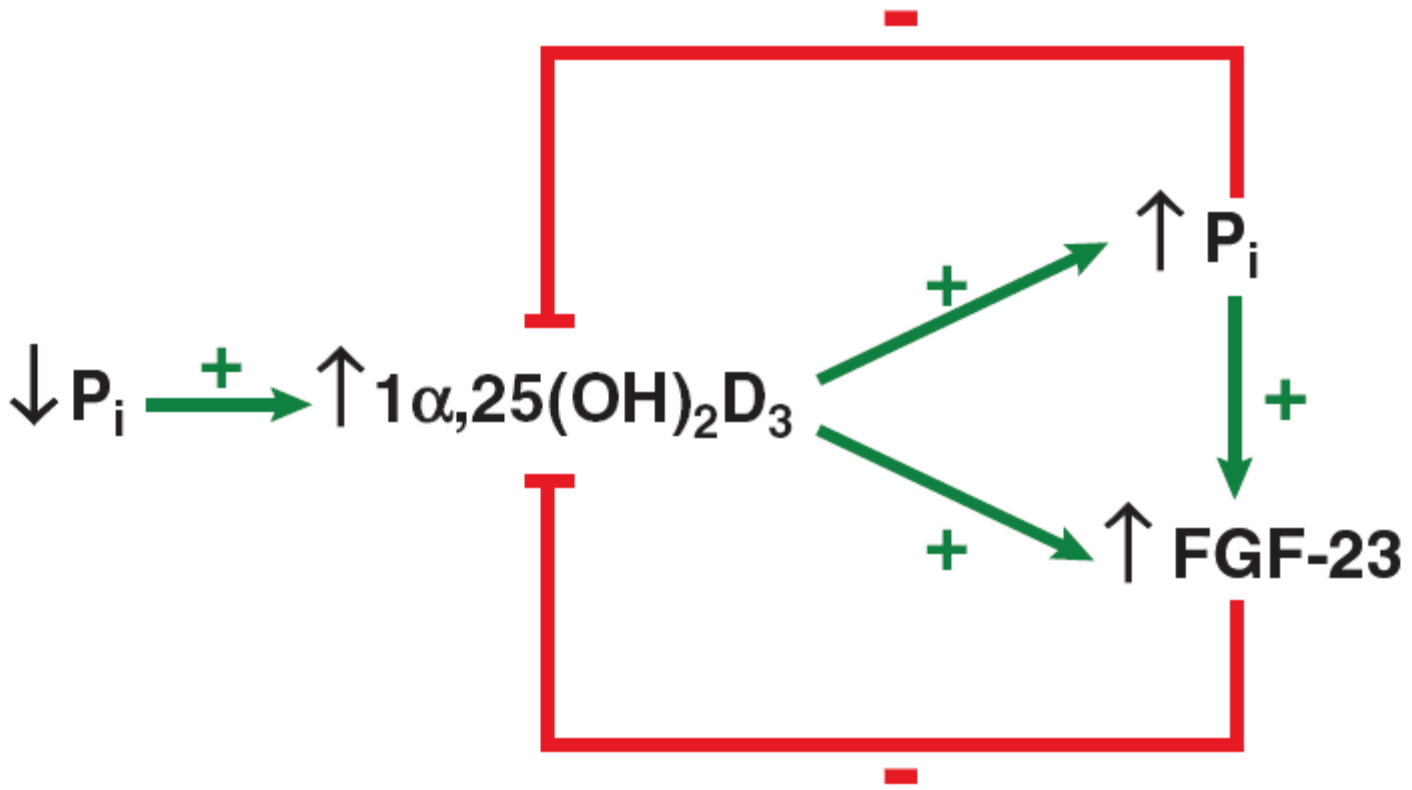
Prié, 2009

Figure 1 | Proteins involved in renal phosphate reabsorption.
Phosphate is reabsorbed in the proximal tubular cells through two sodium phosphate cotransporters, NPT2a and NPT2c, the activity of which is controlled by two hormones; the parathyroid hormone (PTH) and the fibroblast growth factor 23 (FGF23). PTH binds to the PTH type1 receptor (PTHR1) and induces the retrieval of NPT2a from the brush border membrane. Its effect on NPT2c is uncertain. FGF23 decreases the expression of both sodium phosphate cotransporters. NHERF1 binds to NPT2a and type 1 PTH receptor (PTH1R). Mutations in all these proteins have been identified in humans with impaired renal phosphate reabsorption.



Justin Silver1 and Tally Naveh-Many, 2009.
Figure 2 . FGF23 acts on the parathyroid to decrease PTH synthesis and secretion—a novel bone–parathyroid endocrine axis. FGF23 is secreted by bone after the stimulus of a high Pi level. In addition to the action of FGF23 on the kidney to cause Pi excretion and decrease the synthesis of 1,25(OH)2 vitamin D, it is now shown to act on the parathyroid to decrease PTH synthesis and secretion. This new endocrine axis contributes to our understanding of how the metabolism of bone Pi and Ca2þ is so tightly regulated. PTH is the major regulator of Ca2þ and FGF23 of Pi, and together with vitamin D they contribute to normal mineral and bone metabolism. This new endocrine axis may be useful for the discovery of new drugs to regulate PTH secretion. FGF23, fibroblast growth factor 23; FGFR, fibroblast growth factor receptor; CaR, calcium receptor; PTH, parathyroid hormone; VDR, vitamin D receptor. The red arrows indicate stimulatory pathways.

RELAÇÃO ENTRE 1α,25(OH)2D3, FÓSFORO E FGF23



2007, Berndt and Rajiv Kumar

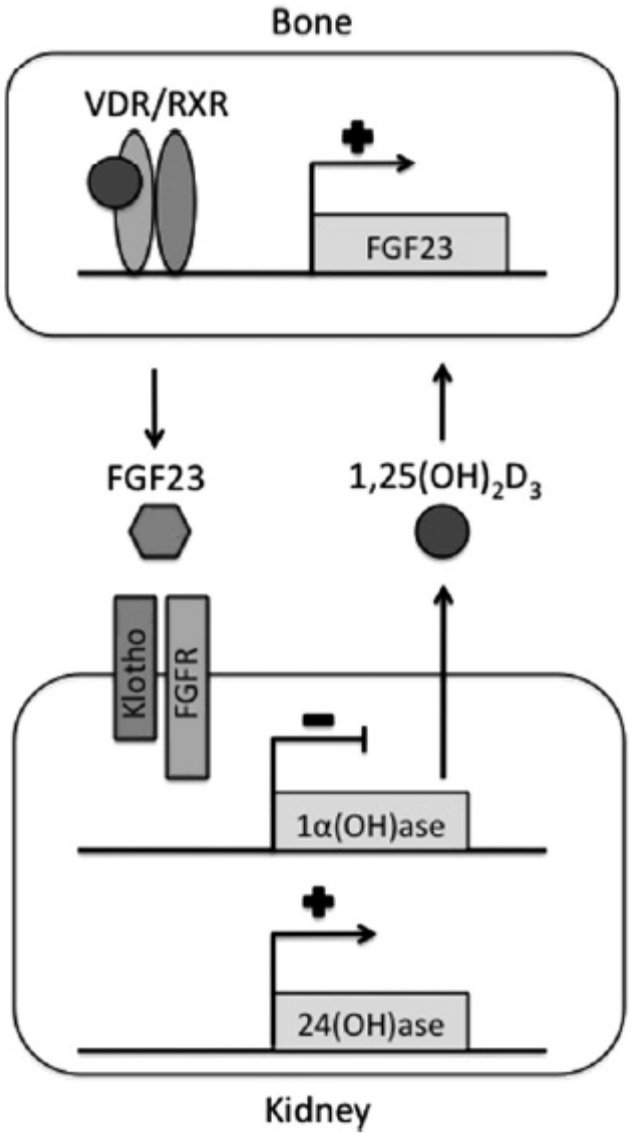


Fig. 2. Regulation of vitamin D hydroxylases by FGF23-Klotho. 1,25(OH)2D3 binds to VDR. The ligand-bound VDR forms a heterodimer with nuclear retinoid X receptor (RXR) resulting in increased expression of FGF23 in osteocytes. Secreted FGF23 activates FGF receptor (FGFR) bound by Klotho in renal tubular cells. FGF signaling suppresses expression of 1a(OH)ase and induces 24(OH)ase, thereby inhibiting synthesis and promoting catabolism of 1,25(OH)2D3. Thus, the FGF23-Klotho results in decreased levels of 1,25(OH)2D3. (

