

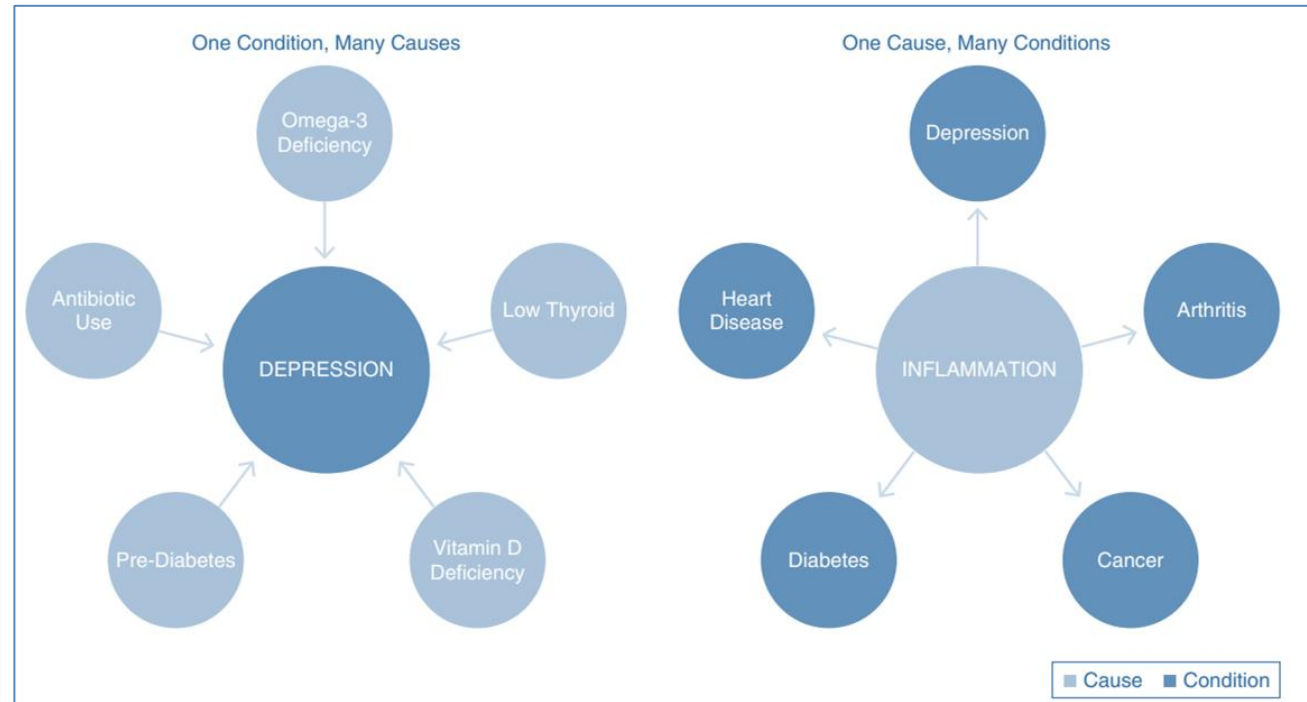
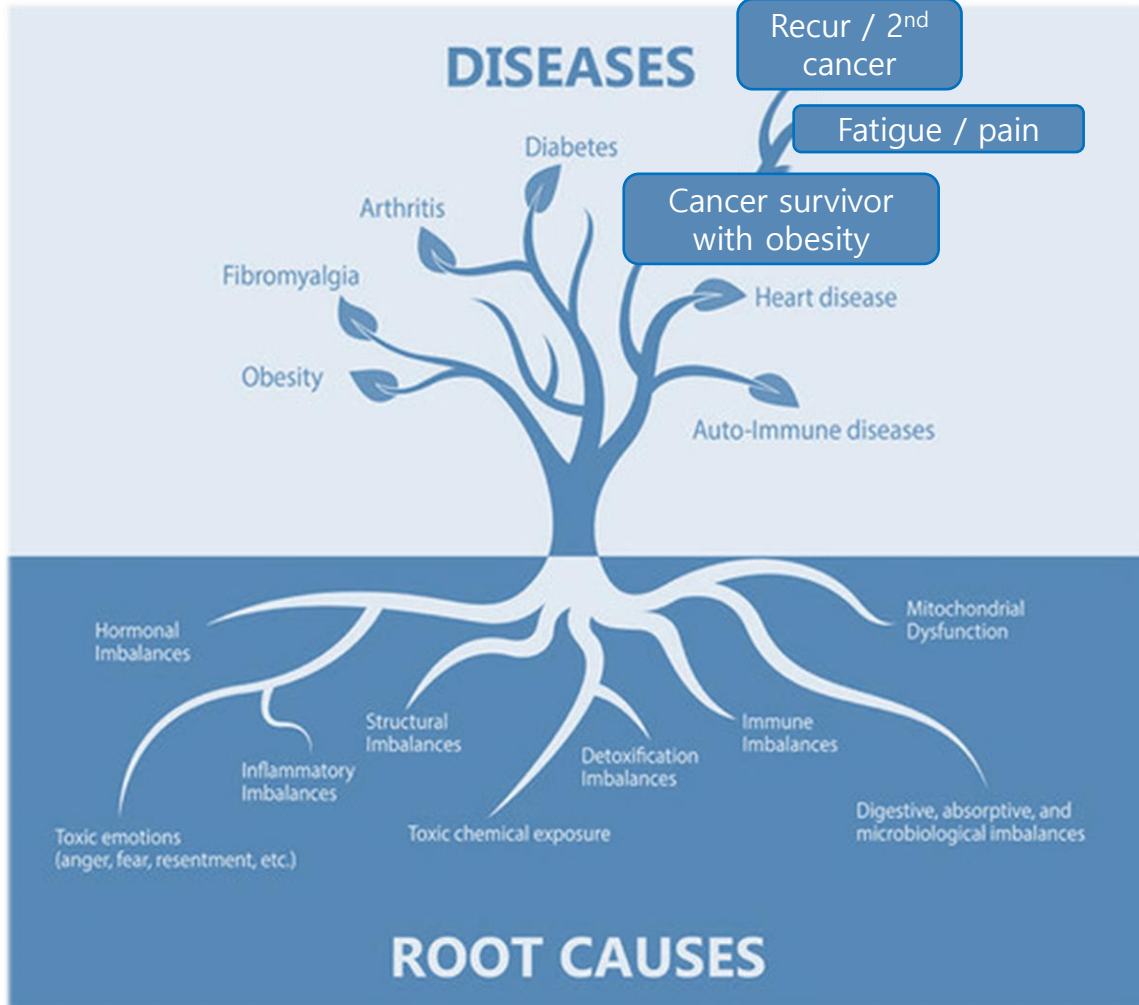
Functional medicine for cancer survivors with obesity

비만한 암환자에 대한 기능의학

March 25th 2023

아주대병원 정수지

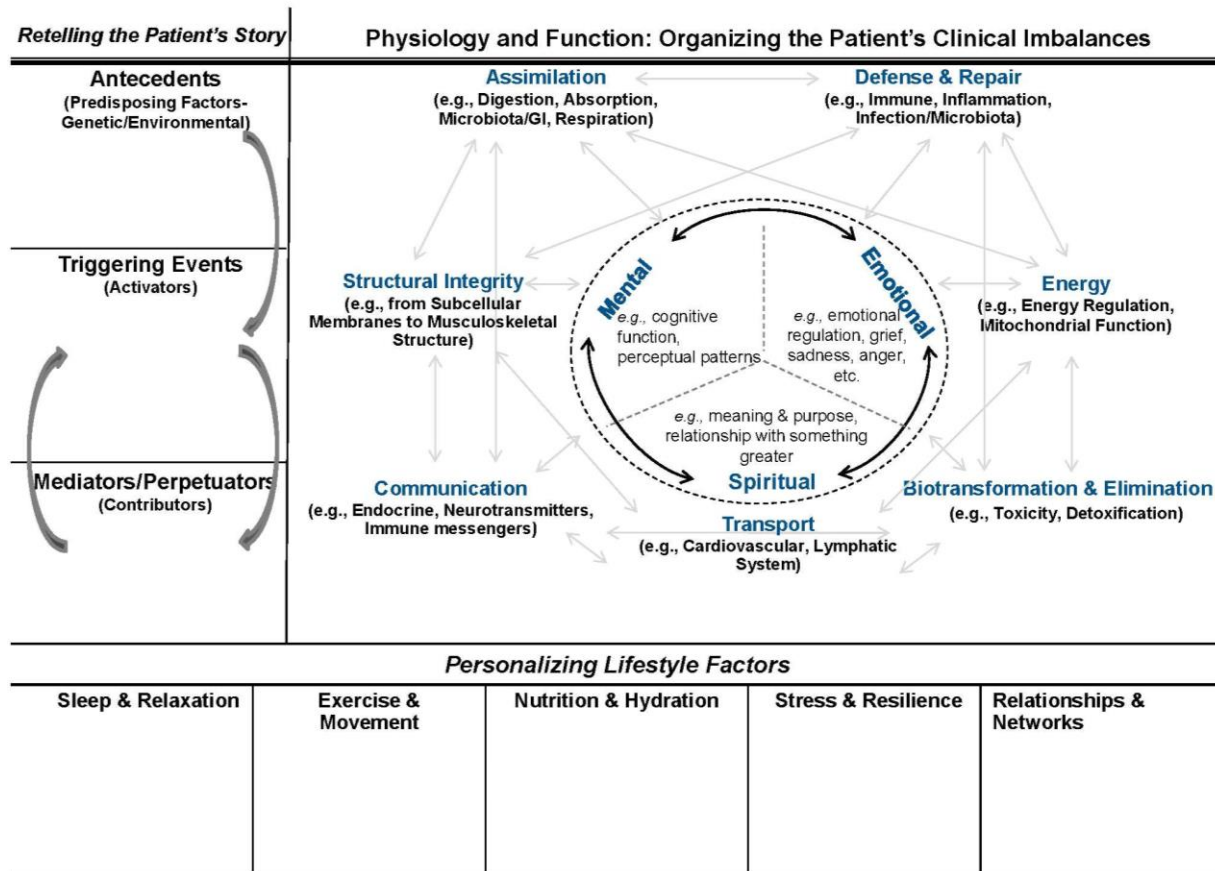
Cancer survivor with obesity 기능의학적 접근



- a **comprehensive** and **personalized** approach
- addresses the **root causes** of the individual's health concerns
- 암 생존자에서 **추가적인 암 및 질병 예방**, 기능의 회복, 증상 조절을 통한 **삶의 질 향상**을 목표
- 비만(obesity)이 암 생존자(cancer survivor)에게 주는 **7-core dysregulation**에 초점

Cancer survivor with obesity

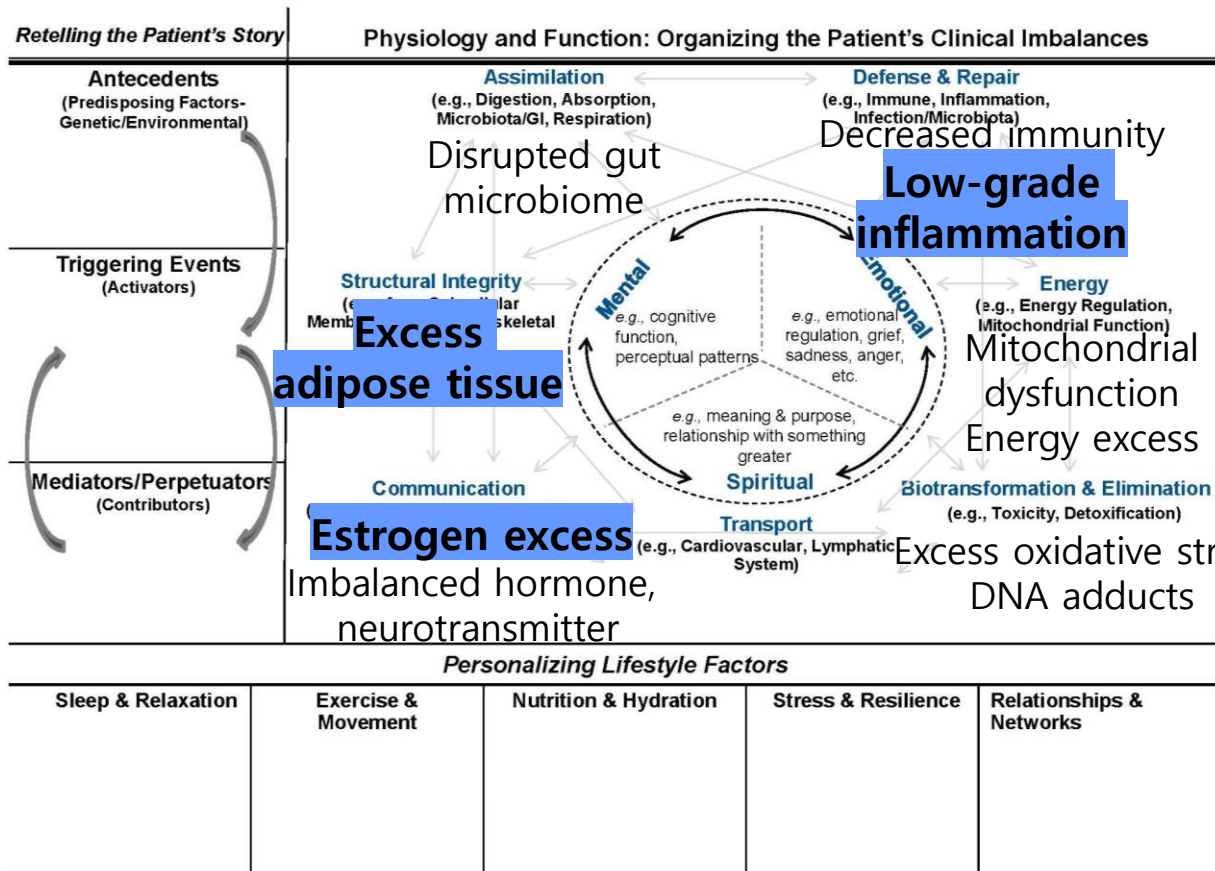
7-core imbalance in functional medicine



- **Assimilation imbalance** (impaired gut integrity, GI dysbiosis)
- **Defense & repair imbalance** (immune, chronic inflammation)
- **Energy imbalance** (energy regulation, mitochondrial function)
- **Biotransformation & elimination imbalance** (fatigue, toxicity, detoxification reserve)
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- **Communication imbalances** (endocrine, neurotransmitter, immune dysfunction)
- **Structural integrity imbalance** (low muscle, high fat, visceral fat)

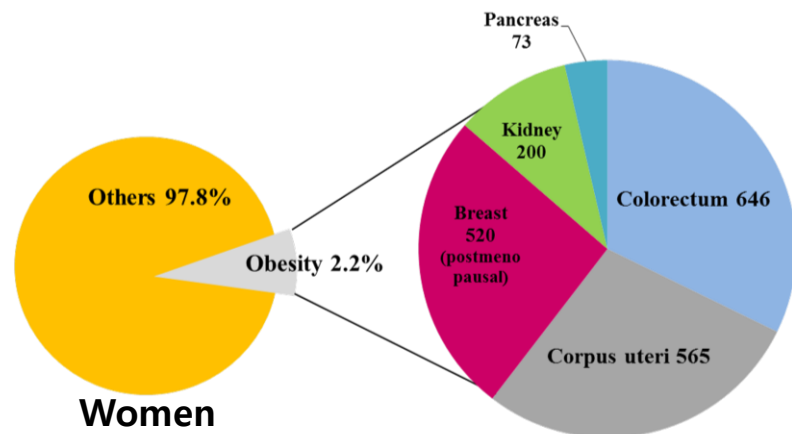
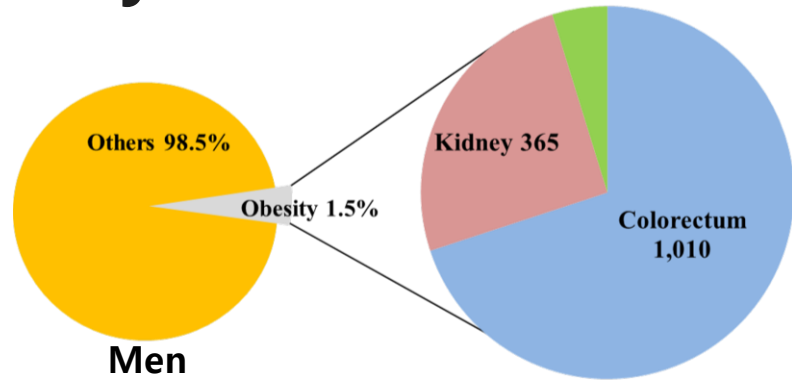
Cancer survivor with obesity

7-core imbalance in functional medicine

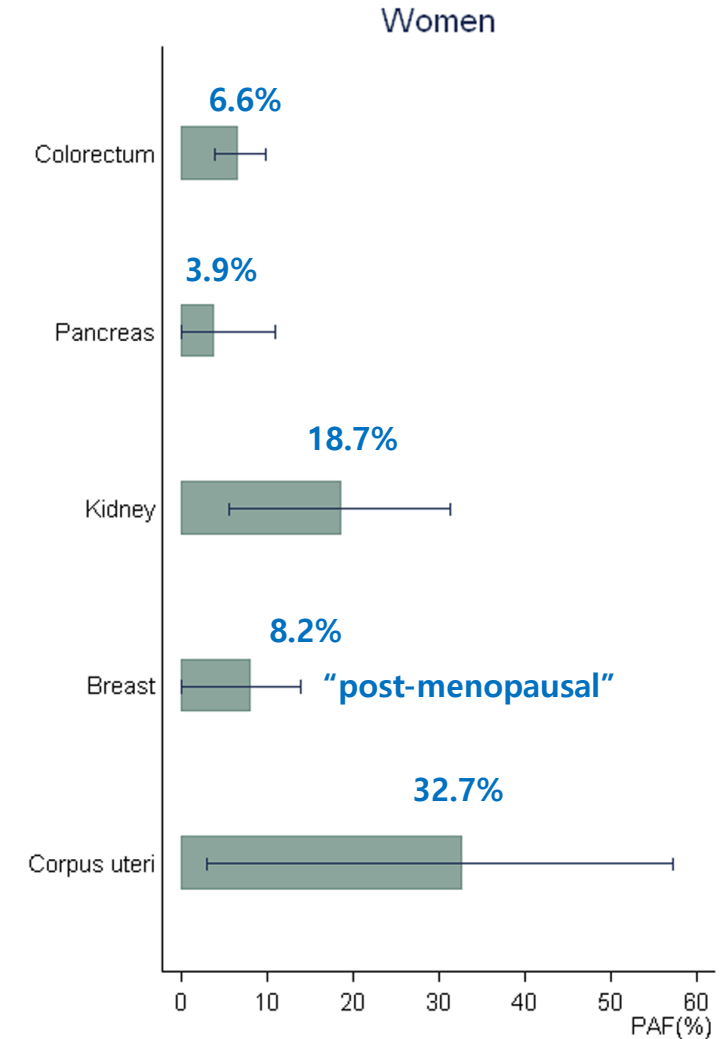
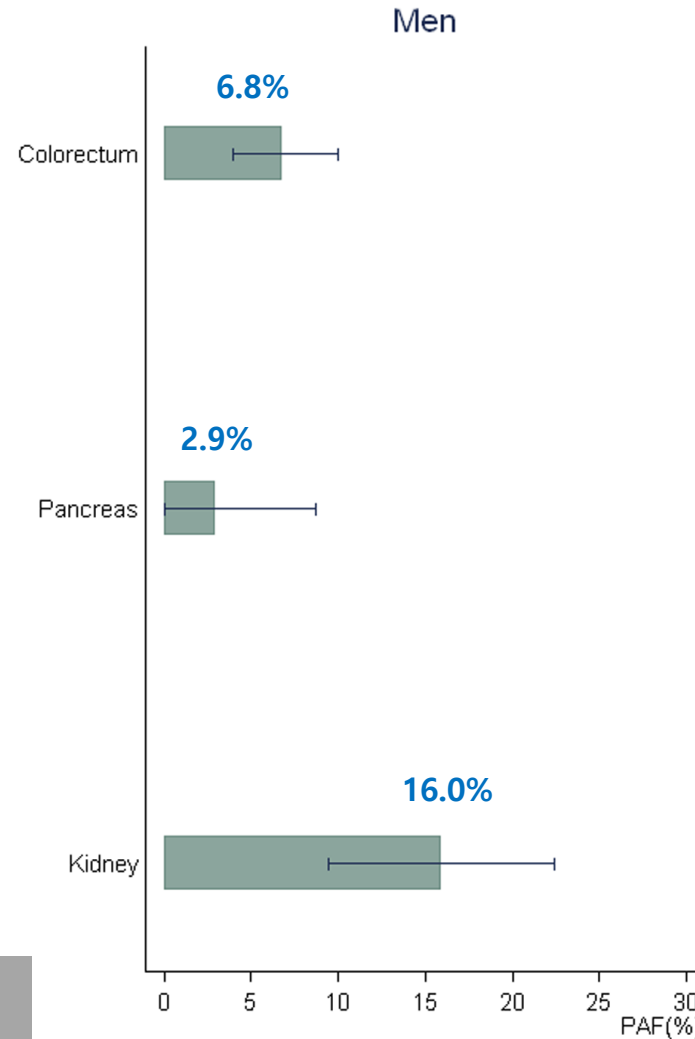


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Population-Attributable Causes of Cancer in Korea (2009): Obesity

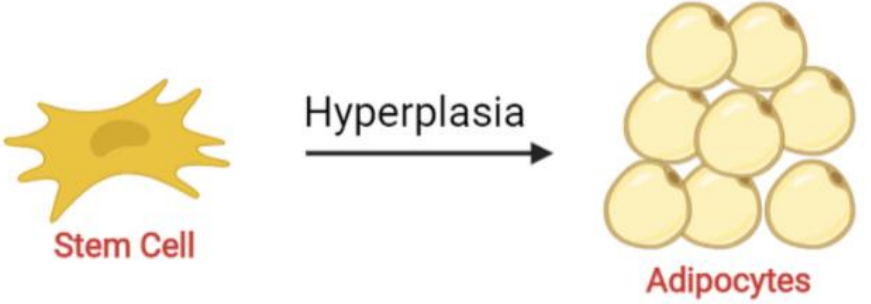


1992-1995년 대규모 전향적코호트 (National Health Insurance Corporation)
2009년 국가암 발생률 (Korea Central Cancer Registry)

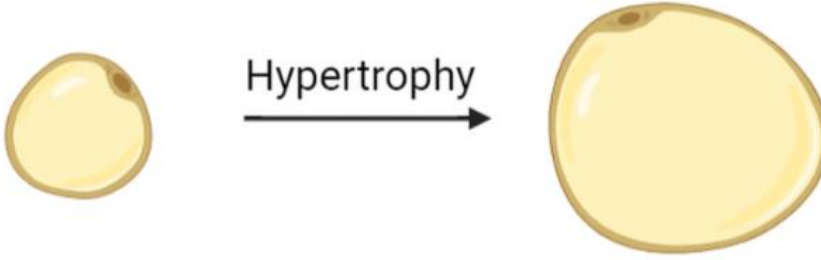


Population-attributable fraction

Excess energy

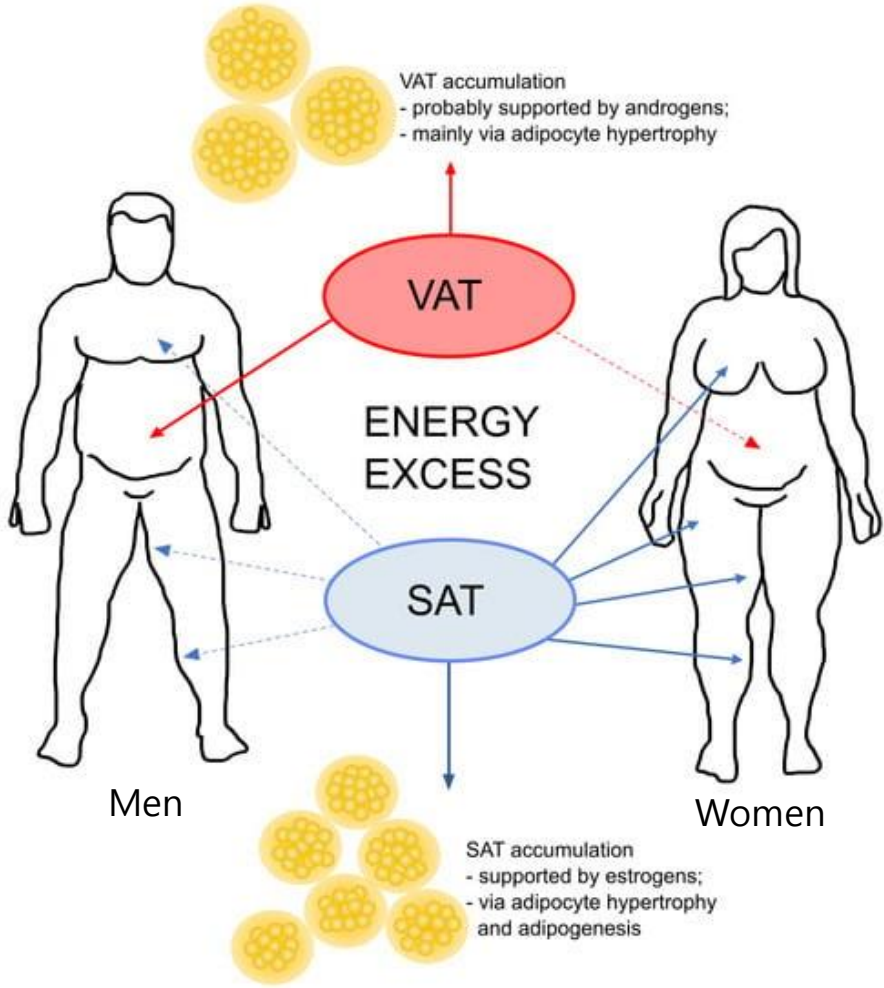


An increase adipose tissue mass through increasing adipocyte number



An increase adipose tissue mass through increasing adipocyte size

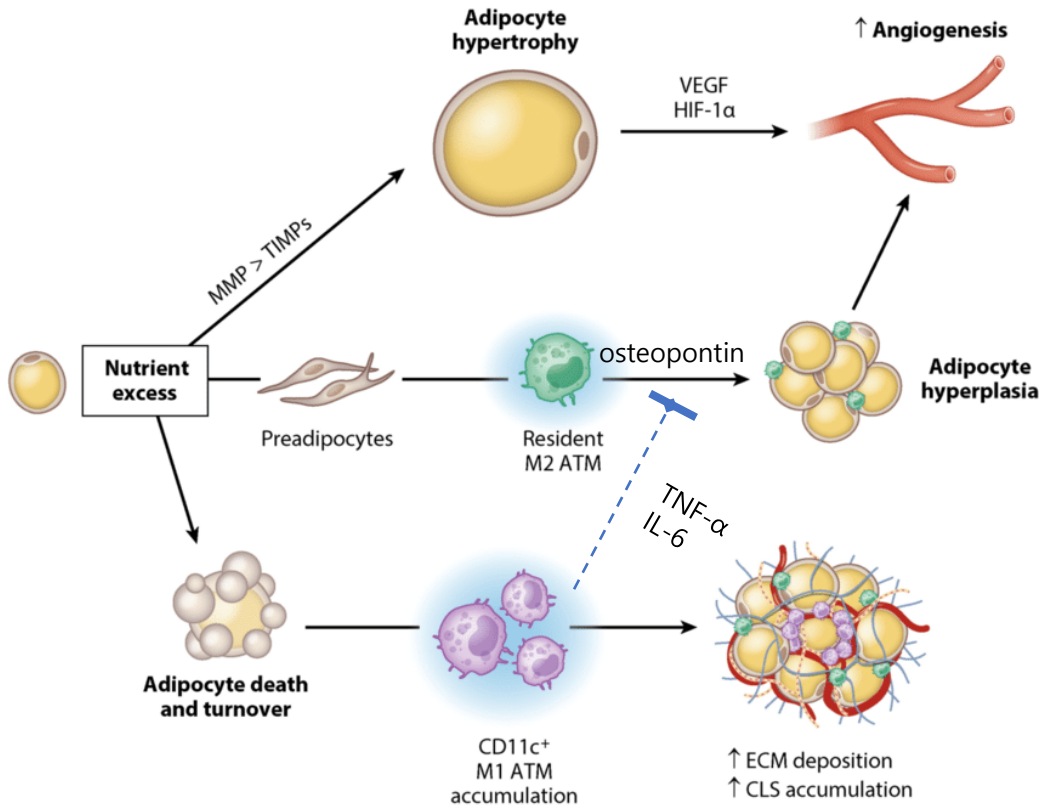
Adipose Hyperplasia vs. Hypertrophy



Visceral vs. Subcutaneous Adipose Tissue

Adipocyte hyperplasia

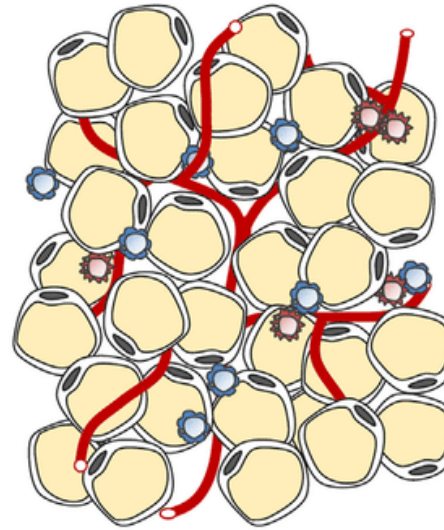
Adipocyte hypertrophy



Adipose hypertrophy
: 지방세포 과사, 노화, M1/M2 ratio ↑
IL-6, TNF-α, IL-8, CRP ↑ & IL-10 ↓

