아연의 생리적인 기능 및 약리적 역할

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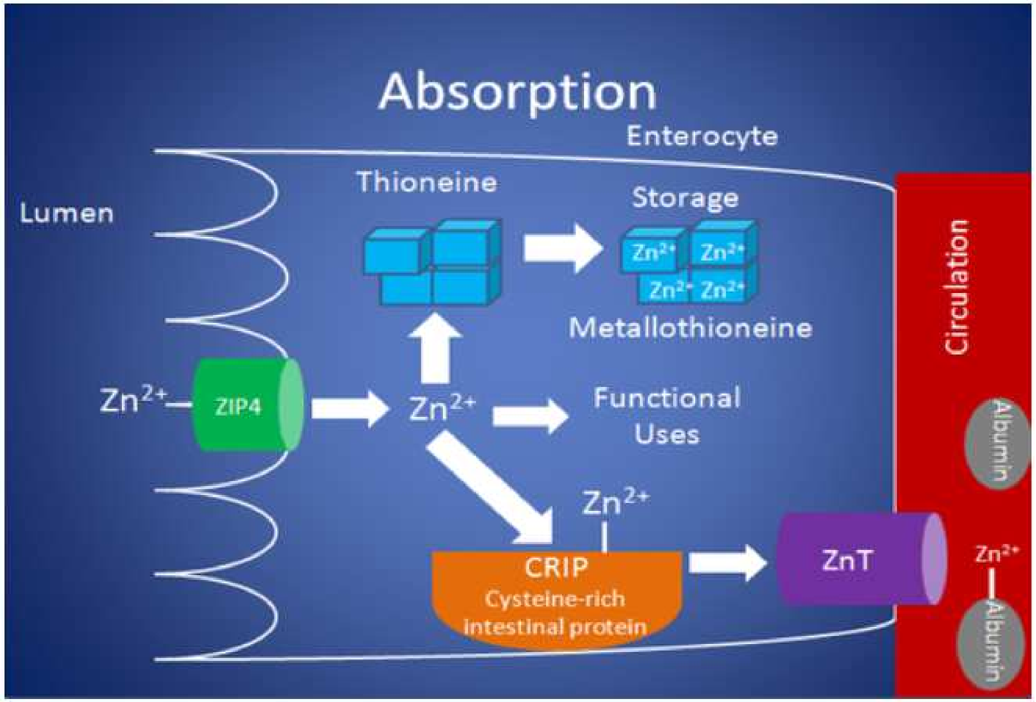
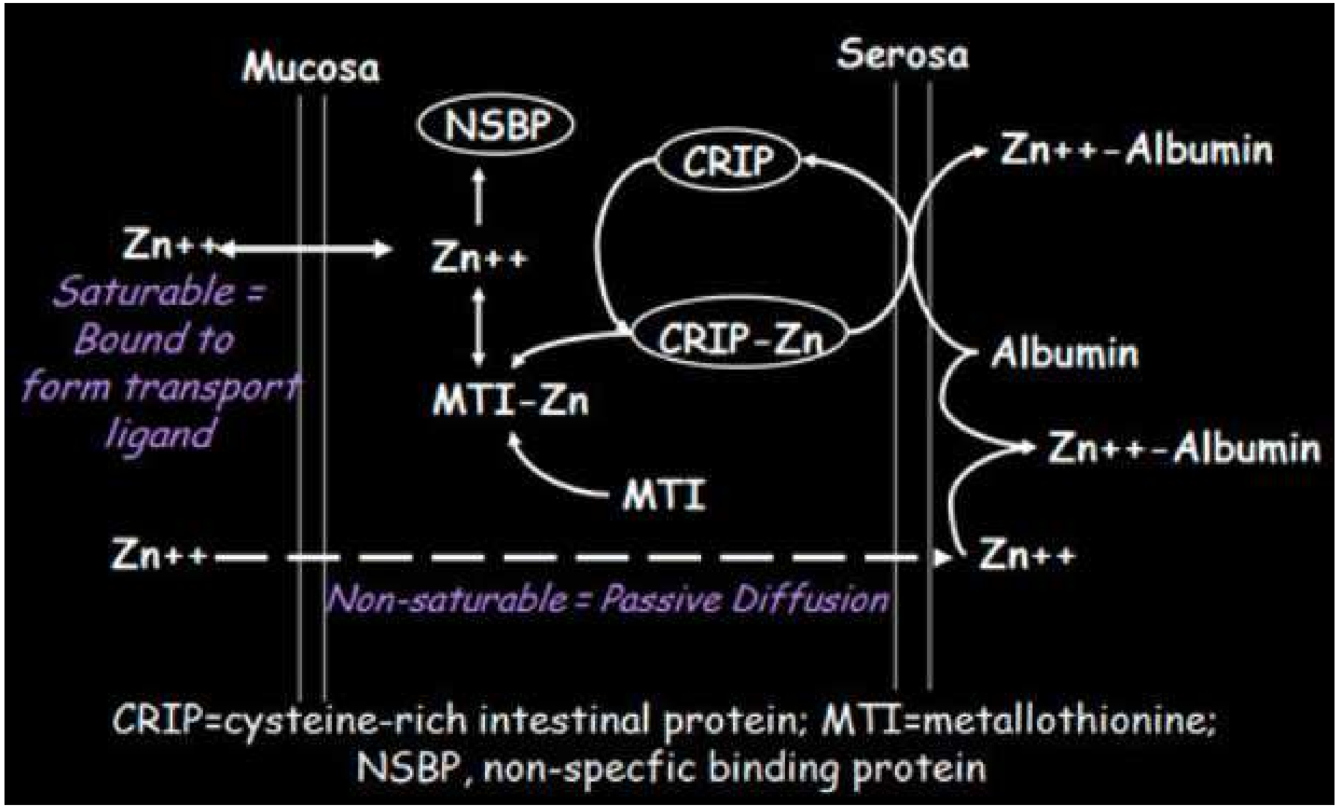
Zinc absorption

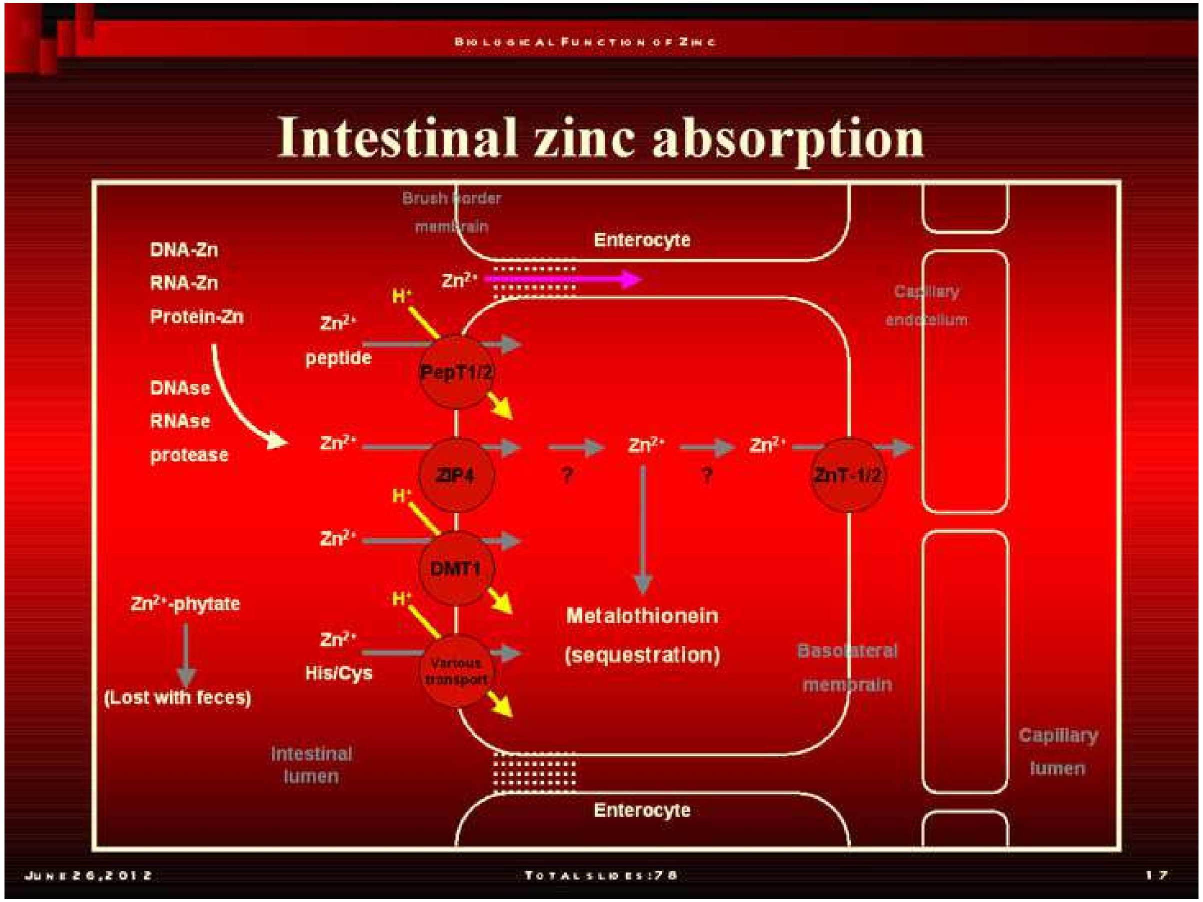
Enterocyte(장세포)에는 thioneine이 발현되어 흡수된 아연과 결합하여 metallothioneine으로 장세포 안에 저장되고 cysteine-rich intestinal protein(CRIP)에 결합되어 아연 transporter를 통해 혈중으로 분비된다.

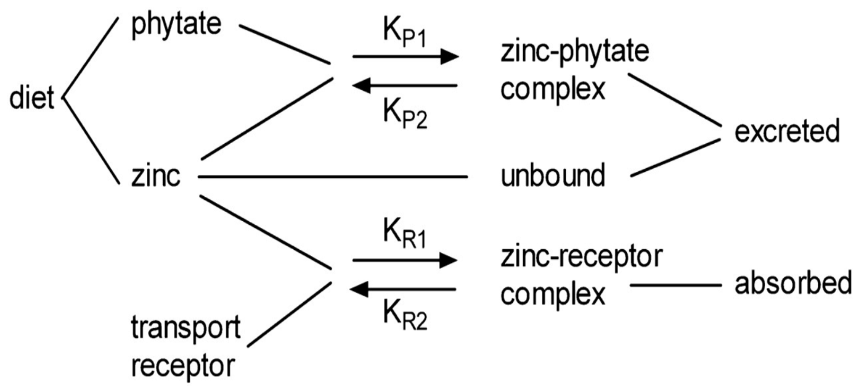


장 내에서 아연 이온은 아연 transporter를 통해 장내 세포로 들어오고 혈중에서는 알부민과 결합된 형태로 움직이게 된다.