Vitamin D: Metabolism
Sylvia Christakos, 2010

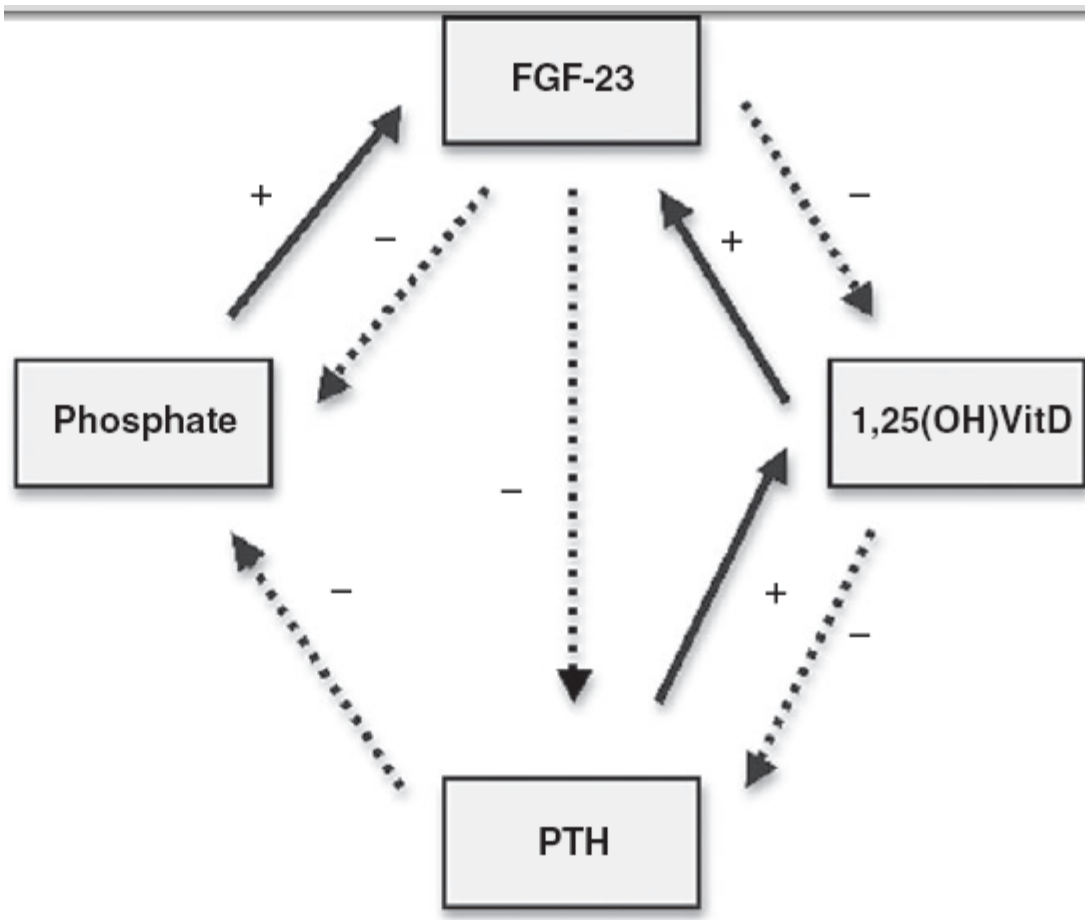
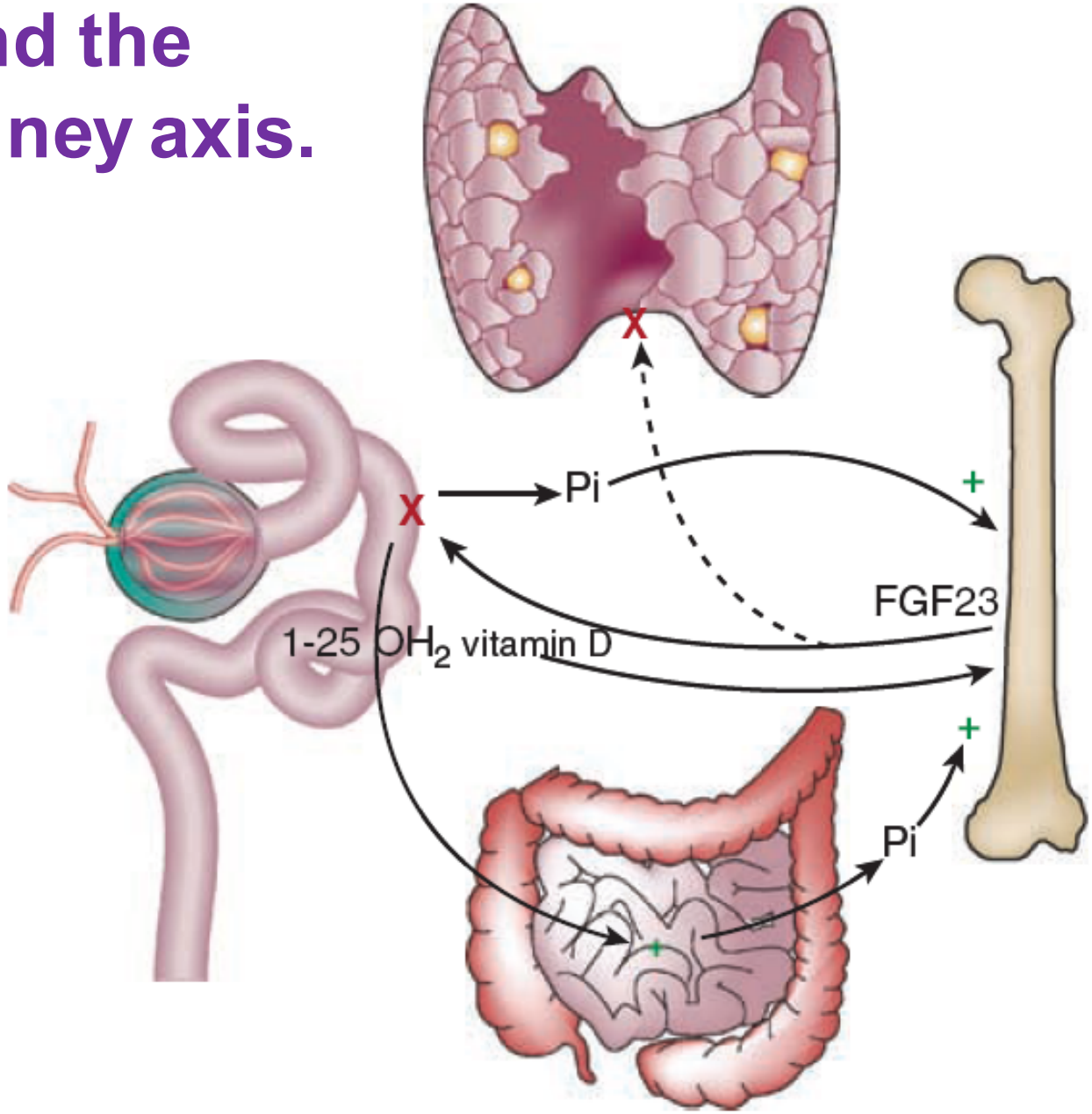


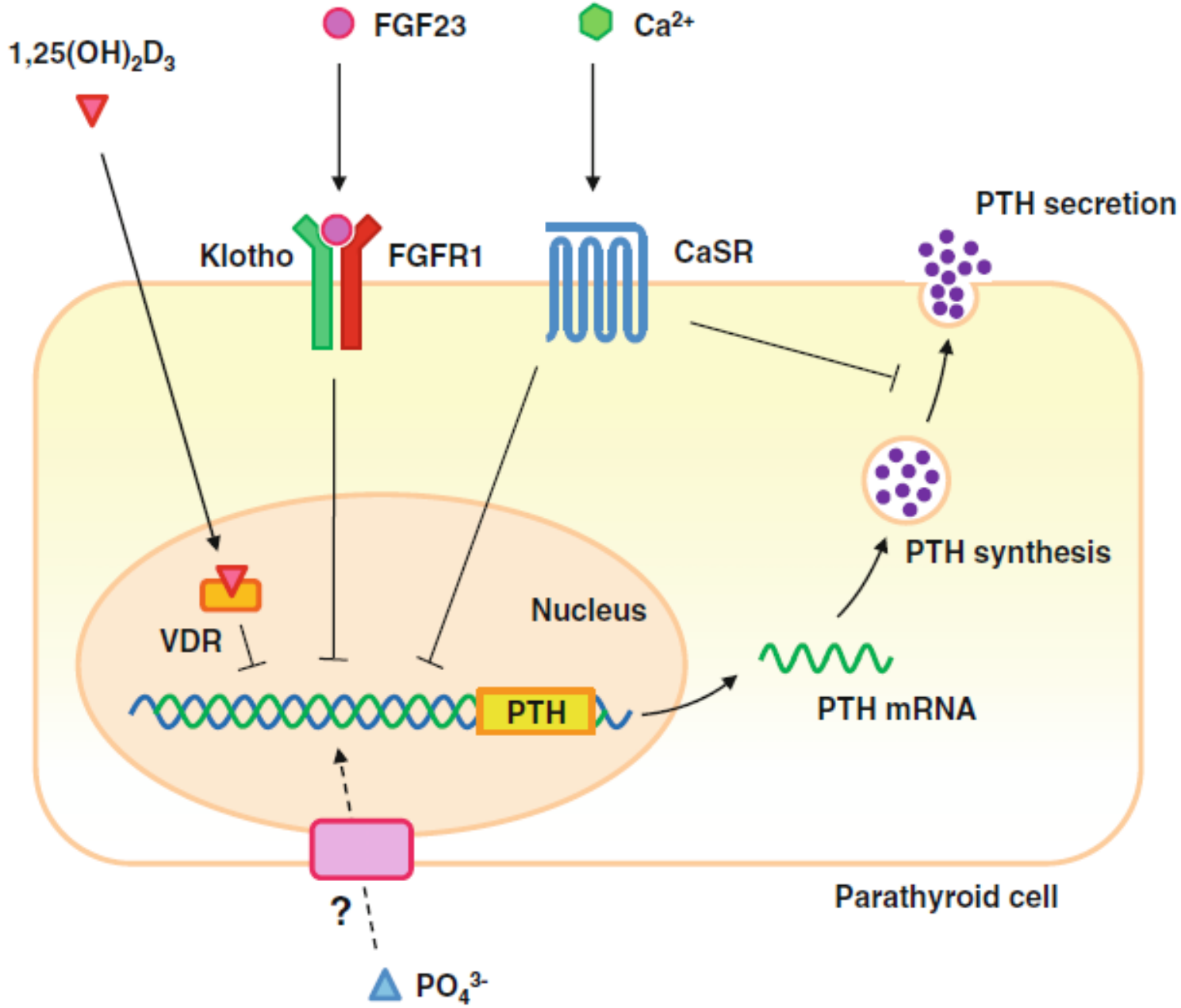
Fig. 1 Feedback loops. Fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH) lower phosphate by stimulating phosphaturia. PTH and FGF-23 have counter-regulatory effects on 1,25(OH) vitamin D. FGF-23 inhibits PTH.