↑ Adiponectin
↓ Inflammatory Adipokines

Good endocrine organ



Hyperplasia

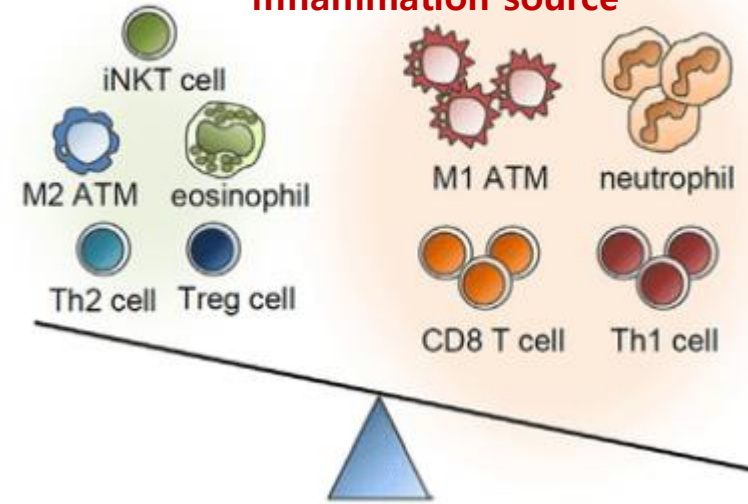
- cell number ↑
- FFA release ↓
- adiponectin ↑
- pro-inflammatory cytokines ↓
- immune cell recruitment ↓
- hypoxia and fibrosis ↓
- insulin sensitivity ↑

↓ Adiponectin
↑ Inflammatory Adipokines

↓ Blood Flow → Hypoxia

anti-inflammatory < pro-inflammatory

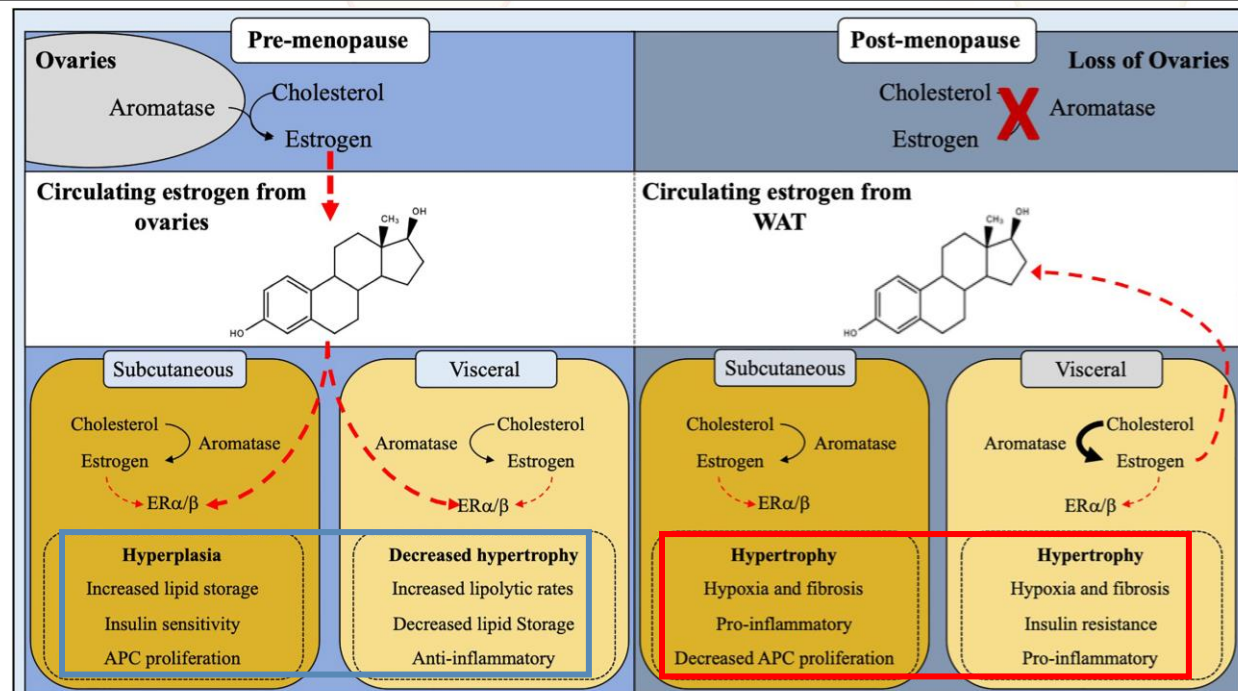
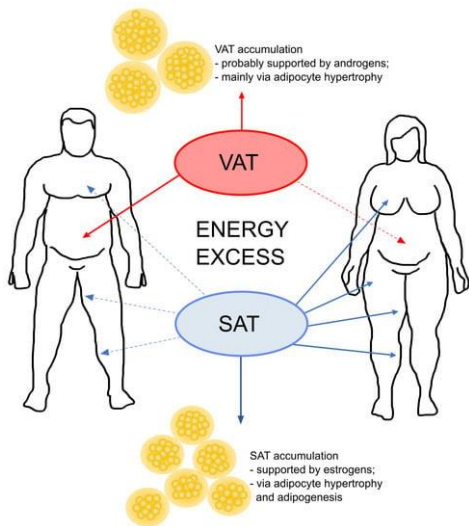
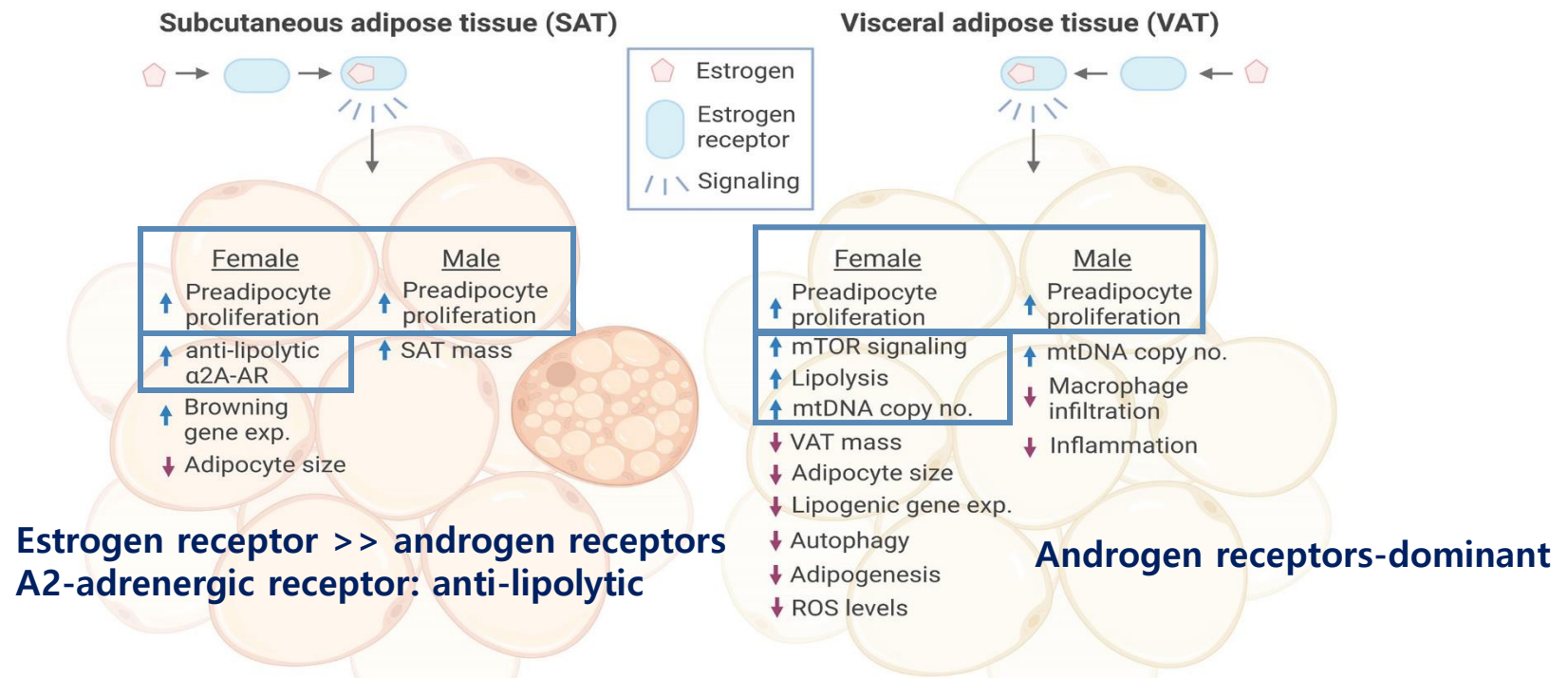
Inflammation source



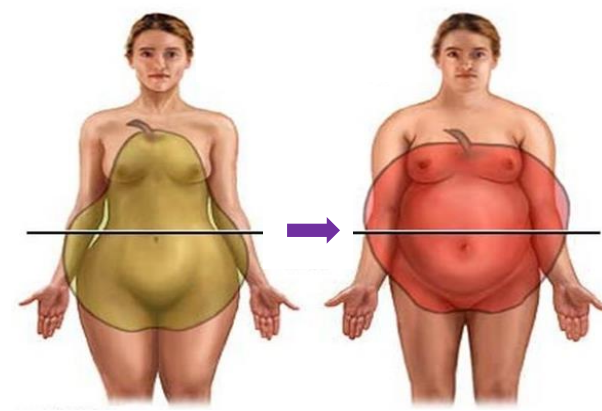
Hypertrophy

- cell size ↑
- FFA release ↑
- adiponectin ↓
- pro-inflammatory cytokines ↑
- immune cell recruitment ↑
- hypoxia and fibrosis ↑
- insulin sensitivity ↓

Estrogen action on SAT and VAT

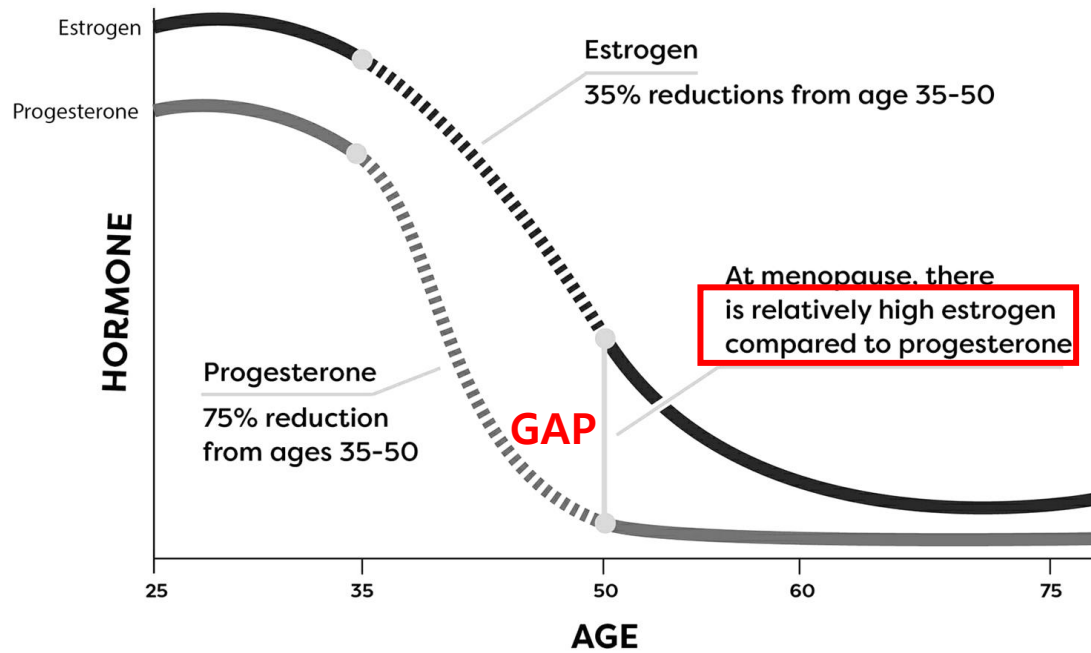


Front Endocrinol (Lausanne). 2022;13:828780.

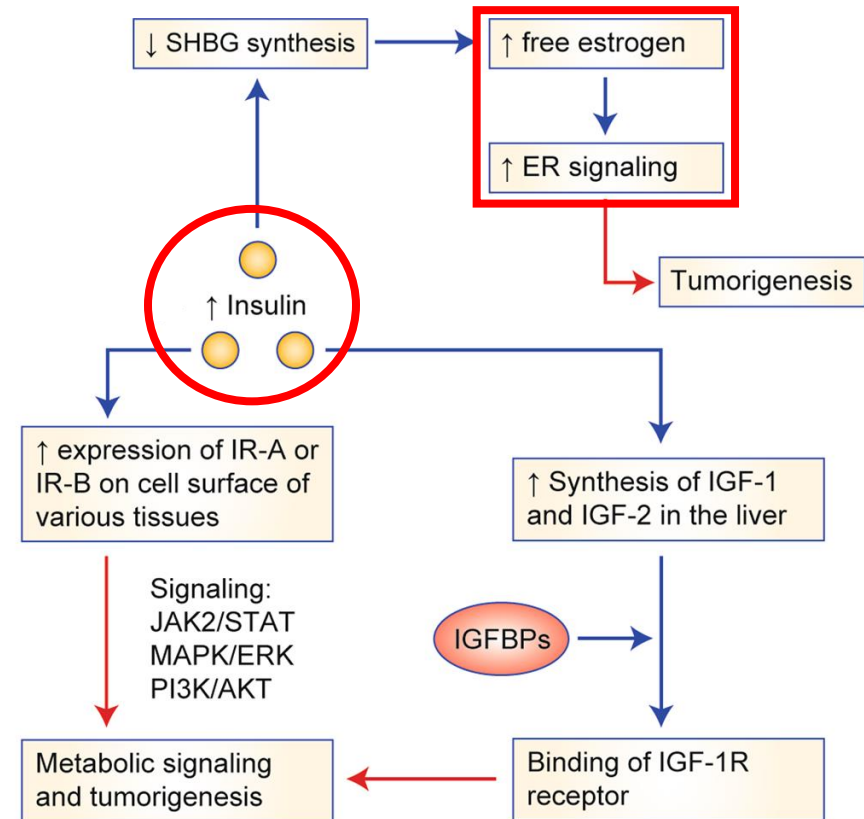


Front Endocrinol (Lausanne). 2022;13:889923.

Unopposed E2 (E2 dominance) around menopause



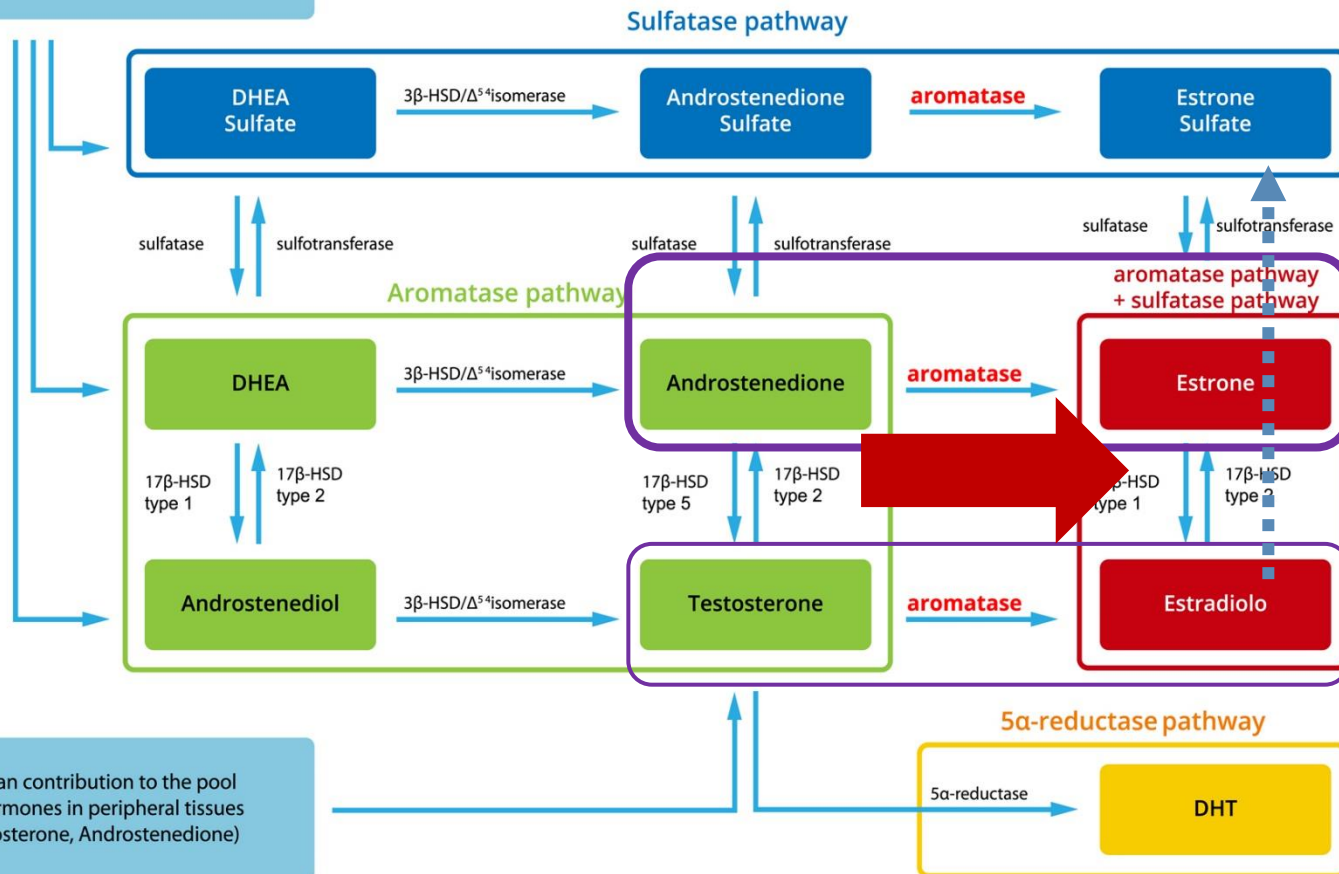
Obesity and estrogen-related cancer elevated free estrogen in obesity



Estrogen & Es receptors

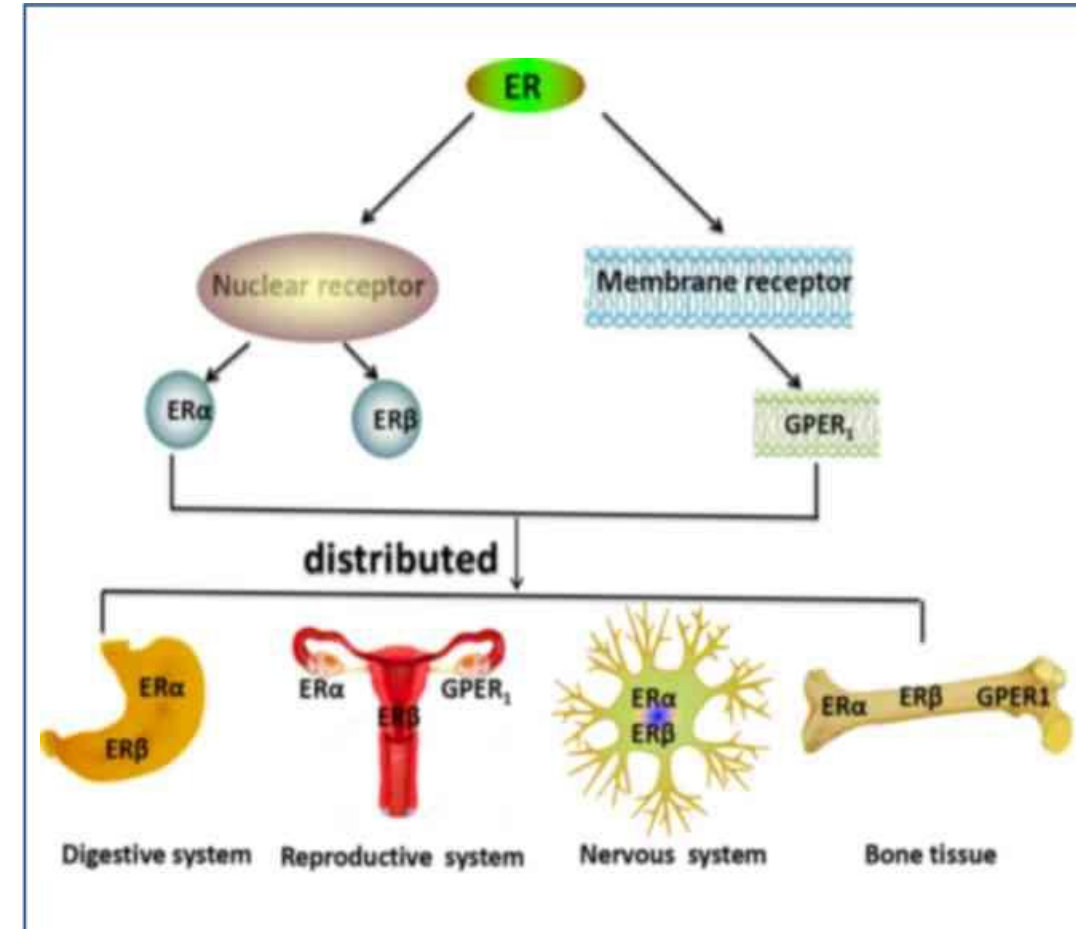
Progesterone: an antagonist of estrogen decreasing the production of ER activation of 17 β -HSD2 and sulfotransferase
Front Endocrinol (Lausanne). 2014;5:192.

Adrenal contribution to the pool of hormones in peripheral tissues (DHEA, DHEAS, Androstenediol, Androstenedione)



Ovarian contribution to the pool of hormones in peripheral tissues (Testosterone, Androstenedione)

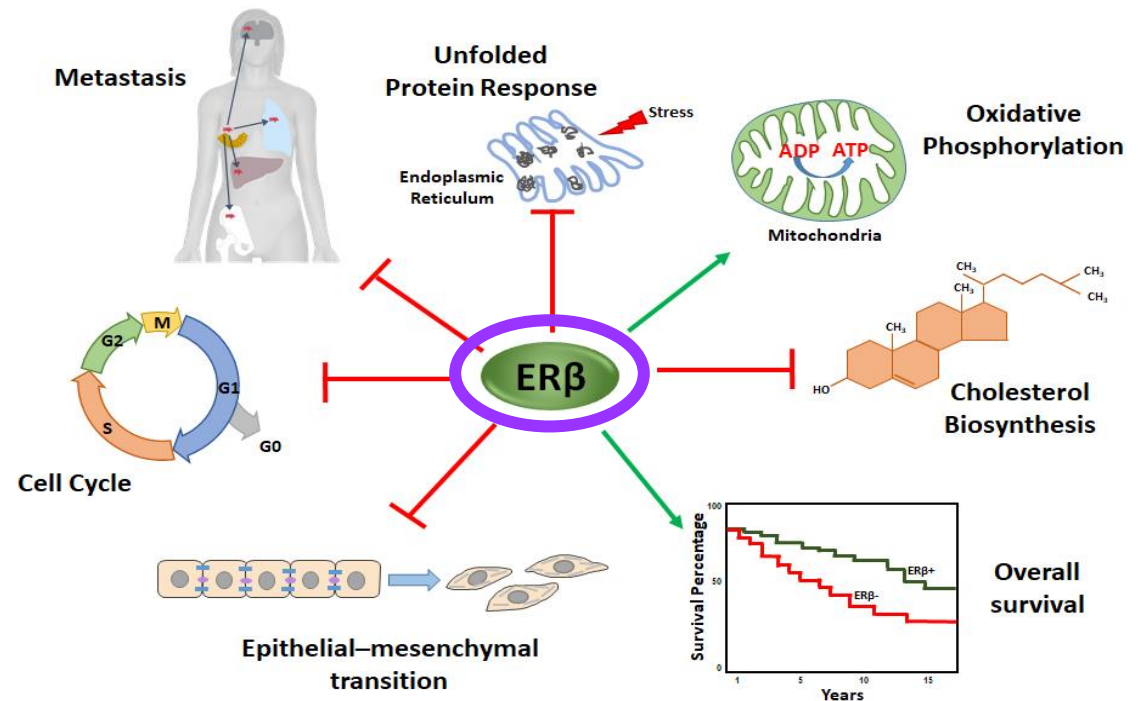
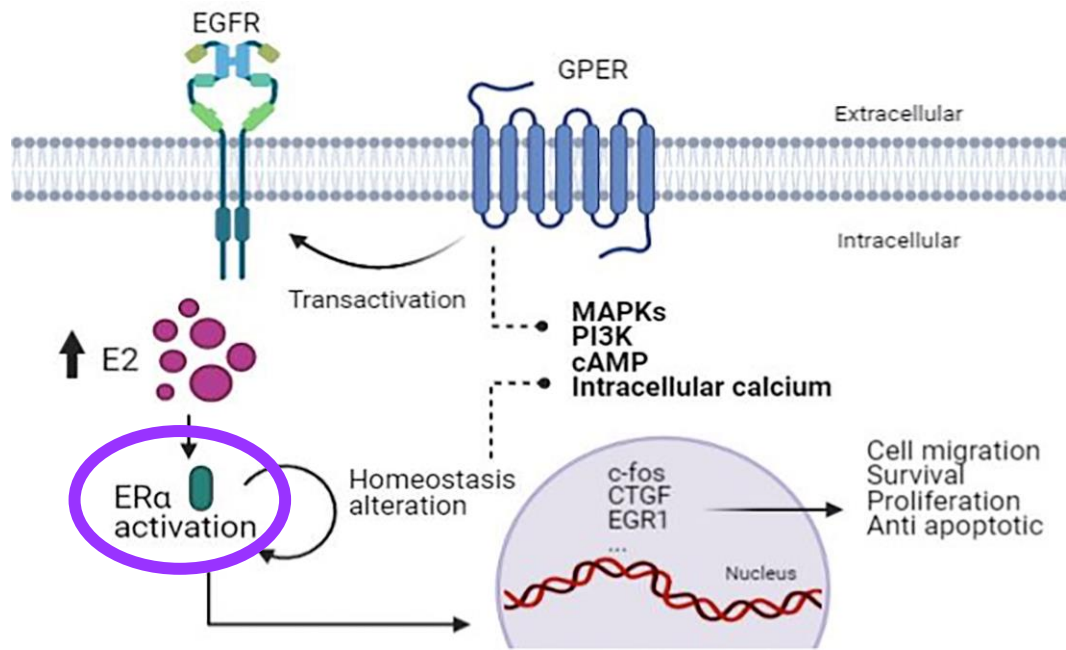
17 β -HSD(17 β -Hydroxysteroid dehydrogenase)
Endocr Relat Cancer. 2019 Feb;26(2):R81-R94.



Estrogen Receptors: ER α / β and GPER1

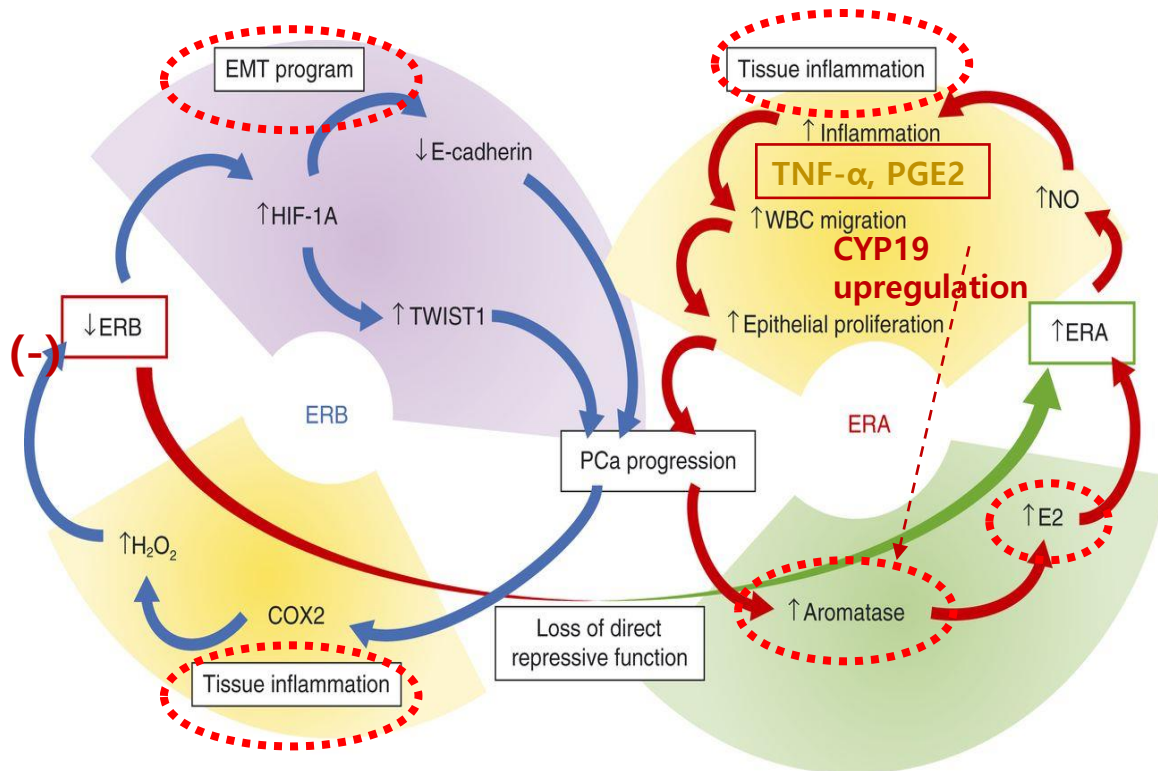
ER α is primarily expressed in breast, uterus and ovaries.

ER β is expressed in the brain, ovary, vascular endothelium, and prostate/ testes.