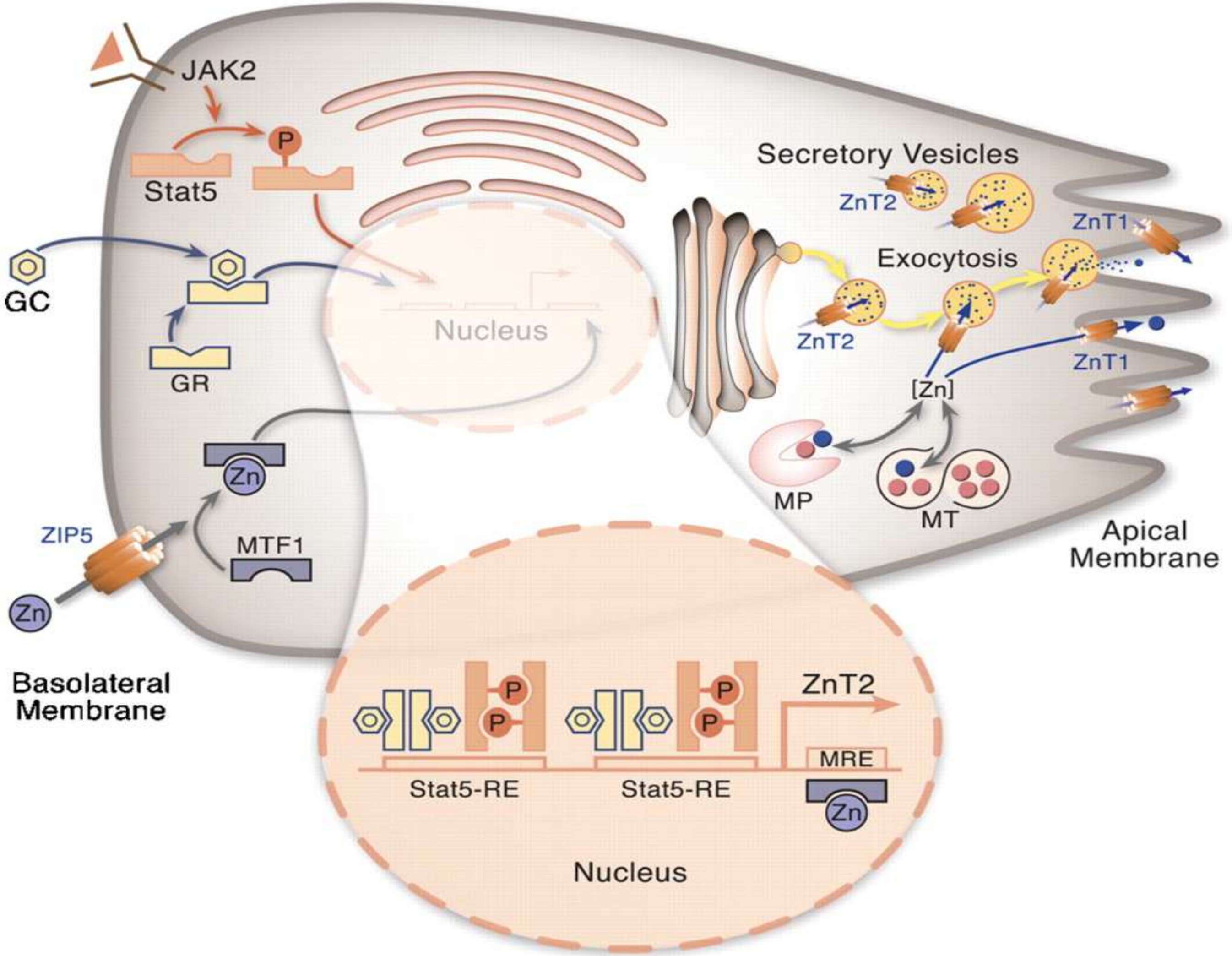


장에 발현되는 Zn transporter의 종류

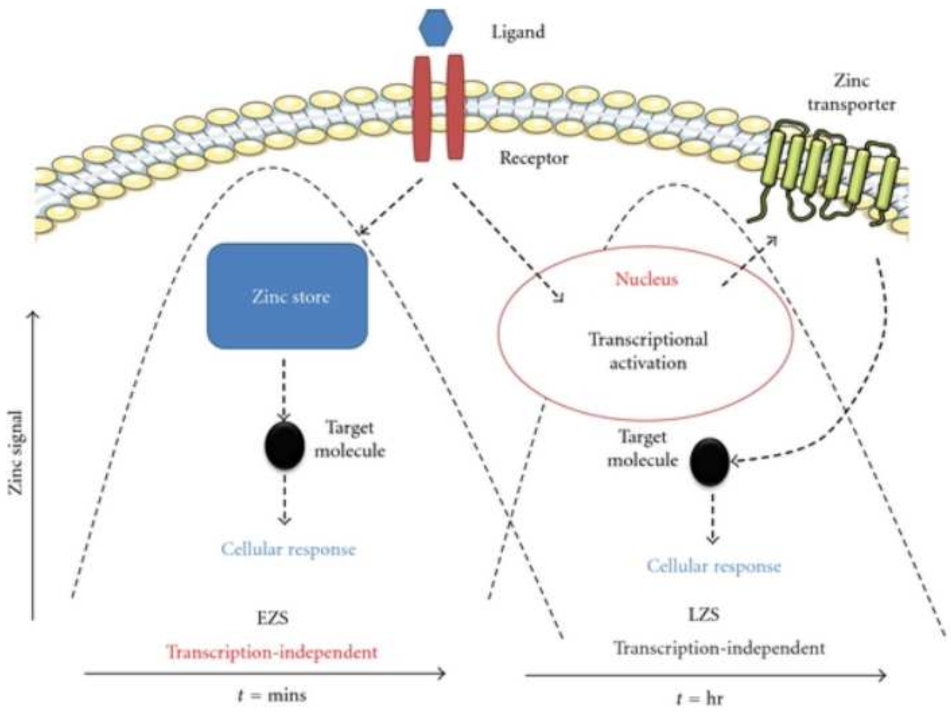


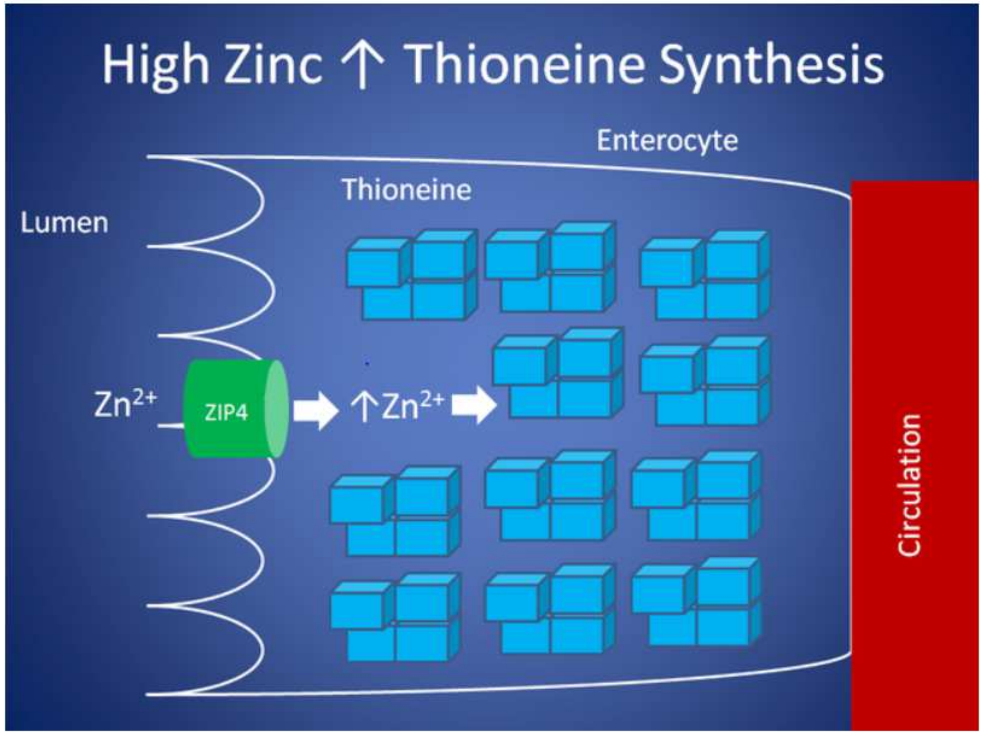


- 피틴산 : 화학식 $C_6H_{18}O_{24}P_6$. 분자량은 660.03이다. 벼의 종자에서 얻어진 쌀겨 또는 옥수수의 종자를 물 또는 산성 수용액으로 추출한 후 정제하여 얻어지는 것으로 주성분이 이노시톨헥사인산(Inositol hexaphosphoric acid)인 엷은 노란색의 시럽상의 액체로, 냄새가 없고 강한 신맛이 있다. 이노시톨의 6개의 하이드록시기가 모두 인산(H_3PO_4)과 결합한 에스터 형태로 된 화합물로 인산의 저장고 역할을 하는 천연식물 항산화제이다. 대부분 콩류, 나무의 열매, 곡류의 외피에 많이 분포되어 있으며, 가장 좋은 급원은 밀기울과 아마인씨로 3% 피트산을 함유하고 있다.
- **피트산 함유식품 섭취 시 체내에서 필수미네랄(Ca^{2+}, Fe^{2+}, Zn^{2+}, K 등)을 흡착하여 불용성인 Phytate-mineral 복합체를 형성, 필수 미네랄 이용성 저하 및 단백질 흡수 저하와 같은 비영양적 대사가 보고**되어 있으나, 최근에는 지방산 및 대장암 억제, 항산화 및 항암작용, 신장 담석증 치료제로서의 이용성이 많이 보고되고 있다.
- 간에 콜레스테롤 농축과 지방산 합성효소를 줄여 주고 간의 말산(malic) 효소 활성을 감소시키며, 암세포의 분화와 세포증식을 줄여 주는 역할을 한다. 또한 인체 내에서 free iron을 킬레이트(집게발 모양) 함으로써 자유라디칼의 형성을 억제하고, 체내에서 두 번째 메신저의 인공적 항원변환 시스템에 작용한다. 이외에도 피트산은 위의 공복감을 줄여 주고 전분소화를 느리게 하여 혈당을 낮추어 주는 역할을 하며, 곡류와 콩류 저장 시 자체에 항산화 효과를 부여한다고 알려져 있다. 식품첨가물로서의 피트산은 발효조성제, 금속봉쇄제로 통조림, 음료, 발효식품, 연제품, 면류에 사용되며, 수산물 통조림에는 스트루바이트 방지제, 흑변 방지제로 쓰인다. 산화방지제, 금속의 부식방지제로 쓰이기도 하며 물의 연화제로 쓰이기도 한다. 건강기능식품 및 특수영양식품에 사용해서는 안 된다.



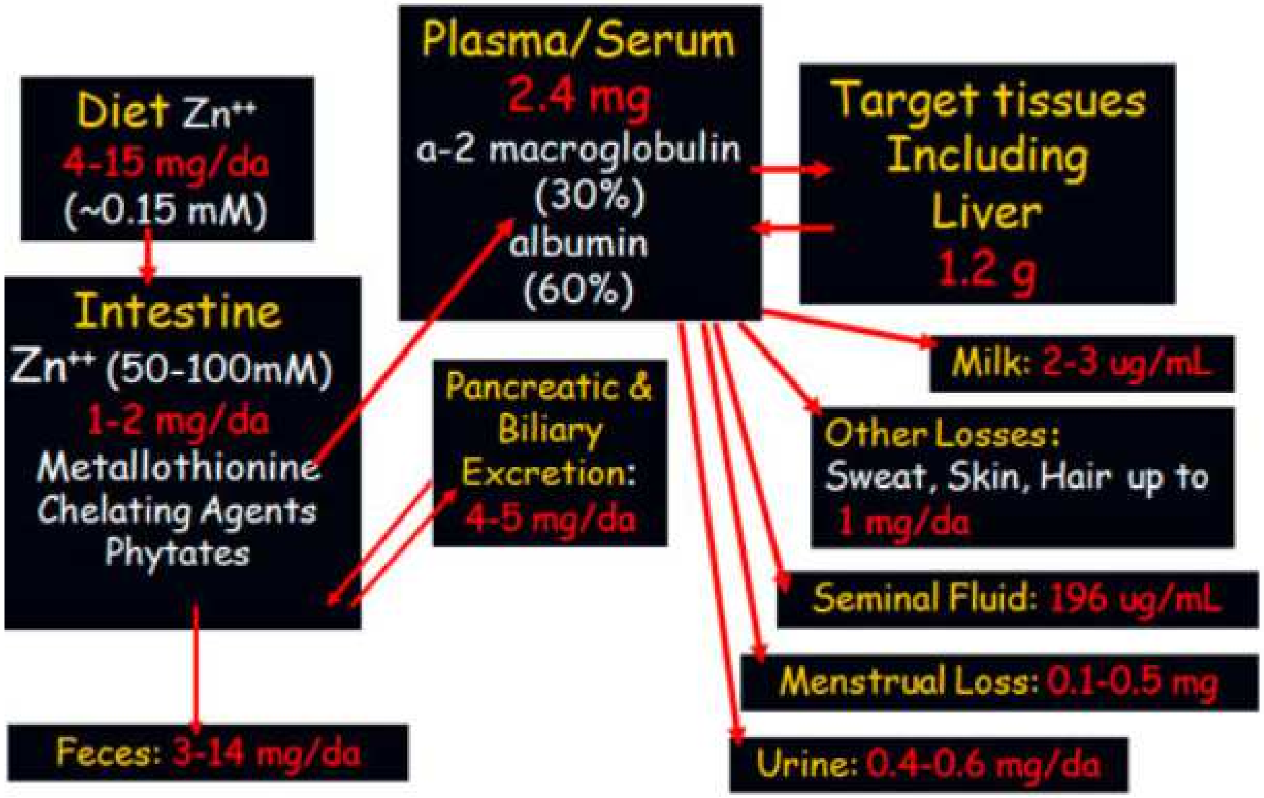
아연은 enterocyte에서 흡수되면 metallothionein과 결합하게 되는데 흡수된 고함량의 아연은 MT의 합성을 촉진하게 되고 **enterocyte에 MT가 많아지면 copper가 MT에 잡혀있게 된다. 그렇기 때문에 고함량 아연 섭취는 구리 부족을 일으킬 수 있다.**



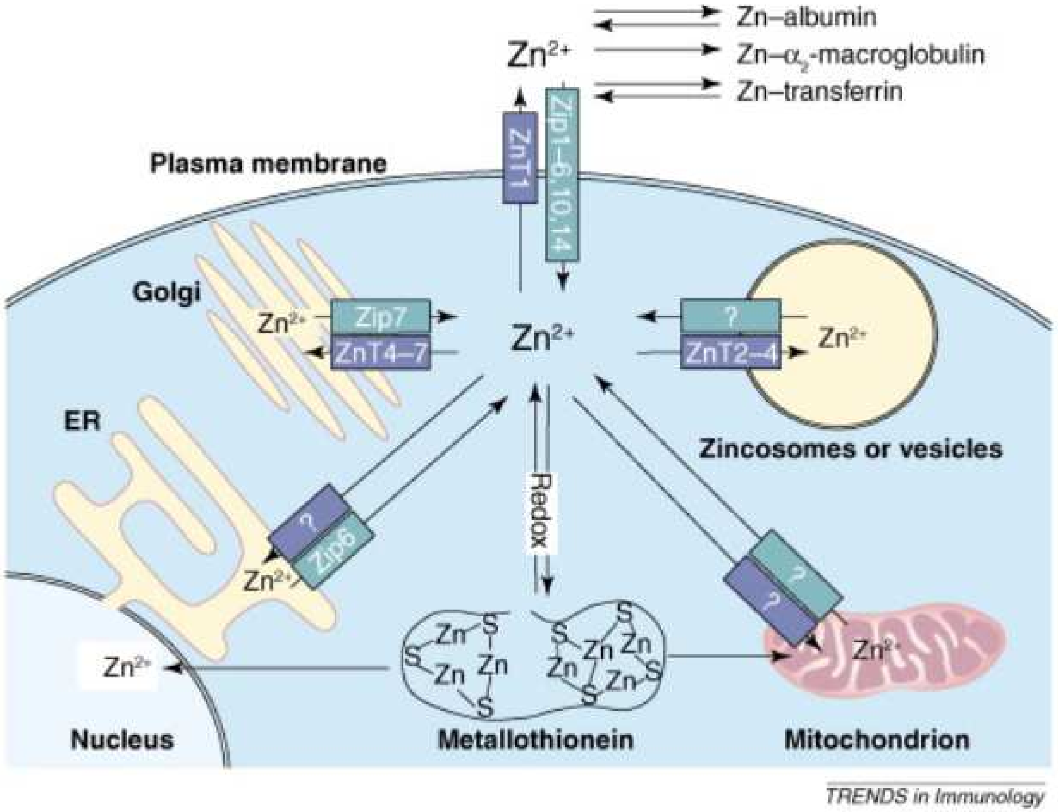


장세포로 고함량의 아연이 흡수되면 혈중으로 아연이 과다 분비되는 것을 막기 위해 thioneine의 합성을 늘어나게 해서 장세포 내에 아연을 저장하게 된다.

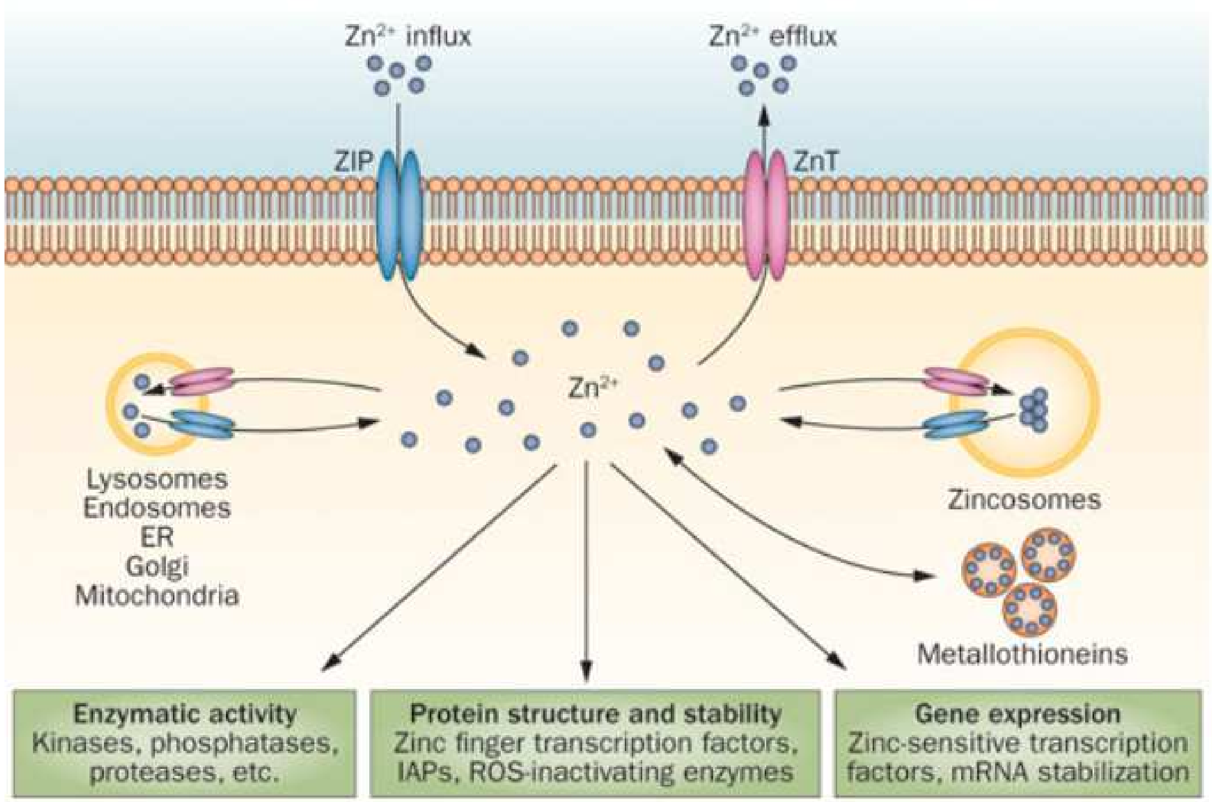
체내 아연의 분포


Diet Zn++
4-15 mg/da
(~0.15 mM)
Plasma/Serum
2.4 mg
a-2 macroglobulin
(30%)
albumin
(60%)
Target tissues
Including
Liver
1.2 g
Intestine
Zn++ (50-100mM)
1-2 mg/da
Metallothionine
Chelating Agents
Phytates
Pancreatic &
Biliary
Excretion:
4-5 mg/da
Milk: 2-3 ug/mL
Other Losses:
Sweat, Skin, Hair up to
1 mg/da
Seminal Fluid: 196 ug/mL
Menstrual Loss: 0.1-0.5 mg
Urine: 0.4-0.6 mg/da
Feces: 3-14 mg/da