Fibroblast growth factor 23 in chronic kidney disease: New insights and clinical implicationsnep, 2011.
MATTHEW J DAMASIEWICZ, NIGEL D TOUSSAINT and KEVAN R POLKINGHORNE

FGF23 and the bone–kidney axis.

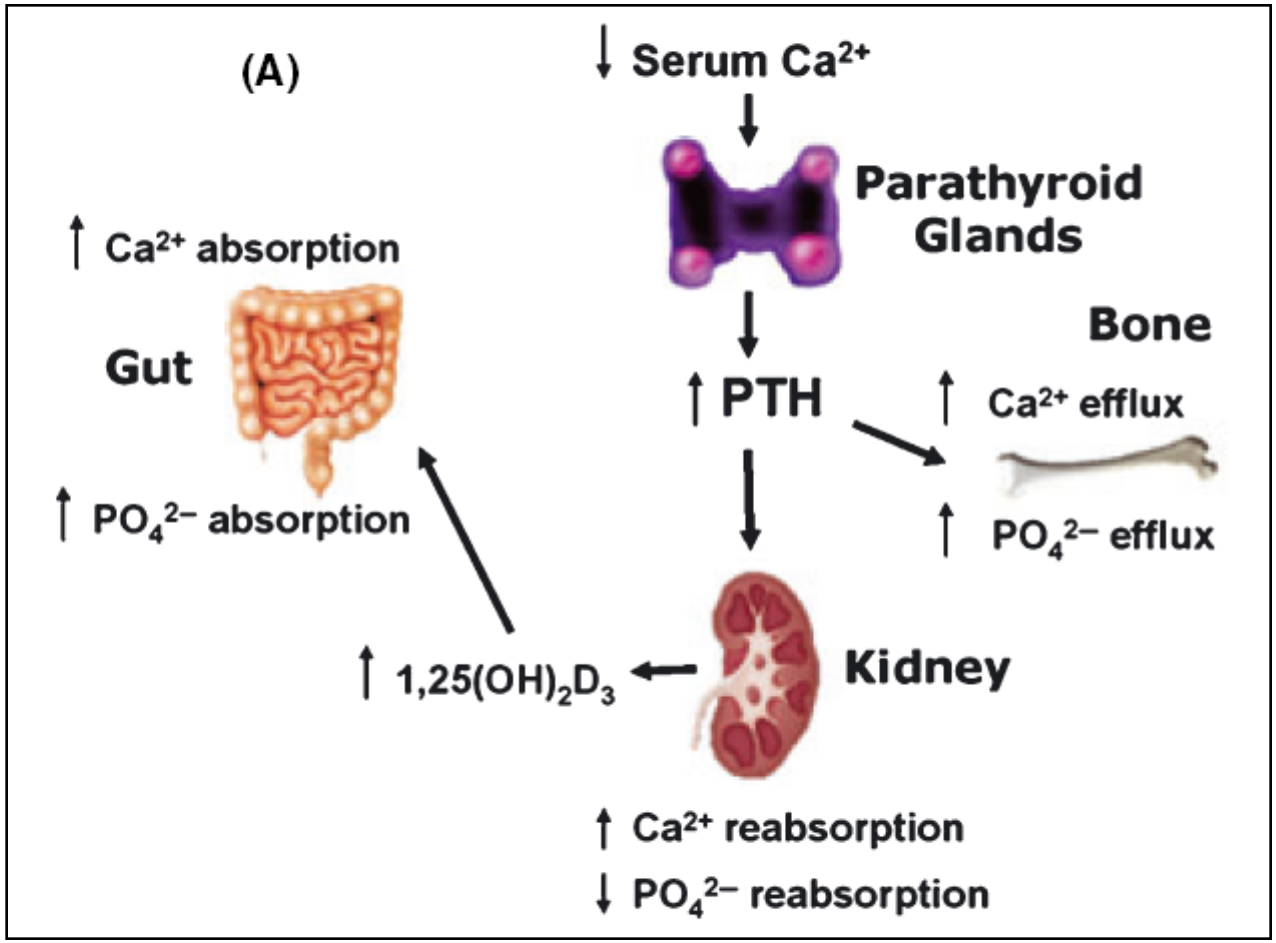


Prié, 2009


1,25(OH)2D3
FGF23
Ca2+
Klotho
FGFR1
CaSR
PTH secretion
PTH synthesis
VDR
Nucleus
PTH
PTH mRNA
?
PO4 3-
Parathyroid cell

Questões Orientadoras:

7. Explicar as variações do PTH e da vitamina D em uma situação de hipocalcemia e de hipofosfatemia.

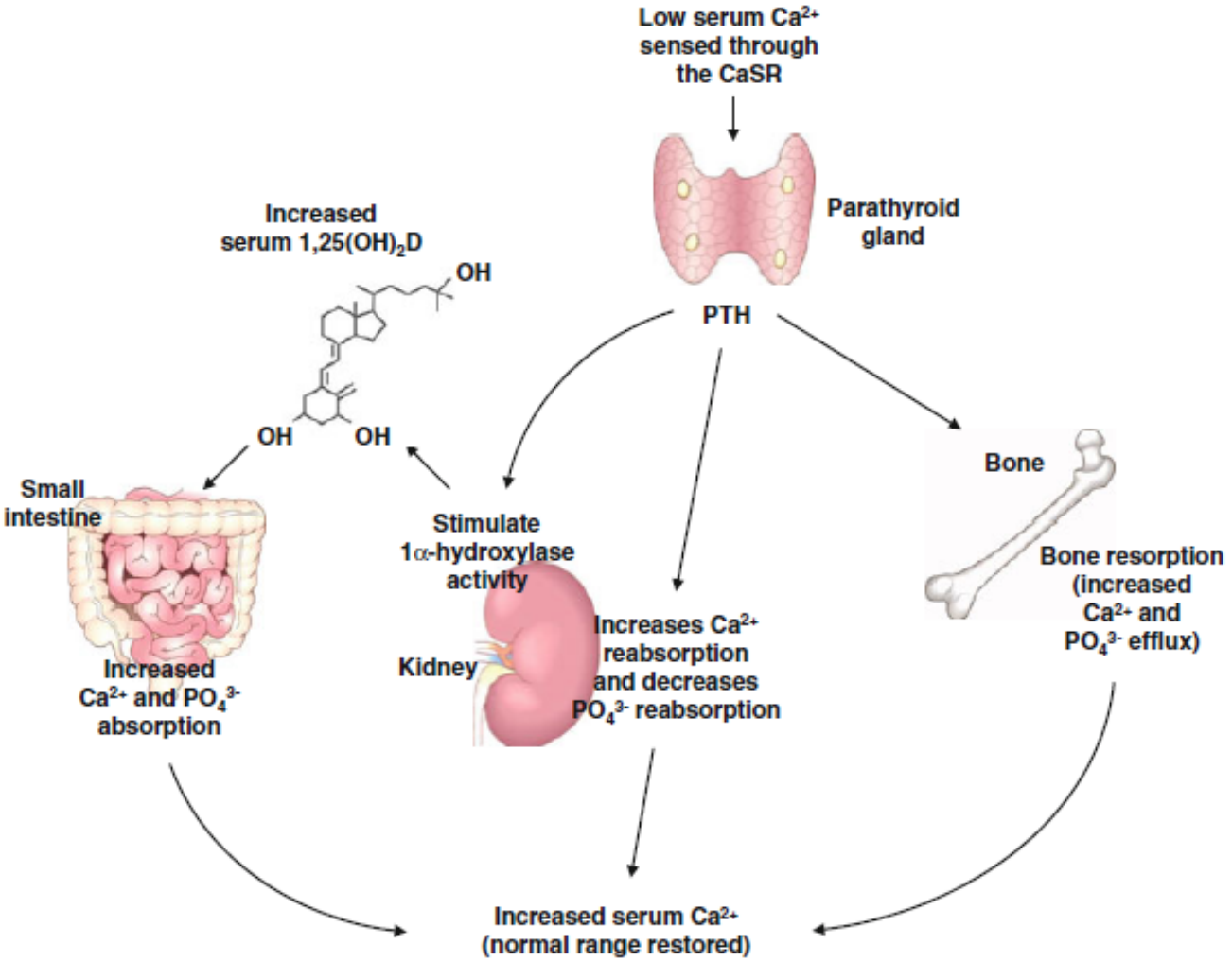


A) Calcium–PTH–vitamin D axis.