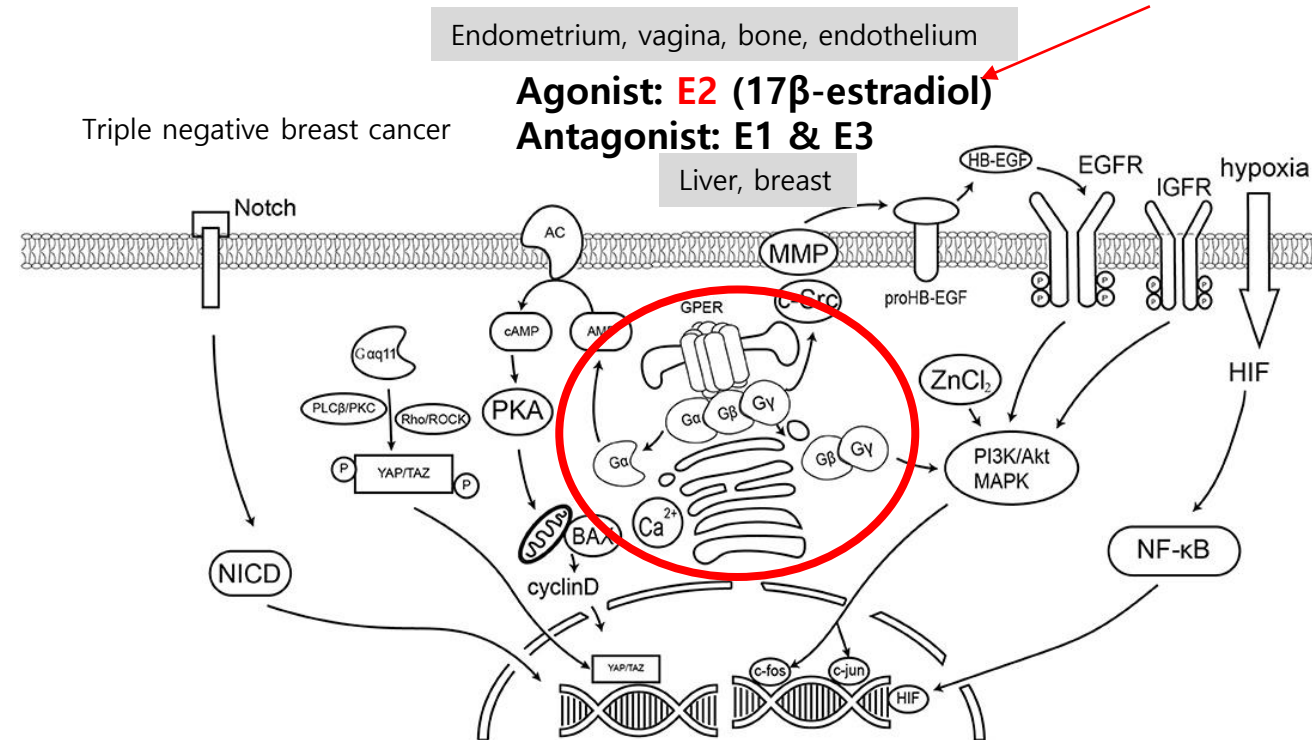


Estrogen Receptors: ER α / β and G Protein-Coupled Estrogen Receptor

Inflammation: estradiol and aromatase

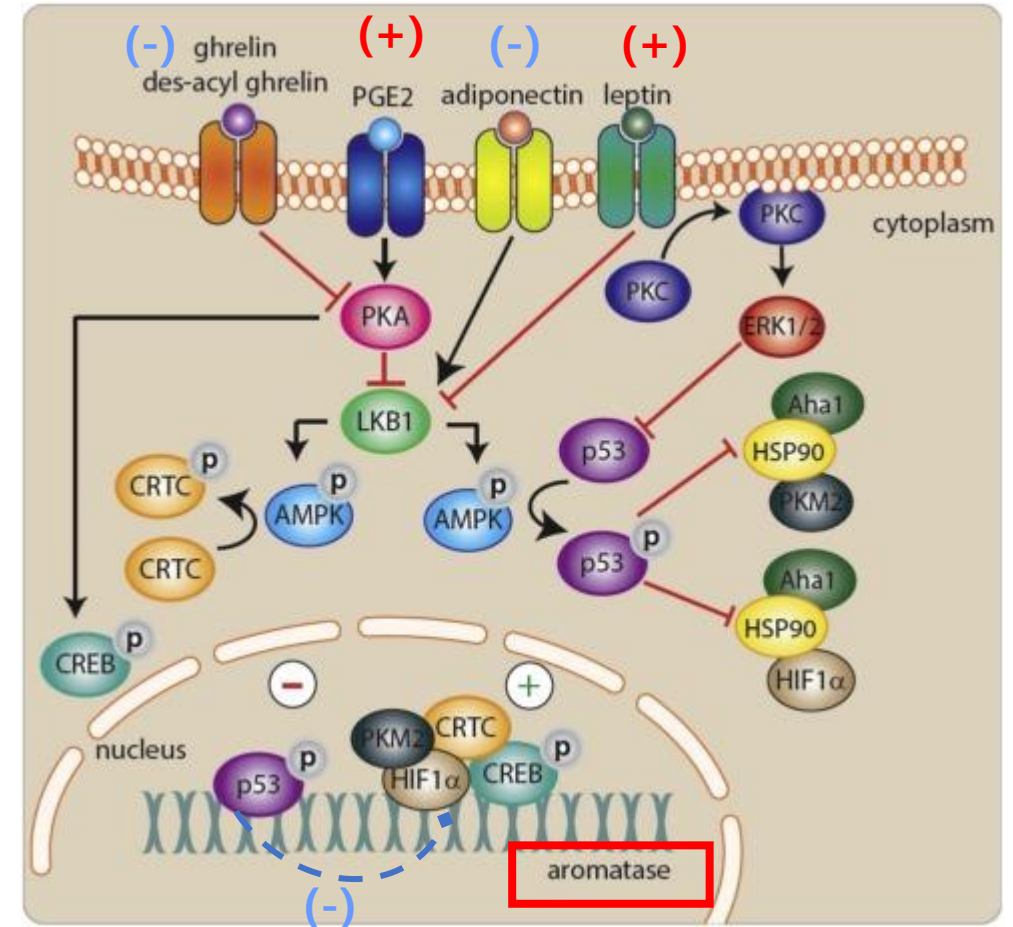
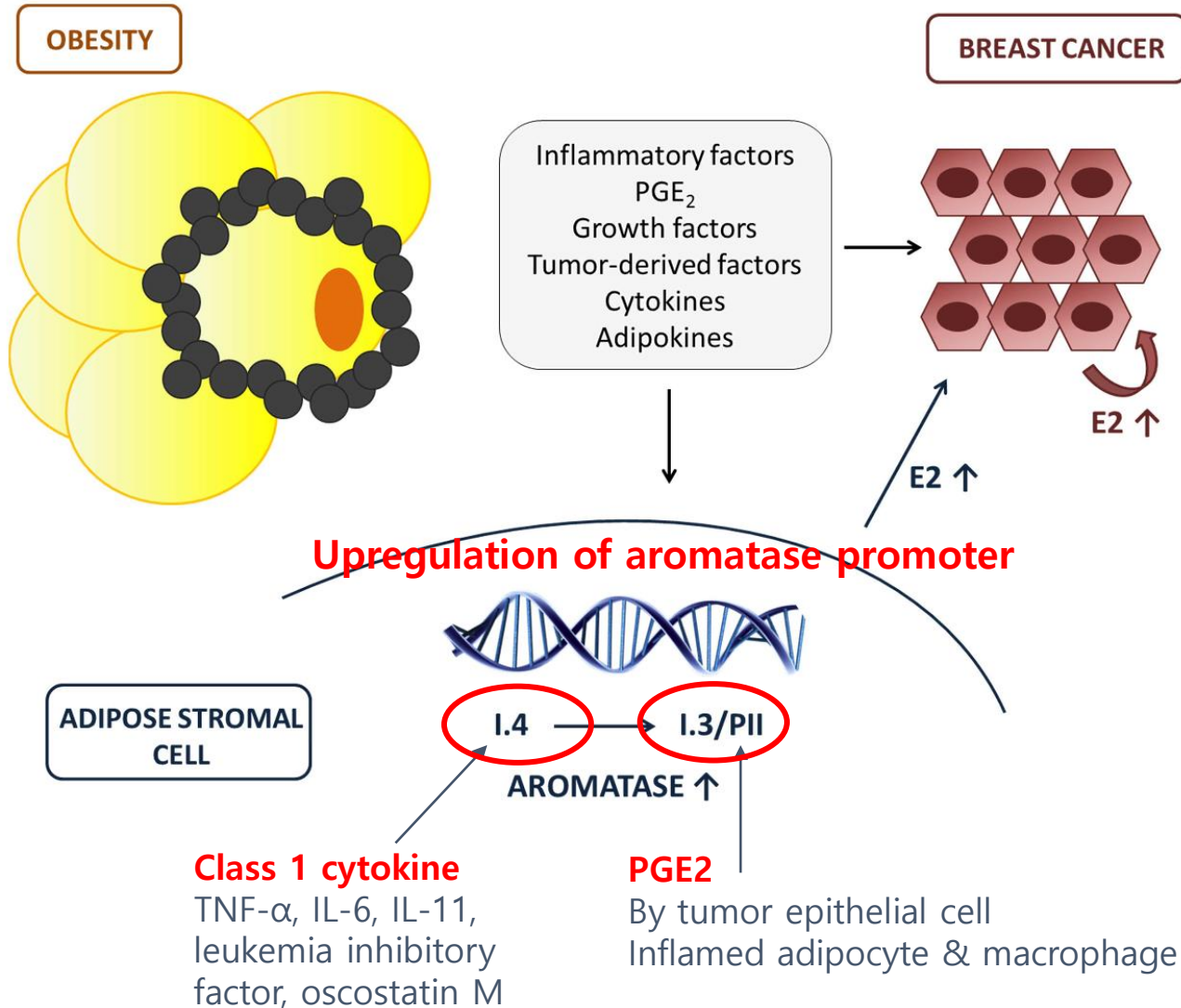


Endocr Relat Cancer. 2014;21(4):T219-T234.



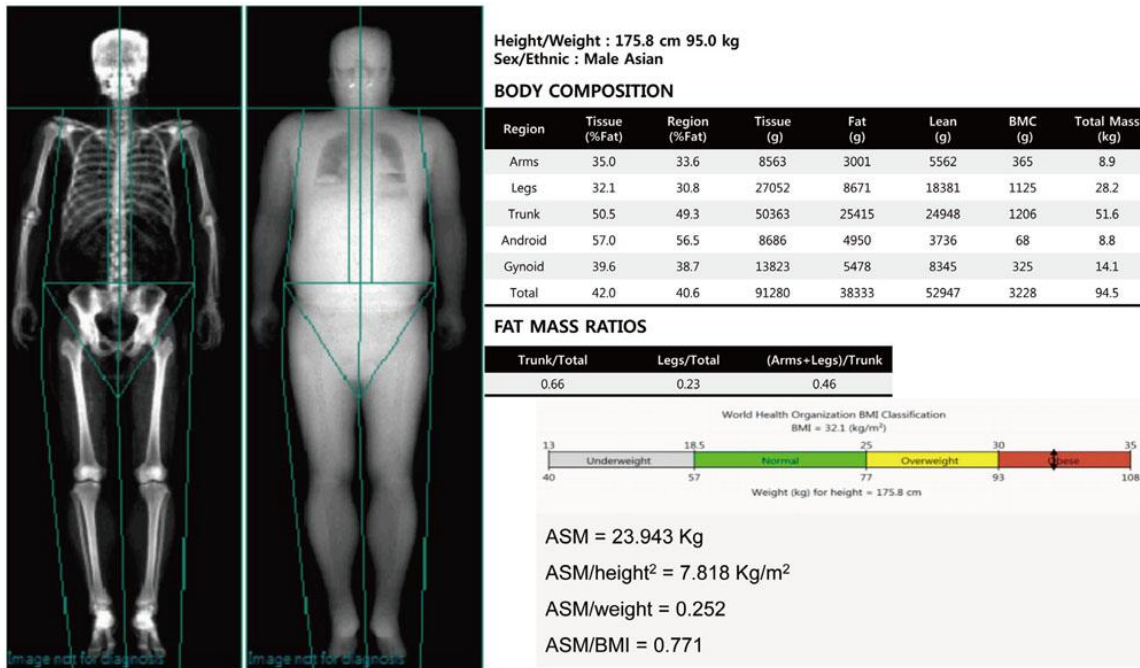
Front Endocrinol (Lausanne). 2019;10:725.

Aromatase activity



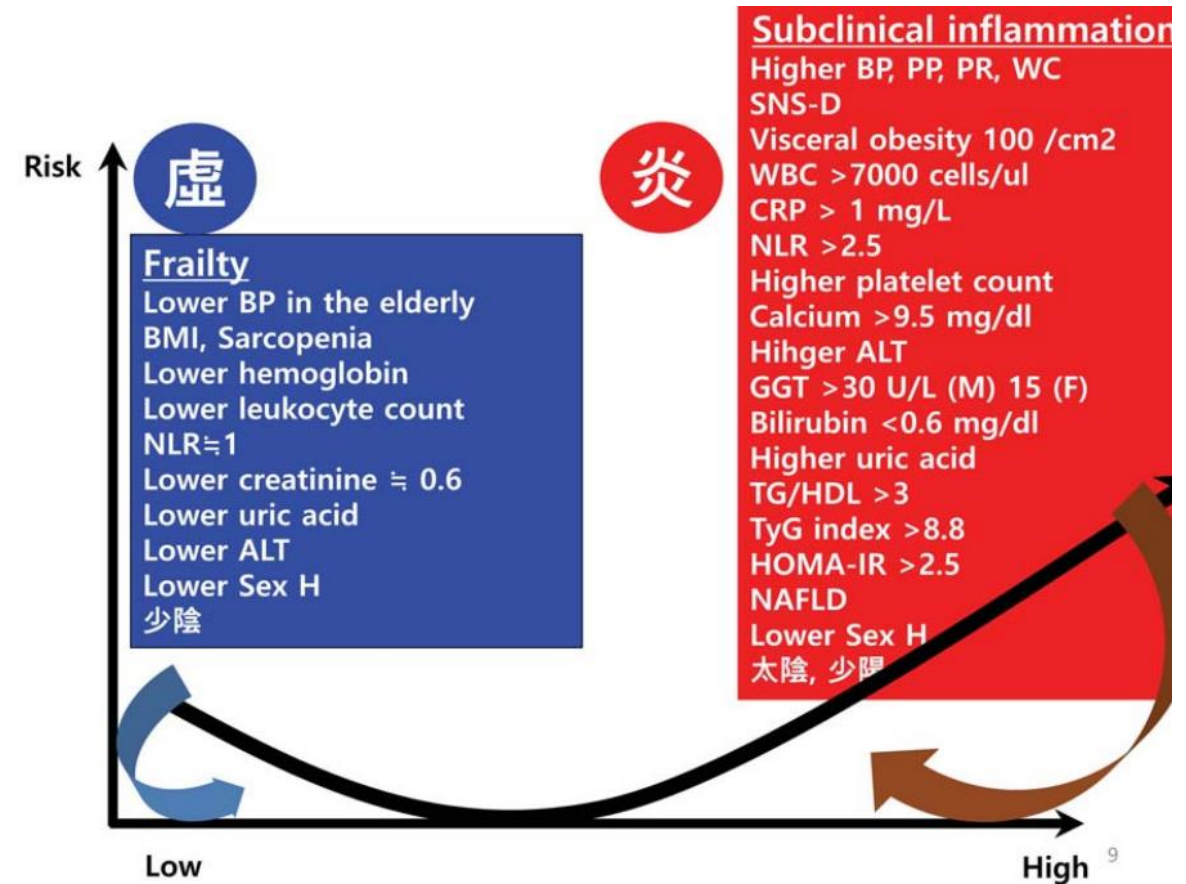
FM marker

- Gender
- Menopause
- Adult-onset obesity

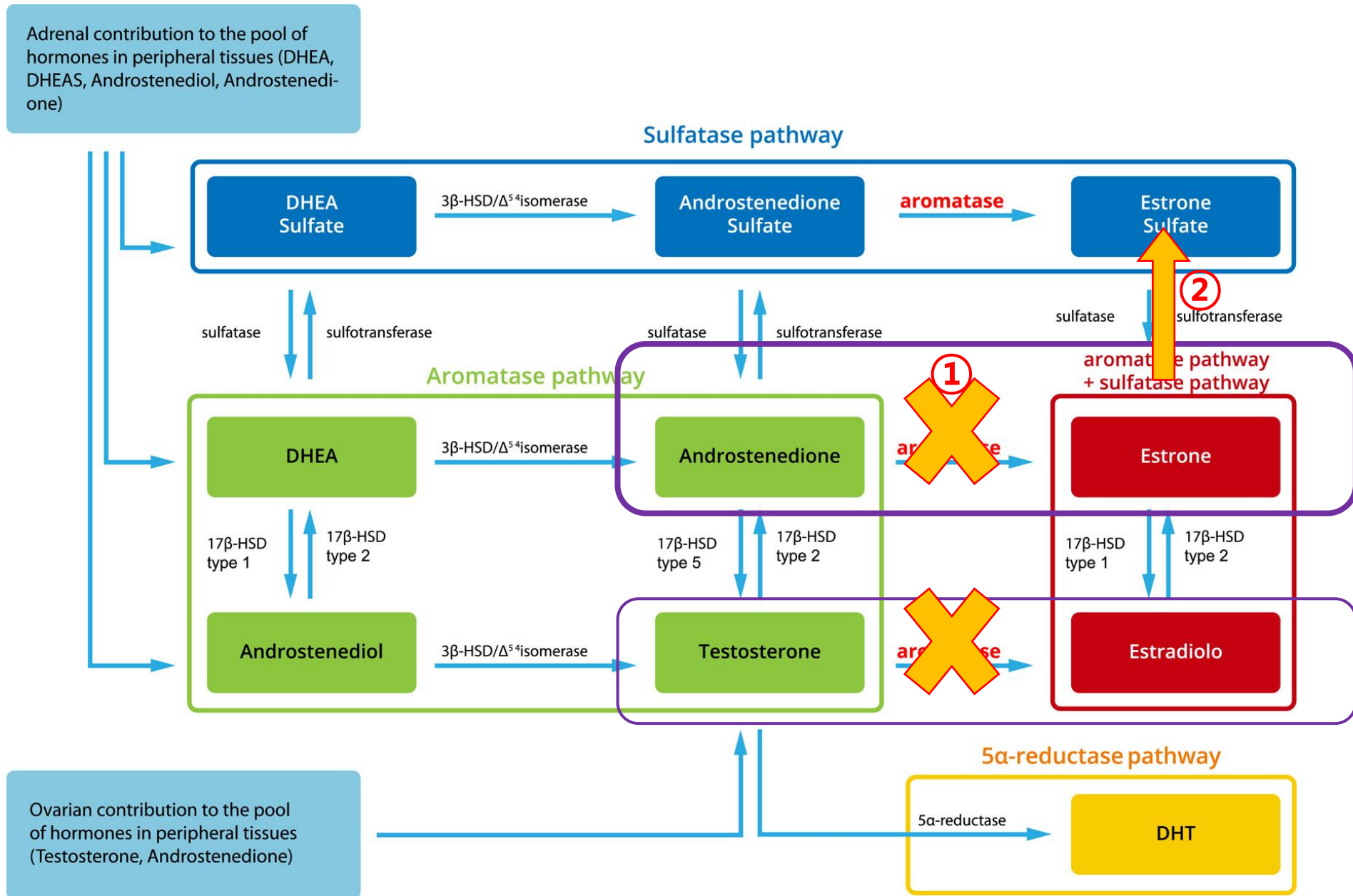


- Sarcopenic obesity
- Central obesity (BIA, DEXA, abd.CT)

- Serum total estrogen, estradiol
- Subclinical inflammatory marker



FM solution



FM solution

① Downregulation of aromatase

- 염증이 발생한 원인 해결 Fat / skin / GI etc
- 꾸준한 운동
- Avoid

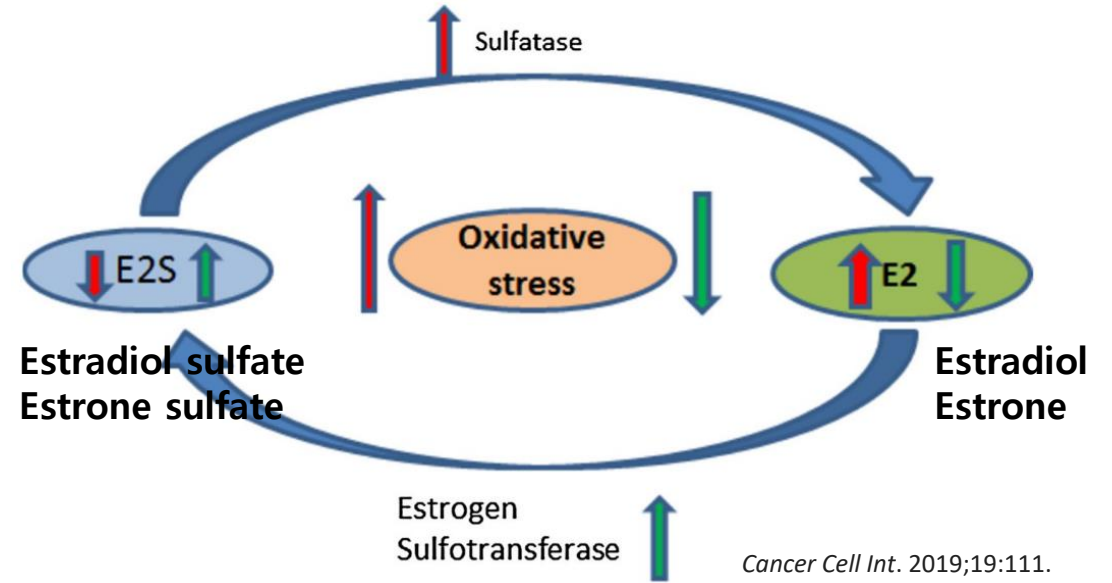
정제된 탄수화물, 설탕 / 가공 식품, 가공육 / 인슐린을 높이는 식사 / 그릴, 튀김, 바비큐 (heterocyclic amines, and advanced glycation end products) / 밀가루(글루텐), 카제인

▪ Recommend

식물성 단백질 / 복합 탄수화물: 전곡, 채소, 정제되지 않은 탄수화물, 과일 / 필수 지방산 $\omega 3:\omega 6 \leq 1:3$ 비율로 섭취

Phytochemicals / 에너지 소비량에 맞는 칼로리 섭취

또는 칼로리 제한 / 꼭꼭 잘 씹어 먹기



② Upregulation of estrogen sulfotransferase

Progesterone (progestin)



규칙적인, 충분한, 질 좋은 수면!!
Melatonin, Tryptophan
 이완 / 긴장근육 풀어주기

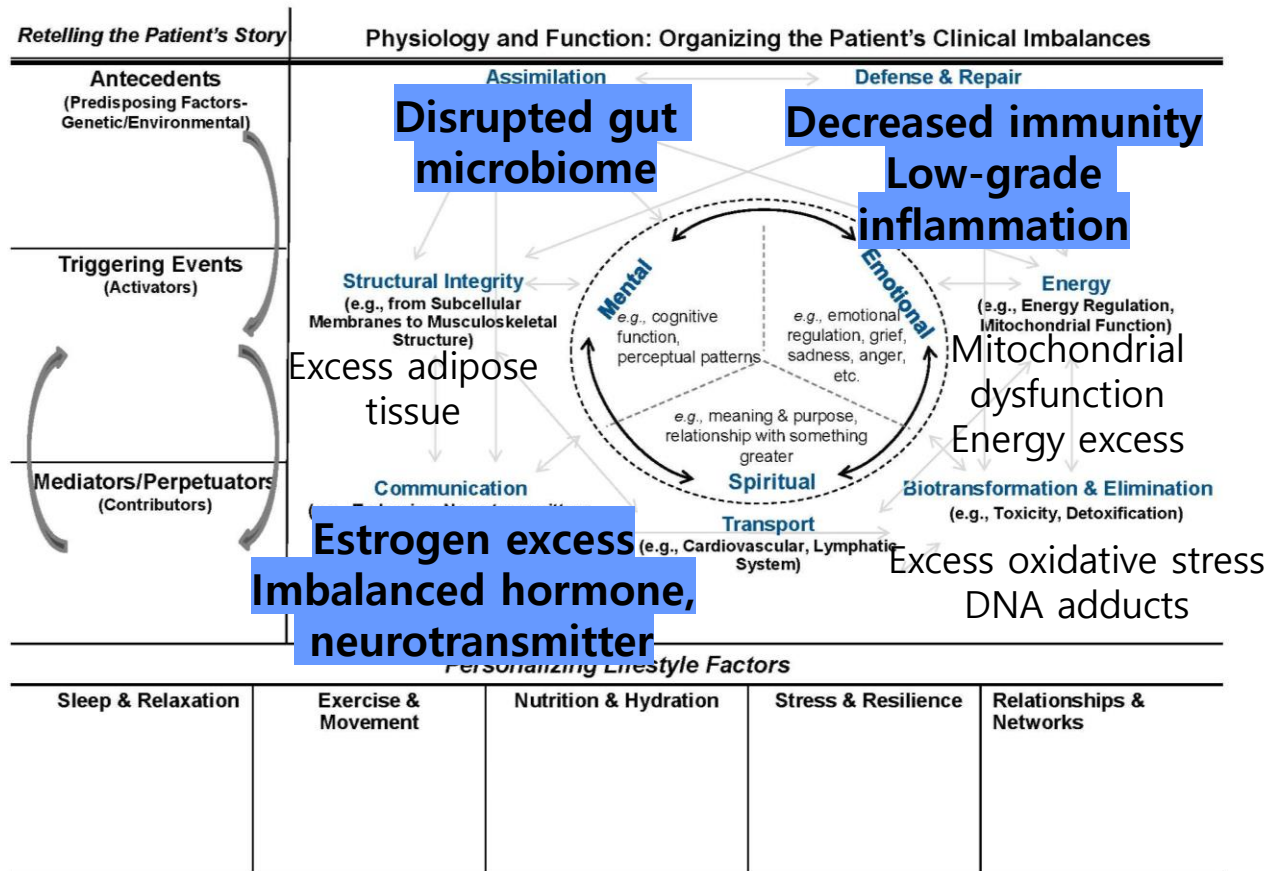


마늘: 알리신
 (DADS, diallyl sulphide)

Cancer survivor with obesity

7-core imbalance in functional medicine

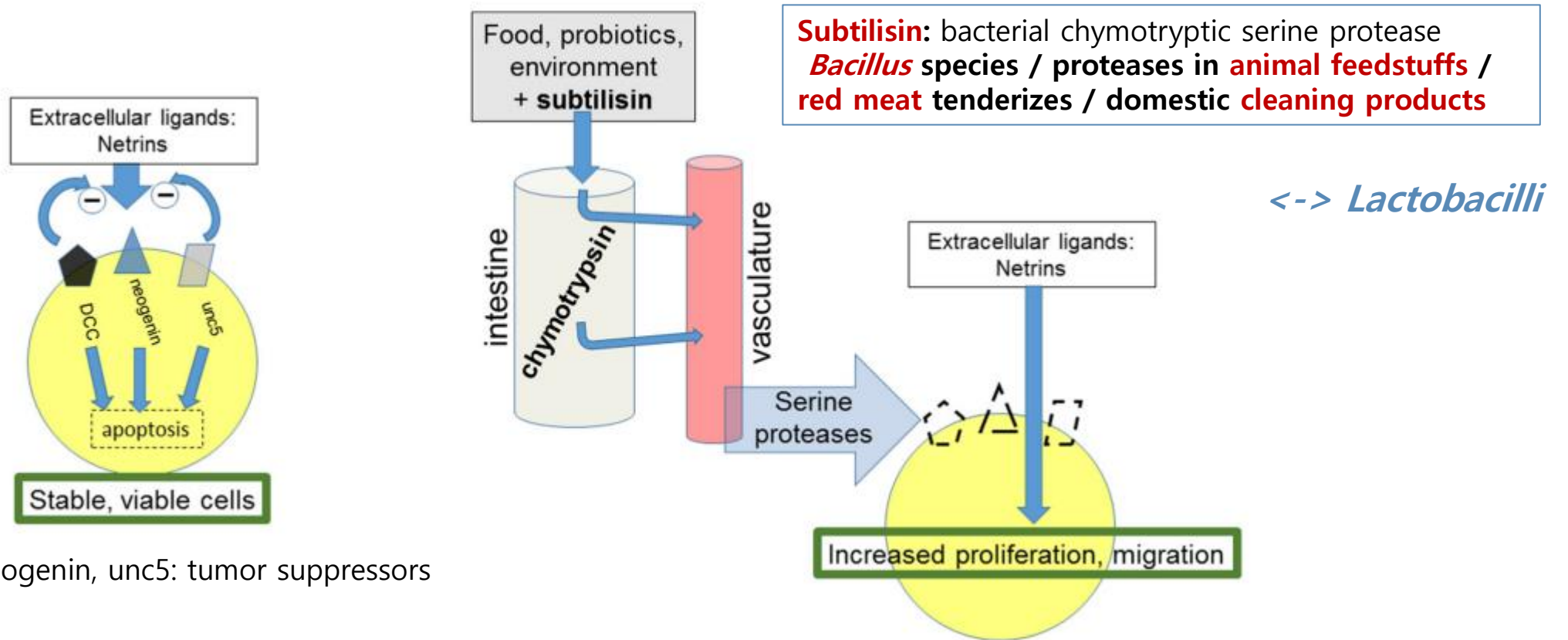
PART ②



- **Assimilation imbalance** (impaired gut integrity, GI dysbiosis)
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Increased serine protease