세포 안의 막에 발현되는 다양한 아연 통로



세포 안에서 아연의 역할



효소활성조절

단백질의 3차 구조
및 구조 안정성 유지

유전자 발현 조절

Physiological functions of zinc

- **Biochemical functions :**
  - Cofactor for enzymes
  - Activity of zinc finger proteins

- **Cellular functions :**
  - Growth & cell development
  - Cell membrane integrity
  - Tissue growth & repair
  - Wound healing

- **Endocrinological functions:**
  - Reproduction: spermatogenesis & oogenesis
  - Thyroid function
  - Pancreatic function
  - Prolactin secretion
  - Thymopoetin synthesis

- **Immunological functions :** function of neutrophils, T cells, B cells and NK cells
- **Neurological function:** Cognition, memory, taste acuity, vision
- **Hematological function :** coagulation factors
- **Skeletal function :** Bone mineralization

5

- Methionine synthase
- 5-methyltetrahydropteroyltriglutamate—homocysteine S-methyltransferase

A

- Alcohol dehydrogenase
- Aspergillus nuclease S1

C

- Carbon monoxide dehydrogenase
- Carbonic anhydrase
- Carboxypeptidase A

D

- D-2-hydroxy-acid dehydrogenase

G

- Galactitol-1-phosphate 5-dehydrogenase

G cont.

- Glutamate carboxypeptidase II
- Glutamyl aminopeptidase

I

- Insulin-degrading enzyme

L

- Lactoylglutathione lyase

M

- Matrix metalloproteinase
- Methionine S-methyltransferase
- Methylmalonyl-CoA carboxytransferase

N

- N-acyl-D-amino-acid deacylase
- N-acyl-D-aspartate deacylase

N cont.

- N-acyl-D-glutamate deacylase
- N-benzyloxycarbonylglycine hydrolase

P

- Phosphonoacetate hydrolase
- Plant matrix metalloproteinase

S

- Stizolobate synthase
- Stizolobinate synthase

Z

- Zinc carboxypeptidase

Categories: Enzymes by cofactor | Zinc proteins

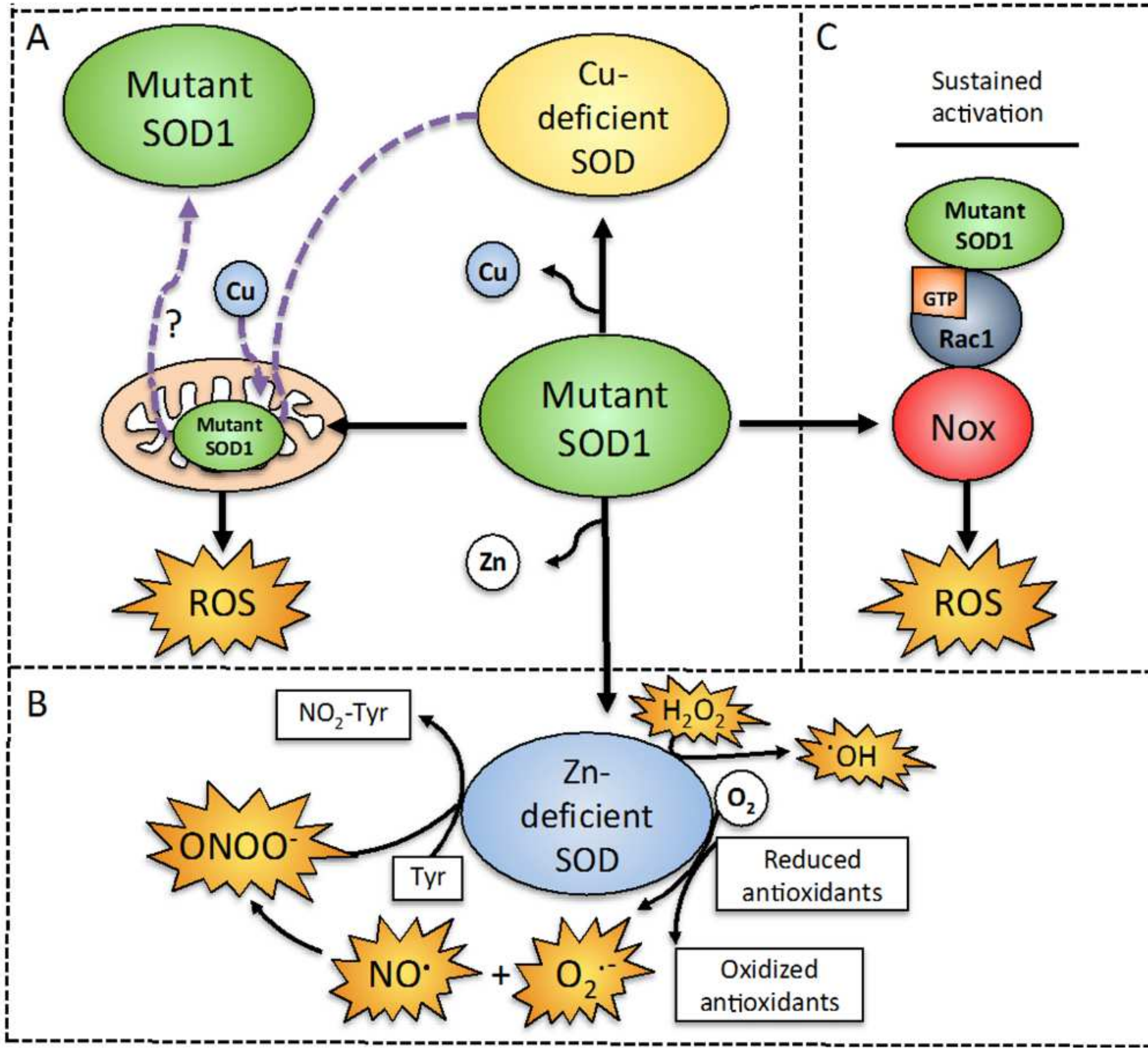
효소 활성 조절 역할 : 아연이 효소에서 하는 역할은 두 가지이다. Catalytic site에서 전자 이동을 돕거나, structural site에서 4개의 아미노산을 입체적으로 배열하는 역할을 한다.

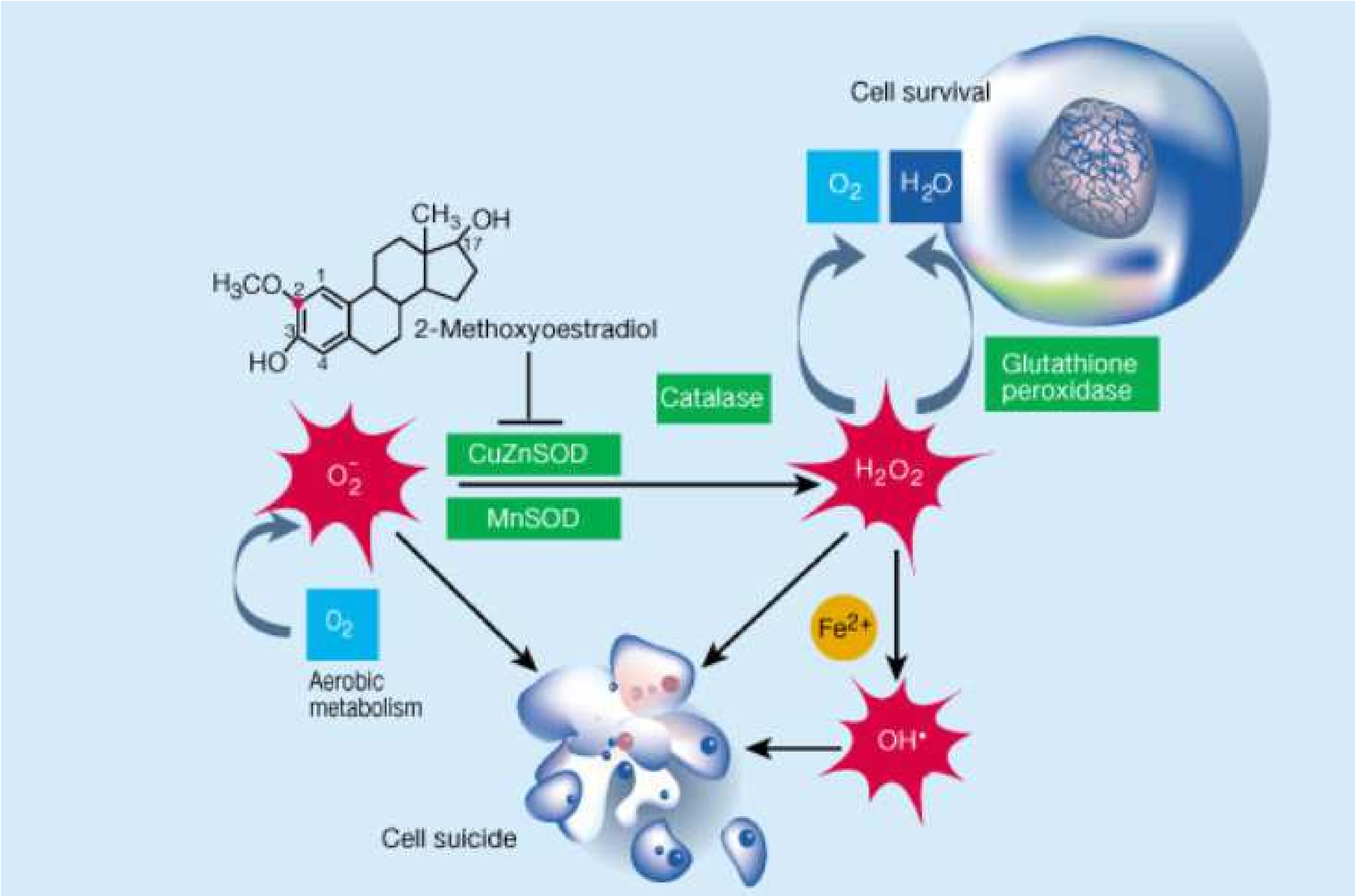
Carbonic anhydrase : Acid-base balance
Alkaline phosphatase : phosphate digestion
Alcohol dehydrogenase : nonspecific aldehyde synthesis
Carboxypeptidases A and B and aminopeptidases : protein digestion
Delta-aminoevulinic acid dehydratase : Heme synthesis
Superoxide dismutase : antioxidant
Phospholipase C : phospholipid metabolism
Polyglutamate hydrolase : folate digestion
Matrix metalloproteinases : wound repair
Polymerases, Kinases, Nucleases, Transferases, phosphorylases, transcriptases : NA synthesis and cell replication and growth.

Zinc dependent enzymes

가장 중요한 아연 포함 단백질 : superoxide dismutase

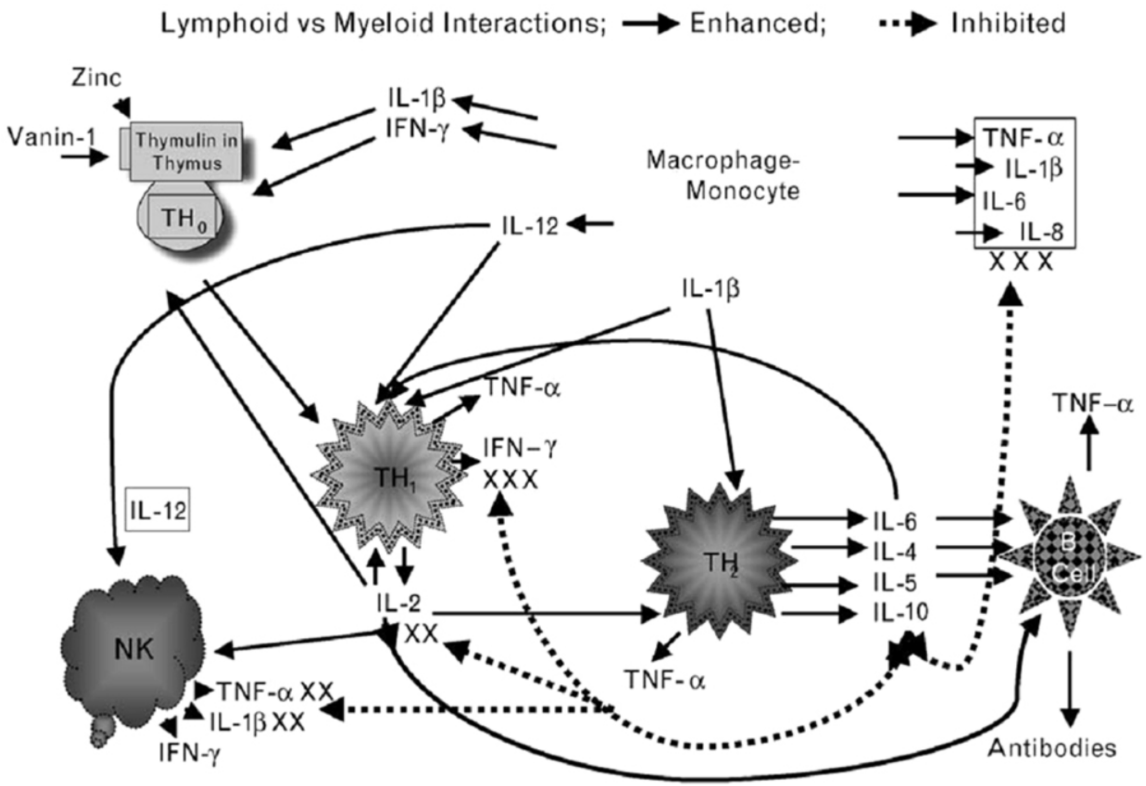
- 세포 안에서 발생하는 활성산소(ROS)를 제거하여 세포를 보호하는 가장 중요한 효소 중의 하나이다. 세포 손상 방지.