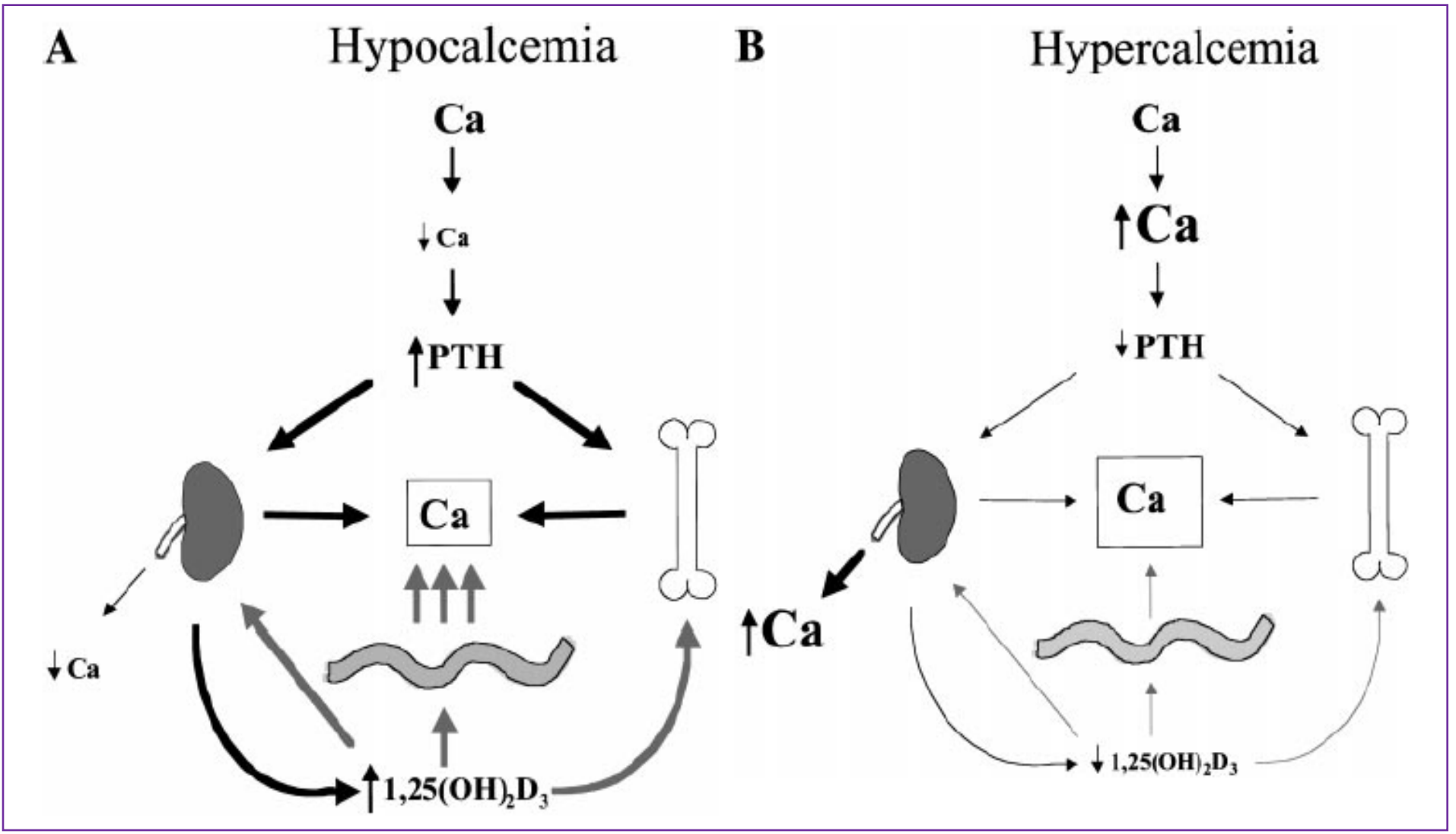
The calcemic hormone **PTH** produced by the parathyroid gland targets kidney to increase calcium absorption and 1,25(OH)2D3 production and bone to increase calcium efflux.

1,25(OH)2D3 stimulates calcium absorption from the gut, which, along with renal and bone calcium, restores serum calcium to normal.

Willians Textbook of Endocrinology


Low serum Ca^{2+} sensed through the CaSR
Parathyroid gland
PTH
Increased serum $1,25(OH)_2D$
OH
OH
OH
Small intestine
Increased Ca^{2+} and PO_4^{3-} absorption
Stimulate 1α-hydroxylase activity
Kidney
Increases Ca^{2+} reabsorption and decreases PO_4^{3-} reabsorption
Bone
Bone resorption (increased Ca^{2+} and PO_4^{3-} efflux)
Increased serum Ca^{2+} (normal range restored)