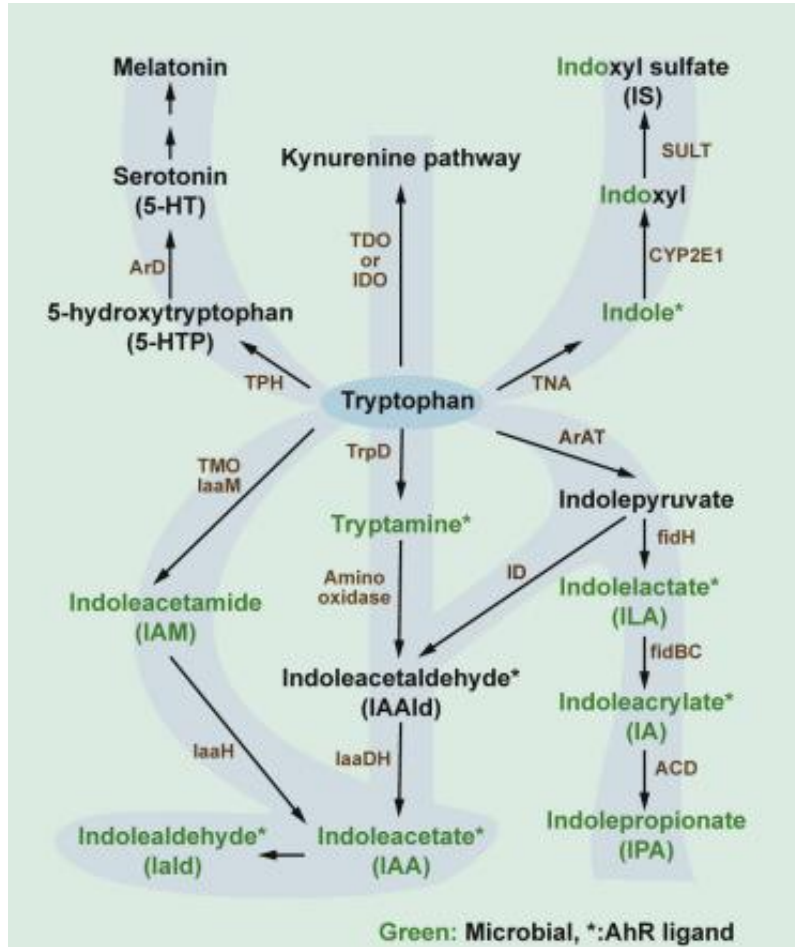
Over-eating & meat-based diet -> high level of fecal chymotrypsin/subtilisin (분해내성, 순환계 흡수)
-> high serum chymotrypsin & low anti-chymotrypsin -> **increased serum "serine protease" activity**



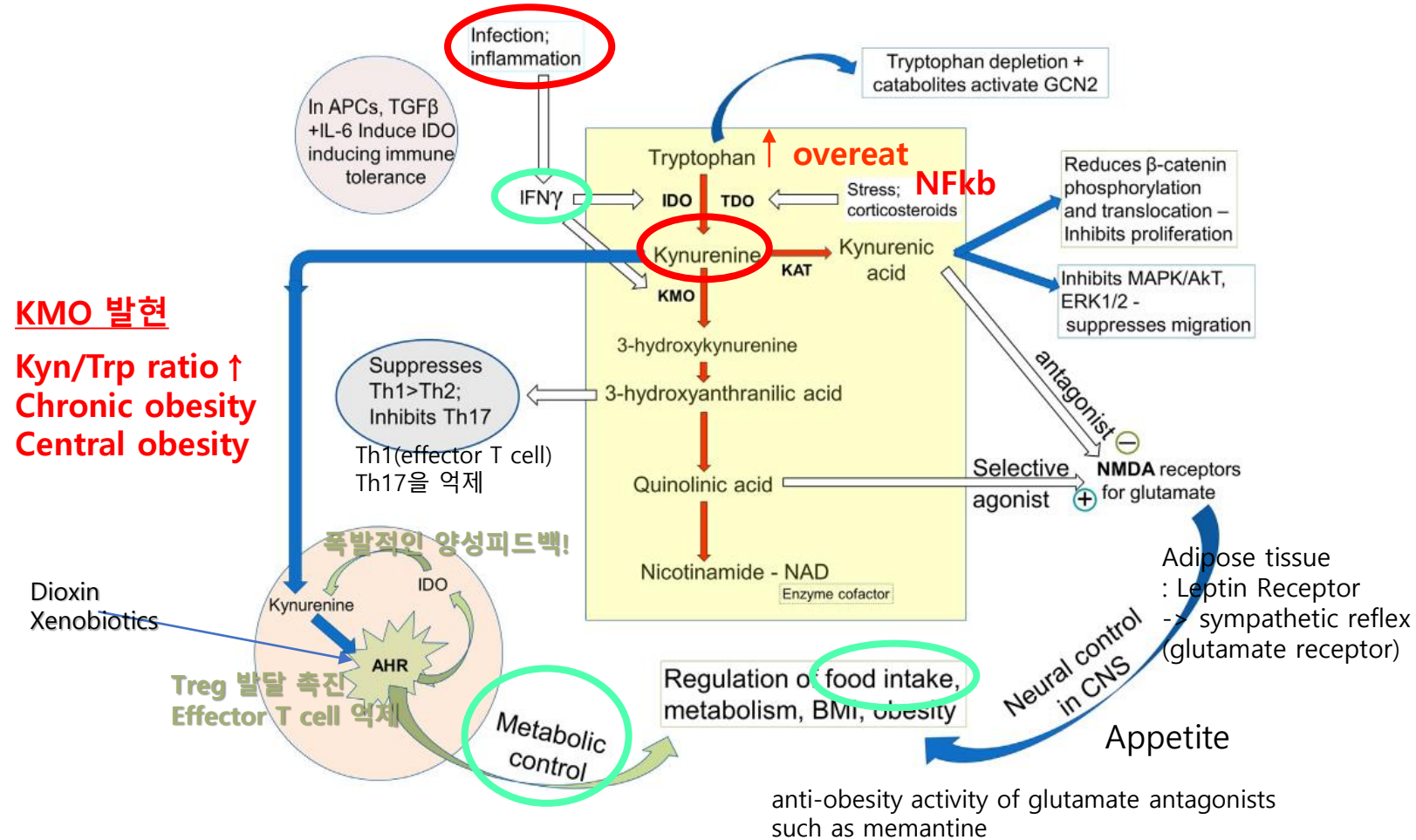
DCC, neogenin, unc5: tumor suppressors

Serine protease: the pancreatic digestive enzymes (trypsin and **chymotrypsin**), liver (pro-protein convertases), leucocytes (neutrophil elastase), prostate glands (prostate specific antigen).

Tryptophan metabolites

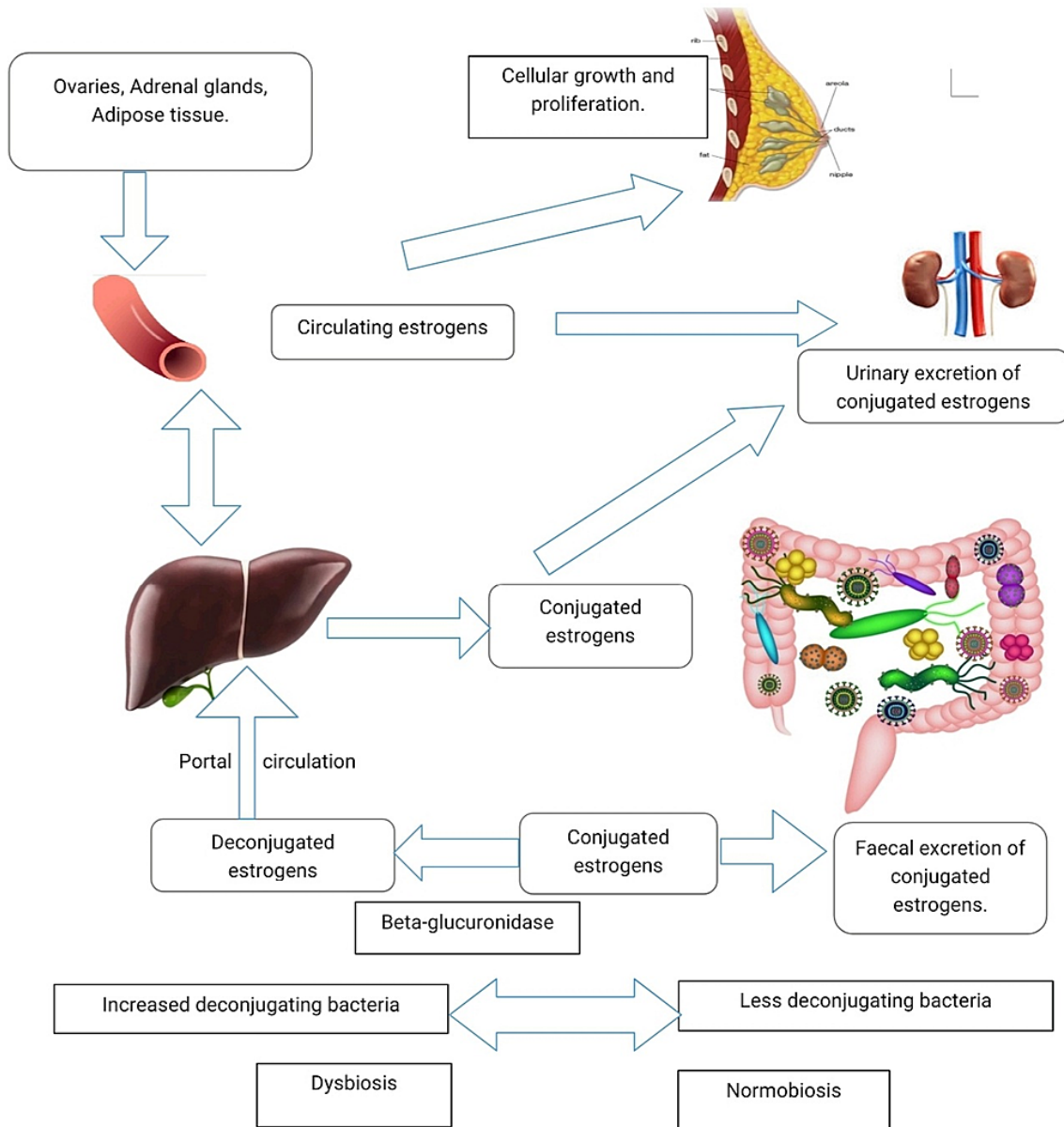


- Tryptophanase 가진 균종: AhR agonists (indole/ indole derivatives) 생성
- Adequate aryl hydrocarbon receptor(AhR): Gut barrier 유지



- **Dysbiosis = Tryptophanase 가진 균종 감소**
 -> **AhR deactivation: GLP1 & IL 22 감소, intestinal permeability 증가**
- **Overeat / inflammation = Trypt-kyn pathway 증가 = kynurenine 증가**
 -> **AhR upregulation : cancer**

Estrobolome



1) Reabsorption (deconjugation by beta-glucuronidase)

Fat & protein diet (Western diet) -> beta-glucuronidase activity ↑

2) Estrogen-like compounds or estrogen mimics from diet

Short-term antibiotics use : beta-glucuronidase activity ↓

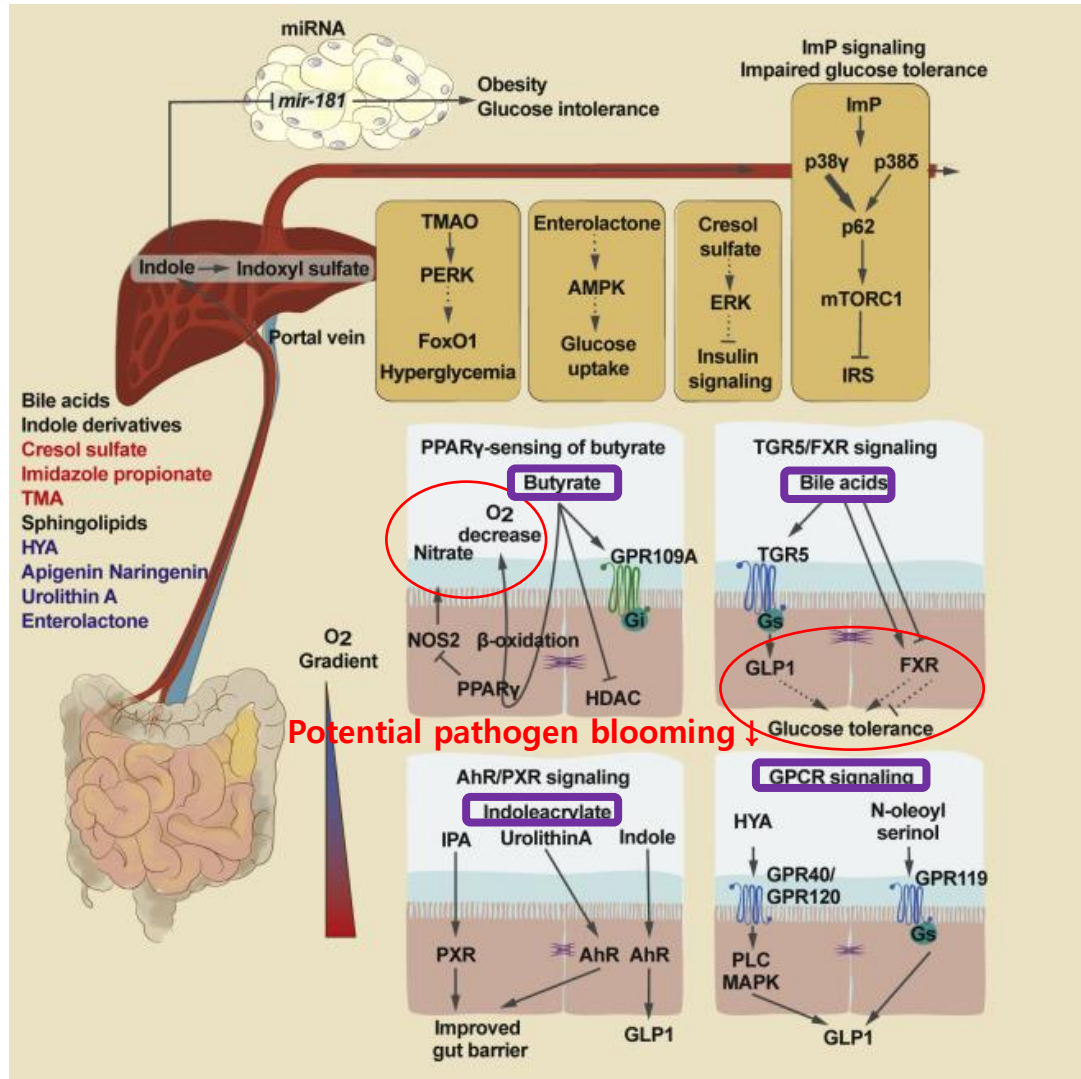
Long-term **antibiotics use** : increased breast cancer risk

Chronic alcohol consumption -> SIBO -> plasma E1 ↑ E2 ↓

😊 **Vegetarians**: conjugated estrogen ↑ (x3) in feces, plasma estrogen (15-20%) ↓ , fecal bacterial beta-glucuronidase activity ↓

😊 **Lactobacillus acidophilus intake** -> fecal bacterial beta-glucuronidase activity ↓

The links between gut microbiota and obesity and cancer



Dietary structure affects the composition of the gut microbiota.

Type of diet	Upregulated	Downregulated
Calorie-restricted	—	Firmicutes to Bacteroidetes ratio
Vegetarian Diet	Bacteroides ↑	Acteroides spp. Bifidobacterium spp. Escherichia coli Enterobacteriaceae spp. Firmicutes ↓
High-Fat Diet	Firmicutes to Bacteroidetes ratio ↑	Clostridia Clostridium leptum Enterobacter spp.

Gut dysbiosis

- Loss of **beneficial** bacteria & Overgrowth of potentially **pathogenic** bacteria
- Decreased overall bacterial **diversity**
- **Small bowel** bacterial overgrowth

FM marker

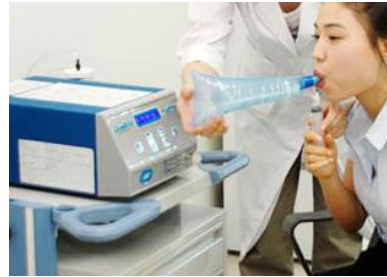
Gut permeability

(hydrogen-methane) Breath test

Fecal calprotectin

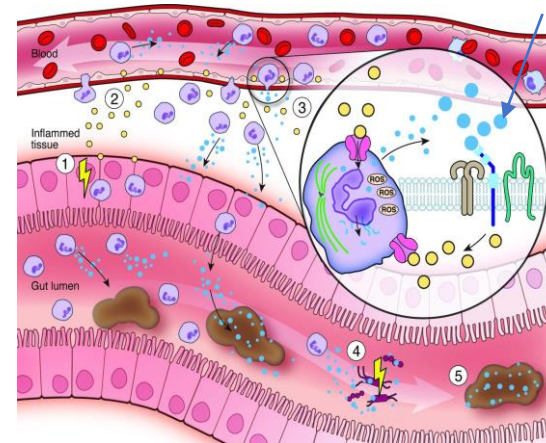
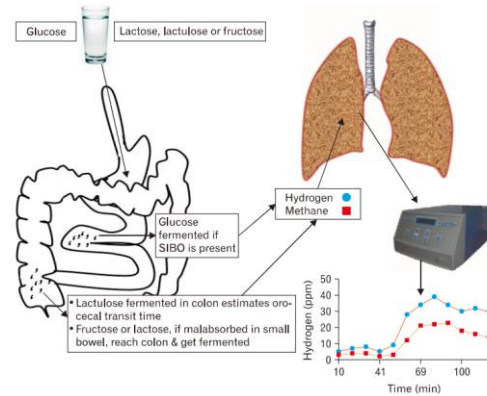
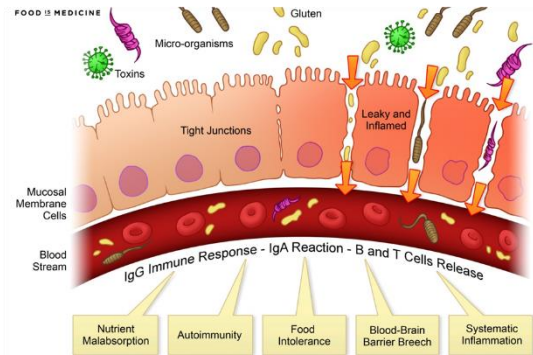
Blood biomarker

※ 8시간 금식후 검사 진행



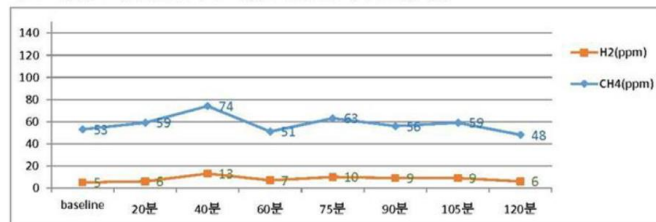
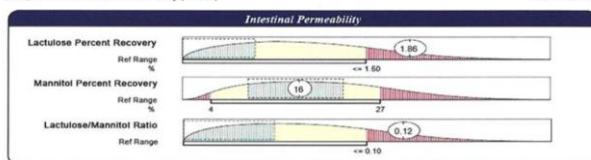
Calprotectin

Total bilirubin
 γ-glutamyl transferase
 Alanine aminotransferase
 Fibrinogen
 Ferritin
 Estradiol



검사종목: Intestinal Permeability(Urine)

Enzymatic assay



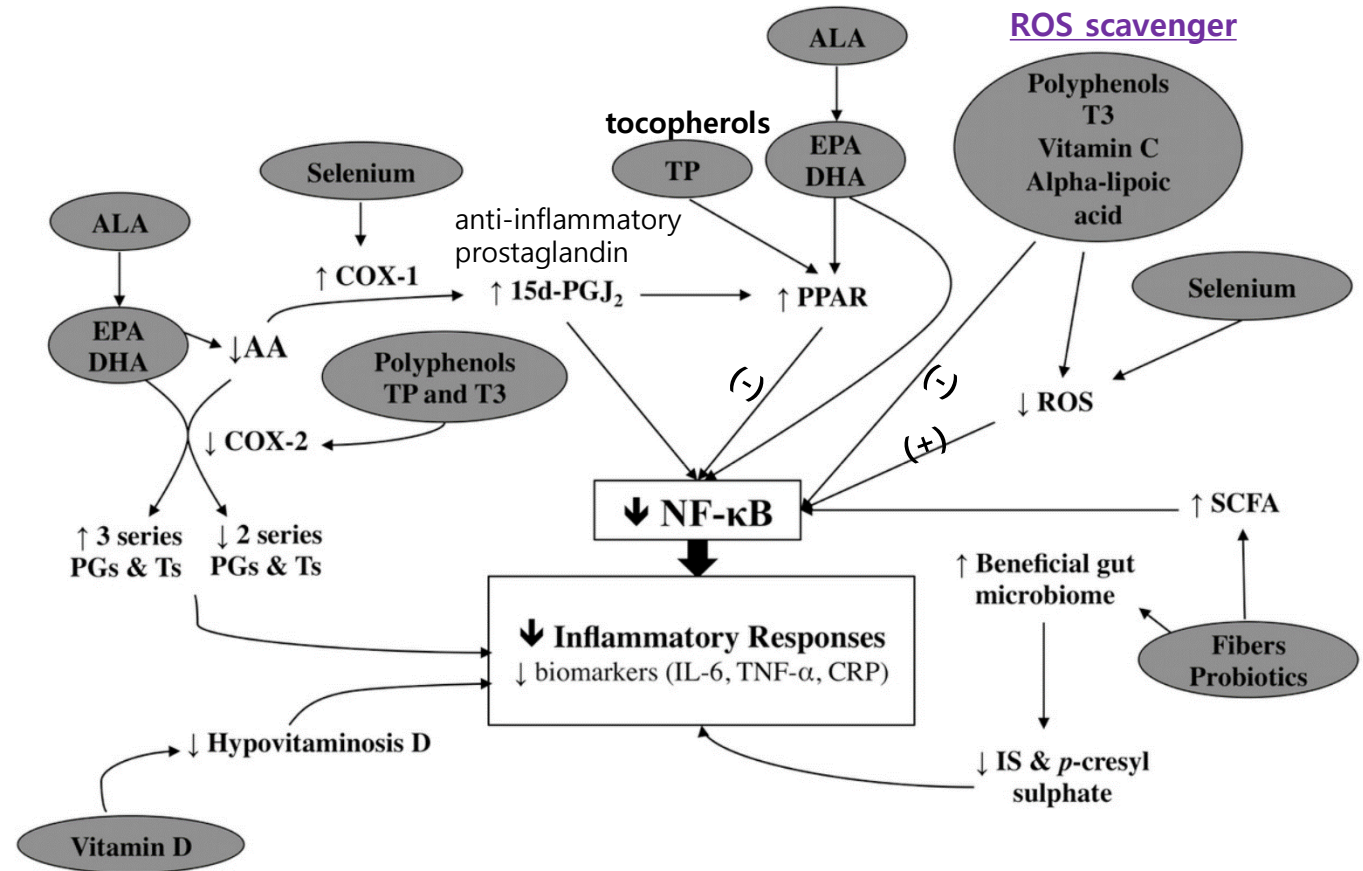
검사명	결과	정상구분	단위
Calprotectin	159,0	H	mg/kg

FM solution

5R

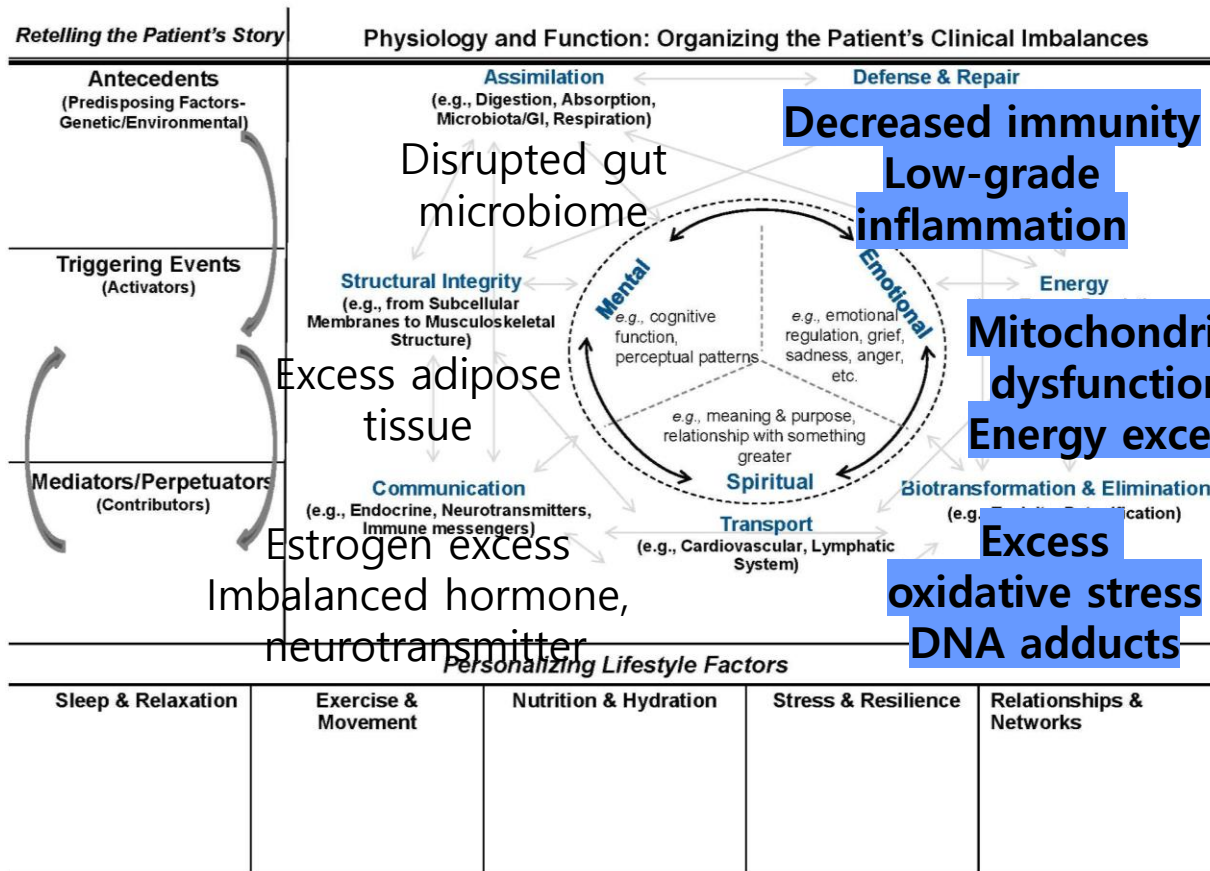
- Remove: rifaximin 1200mg/d
- Replace: Pancreatic enzymes, betaine HCL
- Reinoculate: prebiotics, probiotics, or synbiotics
- Repair: nutrients for GI repair (glutamine, arginine, vitamin D, zinc), GALT function (lactoferrin, whey immunoglobulins), antibiotics, healing (pantothenic acid, vitamin E, carotenoids)
- Rebalance: lifestyle changes (alcohol, sleep, exercise, stress)