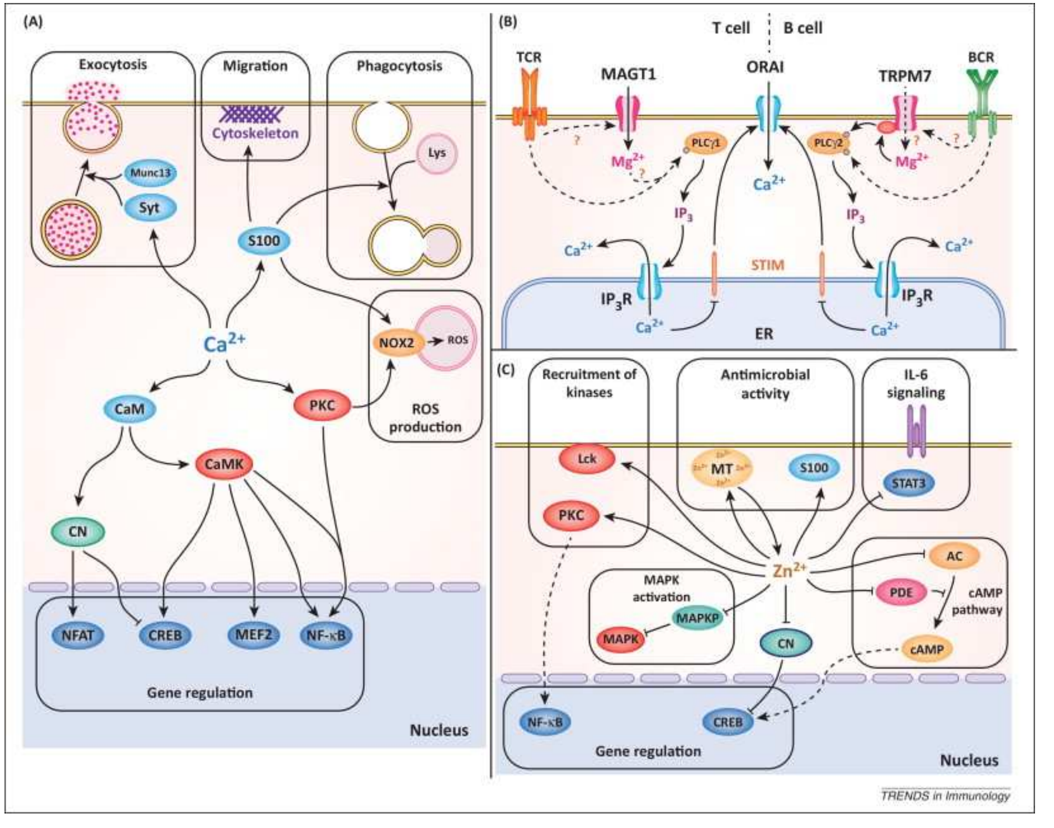

Cell survival
O_2
H_2O
CH_3 OH
17
H_3CO 2 1
3
HO 4
2-Methoxyoestradiol
Catalase
Glutathione peroxidase
O_2^-
CuZnSOD
MnSOD
H_2O_2
O_2
Aerobic metabolism
Fe^{2+}
OH•
Cell suicide

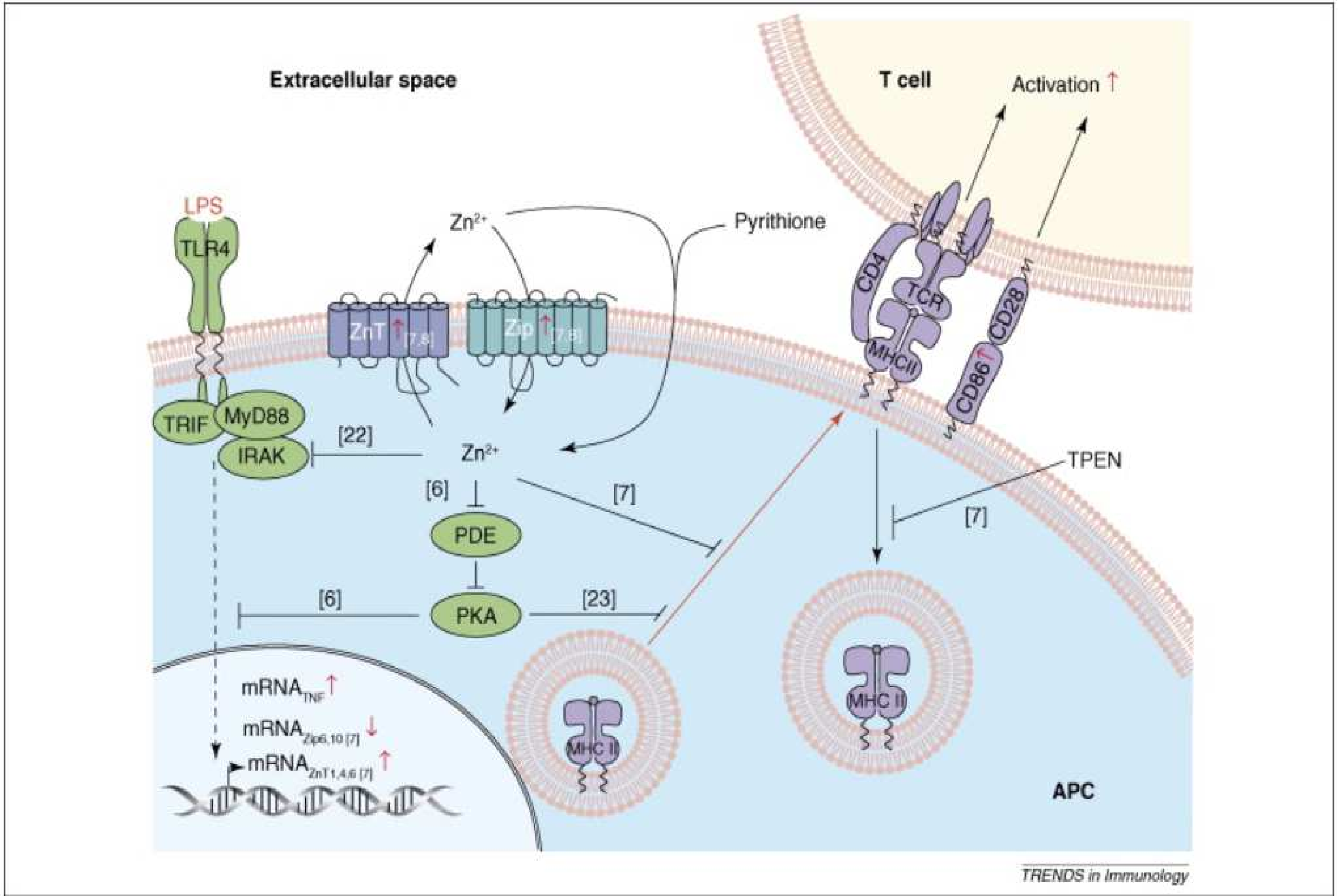
면역계 : 아연은 thymulin(T cell의 성숙을 담당)의 활성을 조절

- Thymic hormone의 integral part. 아연부족 상태는 thymulin 활성을 떨어트려 T cell의 성숙 감소, Th1 에 의한 IL-2, INF-γ의 생성 감소가 나타난다. IL-2 감소는 NK, cytotoxic T cell활성 감소를 일으킨다. Macrophage와 monocyte는 IL-12(Zn dependent cytokine)를 분비한다. Th2 cytokines는 IL-10을 제외하면 아연의 영향을 별로 받지 않는다. 따라서 아연 부족 상황에서는 Th1에서 Th2 기능으로 shift하게 되어 세포 면역 기능이 손상된다. 또한 아연부족은 macrophage-monocytes를 자극하고 활성화하여 염증성 cytokines인 IL-1β, IL-6, IL-8, TNF-α를 증가시킨다.



Divalent cation signaling in immune cells



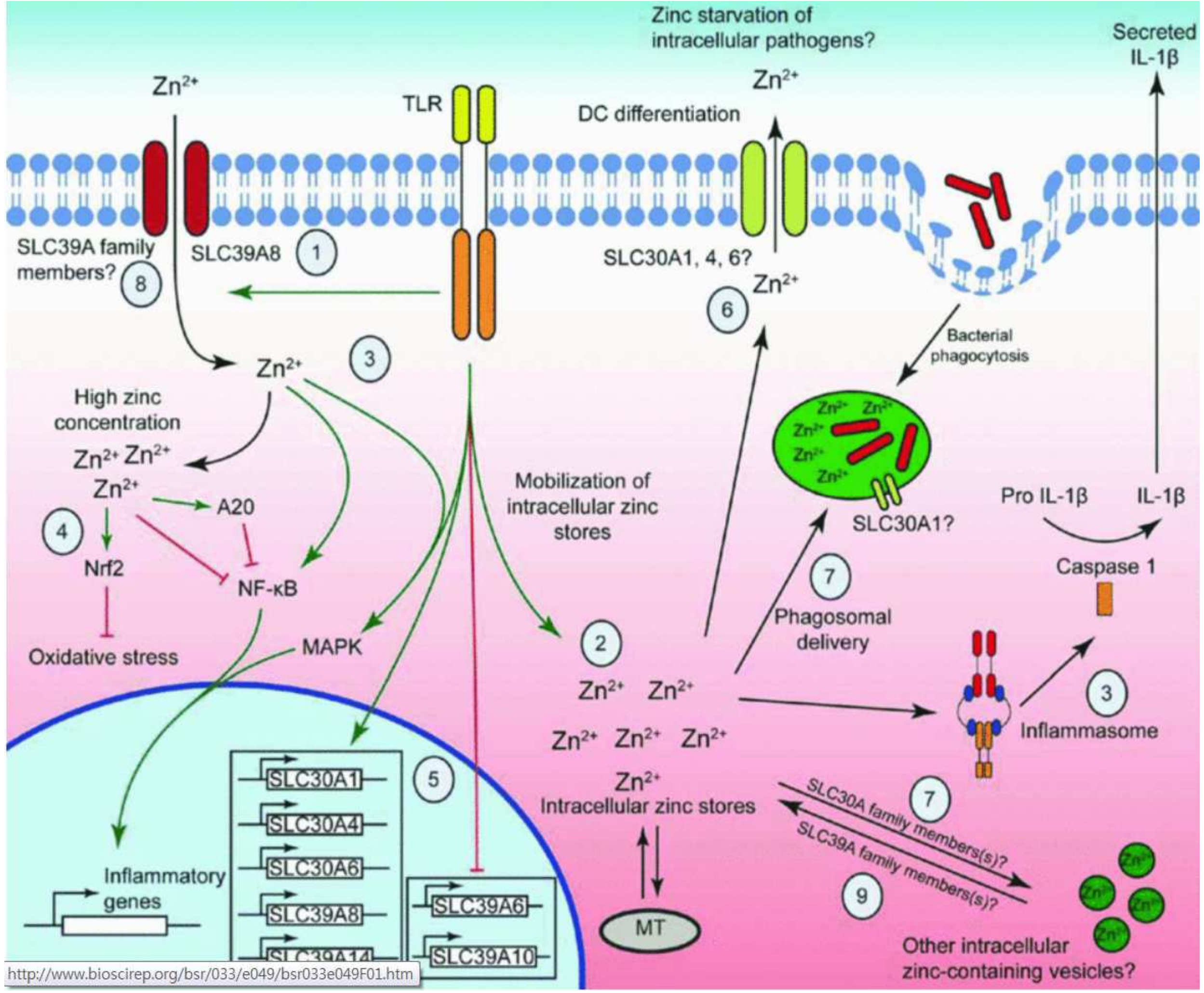


또한 아연은 APC에서 APC와 T cell간의 MHC II interaction을 억제하여 과도한 면역반응을 억제하고 LPS에 의한 세포 기능상실을 막는다.

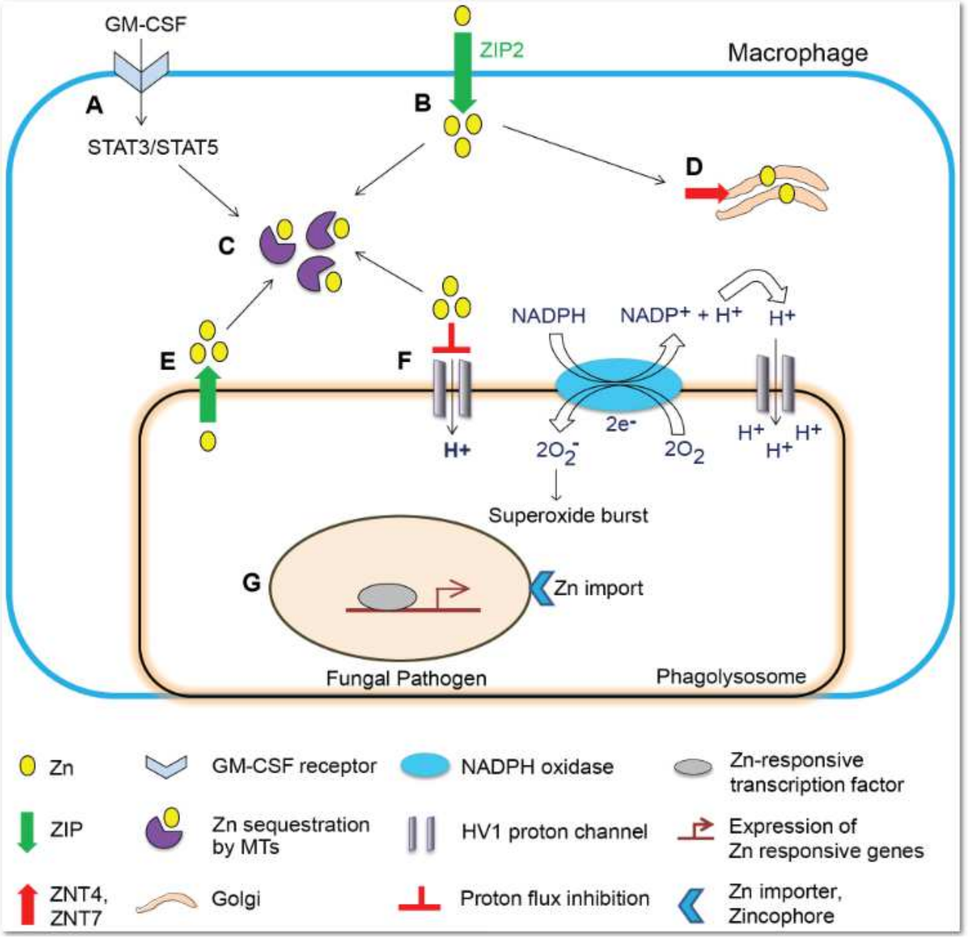
	No stimulation			ox-LDL stimulation		
	Zn−	Zn+	P^b	Zn−	Zn+	P^b
HL-60 cells						
TNF-α (pg/mL)	26.5 ± 25.4	12.1 ± 12.1	0.21	317.2 ± 119.7	152.7 ± 96.4	0.007
IL-1β (pg/mL)	1.4 ± 1.2	0.8 ± 0.7	0.52	3.9 ± 1.4	1.3 ± 0.5	0.042
VCAM-1 (pg/mL)	18.3 ± 4.7	14.2 ± 1.7	0.073	69.9 ± 2.8	32.1 ± 4.3	0.006
MDA + HAE (μM) THP-1 cells	2.6 ± 0.7	1.5 ± 0.6	0.001	5.6 ± 1.4	2.3 ± 0.5	0.046
THP-1 cells						
TNF-α (pg/mL)	32.2 ± 15.1	23.8 ± 12.0	0.022	181.2 ± 13.9	121.0 ± 17.9	0.027
IL-β (pg/mL)	1.5 ± 0.1	0.9 ± 0.4	0.027	4.4 ± 0.7	1.7 ± 0.9	0.004
MDA + HAE (μM)	1.4 ± 0.6	1.0 ± 0.5	0.013	4.5 ± 0.6	2.0 ± 0.7	0.004
HAECs						
TNF-α (pg/mL)	8.0 ± 6.6	4.2 ± 5.0	0.06	22.6 ± 2.3	13.6 ± 2.1	0.034
IL-lβ (pg/mL)	5.8 ± 5.7	2.8 ± 2.7	0.11	13.1 ± 4.8	6.2 ± 1.8	0.028
VCAM-1 (ng/mL)	3.5 ± 1.5	4.5 ± 2.1	0.247	23.8 ± 4.7	13.8 ± 2.1	0.016
MDA + HAE (μm)	1.16 ± 0.36	1.02 ± 0.20	0.18	3.33 ± 1.02	1.45 ± 0.77	0.028