CALCEMIA E A SECREÇÃO DE PTH E SÍNTESE DE 1,25(OH)2D3



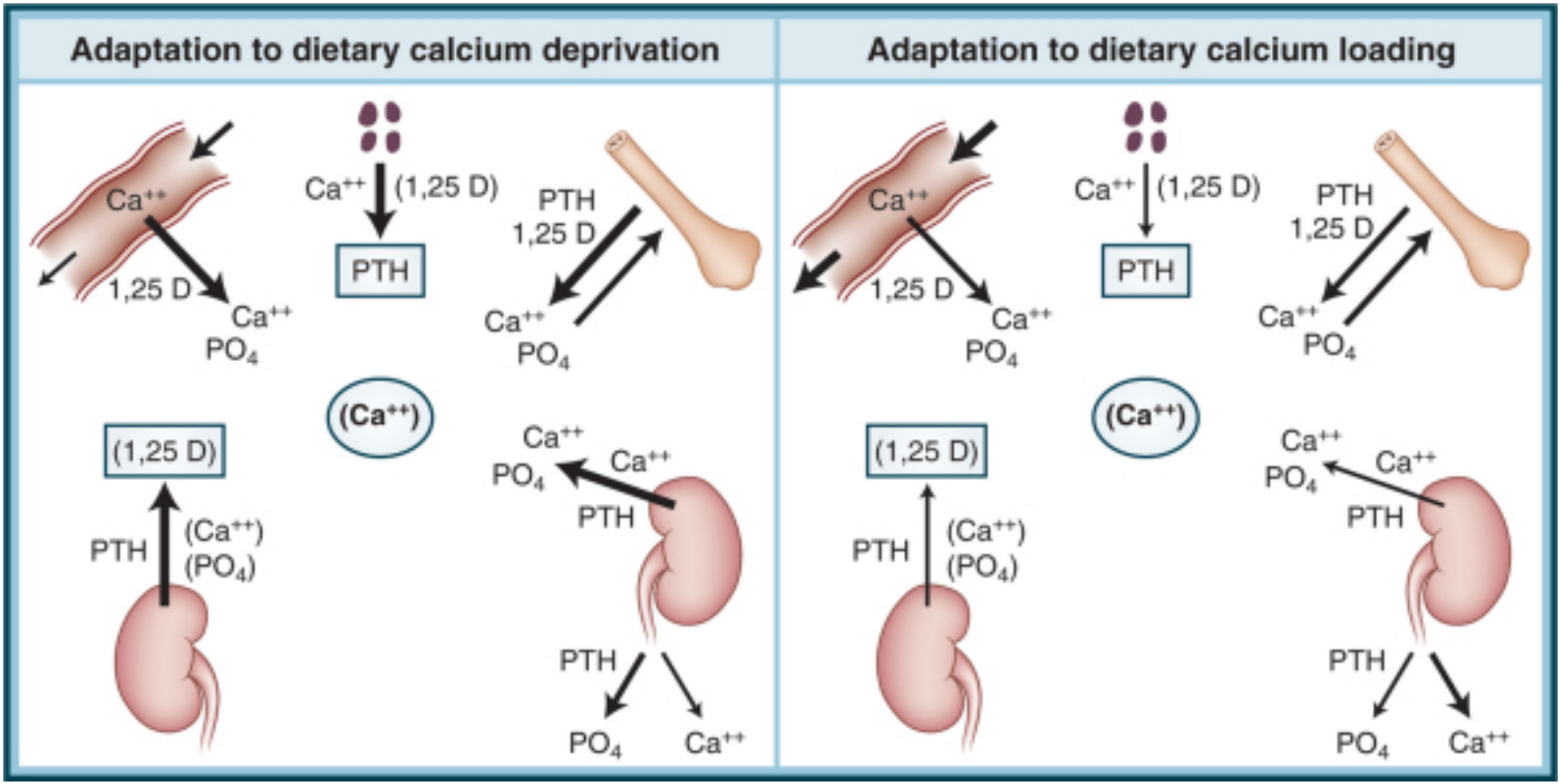
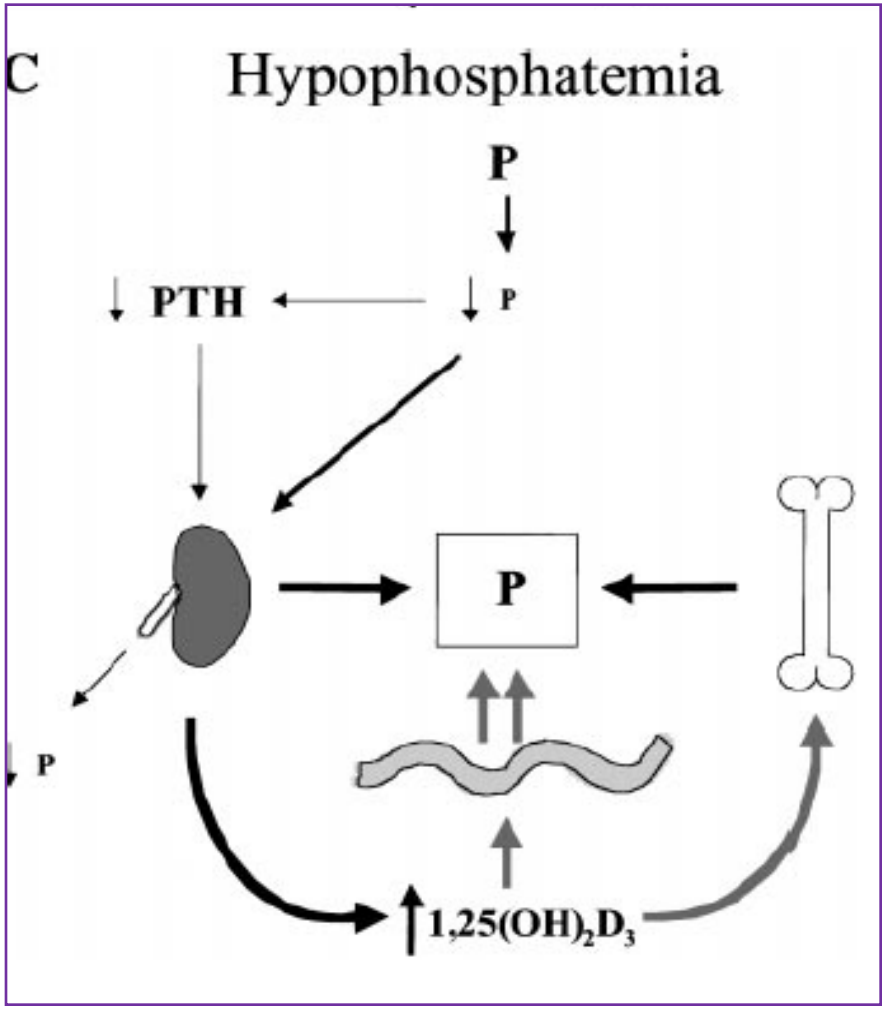


Figure 27-19 Homeostatic responses to variations in dietary calcium content. Major homeostatic responses to dietary calcium deprivation or loading are depicted. Arrow thickness indicates relative activity of transport or secretory mechanisms, whereas amounts of hormones or transported ions are related to the size of their notations. Parentheses indicate an inhibitory regulation. Note that the extracellular calcium concentration is well maintained, although different underlying mechanisms are involved in the two circumstances (see text for details). PTH, parathyroid hormone.

Questões Orientadoras:

7. Explicar as variações do PTH e da vitamina D em uma situação de hipocalcemia e de **hipofosfatemia**.



8. Paciente do sexo feminino, 66 anos, com queixa de fratura vertebral, nefrolitíase apresenta os resultados abaixo. Como podemos explicar os resultados abaixo e as queixas da paciente.

		Valor de referência:
Cálcio sérico	10,9 mg/dl	8,4 – 10,4 mg/dl
Fosforo sérico	2 mg/dl	2,3 – 4,7 mg/dl
PTH sérico	90 pg/ml	15 – 65 pg/ml
Densitometria óssea – coluna lombar	T-score: – 2,8	VER CLASSIFICAÇÃO WHO (abaixo)

Postmenopausal Osteoporosis Guidelines, *Endocr Pract.* 2010;16(Suppl 3)

Table 3
World Health Organization Criteria for Classification of Osteopenia and Osteoporosis

Category	T-score
Normal	−1.0 or above
Low bone mass (osteopenia)[a]	Between −1.0 and −2.5
Osteoporosis	−2.5 or below

T-score

$$\frac{\text{Patient's BMD} - \text{Young-Adult Mean BMD}}{\text{1 SD of Young-Adult Mean BMD}}$$

Example:

$$\text{T-score} = \frac{0.7\ \text{g/cm}^2 - 1.0\ \text{g/cm}^2}{0.1\ \text{g/cm}^2} = -3.0$$

Z-score

$$\frac{\text{Patient's BMD} - \text{Age-Matched Mean BMD}}{\text{1 SD of Age-Matched Mean BMD}}$$

Low Z-score (less than -2.0) has been suggested by some to increase likelihood of secondary osteoporosis, however . . .

- This is not validated in clinical trials
- High index of suspicion for secondary causes of osteoporosis is recommended for all patients

8. A administração de 1,25(OH)2 D3 é um dos tratamentos do hiperparatireodismo secundário à insuficiência renal crônica. Explicar os mecanismos que contribuem para o hiperparatireoidismo secundário na insuficiência renal crônica, e os efeitos do tratamento com 1,25(OH)2 D3.