Anti-inflammatory nutrition



Cancer survivor with obesity

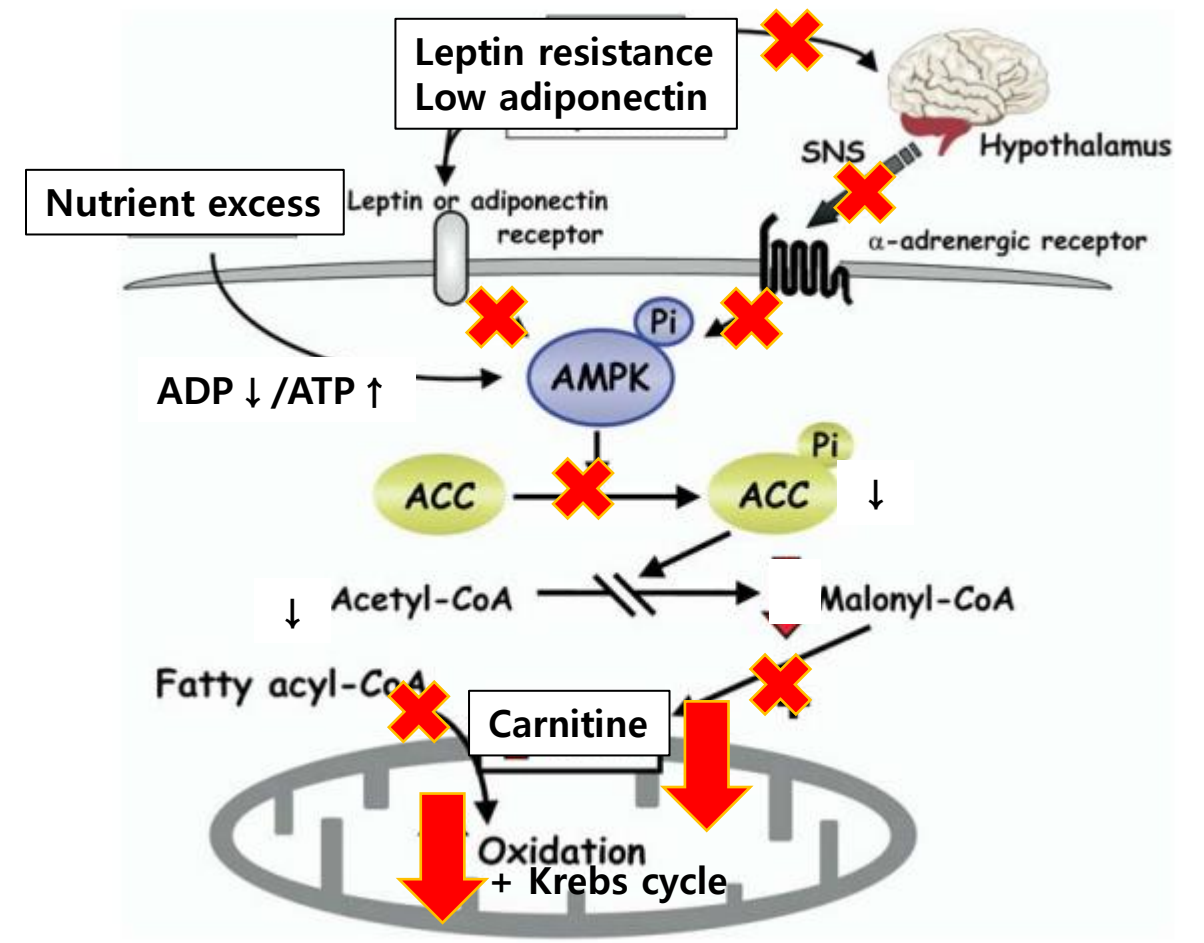
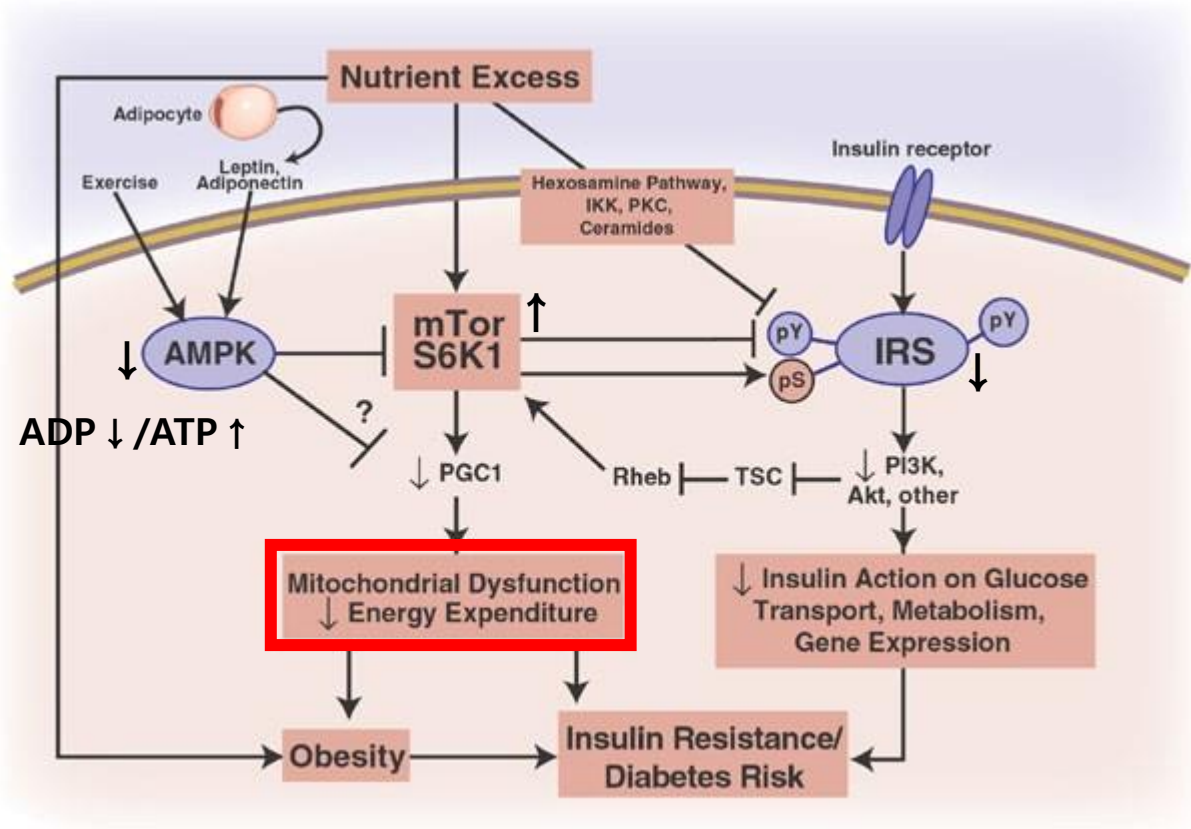
7-core imbalance in functional medicine



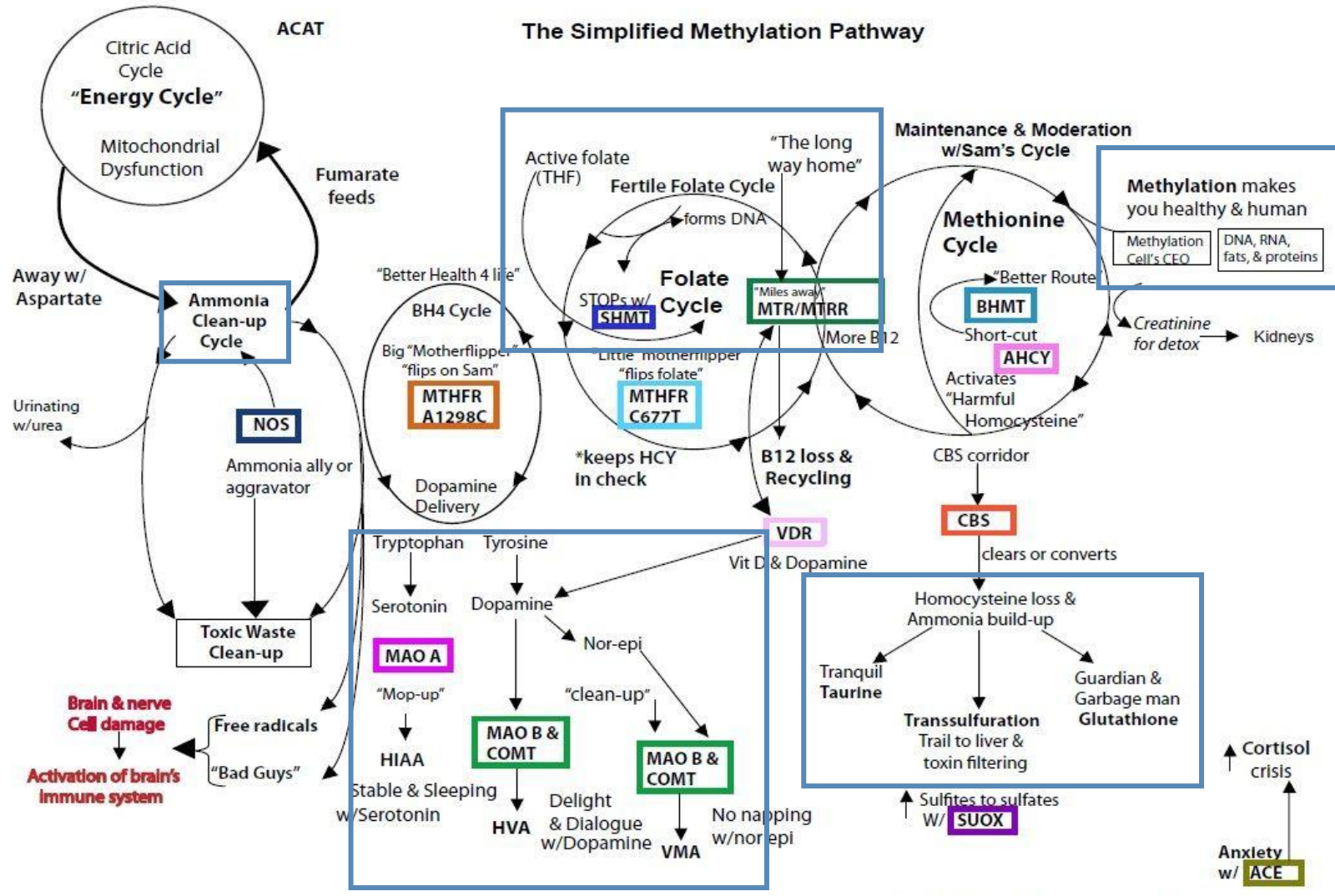
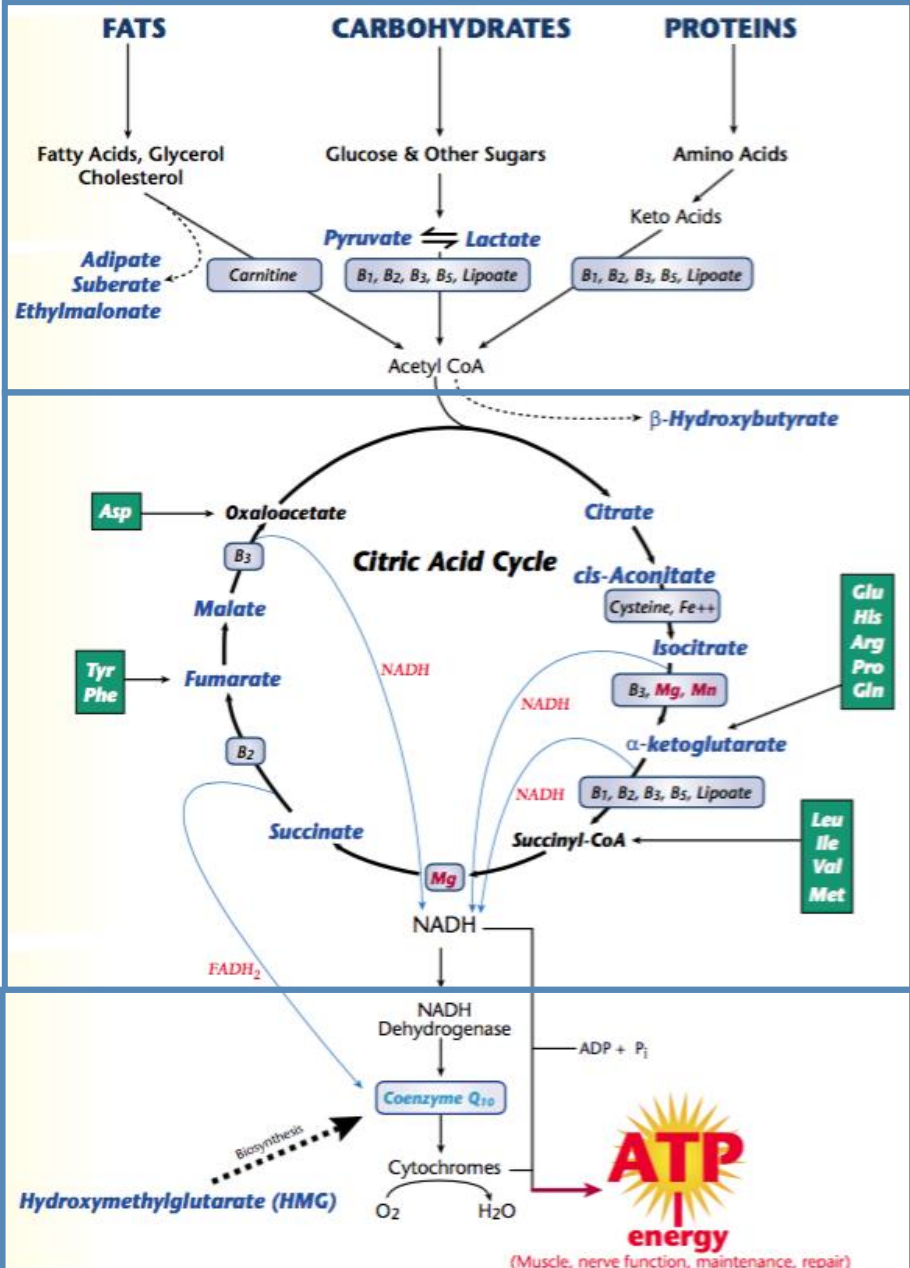
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Nutrient excess and low physical activity

AMPK, Metabolic Master Switch



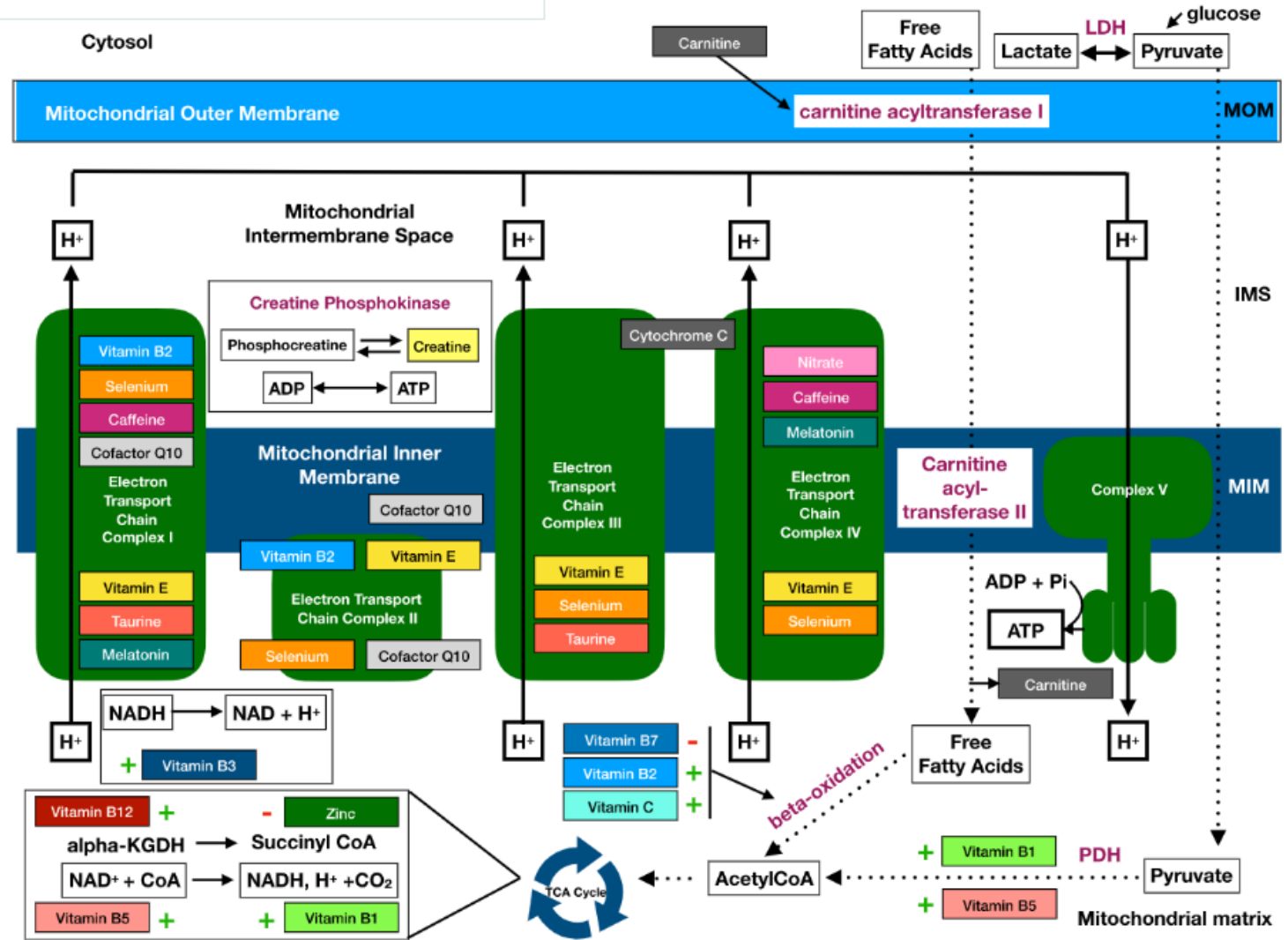
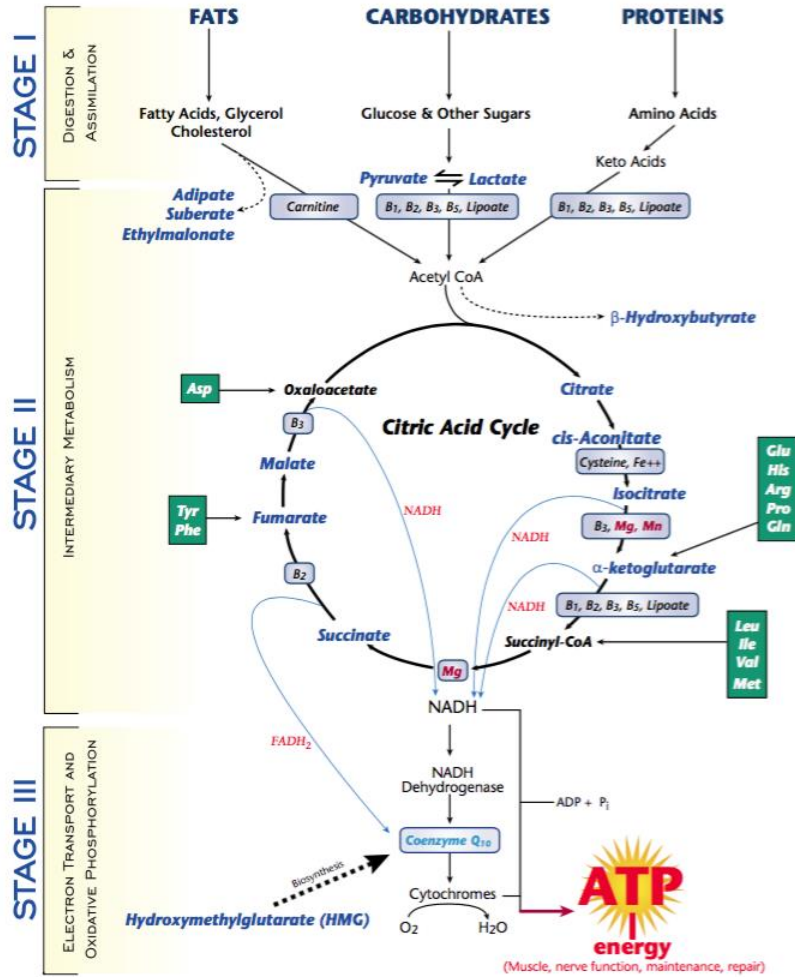
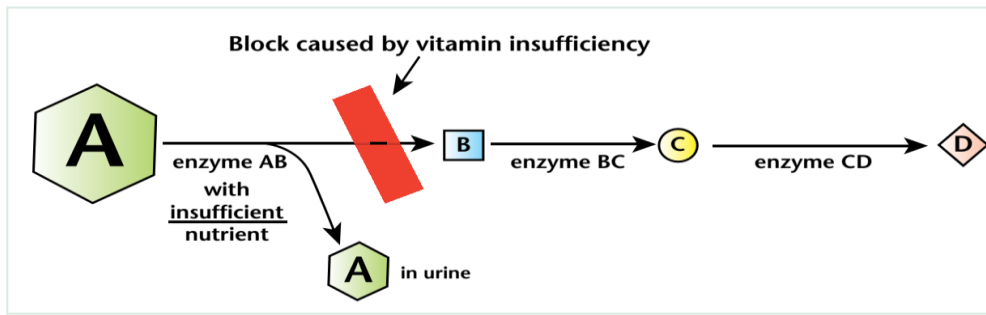
Cell energy metabolism and methylation pathway



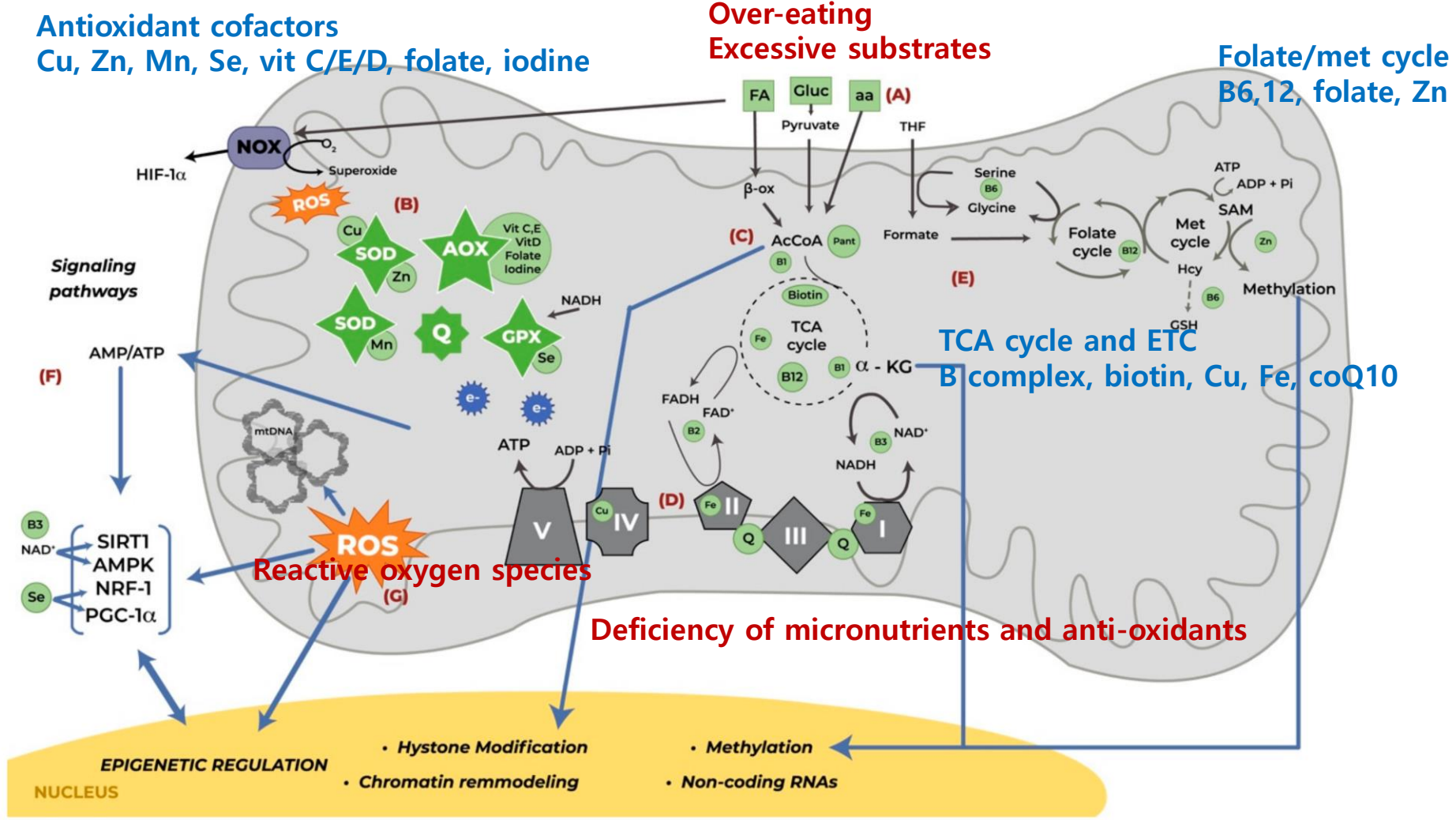
Adapted from the Neurological Research Institute's Diagram and simplified by April Ward-Hauge MS, NP

The Yasko Hypothesis of neurological & autoimmune disorders

Micronutrition

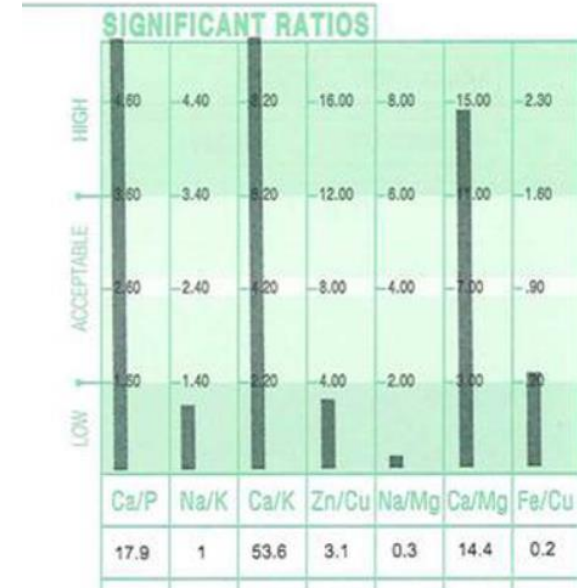
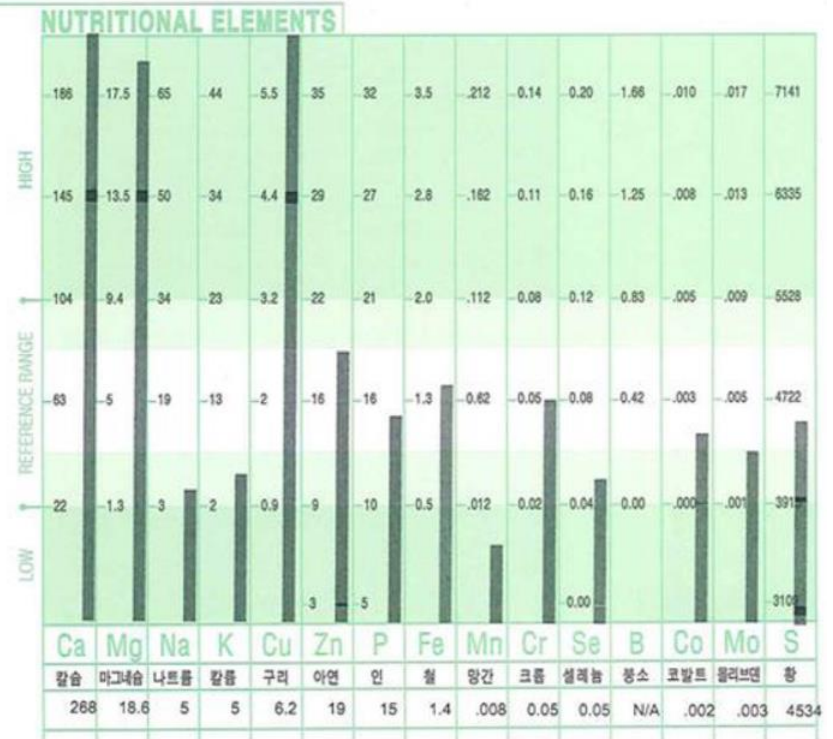
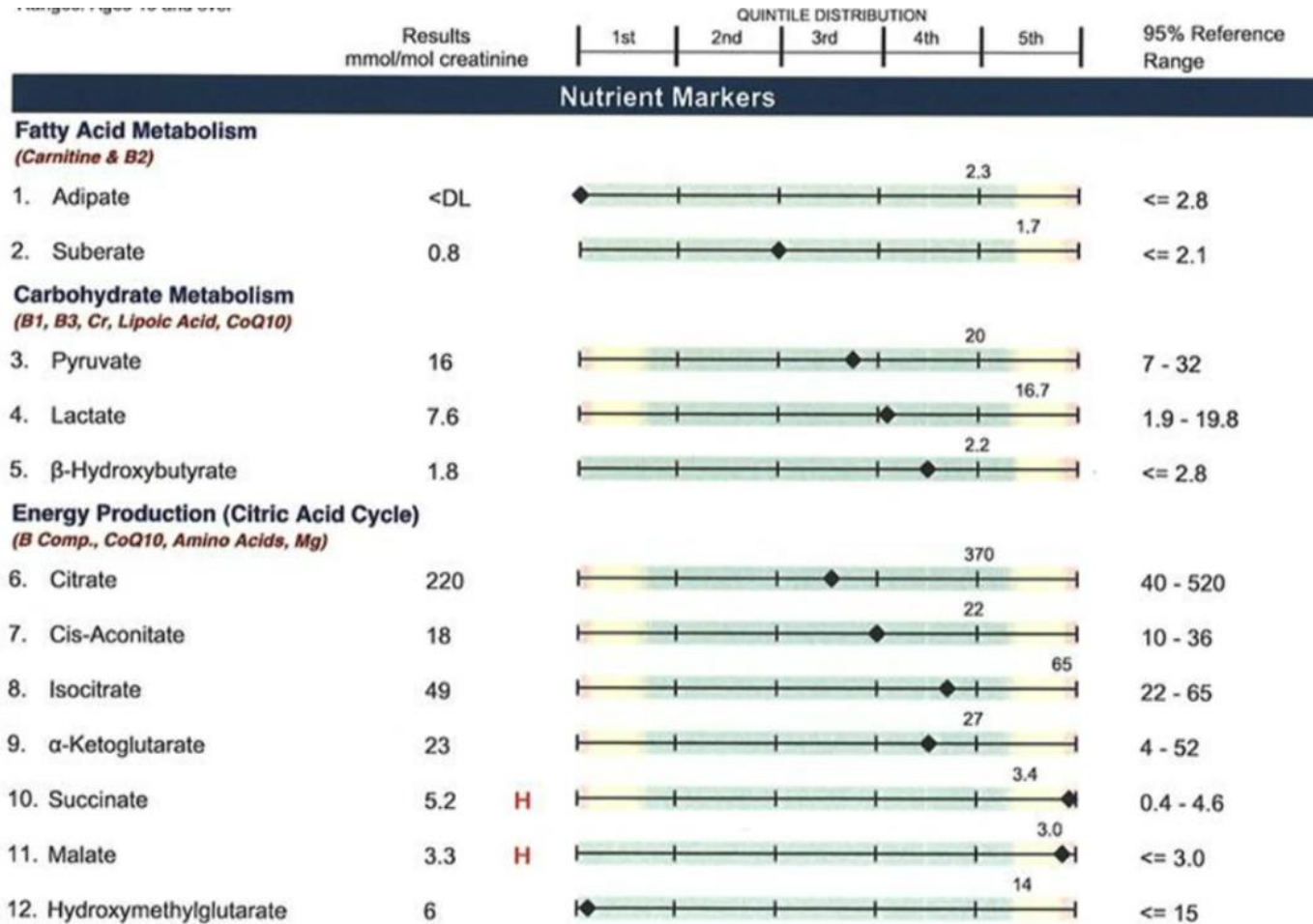