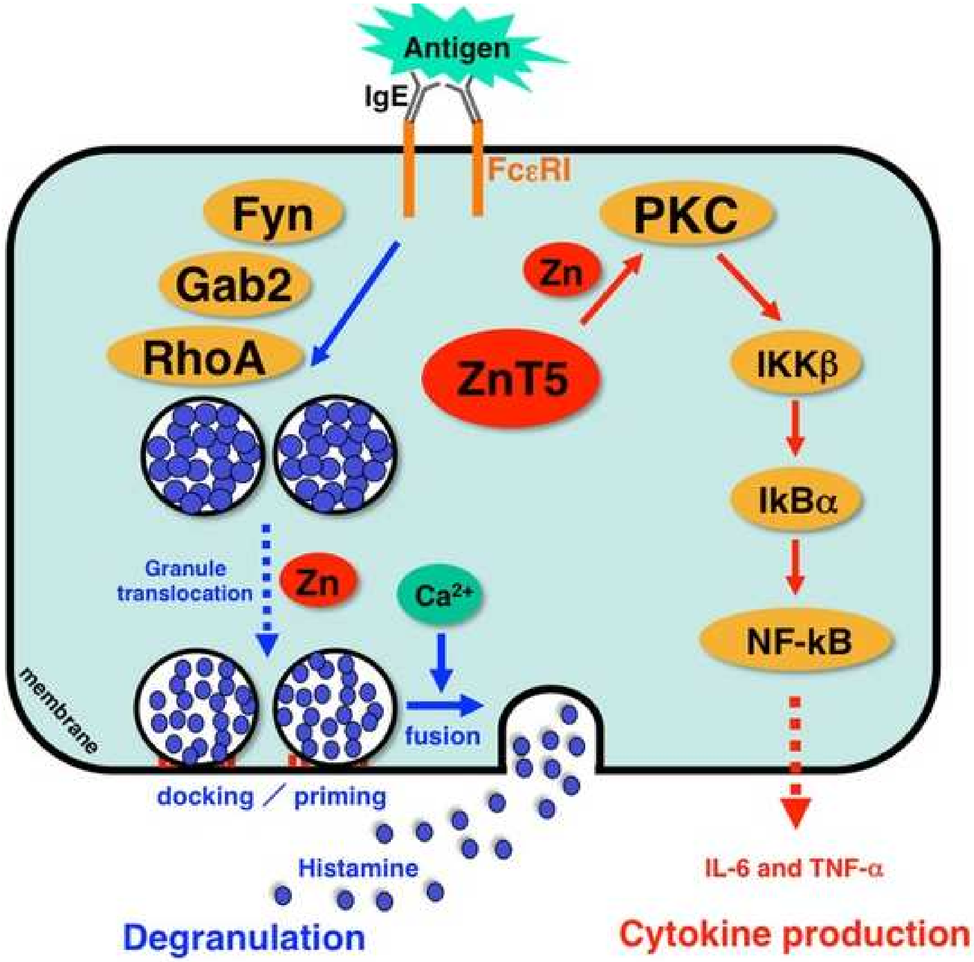
[a] *All values are means ± SDs. Zn−, zinc deficient; Zn+, zinc sufficient.*

[b] *For differences between Zn− (1 μM Zn) and Zn+ (15 μM. Zn) cell groups (Student's t-test; n = 3).*



Zinc starvation of intracellular pathogens?
Secreted IL-1β
Zn2+
TLR
DC differentiation
SLC39A family members?
SLC39A8
1
8
SLC30A1, 4, 6?
6
Bacterial phagocytosis
3
High zinc concentration
Zn2+ Zn2+
Zn2+
A20
4
Nrf2
NF-κB
Oxidative stress
MAPK
Mobilization of intracellular zinc stores
2
Pro IL-1β
IL-1β
SLC30A1?
7
Phagosomal delivery
Caspase 1
Inflammasome
Intracellular zinc stores
MT
5
SLC30A1
SLC30A4
SLC30A6
SLC39A8
SLC39A14
SLC39A6
SLC39A10
Inflammatory genes
SLC30A family members(s)?
SLC39A family members(s)?
9
Other intracellular zinc-containing vesicles?
http://www.bioscirep.org/bsr/033/e049/bsr033e049F01.htm


GM-CSF
ZIP2
Macrophage
A
B
STAT3/STAT5
D
C
NADPH
NADP+ + H+
H+
E
F
2e-
H+
H+
H+
H+
2O2-
2O2
Superoxide burst
G
Zn import
Fungal Pathogen
Phagolysosome
Zn
GM-CSF receptor
NADPH oxidase
Zn-responsive transcription factor
ZIP
Zn sequestration by MTs
HV1 proton channel
Expression of Zn responsive genes
ZNT4, ZNT7
Golgi
Proton flux inhibition
Zn importer, Zincophore


Antigen
IgE
FcεRI
Fyn
Gab2
RhoA
PKC
Zn
ZnT5
IKKβ
IkBα
NF-kB
Granule translocation
Zn
Ca2+
fusion
membrane
docking / priming
Histamine
IL-6 and TNF-α
Degranulation
Cytokine production

면역 기능에서의 아연의 역할

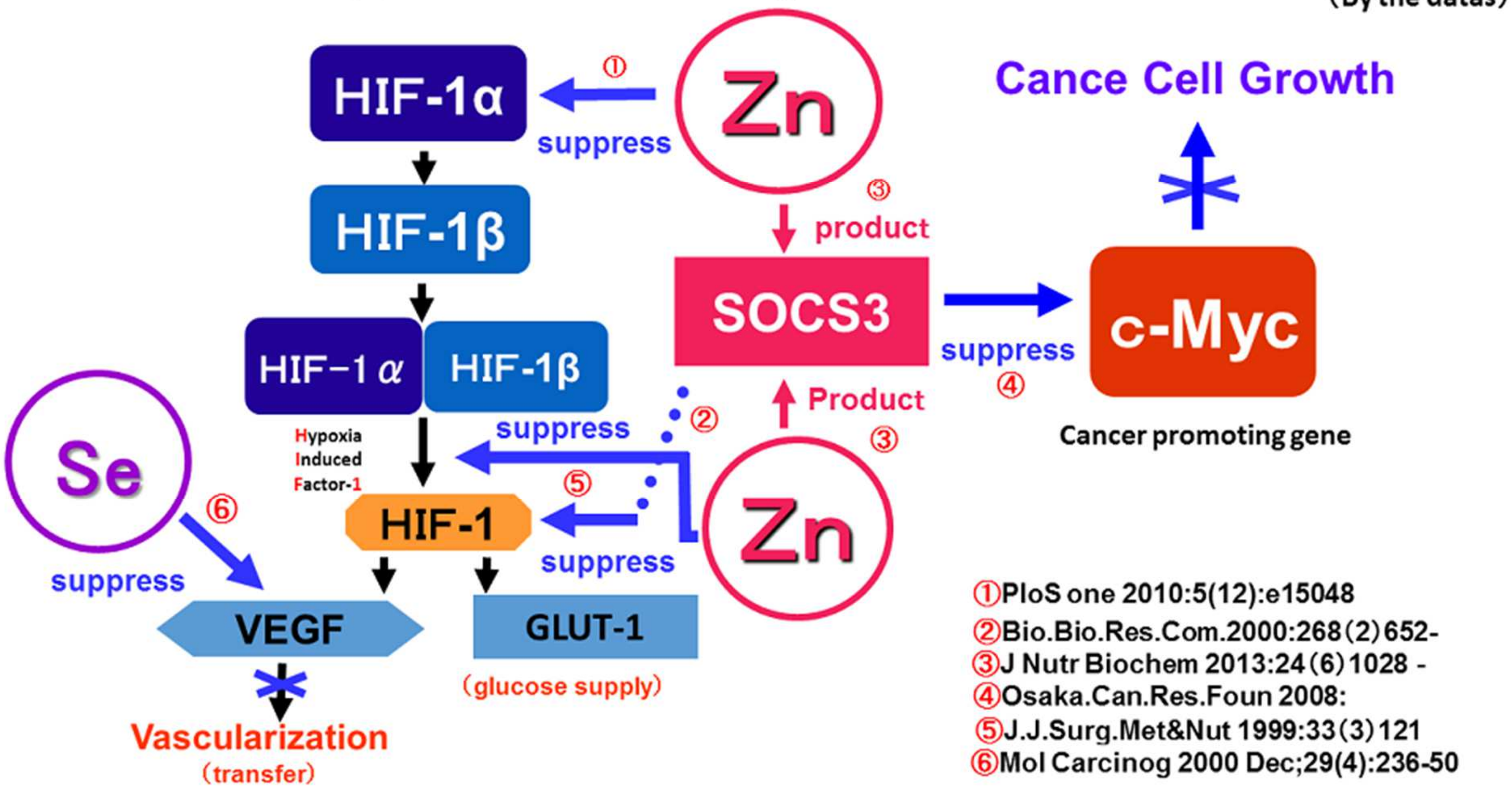
MECHANISMS RESPONSIBLE FOR THE ROLE OF ZINC ON IMMUNE FUNCTION

Nestlé Nutrition Institute

Function	Proposed Mechanisms
Macrophage and neutrophil function: generation of oxygen radicals	Zn is required by Zn-dependent enzymes or reactions for production of oxygen radicals (e.g. peroxide superdismutase)
Lymphocyte maturation	Important for formation of precursor T and B cells in the bone marrow Deficiency increases the CD4+CD45RA+ to CD4+CD45RO+ ratio, thus it appears that zinc is required for regeneration of new CD4+ memory T cells following antigen exposure
Thymulin production	Zn is required by this Zn-dependent thymus-specific hormone that binds to high-affinity receptors on T cells; thymulin induces several T cell markers, and promotes T cell function, including allogeneic cytotoxicity, suppressor function, and IL-2 production
Cytokine production	In humans, Zn deficiency caused an imbalance in cytokine production with ↓ IFN-γ, IL-2 & TNF-α (Th1-type), without changing the production of IL-4, IL-6 and IL-10 (Th2-type)
Apoptosis regulation	Low levels of Zn *in vitro* ↑ apoptosis in murine CD4+CD8+ thymocytes High levels of Zn *in vitro:* ↓ apoptosis by preventing activation of the endonuclease ↓ apoptosis by inhibiting steroid binding to the glucocorticoid receptor, thus inhibiting binding of the receptor to specific glucocorticoid response elements in DNA that signal apoptosis
Gene regulation	Deficiency ↓ activation of NFκB, thus ↓ gene expression of IL2-IL2R Deficiency ↓ thymidine kinase activity delaying cell cycle and ↓ cell growth ↓ activity of Zn-dependent metalloenzymes involved in cytokine production
Role in basic cellular functions	Many enzymes responsible for DNA replication, RNA transcription, cell division, and cell activation are Zn dependent Skin lesions, poor wound healing observed with deficiency Maintaining the barrier of the skin Zn itself has some antioxidant properties

【Figure1】

The role of Zinc and Selenium to suppress cancer cell growth and trasfer



Function of Zinc,Selenium on cancer

【Zinc】

Suppress to make new blood vessels by cancer cell

PloS one 2010:5(12):e15048　　Bio.Bio.Res.Com.2000:268（2）652-

Prevent the way to send the nutrition (glucose) in cancer cell

Surg.Metab.&Nutr.1999:33（3）121　　J Nutr Biochem 2013:24（6）1028-

Zinc inhibits STAT3※ (cancer gene)and is related to the suppression of carcinogenesis and proliferation

Nature, 429: 298-302 (2004)　Osaka univ.,RIKEN

※STAT3 (Signal Transducer and Activator of Transcription 3)

One of the cancer genes associated with carcinogenesis

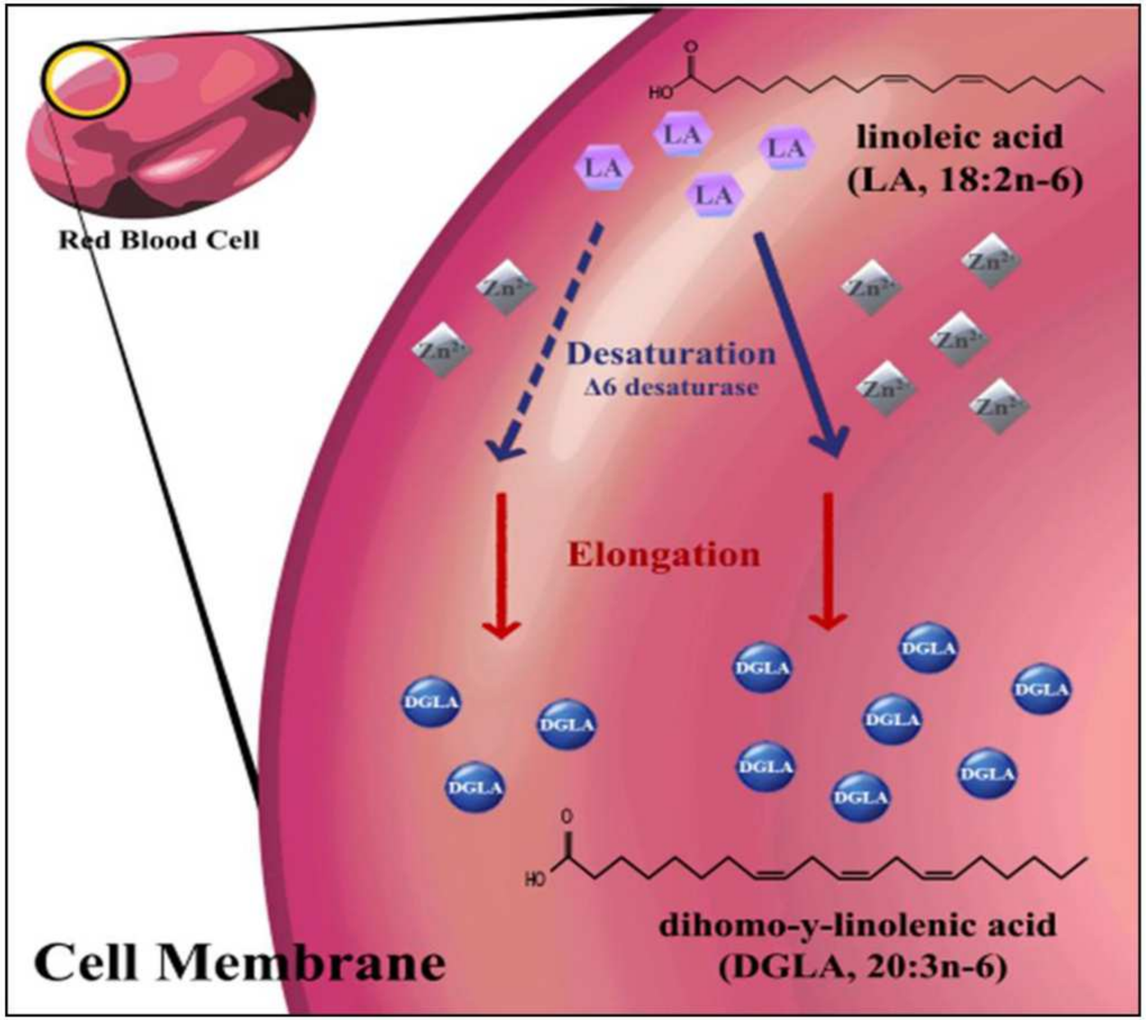
Zinc reduce iron and copper vales to make reactive oxygen species in serum and liver.