Phosphate Retention and Secondary Hyperparathyroidism

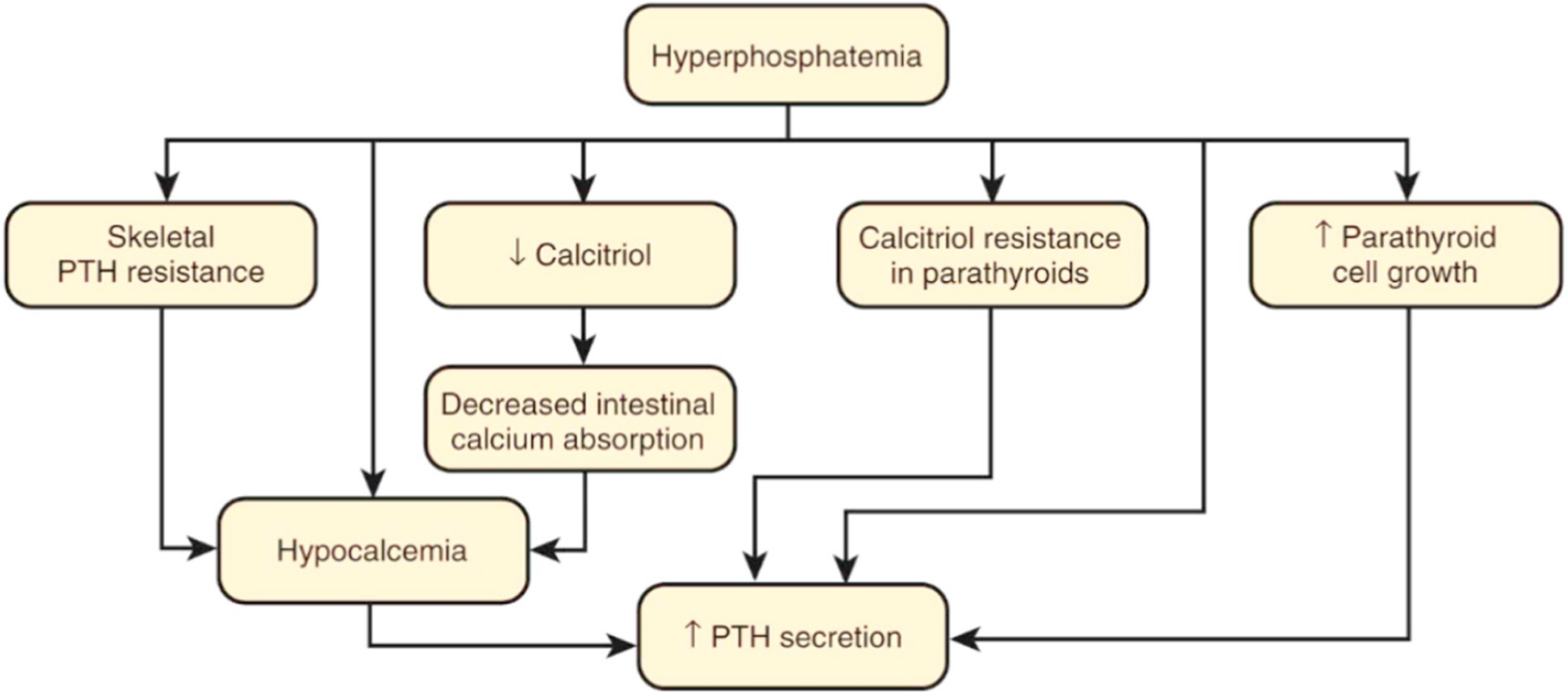


Fig. 2. Role of phosphate retention in the pathogenesis of secondary hyperparathyroidism. Hyperphosphatemia stimulates parathyroid hormone (PTH) secretion indirectly by inducing hypocalcemia, skeletal resistance to PTH, low levels of calcitriol, and calcitriol...

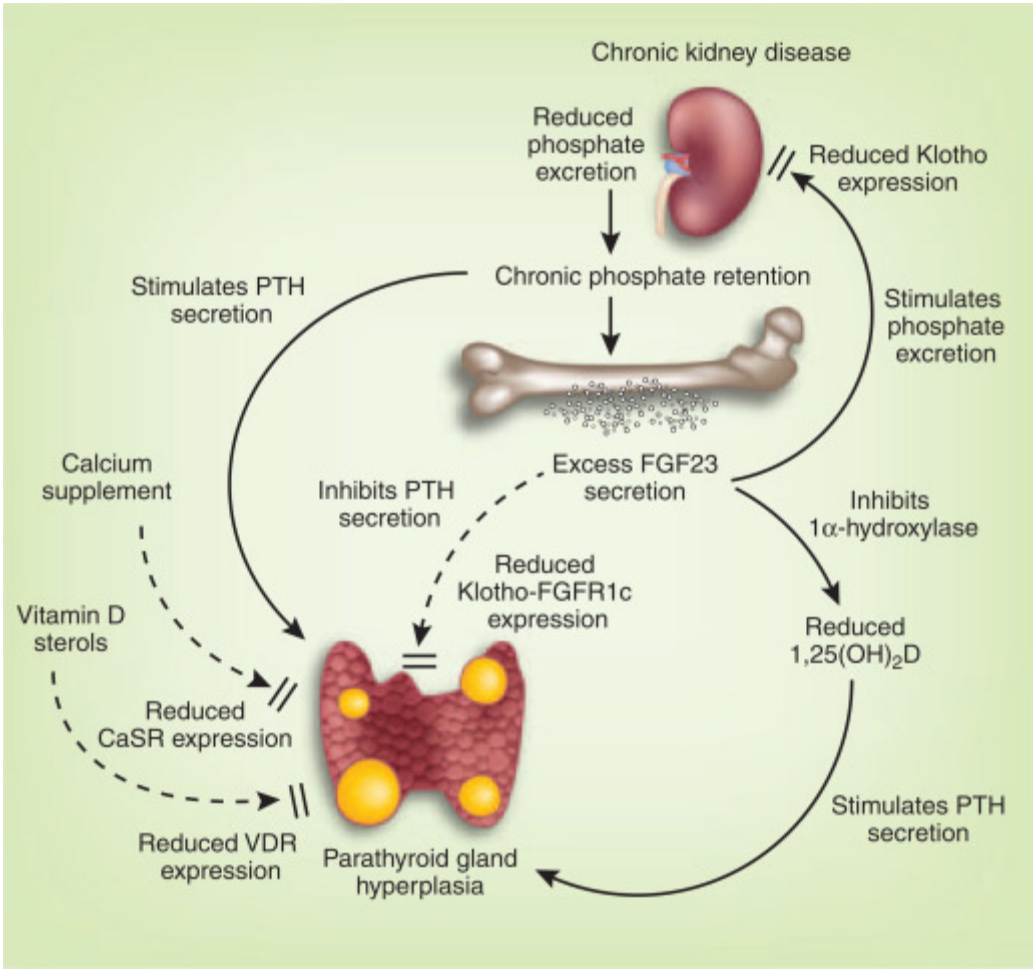
Malgorzata Kochanek, Albara Said, Edgar V. Lerma

Mineral metabolism in chronic kidney disease

Disease-a-Month, Volume 61, Issue 10, 2015, 425–433

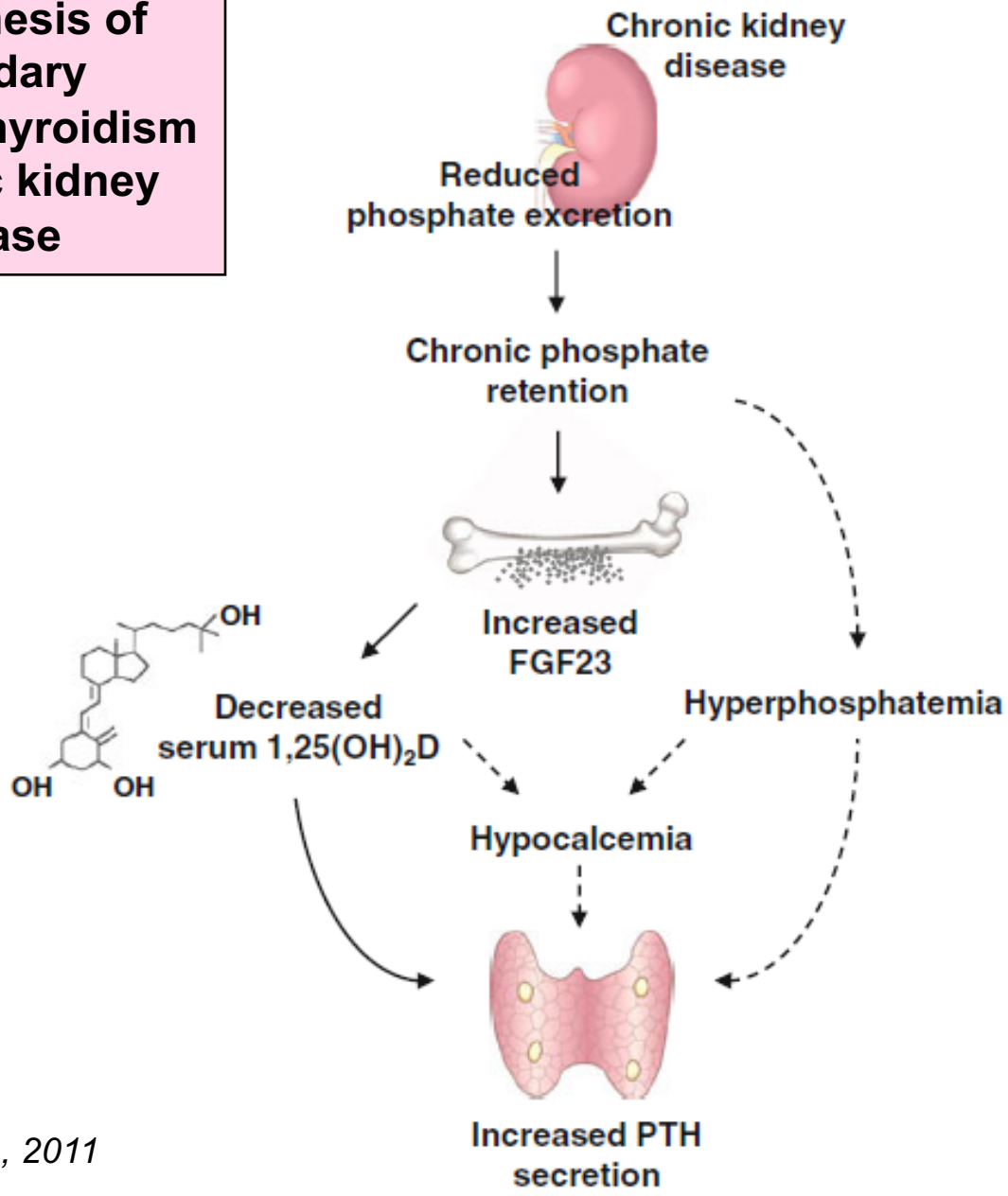
http://dx.doi.org/10.1016/j.disamonth.2015.08.003

Secondary hyperparathyroidism in chronic kidney disease



Hirotaka Komaba, Masafumi Fukagawa. Kidney International, 2010.