Mitochondria and oxidative stress

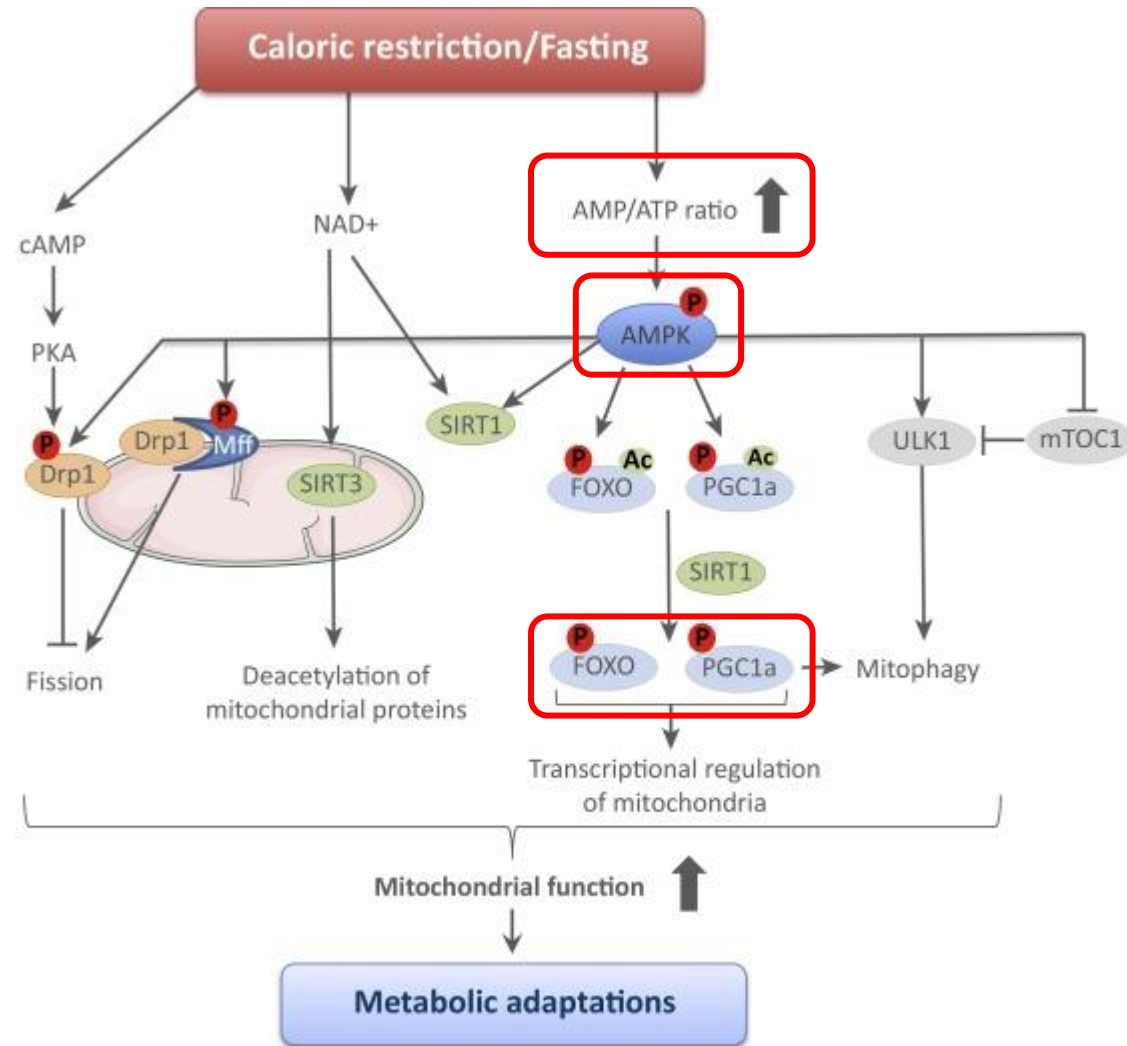


FM marker

소변 유기산 검사: 대사, 신경전달물질, 해독, 산화스트레스
 모발미네랄 검사: 주요 미네랄 과잉/부족, 불균형



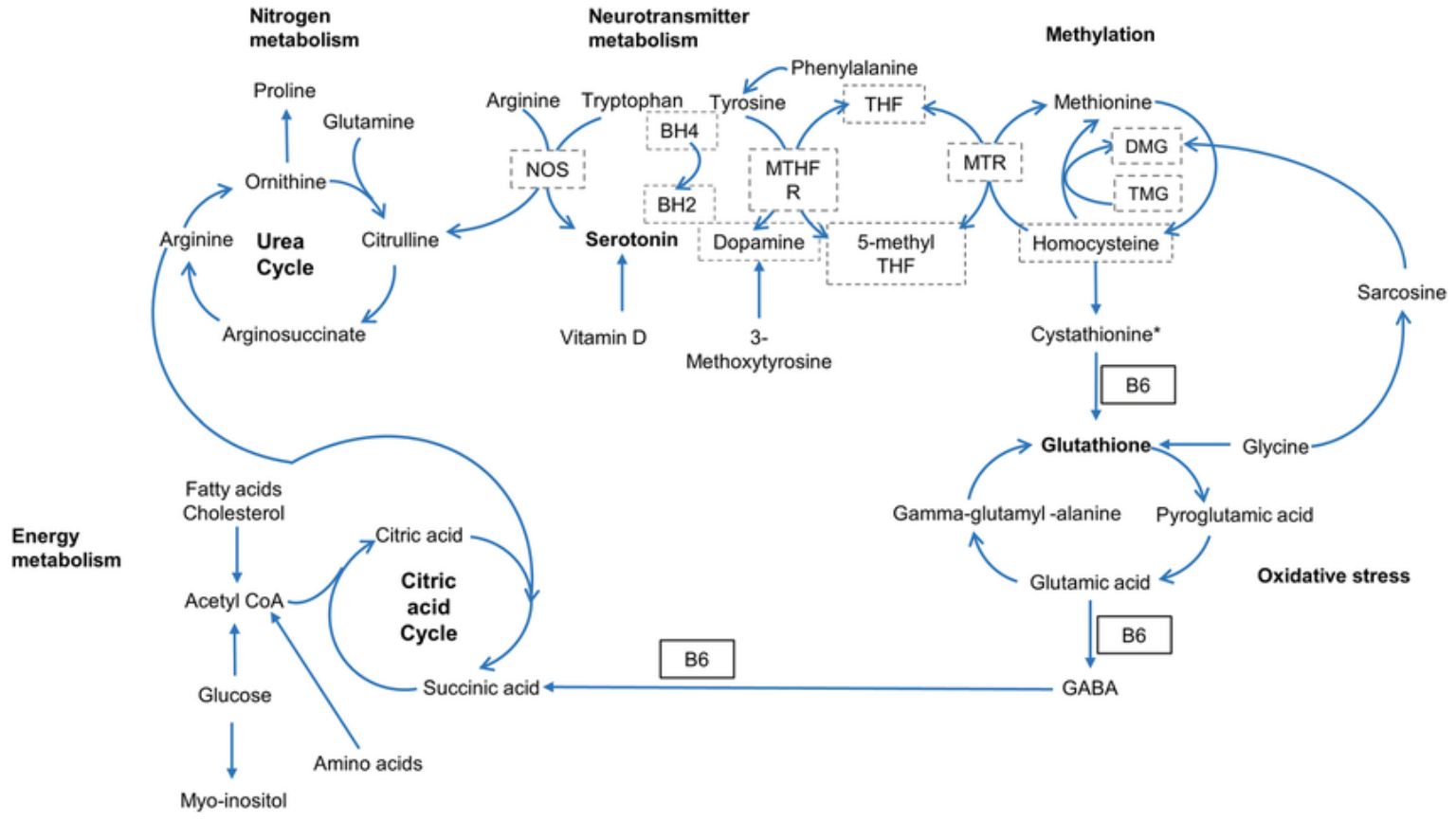
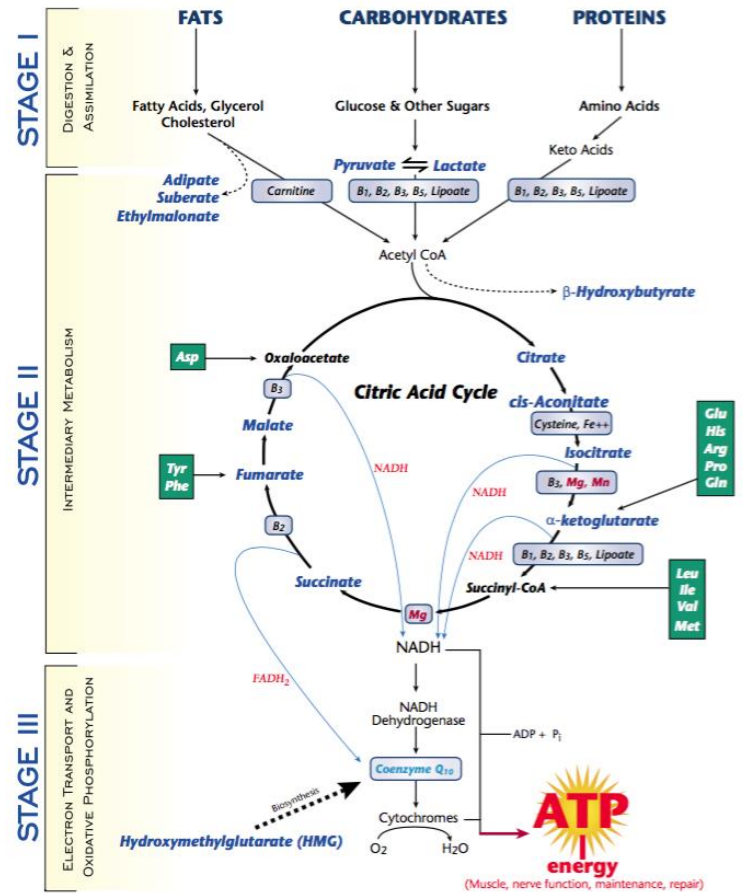
FM solution



FM solution

The Myers' Cocktail

Components: Mg, high dose vitamin B complex, vitamin C

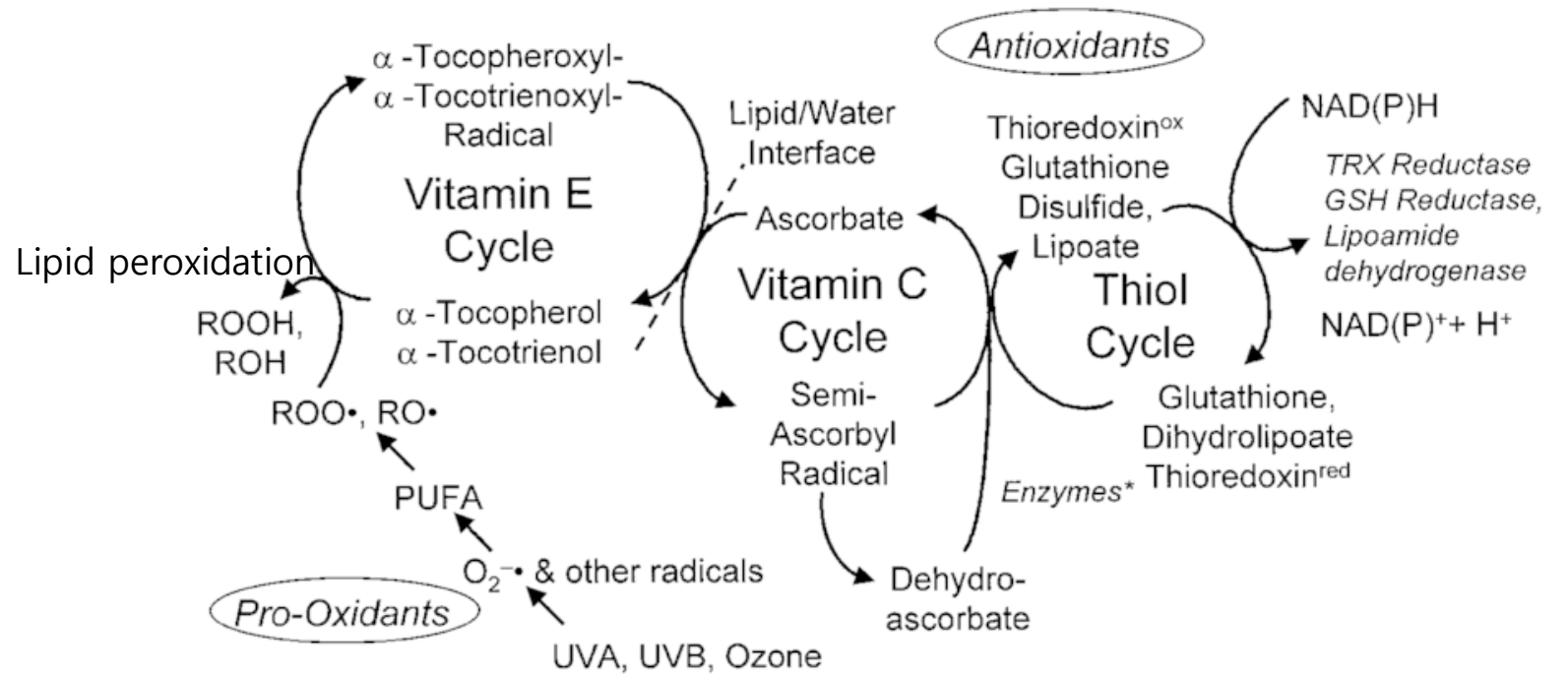


FM solution

Antioxidants

Enzymatic antioxidants

SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase



* 1) Thiol transferase (glutaredoxin)
3) Protein disulfide isomerase

2) Glutathione (GSH)-dependent dehydroascorbate reductase
4) Thioredoxin (TRX) reductase

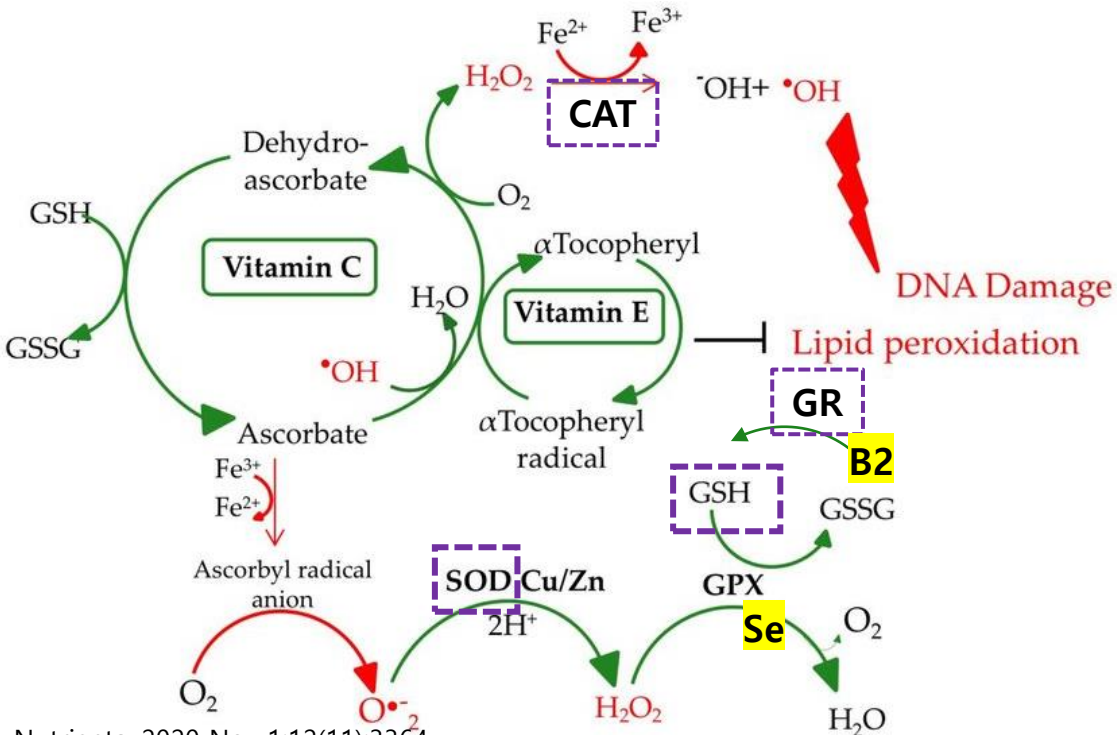
J Nutr. 2001;131(2):369S-73S.

Non-enzymatic antioxidants

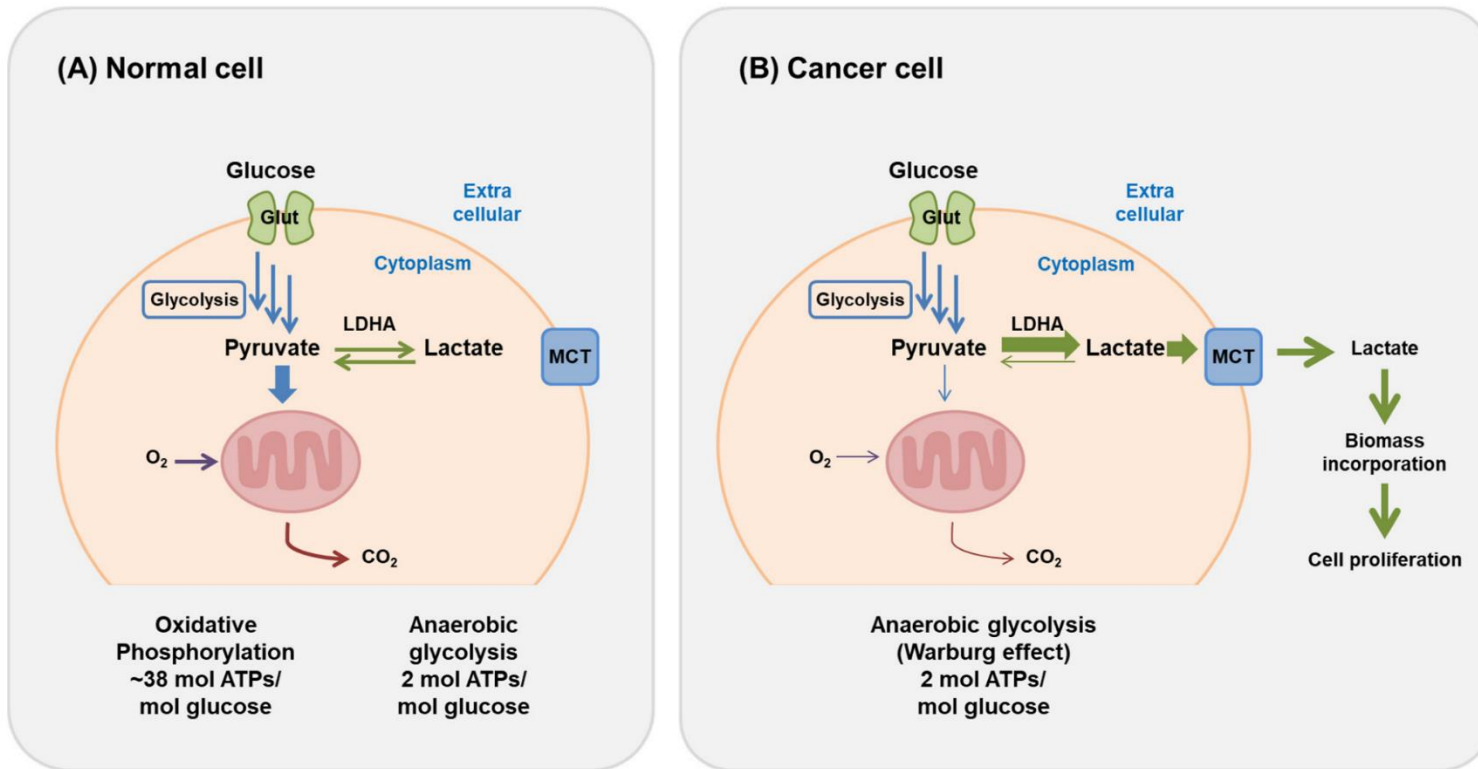
Endogenous: GSH, glutathione, uric acid, lipoic acid, NADPH, coenzyme Q, albumin, bilirubin

Dietary:

vitamin C, E
Zn, Se
Carotenoids: beta-carotene, zeaxanthin
Flavonoids
Anthocyanidins
Phenolic acids



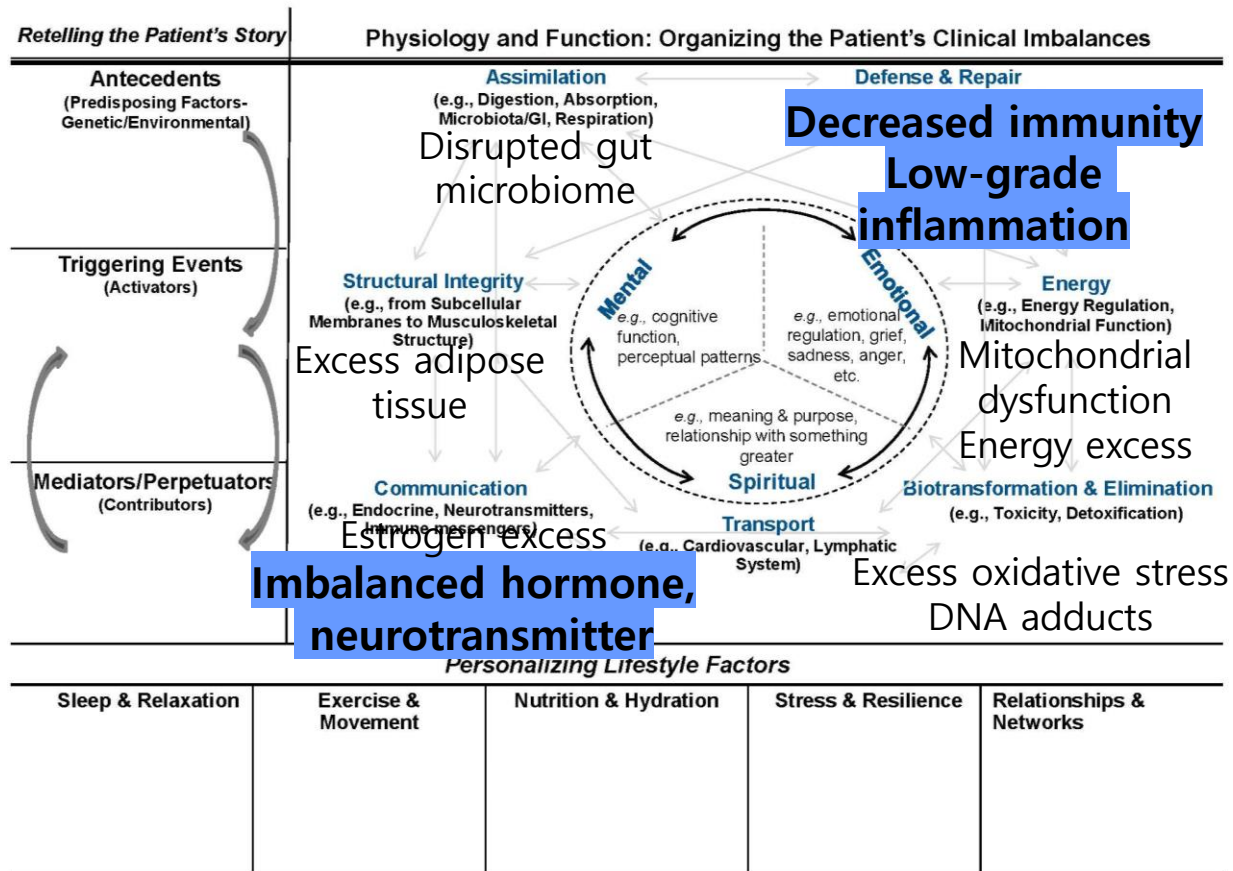
암의 대사방식: 암 대사 재설정



- Mitochondrial dysfunction: 유전, 대사, 면역 이상의 중심
- **Warburg effect** : “aerobic” glycolysis
 - 초기 암
- **역 Warburg effect**
 - 진화된 암 (공격적인 암): 전이, 확산, 신생혈관생성, 항암제 내성
- Nucleotide level ↑
salvage > de novo pathway
- Serine / FA / Glutamine pathway

Cancer survivor with obesity

7-core imbalance in functional medicine



- **Assimilation imbalance** (impaired gut integrity, GI dysbiosis)
- **Defense & repair imbalance** (immune, chronic inflammation)
- **Energy imbalance** (energy regulation, mitochondrial function)
- **Biotransformation & elimination imbalance** (fatigue, toxicity, detoxification reserve)
- **Transport imbalance** (cardiovascular, lymphatic dysfunction)
- **Communication imbalances** (endocrine, neurotransmitter, immune dysfunction)
- **Structural integrity imbalance** (low muscle, high fat, visceral fat)

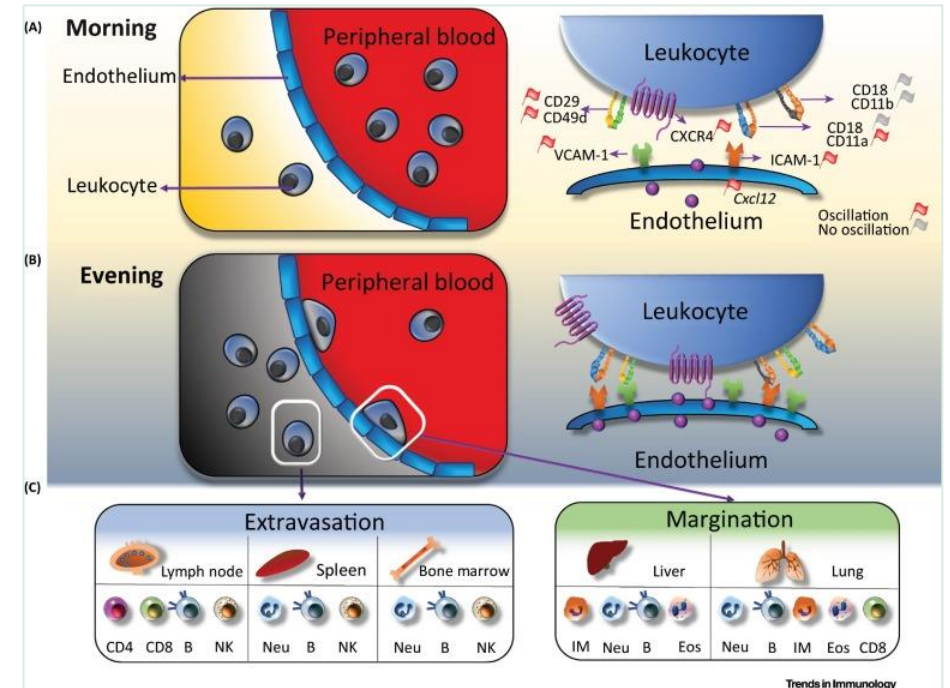
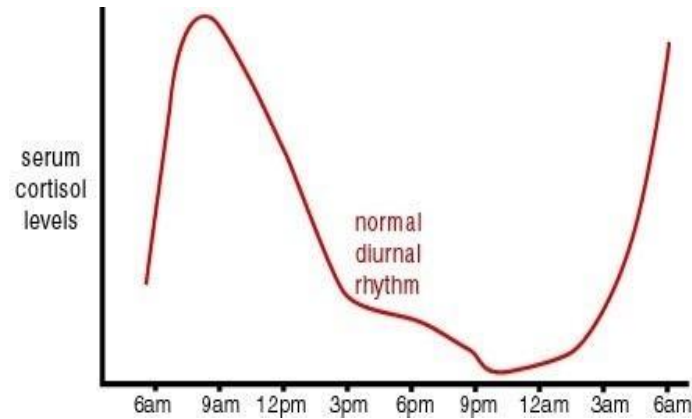
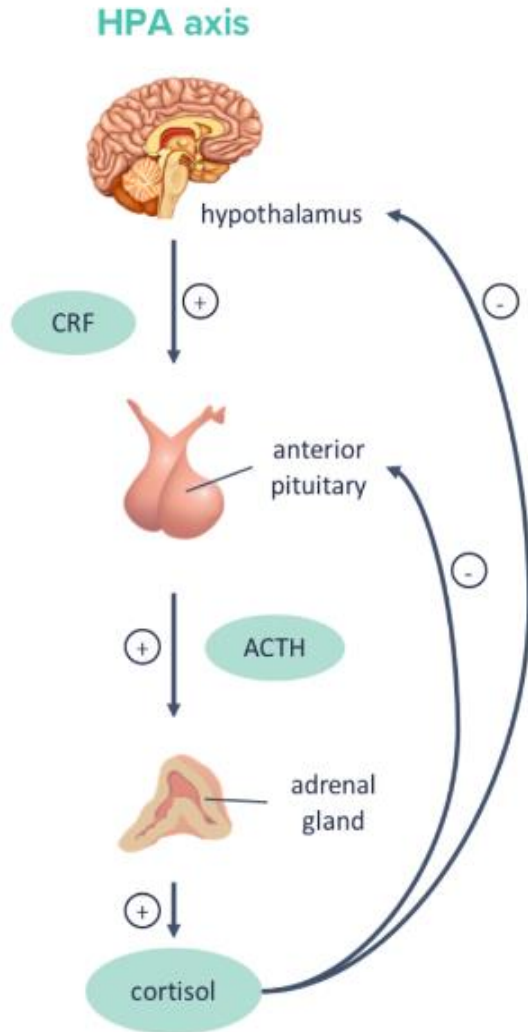
Symptoms and long-term effects experienced by cancer survivors

▪ **Fatigue**

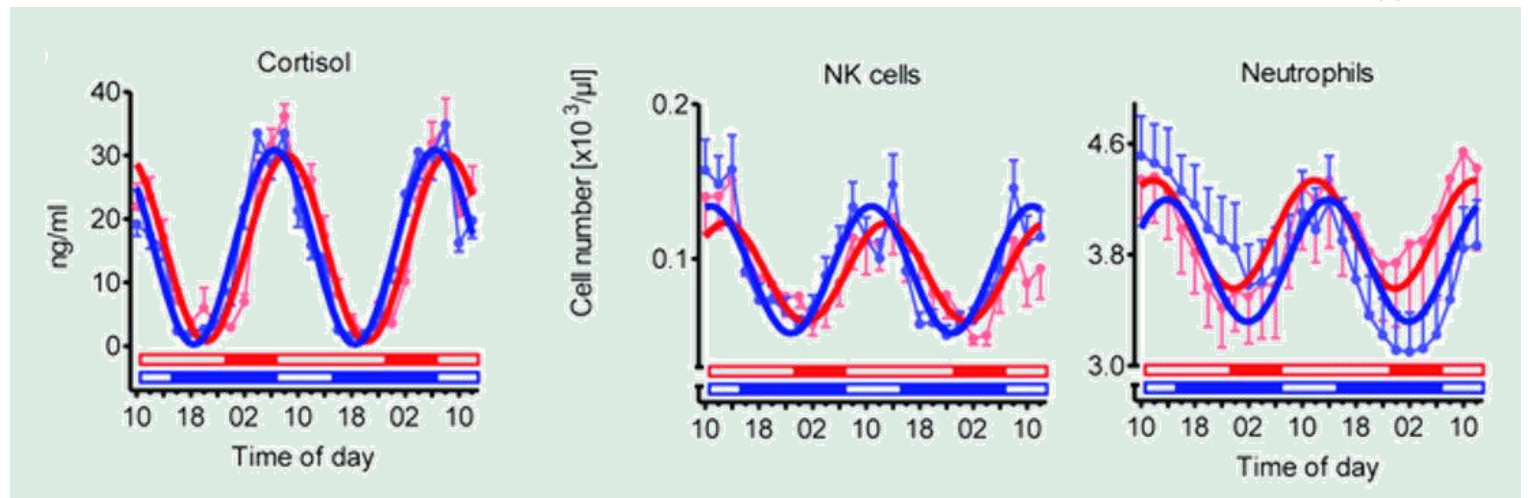
- Depressive symptoms
- Sleep disturbances
- Pain
- Cognitive limitation

- Anemia
- Cytokine dysregulation; inflammation
- HPA axis dysregulation
- 5-HT/NTs dysregulation (low serotonin / high quinolinic acid -> NMDA Rc) (low dopamine)
- Alterations in ATP and muscle metabolisms
- Mitochondrial dysfunction

Cortisol and immune cell



Trends Immunol. 2019 Jun;40(6):524-537.