【Selenium】

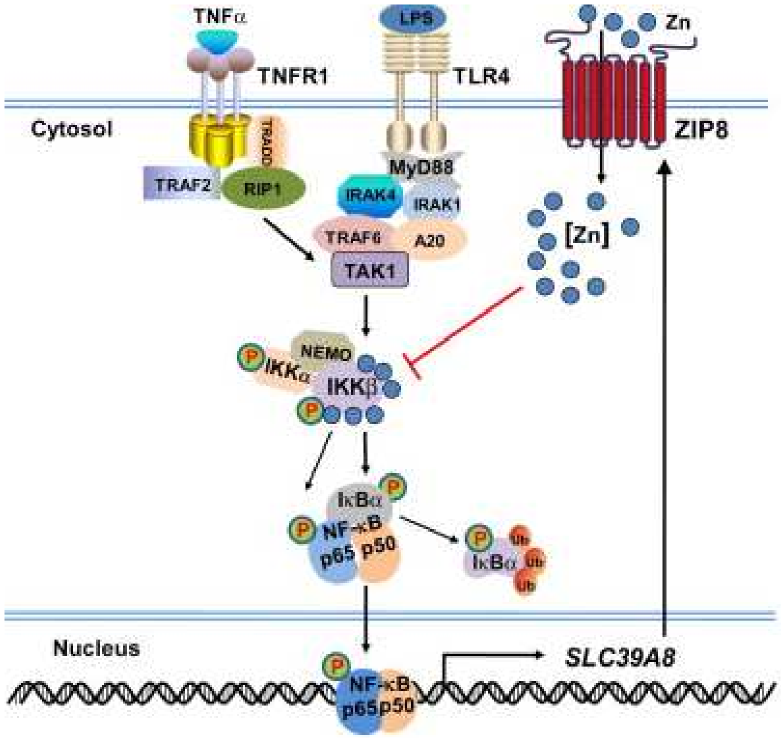
Selenium reduce iron and copper vales to make reactive oxygen species in serum and liver. It is stronger than zinc.

Selenium is believed mineral work synergistically with zinc

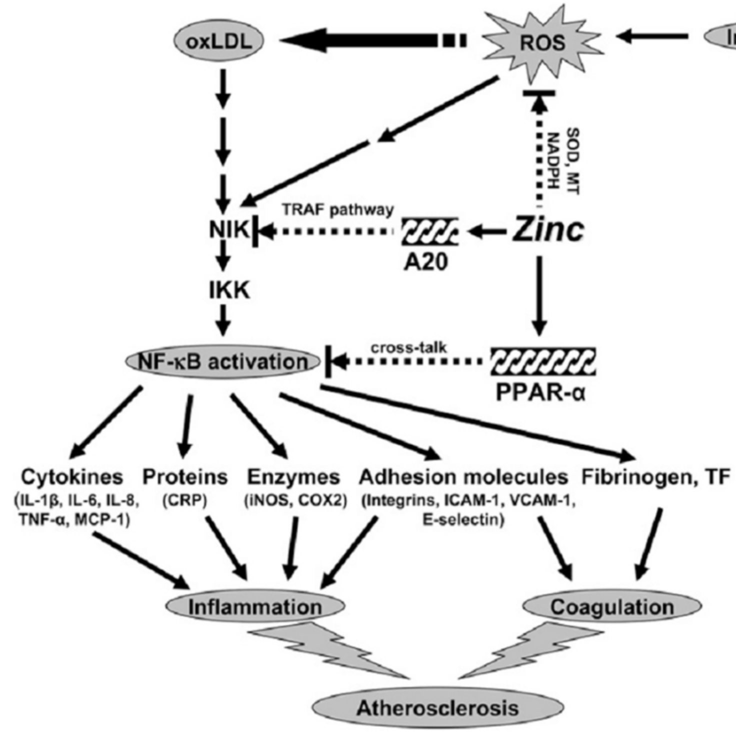
CCLM 2002 vol.40 issue11　　Jour.of Zinc Nutr.Therp.Suppl.1 2013



Linoleic acid에서 시작되는 오메가 6의 대사과정과 alpha-linoleic acid에서 시작되는 오메가 3의 대사과정에 공통적으로 작용하는 desaturase의 활성 또한 아연의 영향을 받기 때문에 아연 부족 상태에서는 지질대사도 제대로 일어날 수 없다.

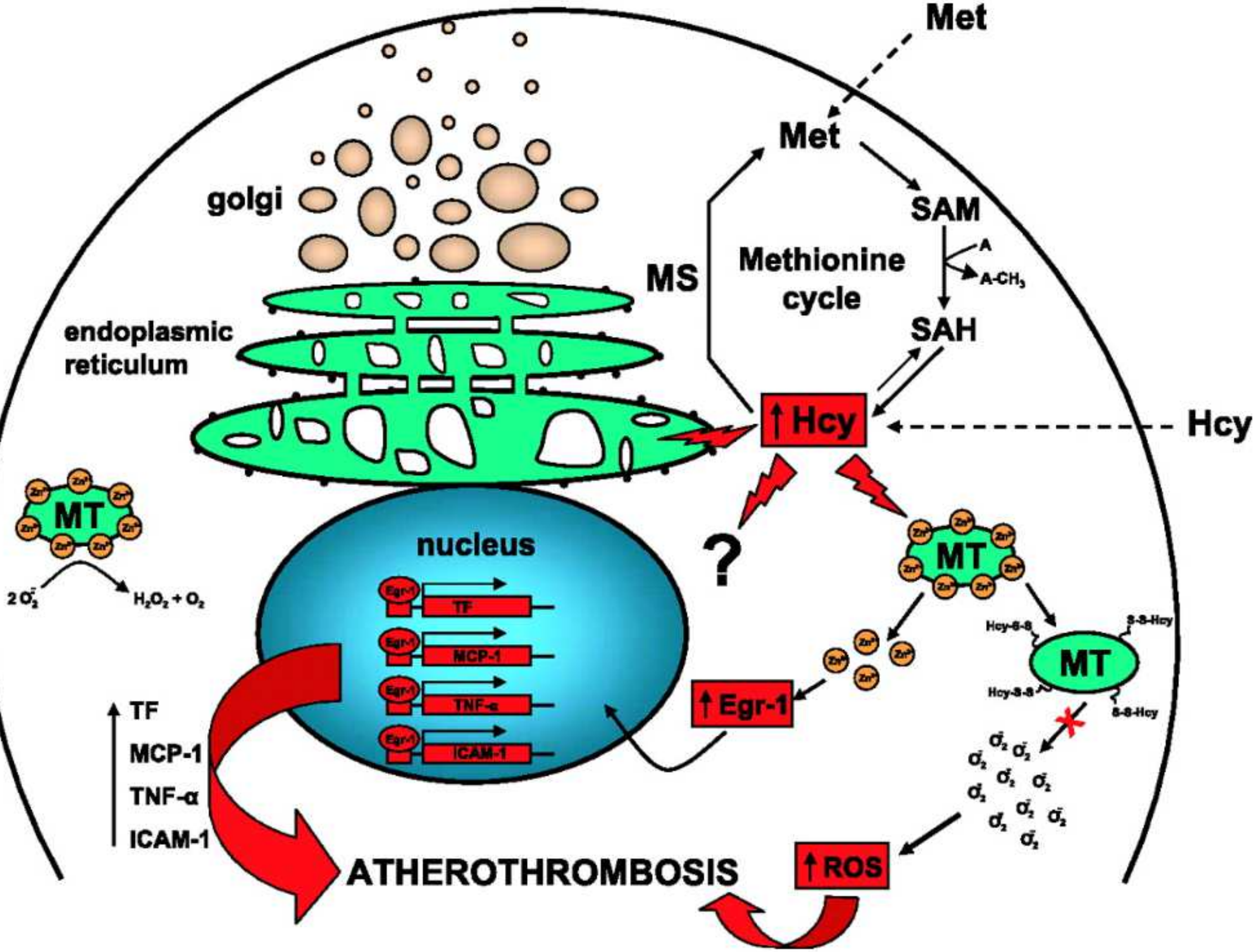


TNFα
TNFR1
LPS
TLR4
Zn
ZIP8
Cytosol
TRADD
TRAF2
RIP1
MyD88
IRAK4
IRAK1
TRAF6
A20
TAK1
[Zn]
NEMO
IKKα
IKKβ
IκBα
NF-κB
p65
p50
Nucleus
SLC39A8



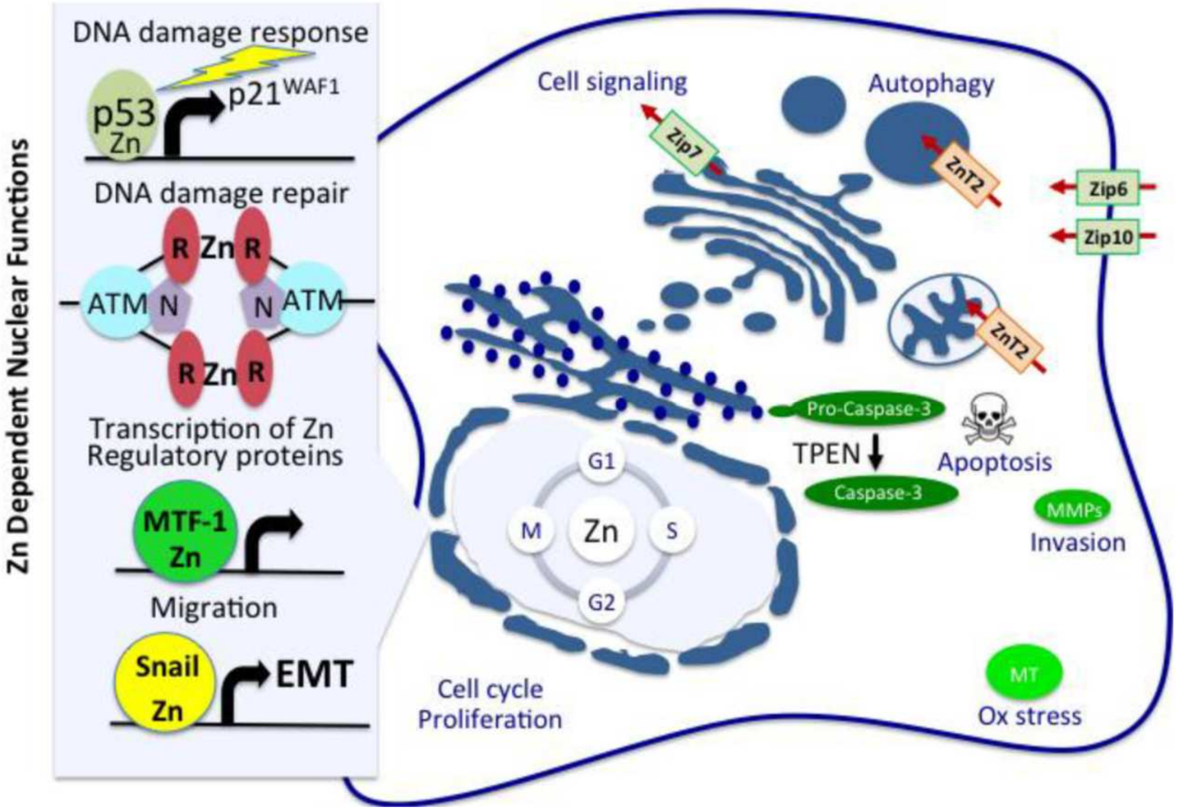
oxLDL
ROS
Inflammation
SOD, MT
NADPH
TRAF pathway
NIK
A20
Zinc
IKK
NF-κB activation
cross-talk
PPAR-α
Cytokines
(IL-1β, IL-6, IL-8, TNF-α, MCP-1)
Proteins
(CRP)
Enzymes
(iNOS, COX2)
Adhesion molecules
(Integrins, ICAM-1, VCAM-1, E-selectin)
Fibrinogen, TF
Inflammation
Coagulation
Atherosclerosis

염증상태와 아연 부족



Met
Met
SAM
A
A-CH3
SAH
MS
Methionine cycle
golgi
endoplasmic reticulum
↑Hcy
Hcy
?
MT
MT
MT
2 O2
H2O2 + O2
nucleus
Egr-1
TF
MCP-1
TNF-α
ICAM-1
↑Egr-1
Hcy-S-S
S-S-Hcy
↑TF
MCP-1
TNF-α
ICAM-1
ATHEROTHROMBOSIS
↑ROS

아연의 DNA 보호 효과



Zn Dependent Nuclear Functions
DNA damage response
p53
Zn
p21WAF1
DNA damage repair
R Zn R
ATM N
N ATM
R Zn R
Transcription of Zn Regulatory proteins
MTF-1
Zn
Migration
Snail
Zn
EMT
Cell signaling
Zip7
Autophagy
ZnT2
Zip6
Zip10
ZnT2
Pro-Caspase-3
TPEN
Caspase-3
Apoptosis
MMPs
Invasion
G1
M
Zn
S
G2
Cell cycle
Proliferation
MT
Ox stress