Pathogenesis of secondary hyperparathyroidism in chronic kidney desease



Komaba et al., 2011

TABLE 3. Causes of low serum $1,25(OH)_2D_3$ levels in CKD

Reduced renal mass decreases 1α-OHase activity
Functional suppression of the 1α-OHase enzyme by
Hyperphosphatemia (26)
Hyperuricemia (16,17)
Metabolic acidosis (19)
Other uremic toxins (e.g., xanthine, hypoxanthine) (20)
Low $25(OH)D_3$ levels from
Nutritional vitamin D deficiency (little sunlight exposure, inadequate intake, age, dark-pigmented skin) (14,21)
Renal losses of 25-hydroxyvitamin D due to proteinuria (22)
Uremia-induced decreased skin photoconversion of 7-dehydrocholesterol (23)
Low renal megalin levels (from renal disease) (24)

Andress, 2005

Fig. 7. Brown tumor in the distal portion of the femur demonstrated as central, lytic, sharply demarcated lesion (small arrows). Ill-defined subchondral surface of the medial femoral condyle reflects subchondral bone resorption (curved arrow).

Imaging of renal osteodystrophy
V. Jevtic. 2003

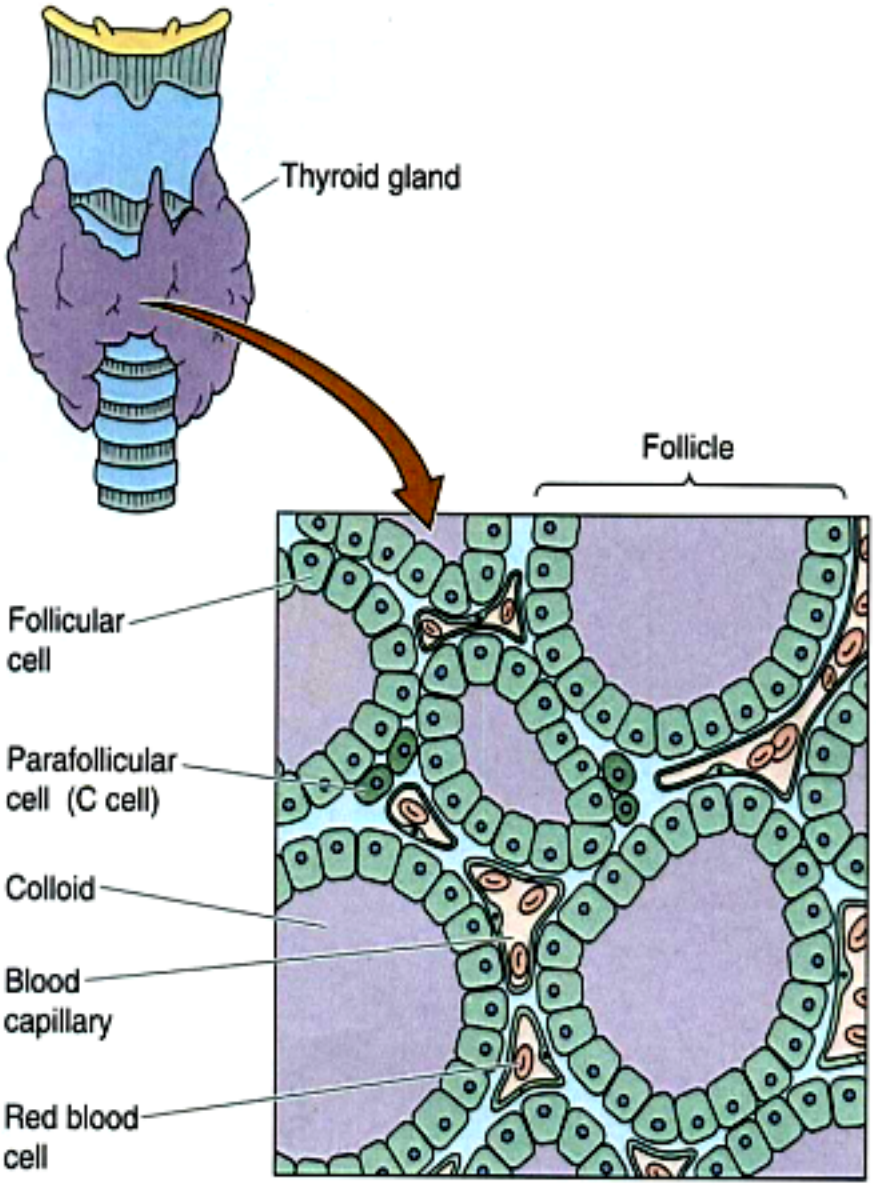
Brown tumors (osteoclastomas)

Calcitonina

Calcitonina

- Hormônio protéico (32aa)
- Produzido nas células parafoliculares (C) tireóide
- Circula livre
- Concentração plasmática de 20 pg/ml or 5×10^{-12} M

Células parafoliculares
ou
células C secretam
calcitonina



Controle da Secreção de Calcitonina

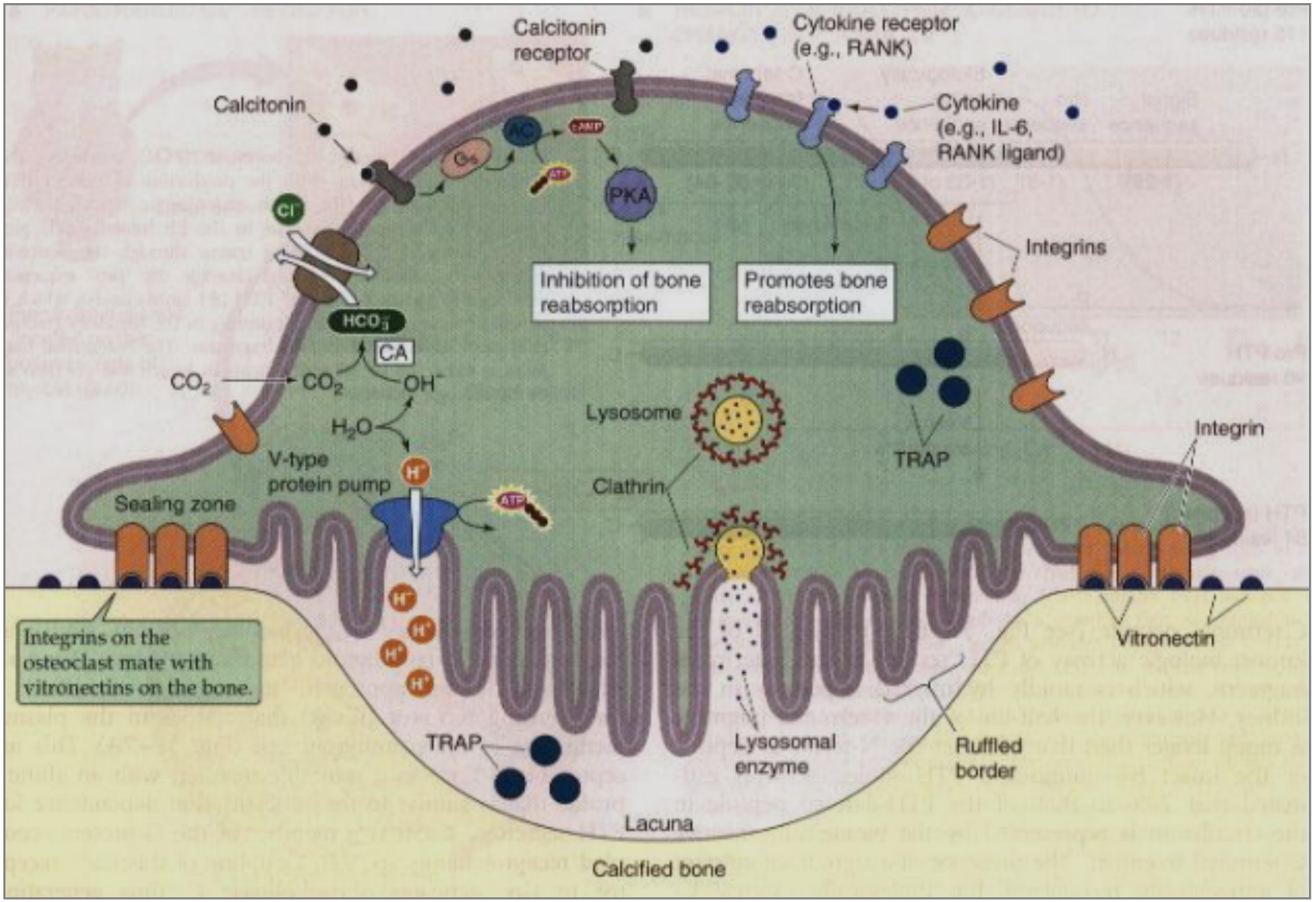
- Aumento do [Ca+] extracellular estimula a secreção de calcitonina (receptor sensível ao cálcio)