Front Immunol. 2019;10:393.

Cortisol and immune aspect

Cortisol function; the **number** and **function** of immune cells

Cortisol rhythm dysfunction

- Disturbance of immune function; suppression of **natural killer cell function**
- Disrupt the suppressive effects of cortisol on proinflammatory **cytokine** production; elevation in circulating cytokines
- Chronic inflammatory processes and associated behavioral symptoms might drive changes in cortisol rhythm

Cortisol rhythm dysfunction and NK cell number/activity in metastatic breast cancer

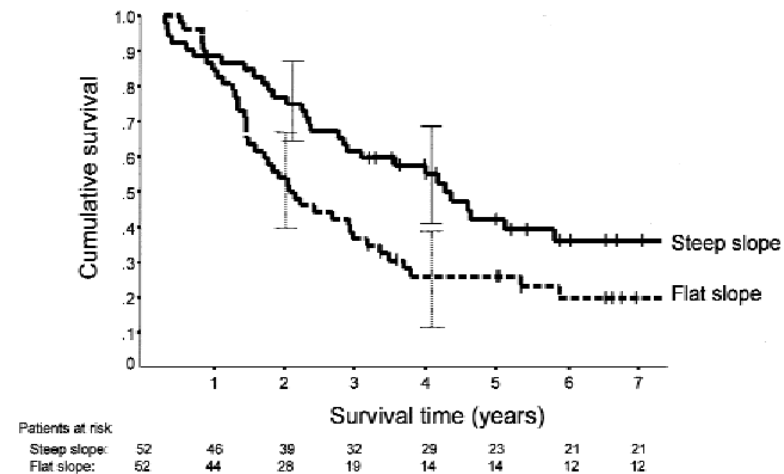
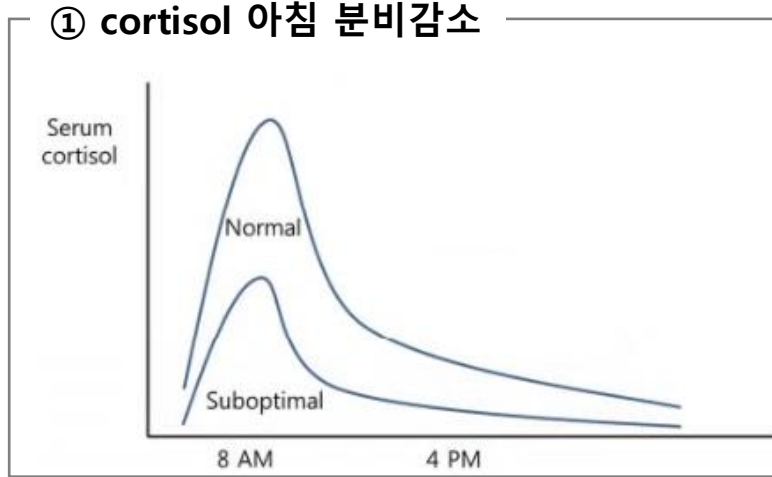


Table 2. Mean (standard deviation) numbers and functional activity* of natural killer (NK) cells in groups of patients with metastatic breast cancer dichotomized at the median diurnal cortisol slope

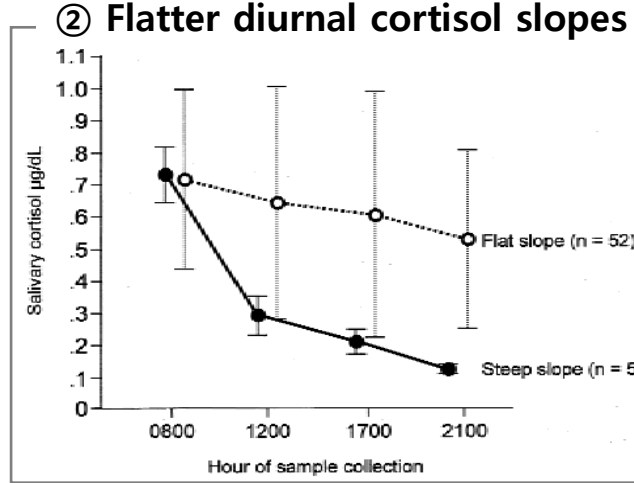
Cortisol slope log, μg/dL per h	NK cells per mm ³ whole blood	Lytic units,* 20% lysis	% lysis by effector-to-target cell ratio				
			100 : 1	50 : 1	25 : 1	12 : 1	6 : 1
Steep slope, ≤-.091	212 (131)	800 (473)	49 (22)	45 (21)	39 (19)	28 (14)	18 (9)
Flat slope, >-.091	164 (134)	851 (520)	44 (19)	39 (19)	33 (17)	25 (14)	16 (9)

*Lytic units are corrected for NK cell numbers and are expressed as the number of NK cells required to kill 20% of the targets in a suspension of 10⁷ cells per mm³.

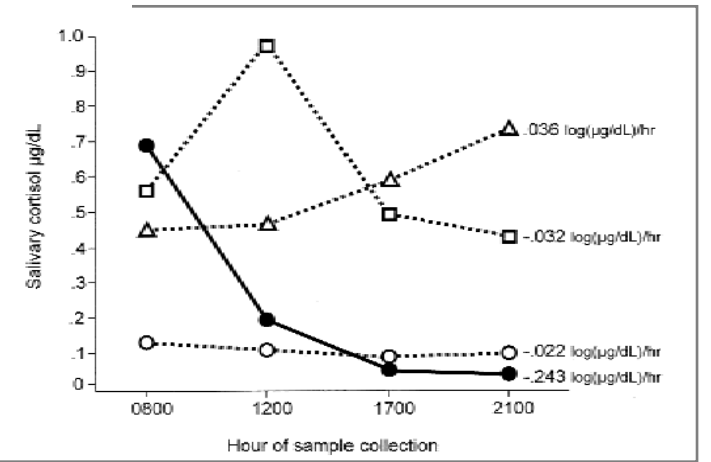
Cortisol rhythm dysfunction in cancer survivors



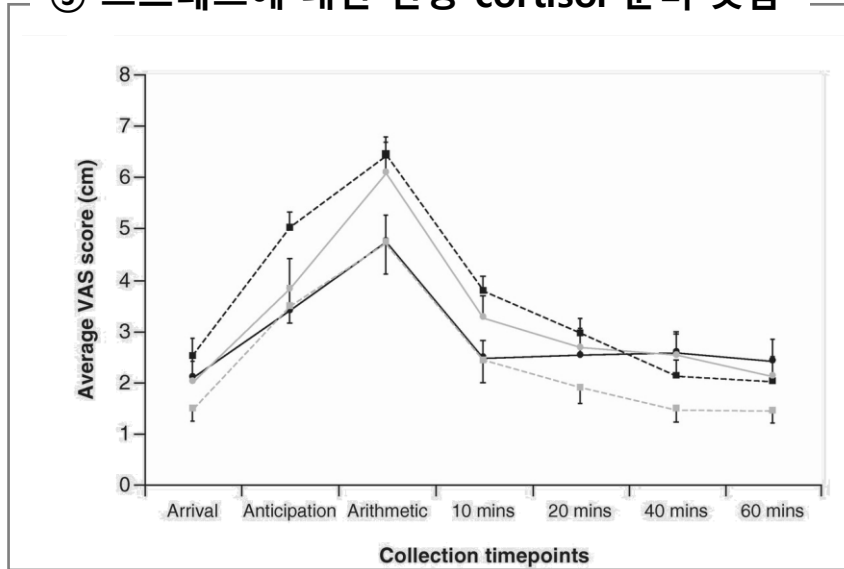
Psychoneuroendocrinology. 2005 Jan;30(1):92-100.



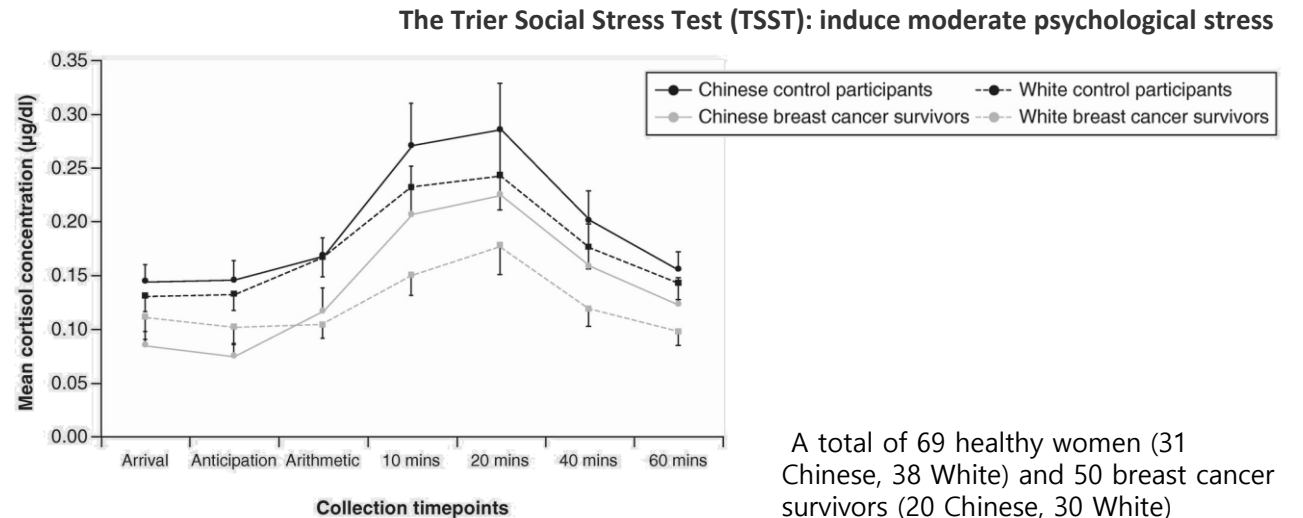
Brain Behav Immun. 2013 Mar;30 Suppl:S163-70.



③ 스트레스에 대한 반응 cortisol 분비 낮음



Breast cancer management. 2019. Vol 8, No. 1



A total of 69 healthy women (31 Chinese, 38 White) and 50 breast cancer survivors (20 Chinese, 30 White)

FM marker

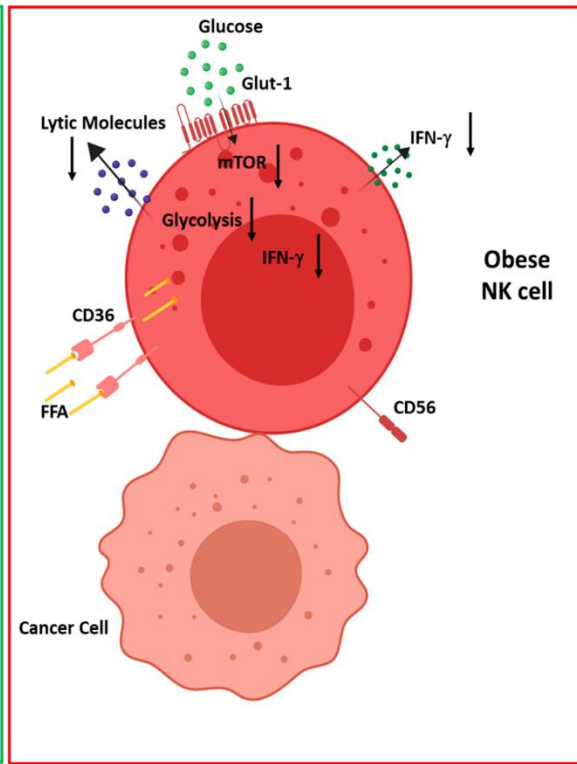
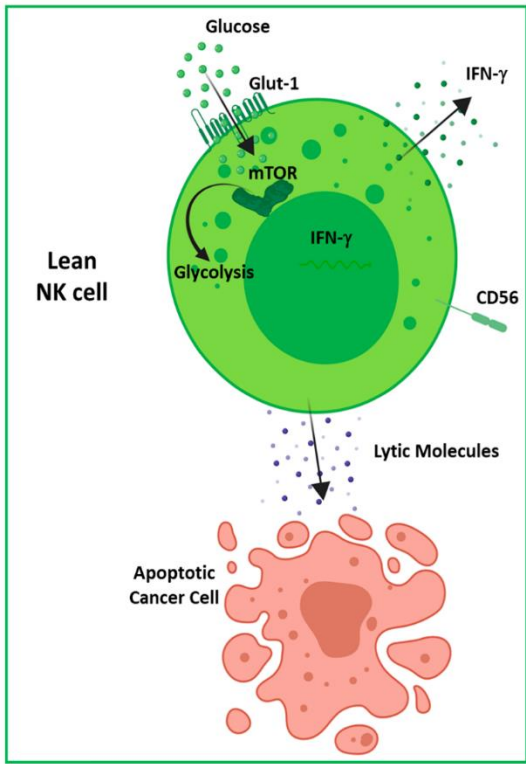
NK cell activity

Weight Loss

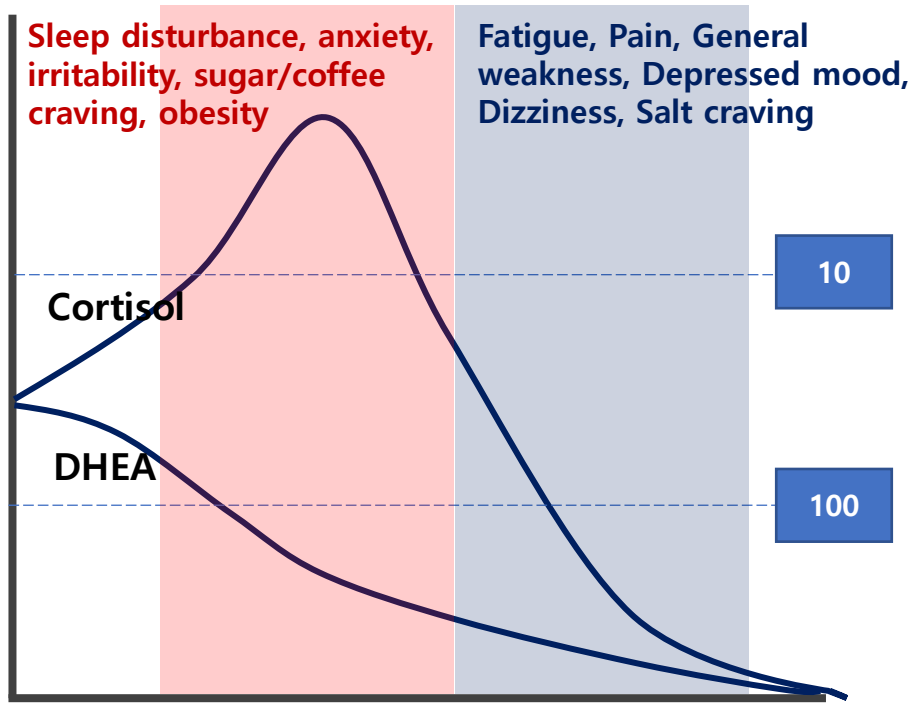
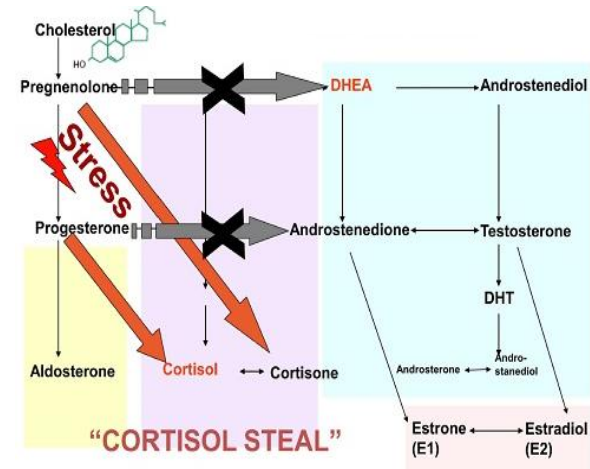
- Restored NK cell frequencies
- Restored cytokine production
- Restored perforin & granzyme
- Restored cytotoxicity

Obesity

- Lower NK cell frequencies
- Reduced cytokine production
- Reduced perforin & granzyme
- Reduced cytotoxicity

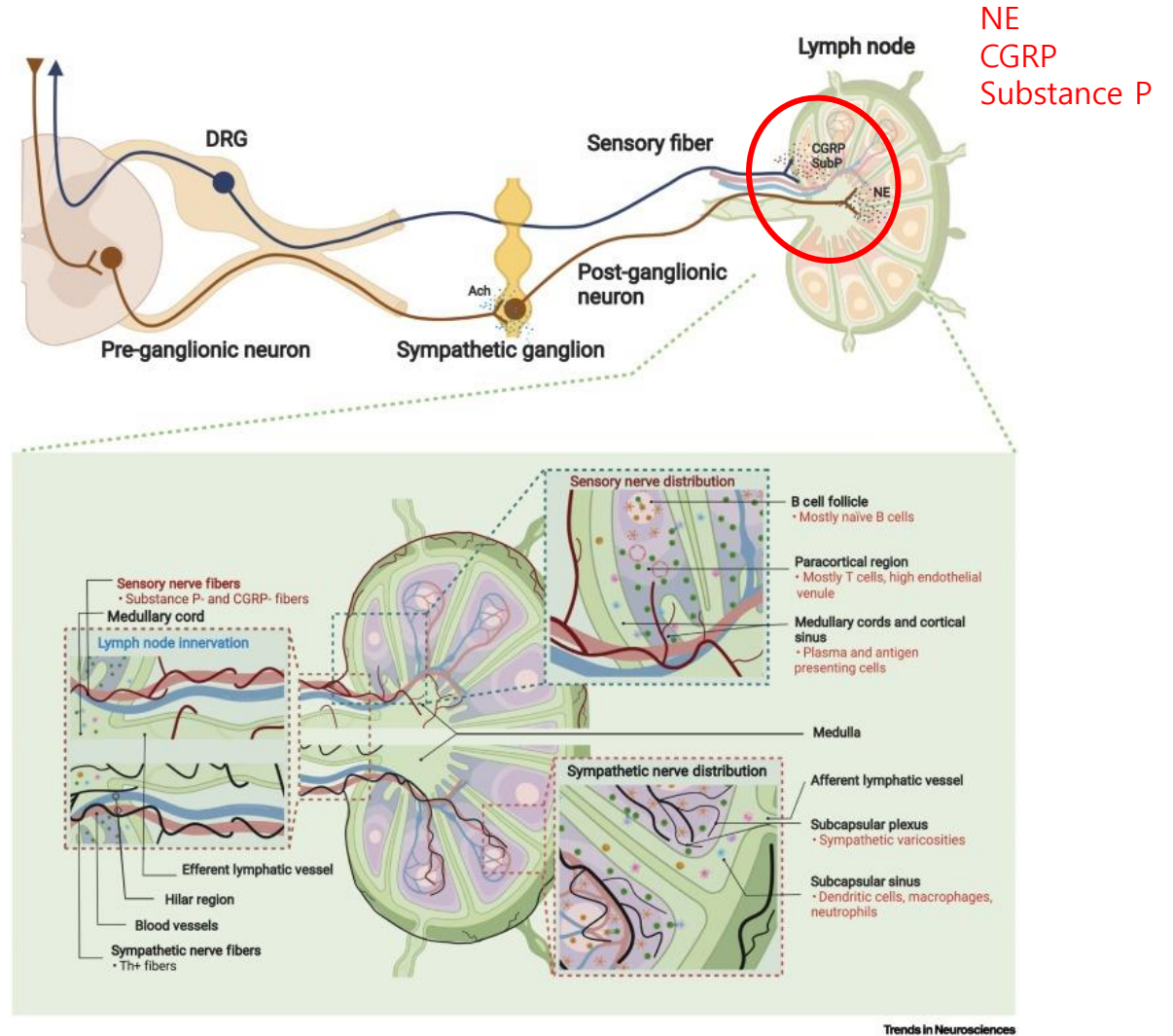
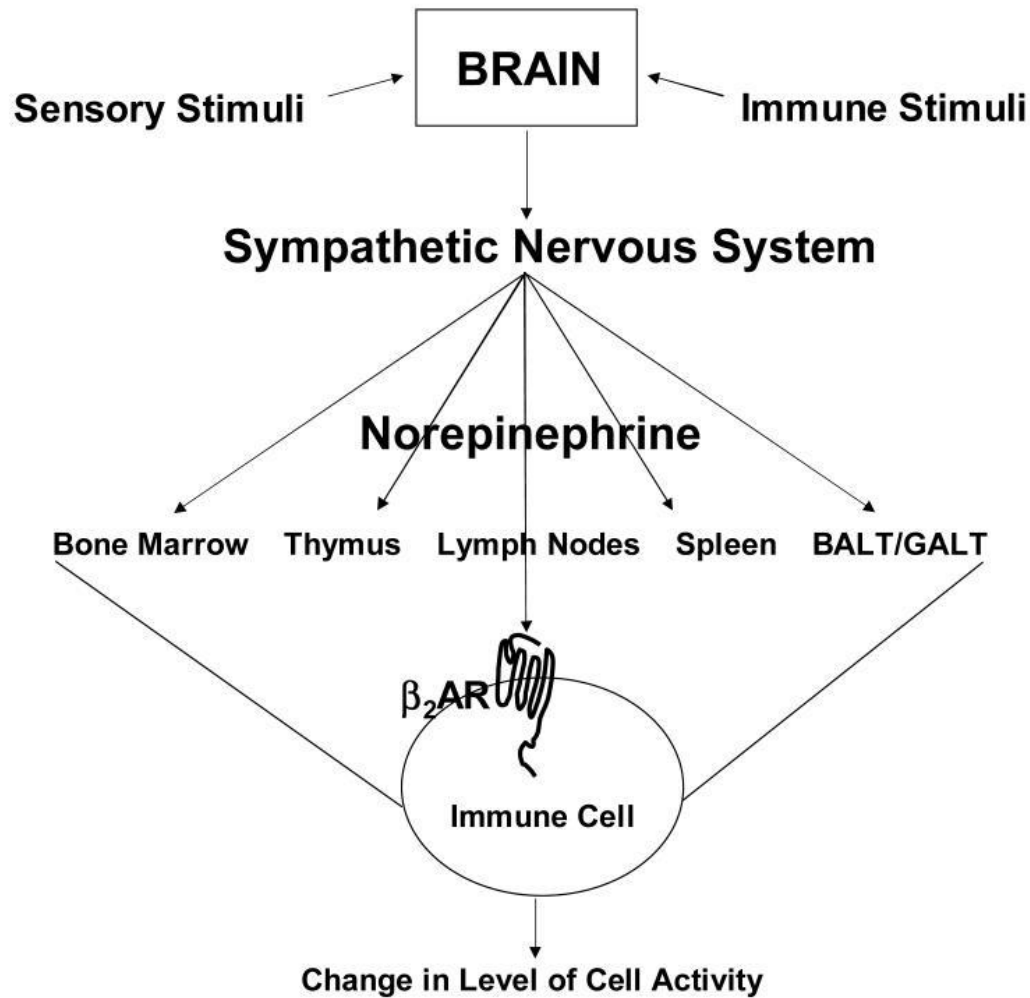


Adrenal exhaustion/fatigue : cortisol, DHEA-S, ACTH



Autonomic nervous system and immune cell

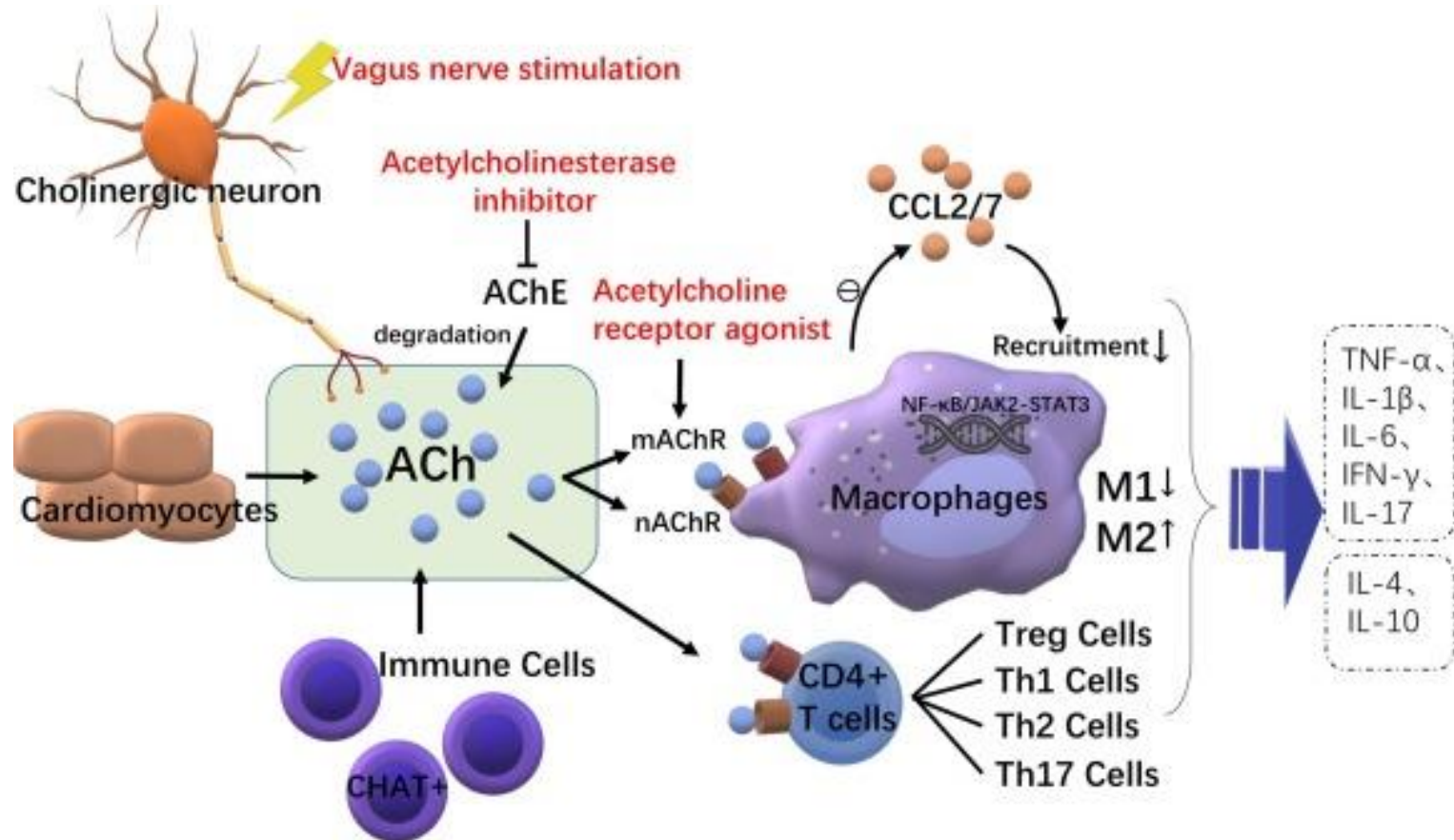
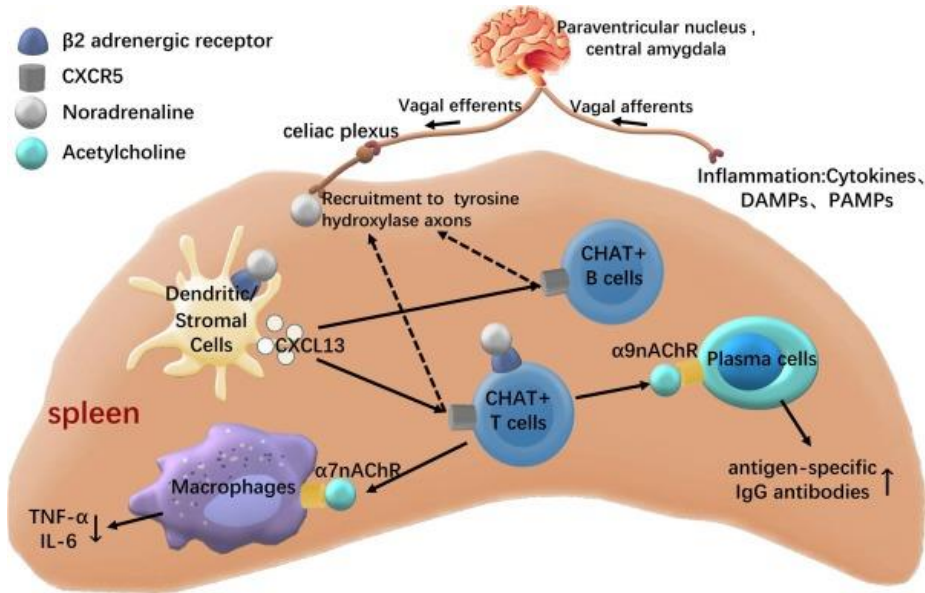
적절한 교감신경 - 선천면역 유지