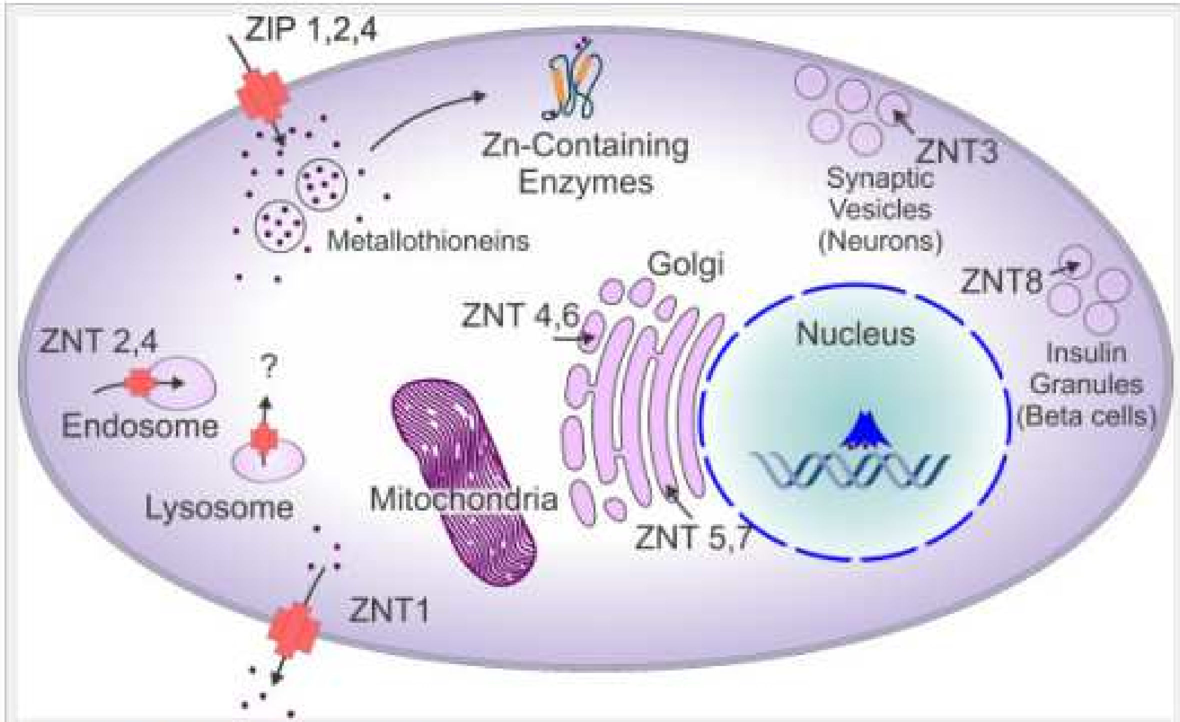
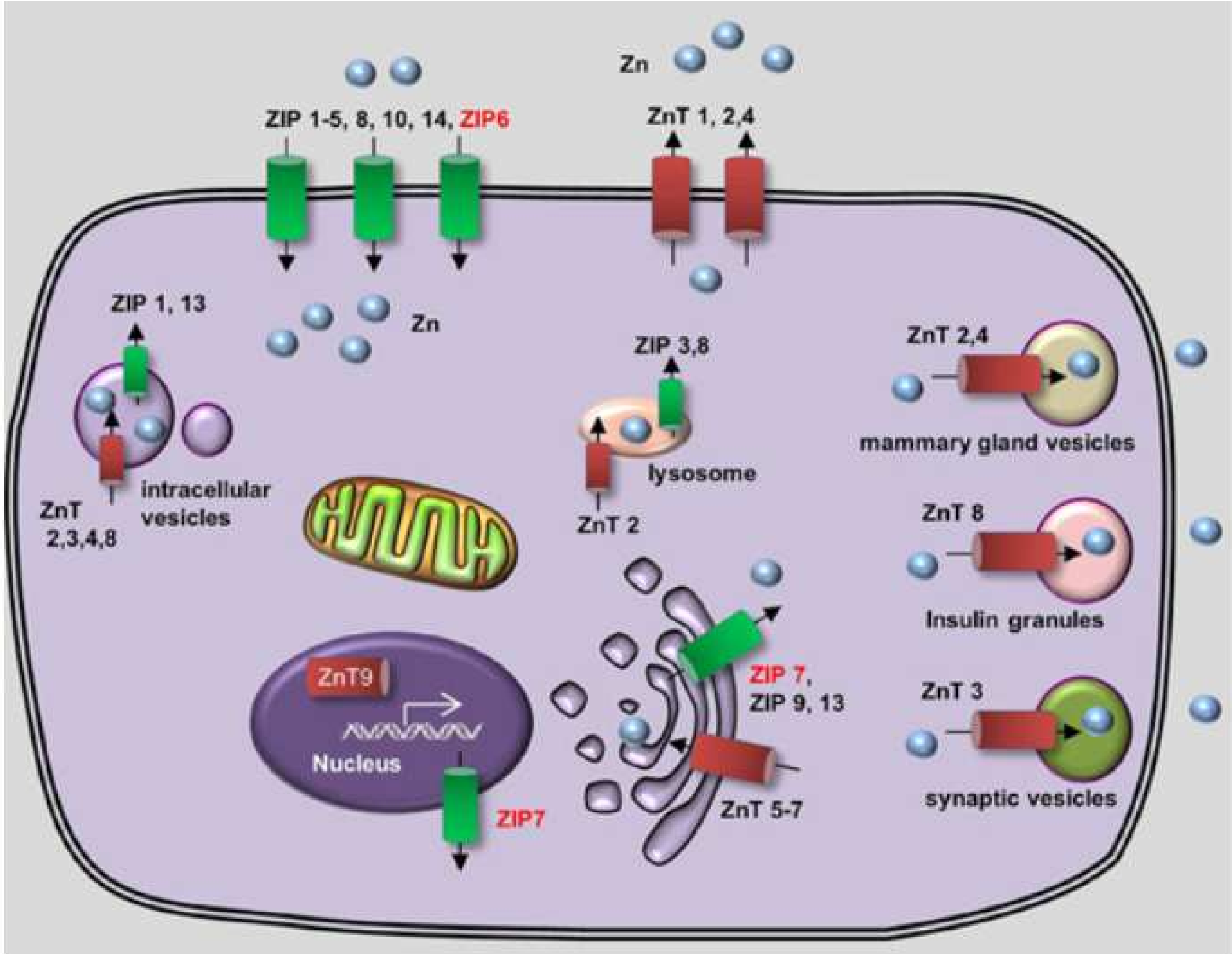
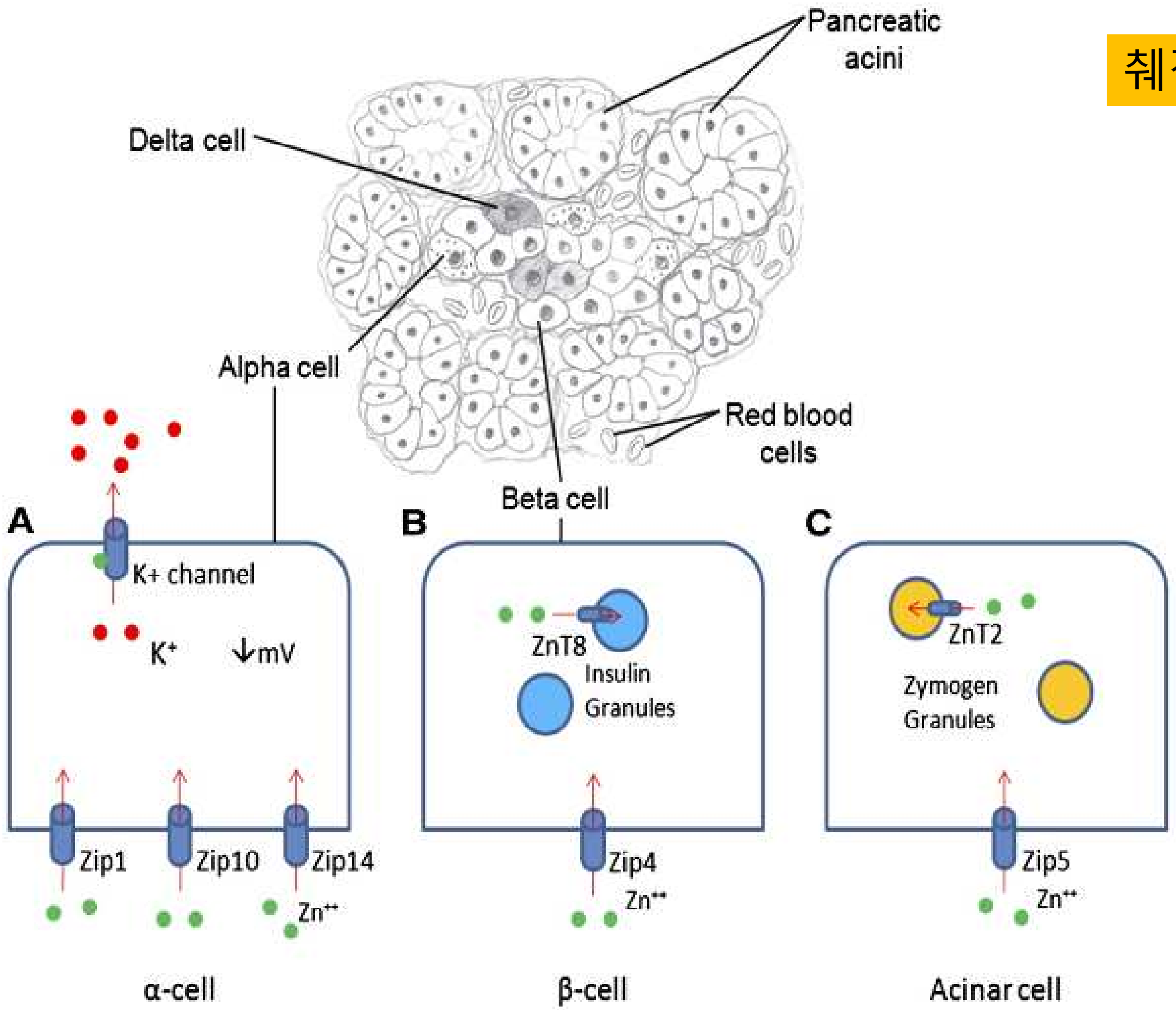


Figure 2: Localization and transport of zinc in a mammalian cell. Cellular localization and function of ZIP and ZNT zinc transporter family members. Arrows indicate the direction of zinc mobilization. ZIP1, 2 and 4 are induced in zinc deficient conditions, while ZNT-1 and 2 members are induced by zinc administration. In general zinc efflux is associated with enhanced susceptibility to apoptosis and higher levels with protection/autophagy.



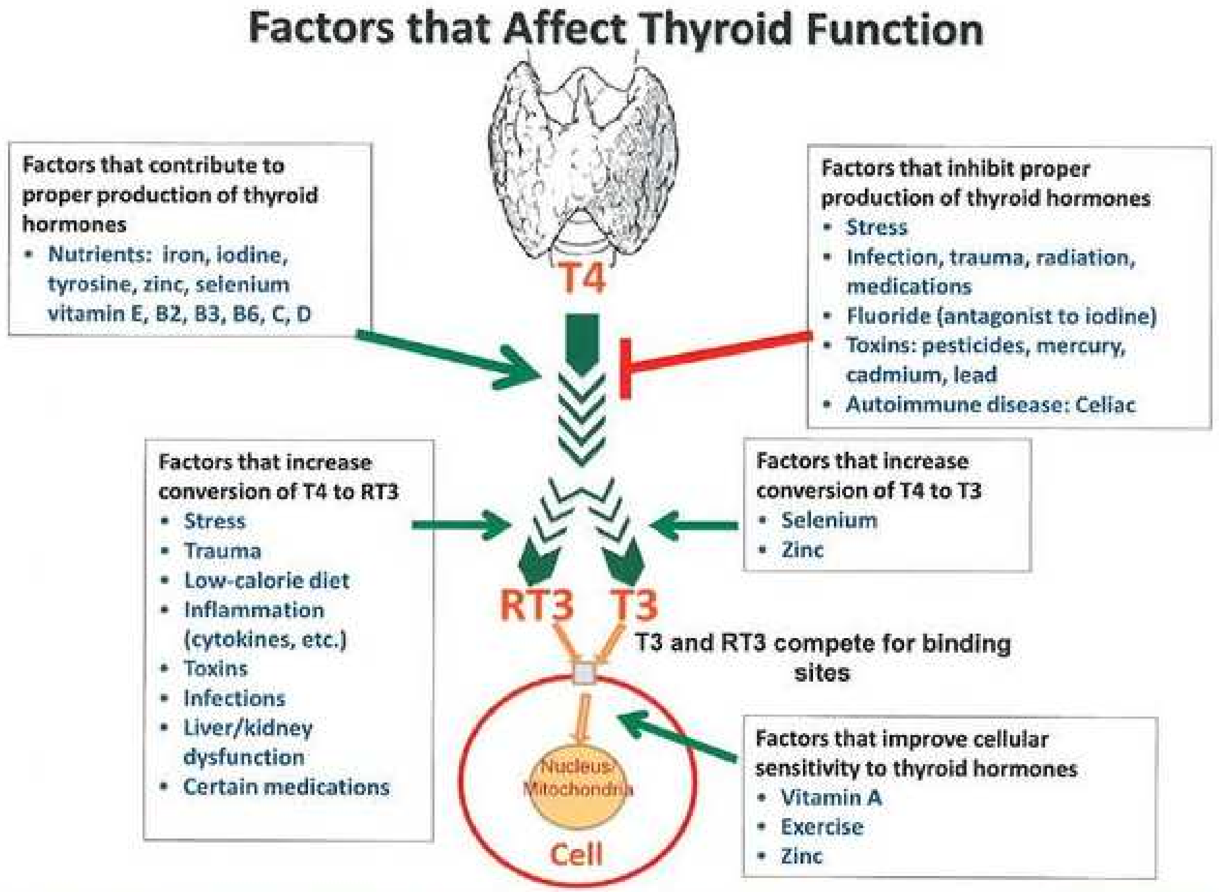
Zn
ZIP 1-5, 8, 10, 14, ZIP6
ZnT 1, 2,4
ZIP 1, 13
Zn
ZIP 3,8
ZnT 2,4
intracellular vesicles
ZnT 2,3,4,8
lysosome
ZnT 2
mammary gland vesicles
ZnT 8
Insulin granules
ZnT9
Nucleus
ZIP 7, ZIP 9, 13
ZnT 3
ZIP7
ZnT 5-7
synaptic vesicles

췌장의 내분비기능에 미치는 아연의 역할

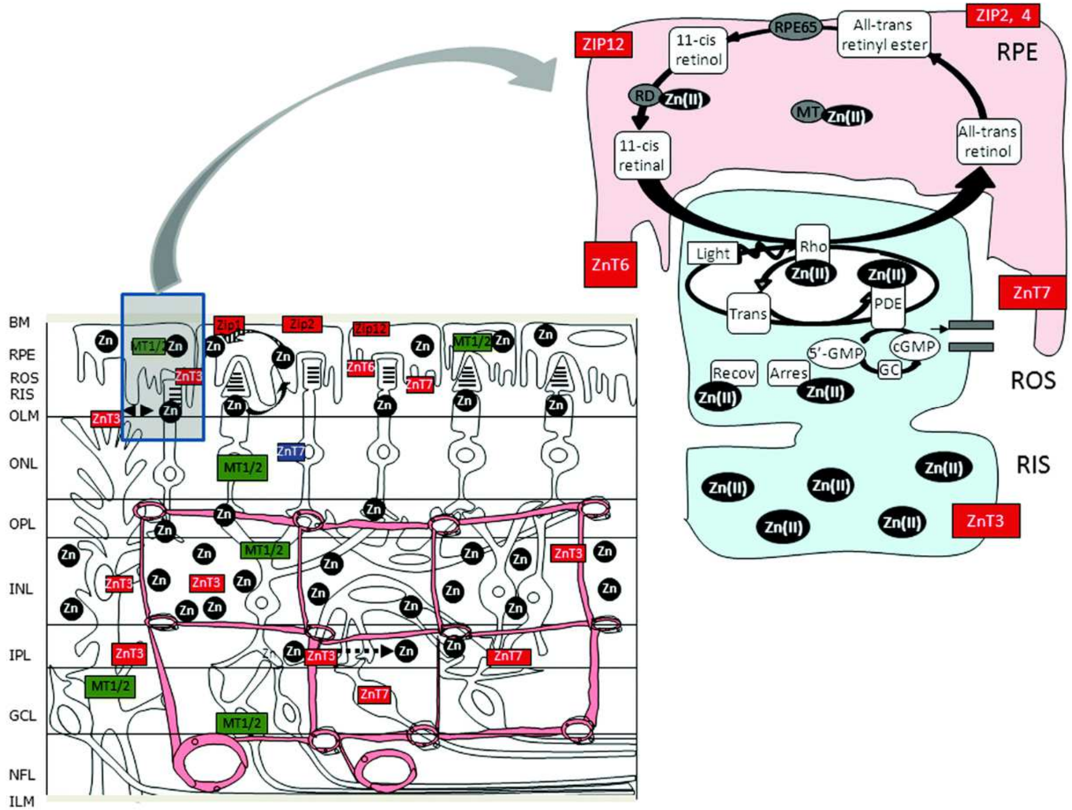


Zn transport in various pancreatic cell types. (*A*) Localization of Zip1, Zip10, and Zip14 to pancreatic α-cells suggests that these transporters are responsible for importing Zn into the cell. Zn binds to and opens ATP dependent K(+) channels, allowing the efflux of Zn from the α-cell and inactivation of voltage dependent calcium channels, resulting in decreased glucagon secretion. (*B*) Zn is transported into pancreatic β-cell cells via Zip4. ZnT8 is responsible for the transport of Zn into insulin granules. Autoantibodies to ZnT8 and polymorphisms of ZnT8 are associated with the onset of DM. (*C*) Zip5 is responsible for the transport of Zn into pancreatic acinar cells. Zn is transported into zymogen granules by ZnT2 where it binds to and activates digestive enzymes that are subsequently secreted.