- Pode ser facilitada pela ação de hormônios gastrointestinais
  - Gastrina

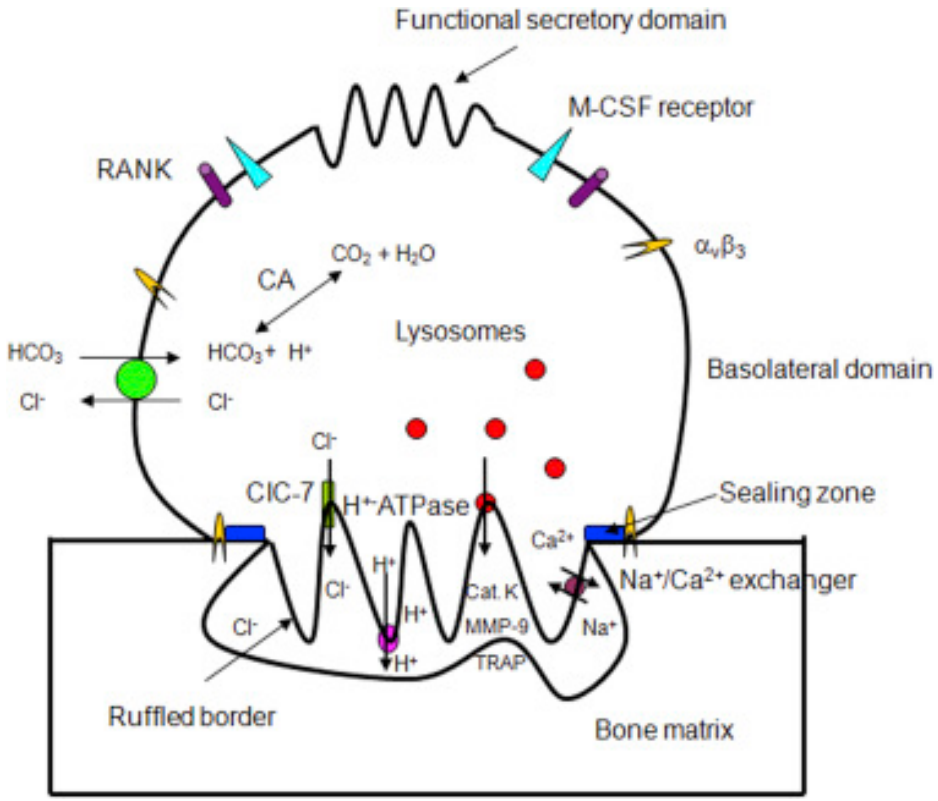
CALCITONINA

INIBIÇÃO DA RESSORÇÃO ÓSSEA PELO OSTEOCLASTO

(Ação mediada por receptor ligado à proteína G)



BONE RESORBING OSTEOCLAST



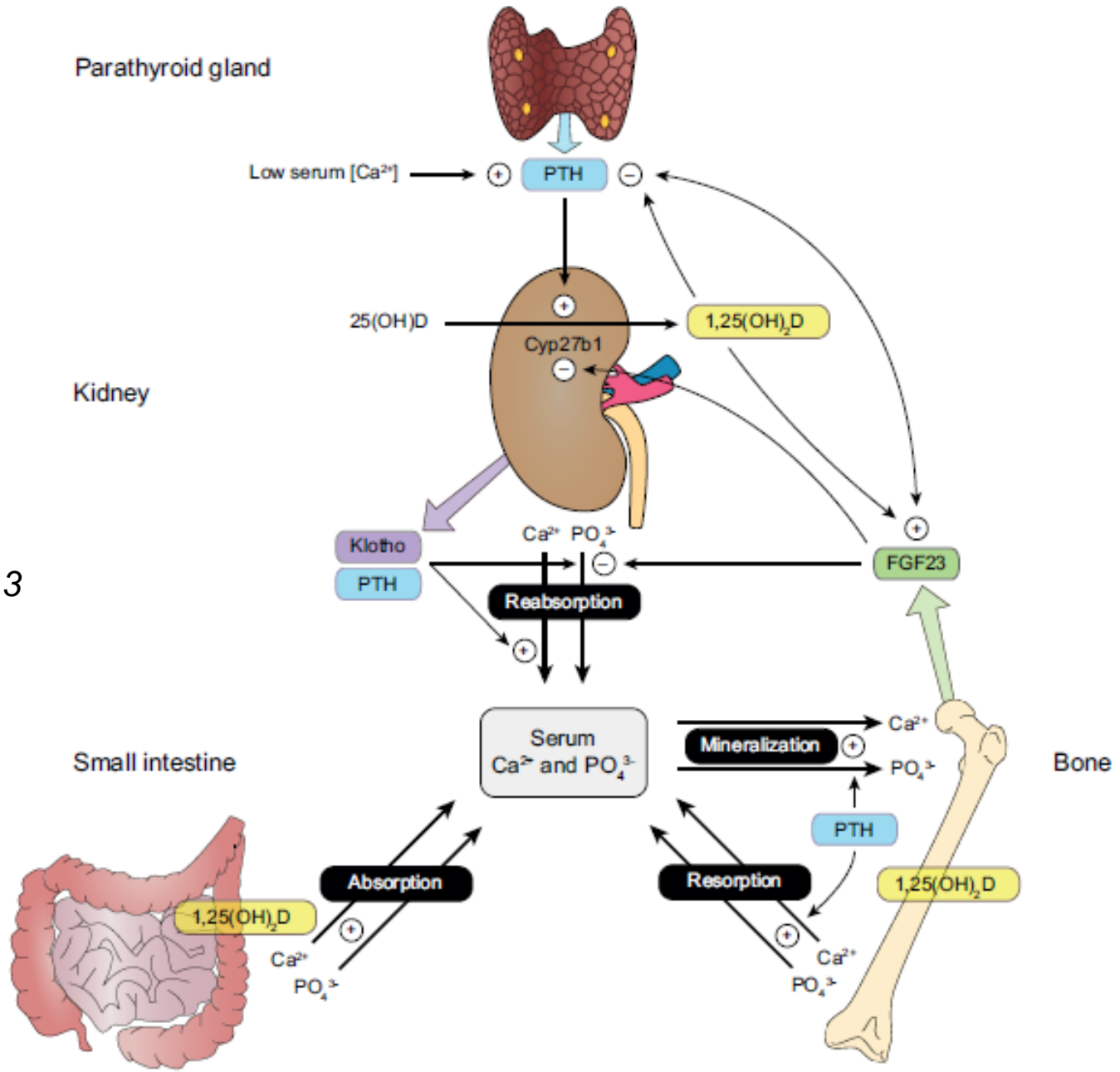
OCs acidify the extracellular vacuole by secreting protons by electrogenic **H^+-transporting adenosine triphosphatase** (v-ATPase) which transports protons provided by the enzyme carbonic anhydrase (CA). **Na^+/Ca^{2+} exchanger** exchanges extracellular Na^+s for intracellular Ca^{2+} during bone resorption. Intracellular alkalization is prevented by extrusion of Cl^- through ClC-7 chloride channel and chloride-bicarbonate exchanges at the basolateral membrane. Collagen is degraded by **proteases** released by lysosomes such as **cathepsin K** and **metalloproteases** (eg.MMP-9) including **collagenase** and **gelatinase**.

Niroshani Surangika Soysa, Neil Alles. **Osteoclast function and bone-resorbing activity: An overview**

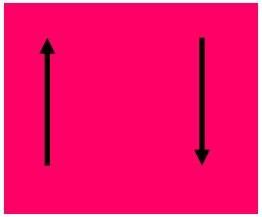
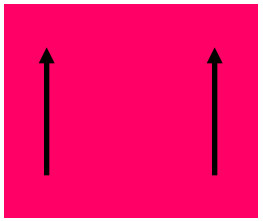
Biochemical and Biophysical Research Communications, Volume 476, Issue 3, 2016, 115–120

Endocrine regulation of calcium (Ca2+) and phosphate metabolism.

Hannes Olauson, 2013



Efeitos dos hormônios que regulam a homeostase do $[Ca^{2+}]$ e fosfato

Hormônio	Estímulo para secreção	Ações no osso	Ações no rim	Ações no intestino	Efeitos no [Ca] sérico	Efeitos no [P] sérico
PTH	↓ $[Ca^{2+}]$	↑ Aumenta a ressorção óssea	↓ Reabsorção de [P] no TP (Ef. Fosfatúrico) ↑ AMPc urinário ↑ Reabsorção de $[Ca^{2+}]$ no TD (Ef. Hipocalciúrico)	↑ Absorção de $[Ca^{2+}]$ (Ativação da 1α-hidroxilase vit D)		
Vitamina D	↓ $[Ca^{2+}]$ ↑ PTH ↓ [P]	↑ Ressorção (sinergismo com PTH)	↑ Reabsorção de [P] ↑ Reabsorção de $[Ca^{2+}]$	↑ Absorção de $[Ca^{2+}]$ ↑ Absorção de [P]		
Calcitonina	↑ $[Ca^{2+}]$	↓ Ressorção	⇓ Reabsorção de P no TP			
FGF23	↑ [P]		⇓ Reabsorção de P no TP			