Trends in Neurosciences

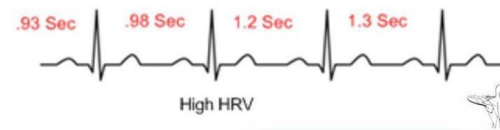
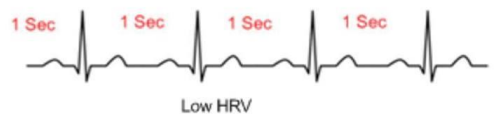
Autonomic nervous system and immune cell

적절한 부교감신경 - 항염 작용



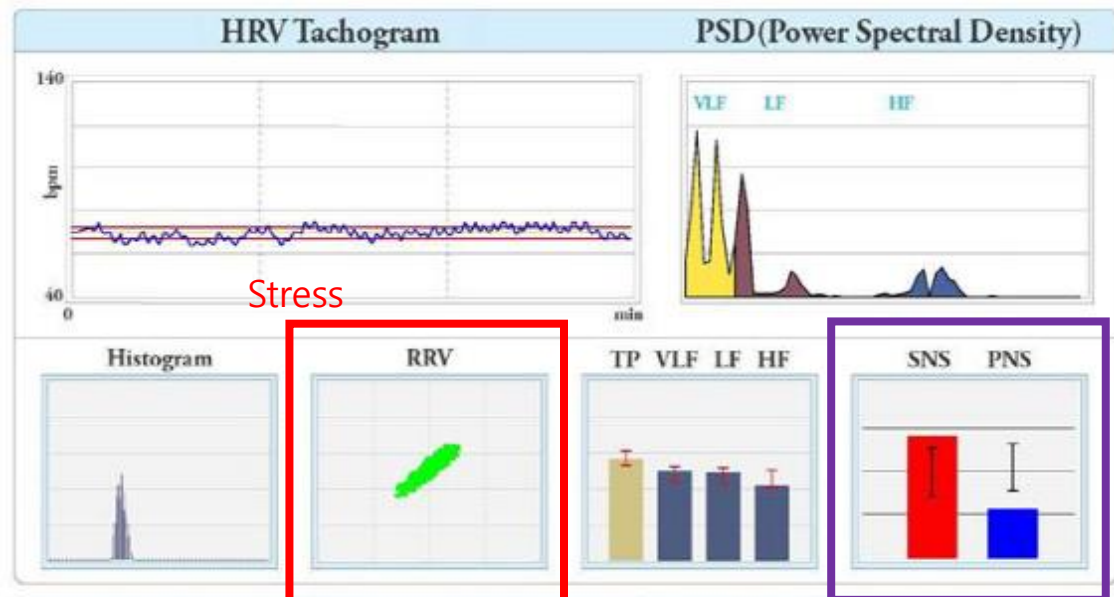
FM marker

Heart Rate Variability

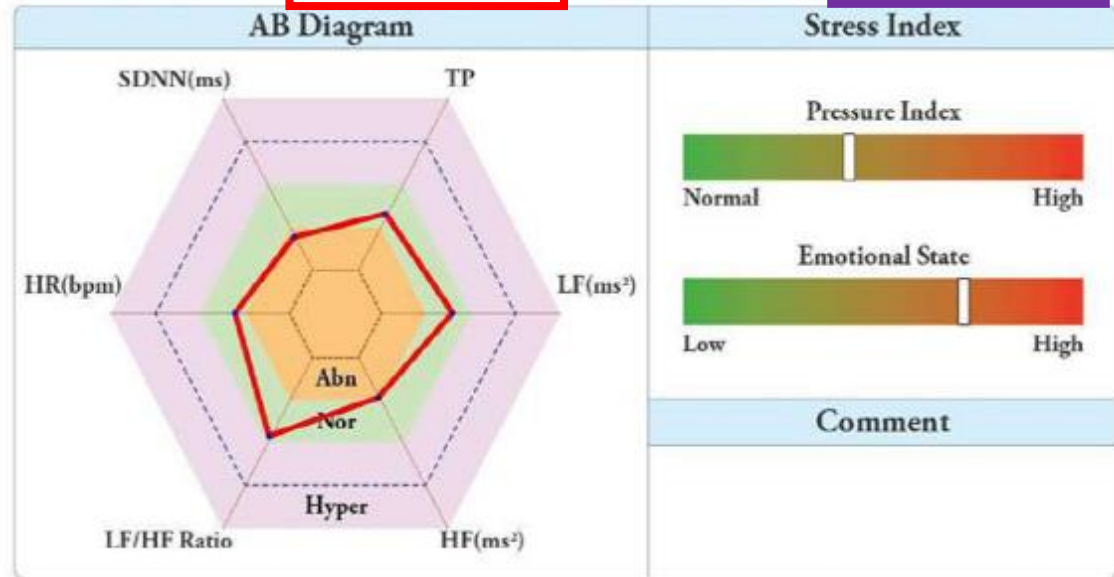


Low HRV
 "Fight or Flight"
 Easily exhausted
 Low Adaptability
 Decreased Cognition

High HRV
 "Rest & Digest"
 Improved Performance
 High Adaptability
 Improved Cognition



Obesity
 HF 감소 = 부교감(미주신경) 기능저하
 인슐린저항성
 LF/HF 증가



HF 부교감신경의 저하
 운동, 체중감량

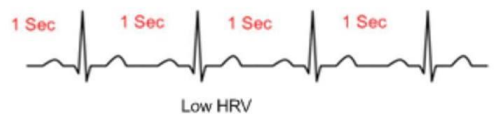
Immunity

30
20

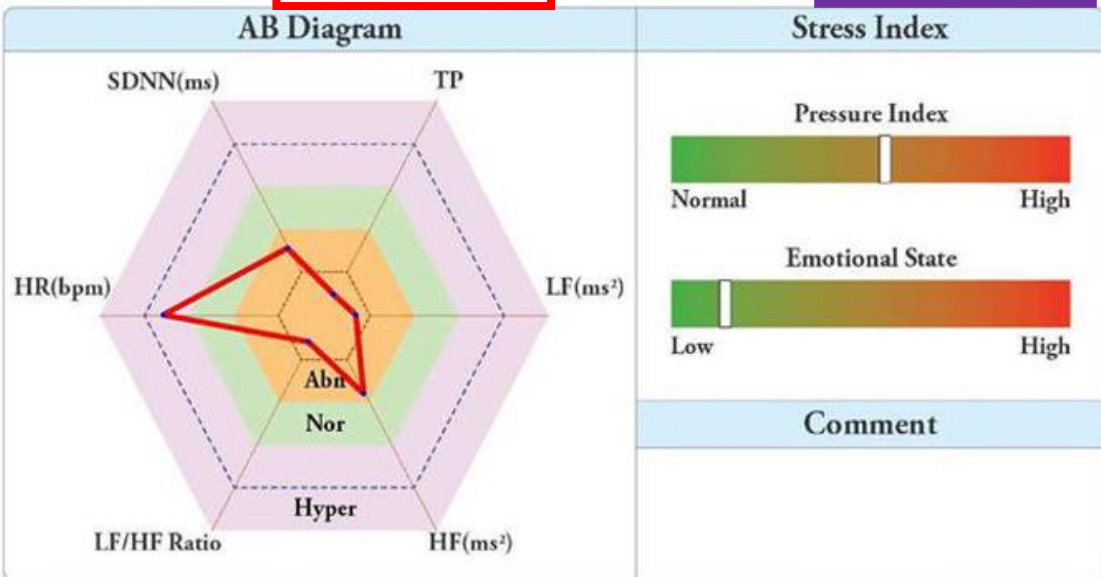
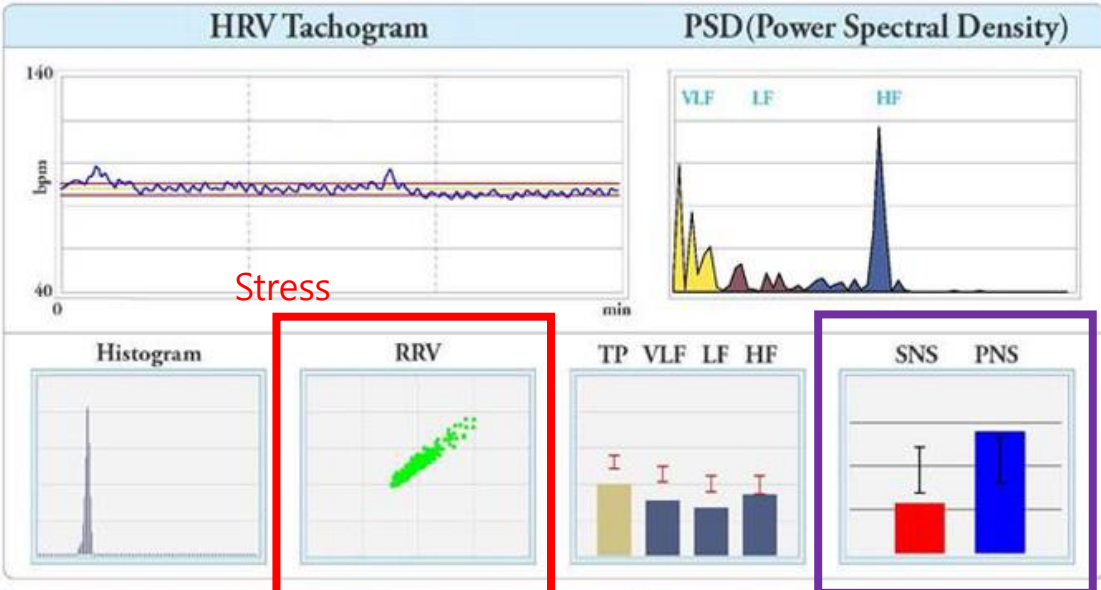
Time Domain Analysis		Frequency Domain Analysis		Others			
MHR(bpm)	69	TP(ms²)	1071.19 / 6.98	LFNorm(n.u.)	71.38	SRD	0.98
SDNN(ms)	35.06	VLF(ms²)	472.02 / 6.16	HFNorm(n.u.)	28.62	ApEn	1.00
RMSSD(ms)	27.93	LF(ms²)	427.68 / 6.06	LF/HF Ratio	2.49		
PSI	43.74	HF(ms²)	171.49 / 5.14	Ectopic Beat	0		0.5-2

FM marker

Heart Rate Variability



Low HRV	High HRV
"Fight or Flight"	"Rest & Digest"
Easily exhausted	Improved Performance
Low Adaptability	High Adaptability
Decreased Cognition	Improved Cognition



교감 vs. 부교감의 우세 비율 3:2

비만이 오래될수록 대사증후군이 있을 수록 암생존자인 경우

SDNN, LF, HF 감소 TP감소

Immunity

30
20

Time Domain Analysis	1000	Frequency Domain Analysis	Others
MHR(bpm)	87	TP(ms ²) 137.06 / 4.92	SRD 1.04
SDNN(ms)	20.89	VLF(ms ²) 43.64 / 3.78	ApEn 0.92
RMSSD(ms)	10.81	LF(ms ²) 27.24 / 3.30	0.5-2
PSI	130.99	HF(ms ²) 66.18 / 4.19	
		LF/HF Ratio 0.41	
		Ectopic Beat 0	

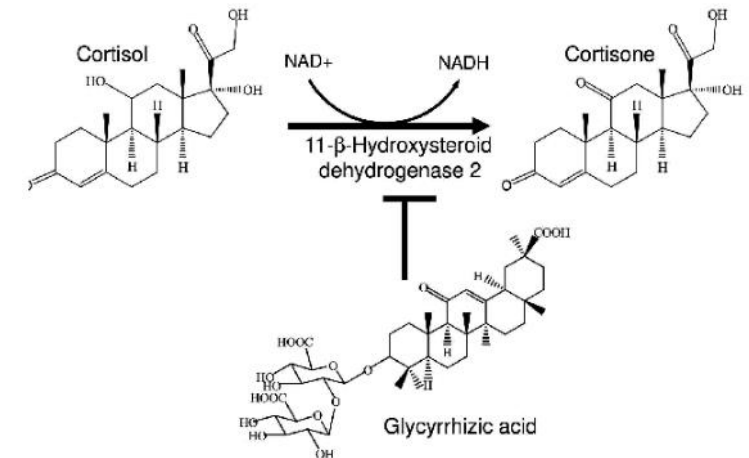
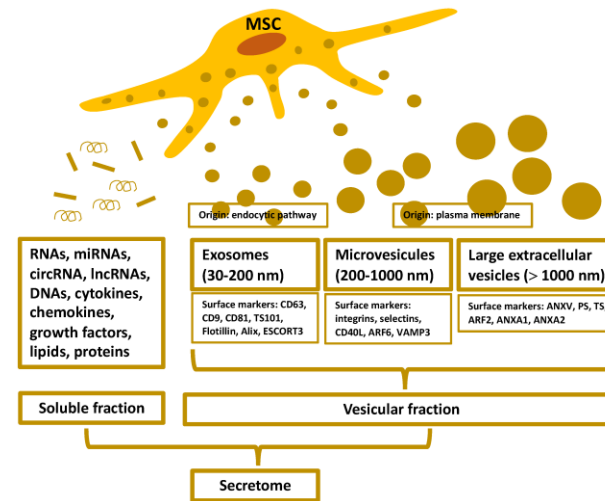
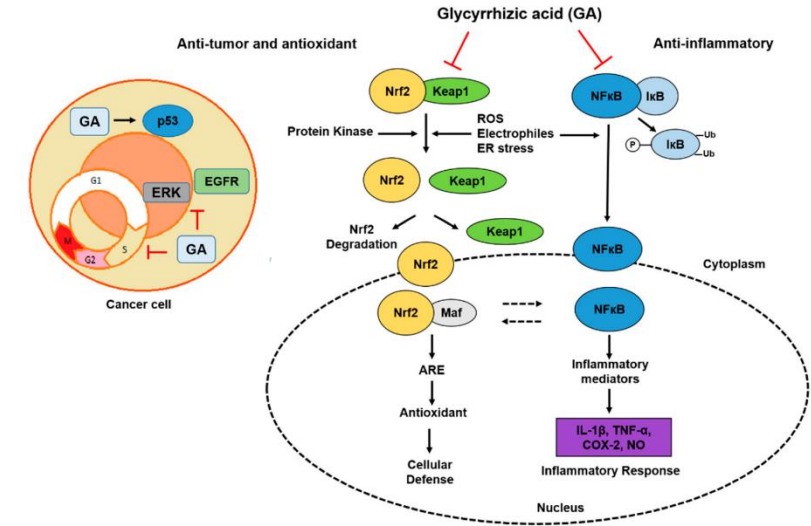
LF 교감신경의 저하 -> 부신기능강화

FM solution

Improving adrenal & immune function

- 일찍 자며 눈 떠질 때 일어난다 (수면으로 내재적 생체리듬 획득이 중요)
- 운동은 규칙적으로, 단 무리는 하면 안된다
- 적절한 스트레스 관리: 명상, 요가, 복식호흡,
- 아침식사는 꼭 한다, 단 GI index 낮은 것으로
- 전곡, 좋은 질의 단백질, 오메가 3, 야채
- (커피, 패스트푸드, 알러지유발음식, 단순당, 포화지방 줄이기)
- 규칙적으로, 충분히 씹어서 삼킨다

- IVNT/PONT : Mg, B군, C, antioxidants
- **Adaptogens**: 감초, 홍삼, 홍경천
- Pregnenolone + DHEA
- **Glycyrrhizin**
- **Placenta hydrolysate**



FM solution

NK cell activity and life-style

경계 구간(100미만)

NK세포의 활성이 매우 낮은 상태로 NK세포의 활성을 저해시키는 질환을 의심할 수 있습니다.

경계 구간(100 ~ 250미만)

NK세포의 활성이 정상인보다 낮은 상태로서 NK세포의 활성을 저하시키는 질환의 전조일 수 있습니다. 또한 일시적인 육체적, 정신적 스트레스로 인해 면역세포의 기능이 저하된 경우에도 경계 값을 보일 수 있습니다.

관심(250 ~ 500미만)

현재의 면역 상태가 질병의 발생과 직접적인 관련이 없는 정상 범위이지만, 그 같이 경계 구간에 가까워 상대적으로 면역력이 저하되어 있는 상태입니다. 면역력을 높이는 활동이 필요합니다.

정상(500이상)

NK세포의 활성이 정상 수준으로서 암과 같은 중증 질환에대한 NK 세포의 면역기능이 이상적인 상태입니다

Cut-off 250 pg/ml

Stressor 제거

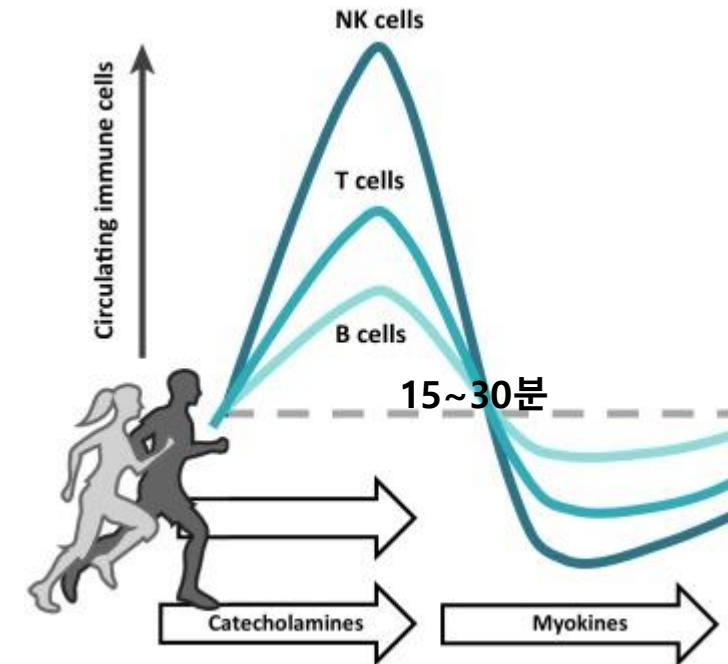
산림욕, 음악감상

금연, 절주

규칙적인 운동 '습관'

'질 좋은 충분한' 수면

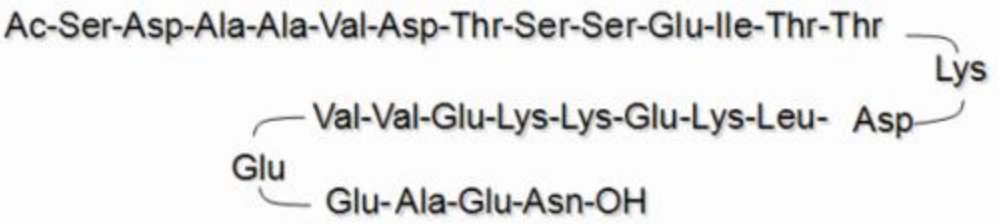
비만에서의 체중감소



FM solution

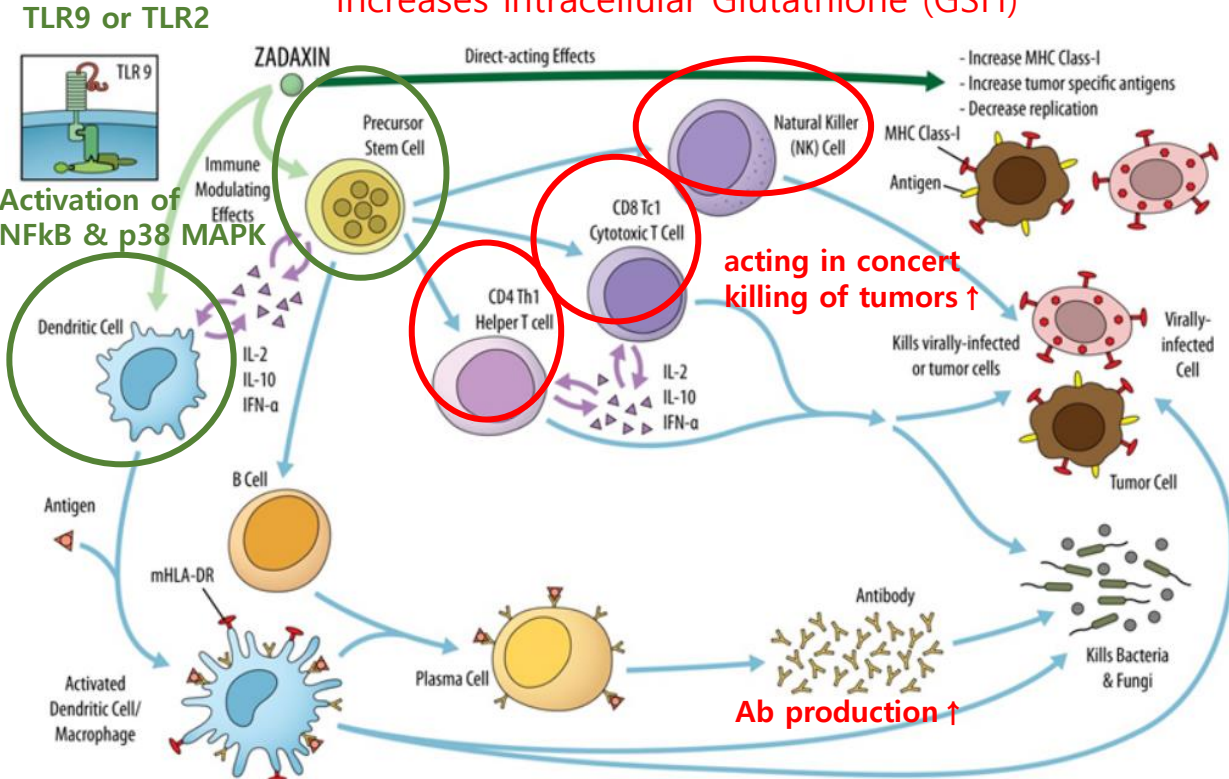
Thymosin alpha-1 (Tα1)

- a naturally occurring peptide produced by the thymus gland
- helps stimulate the development of T cells
- a variety of immune-modulating effect



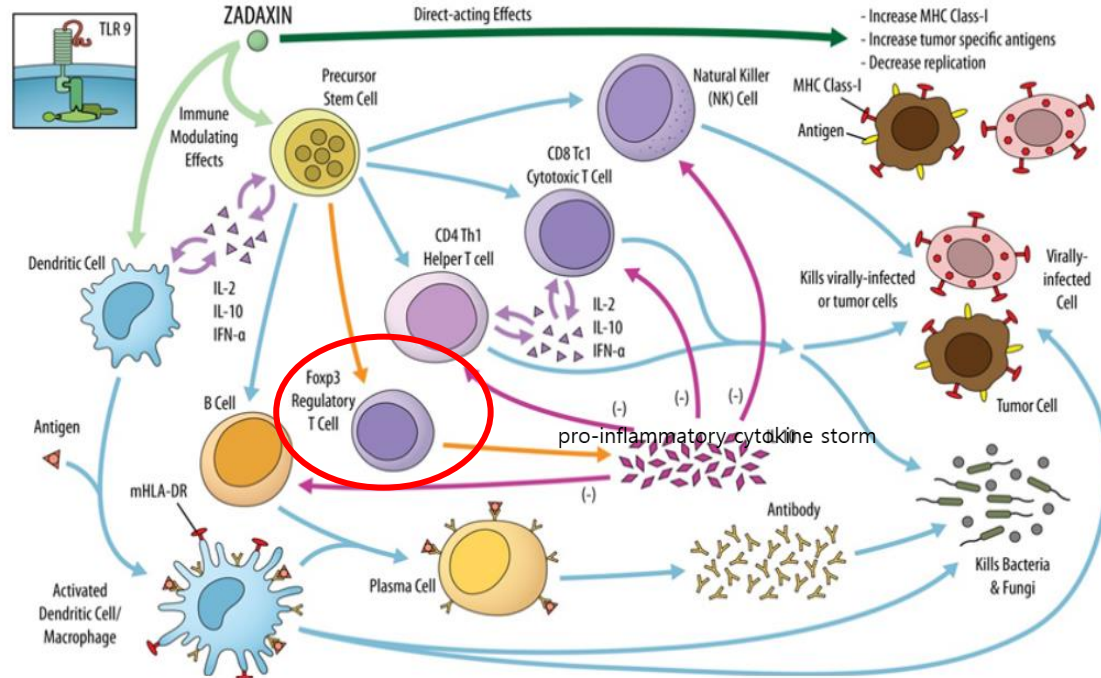
Immune modulating and direct-acting effects

Increase expression of tumor specific antigens
 Increases intracellular Glutathione (GSH)



Immune dampening mechanism of action

stimulates activity of Indoleamine-2,3-Dioxygenase (IDO) in plasmacytoid DCs

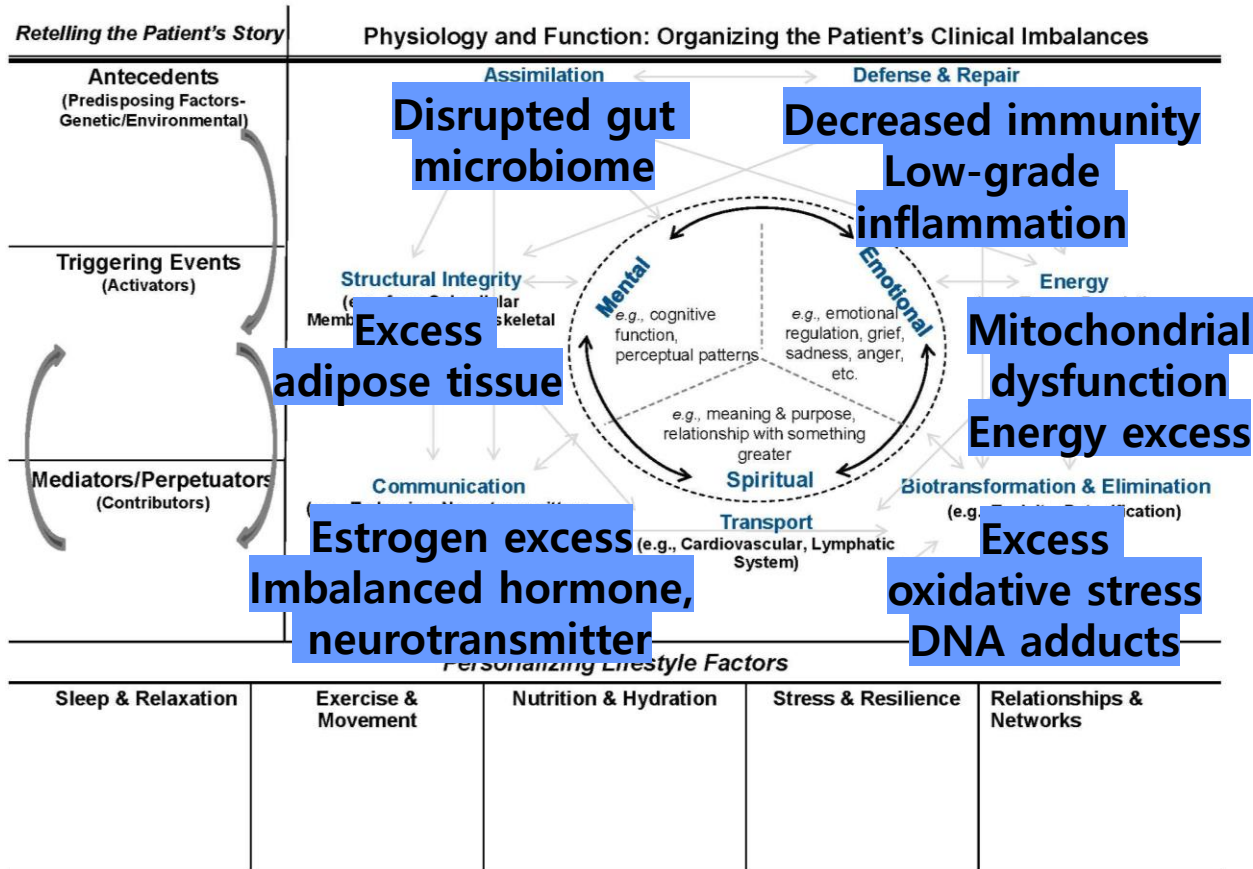


Feedback inhibition of cytokine production
 Prevention of a pro-inflammatory cytokine storm

Vitam Horm. 2016;102:151-78.

Cancer survivor with obesity 7-core imbalance in functional medicine

요약



- 암대사학에서의 맞춤 치료 방향과 유사하게 비만한 암생존자의 관리에도 맞춤 치료가 필요하다
- 비만한 암생존자의 관리의 기능의학적 접근의 핵심은 질병으로 가고 있는 현재의 신체 불균형 상태를 파악하여 가능한 최적의 상태로 기능을 유지 시켜주는 것에 있다.
- 각 개인의 대사 상태, 면역 상태, 호르몬 및 자율신경계, 장 기능 상태를 파악하기 위하여 여러 기능의학적 해석과 기능의학 검사들을 사용해볼 수 있다.
- 각 개별적인 맞춤 영양치료의 근거 수준은 단순 세포수준부터 임상까지 다양하나, 개개인별로 불균형이 달라, 일치된 결과를 얻기는 어려울 것으로 생각되며, 개인의 불균형을 찾아 그 불균형을 균형으로 맞춰주는 것이 치료방침이다.