갑상선호르몬
T4의 T3로의
활성화에도
아연이 필요



안구 조직에는 아연이 고동도로 분포



Signs you need more zinc

- White spots on fingernail beds
- Craving salty or sweet foods
- Diarrhea
- Low energy
- Catch colds easily
- Ringing in the ears
- Trouble focusing/ADD symptoms
- Low fertility
- Nerve dysfunction
- Faulty memory
- Wounds heal slowly

ACTION STEPS

Zinc and Men's Health

To ensure that your male patients are receiving enough zinc, consider implementing the following strategies:

- ✓ Assure that male patients receive a maintenance dose of 15 mg/day zinc.
- ✓ Supplement 50 mg/day zinc to patients at risk for prostate cancer.
- ✓ Supplement 50 mg/day zinc to patients with low testosterone levels.
- ✓ Supplement 25-50 mg/day zinc to patients with low semen volume.
- ✓ Supplement 25-50 mg/day zinc to patients with low sperm count.
- ✓ Some nutritional experts recommend the use of copper while supplementing with zinc in amounts above 25-30 mg per day long-term. Recommended dosage is 0.5-1 mg of copper per 30-50 mg of zinc.

아연이 부족한 경우의 증상과 필요 용량

Top five signs of zinc deficiency are:

Compromised immune system: Zinc affects cell activities. Zinc deficiency can cause reduced or weakened antibodies and compromise the immune system. Thus the deficient person will be prone to infection or flu.

Diarrhea: A compromised immune system makes one susceptible to infection. One of these infections is a bacteria that causes diarrhea.

Hair loss and skin lesions: Zinc is important for normal cell growth. Zinc nutrition deficiency weakens the cells, which can result in hair loss in case of cells on the scalp and lesions on the skin. This is one of the prominent signs of zinc deficiency.

Loss of appetite and/or anorexia: A deficiency of zinc causes decreased loss of appetite. If zinc deficiency is not identified and treated, decreased loss of appetite can eventually lead to anorexia.

Impairment of cognitive and motor functions: Zinc deficiency in a pregnant mother can not only weaken the mother, but can also cause damage to the fetus's neurological system, impairing the motor skills and cognitive skills of the infant.

Other signs of zinc deficiency are reduced fertility, rashes on the skin, spots on fingernails, sleep disturbance, loss of sex drive, loss of taste or smell, and in some cases mild anemia.

Zinc in diarrhoea management - role

- Multiple functions of zinc help to maintain the gut mucosal integrity to reduce or prevent fluid loss
- Thus, in diarrhoea, zinc deficiency affects various mucosal functions:
    - Disrupts intestinal mucosa
    - Reduces brush border enzymes
    - Increases mucosal permeability
    - Increases intestinal secretion
- Note: these responses can occur within 48 hours –
    - much faster than the direct effects of zinc on cellular development.

설사와 아연의 관계

- Significant ↓ in both tissue & serum Zn common in acute and chronic diarrhea.
- Zinc depletion occurs in diarrhea, more so in chronic state.
- Significant negative correlation between serum *zinc* & *diarrheal duration*.
- In a study, mean serum and tissue zinc levels in children with acute and chronic diarrhea were found to be significantly *lower* than healthy and infected controls.
- Zinc supplements have been shown to have a beneficial effect on acute diarrhea in children.
- It is reported that zinc supplementation leads to accelerated regeneration of intestinal mucosa, ↑ levels of brush-border enzymes, ↑ cellular immunity & ↑ levels of secretory antibodies.

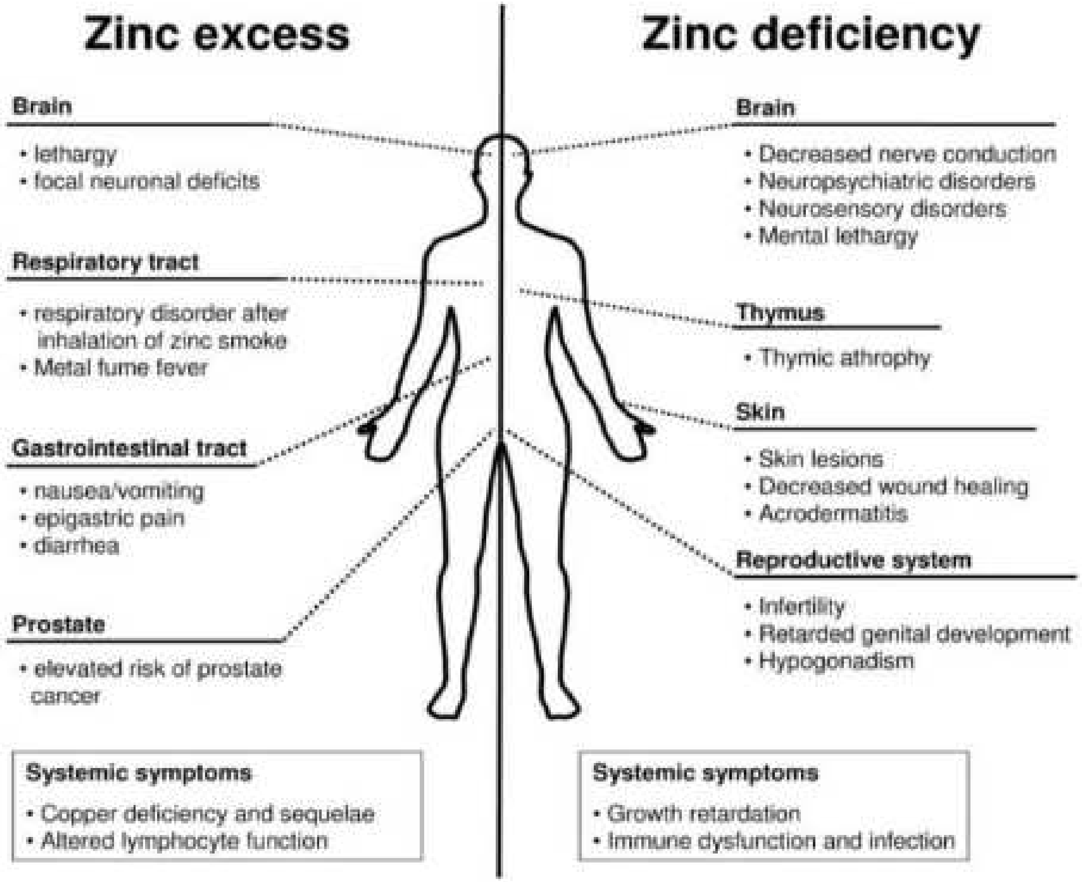
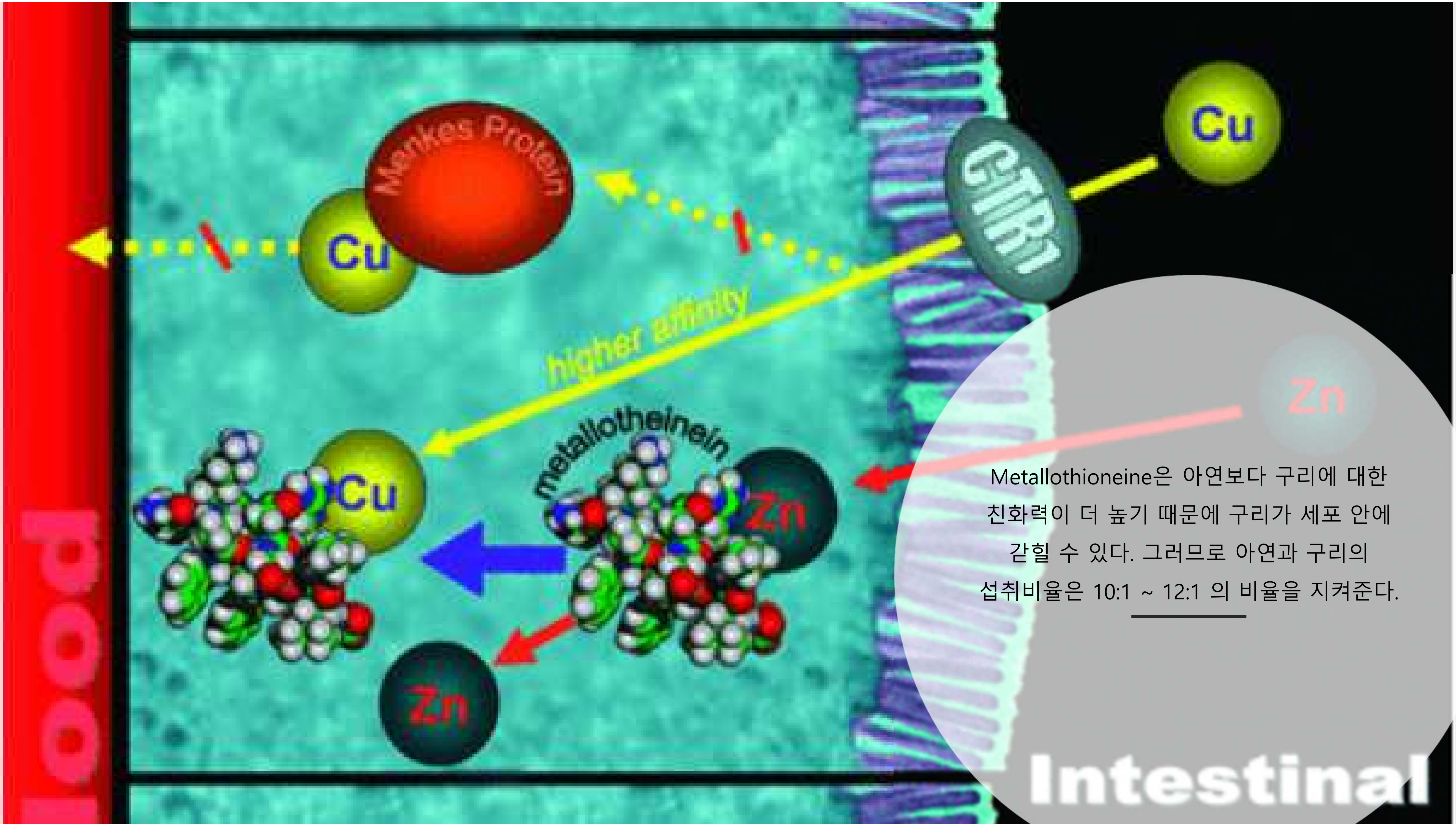


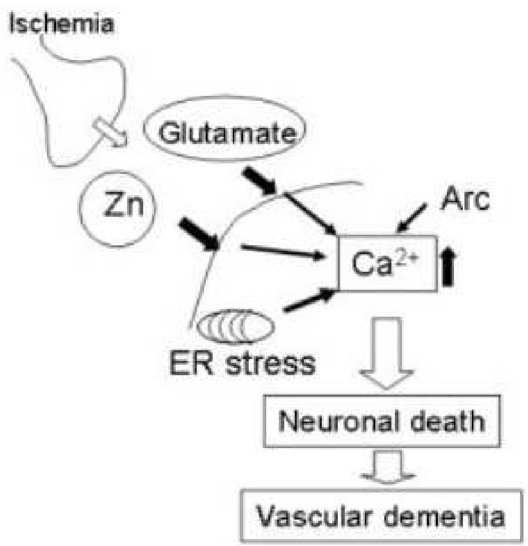
Figure 2. Comparison of the effects of zinc intoxication versus deficiency. Intoxication by excessive exposure to, or intake of, zinc (left hand side), and deprivation of zinc by malnutrition or medical conditions (right hand side), have detrimental effects on different organ systems. Effects that could not be attributed to a certain organ system or affect several organs are classified as systemic symptoms.



Metallothioneine은 아연보다 구리에 대한 친화력이 더 높기 때문에 구리가 세포 안에 갇힐 수 있다. 그러므로 아연과 구리의 섭취비율은 10:1 ~ 12:1 의 비율을 지켜준다.

Abstract: Zinc (Zn) is an essential trace element that is abundantly present in the brain. Despite its importance in normal brain functions, excess Zn is neurotoxic and causes neurodegeneration following transient global ischemia and plays a crucial role in the pathogenesis of vascular-type dementia (VD). We have investigated the molecular mechanisms of Zn-induced neurotoxicity using immortalized hypothalamic neurons (GT1-7 cells) and found that carnosine (β-alanyl histidine) and histidine (His) inhibited Zn^{2+}-induced neuronal death. A DNA microarray analysis revealed that the expression of several genes, including metal-related genes (metallothionein and Zn transporter 1), endoplasmic reticulum (ER)-stress related genes (*GADD34*, *GADD45*, and *p8*), and the calcium (Ca)-related gene *Arc* (activity-related cytoskeleton protein), were affected after Zn exposure. The co-existence of carnosine or His inhibited the expression of *GADD34*, *p8*, and *Arc*, although they did not influence the expression of the metal-related genes. Therefore, ER-stress and the disruption of Ca homeostasis may underlie the mechanisms of Zn-induced neurotoxicity, and carnosine might be a possible drug candidate for the treatment of VD.

Keywords: Zinc; carnosine; histidine; vascular-type dementia



Excess zinc

- 적정량의 아연을 보급하는 것은 전립선 세포를 보호하지만 과량을 지속적으로 복용한 경우 오히려 전립선 암이 증가하였음에 유의. 과량으로 독성을 나타내는 아연 농도의 기준은 조직마다 다르지만 통상 plsama 300 ug/ml이상이면 구리 부족을 비롯한 독성이 나타날 수 있고 일일 섭취량 기준으로 100mg이다.
  (식품의 경우 함량이 높은 것들이 있으므로 총량 100mg을 초과하지 않도록 환자에게 주의를 줄 필요가 있다.)