OBESITA' E MALATTIA

PAOLO FORNENGO
SCDU MEDICINA INTERNA 3
CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO

Sovrappeso: BMI > 25 e < 30

Obesità: BMI ≥ 30

Body Mass Index (BMI): misura del peso di un adulto in relazione alla propria altezza

Kg/m²

DISEASES ASSOCIATED WITH OBESITY

Diabetes: 80% related to obesity

Hypertension: prevalence is >40% in obesity

Heart disease: 70% related to obesity

Restrictive respiratory disease and OSAS

Cancer: Obesity accounts for 15-20% of cancer-related deaths

Death: Obese individuals have a 50-100% increased risk of death from all causes compared to lean individuals (most of this risk is due to cardiovascular disease)

- **Eccesso di peso ed obesità sono responsabili 14% morti per cancro nel maschio e del 20% nelle donne**

- **Outcome è peggiore nei sovrappeso-obesi, sia come risposta alla terapia sia relativamente al rischio di recidive**

- **Eccesso ponderale in adolescenti**
  - RR 2.1 mortalità per neoplasia nel maschio
  - RR 2.0 mortalità per neoplasia nella donna

Cancer Epidemiol Biomarkers Prev 2009;18(10). October 2009

LA DEFINIZIONE

Girovita

È la circonferenza minima tra la gabbia toracica e l'ombelico con la persona in piedi e con i muscoli addominali rilassati.

VALUTA IL TUO RISCHIO

Se il tuo girovita è	> 80 CM
il tuo richio è	MODERATO

Se il tuo girovita è	> 88 CM
il tuo richio è	ELEVATO

Se il tuo girovita è	> 110 CM
il tuo richio è	MOLTO ELEVATO

Se il tuo girovita è	> 92 CM
il tuo richio è	MODERATO

Se il tuo girovita è	> 102 CM
il tuo richio è	ELEVATO

Se il tuo girovita è	> 120 CM
il tuo richio è	MOLTO ELEVATO

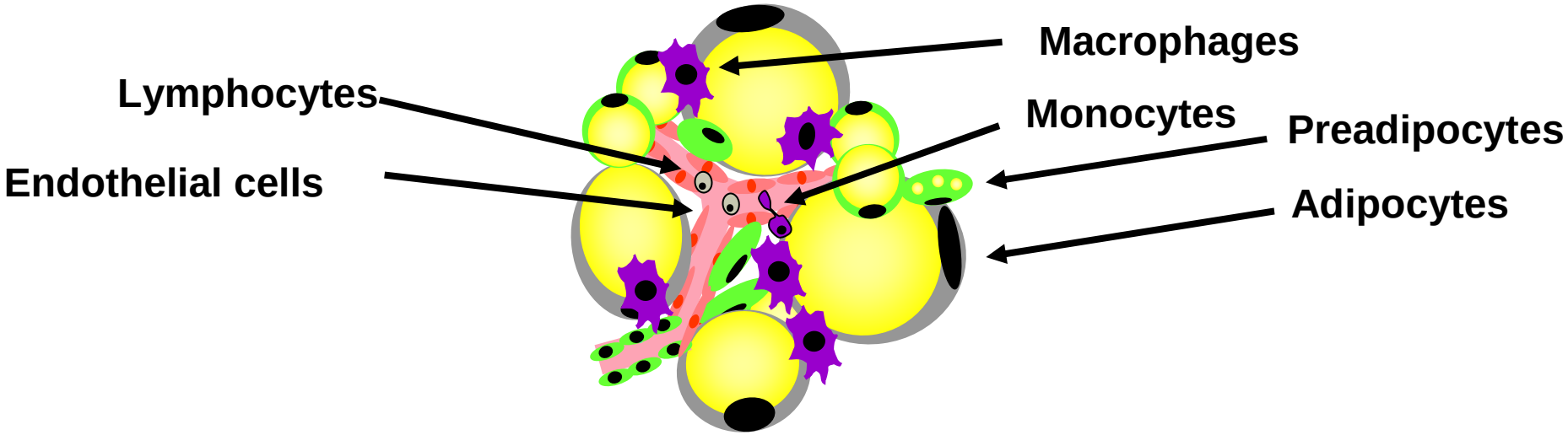
THE METABOLIC SYNDROME

Central obesity
Glucose intolerance
Hypertension
Insulin resistance

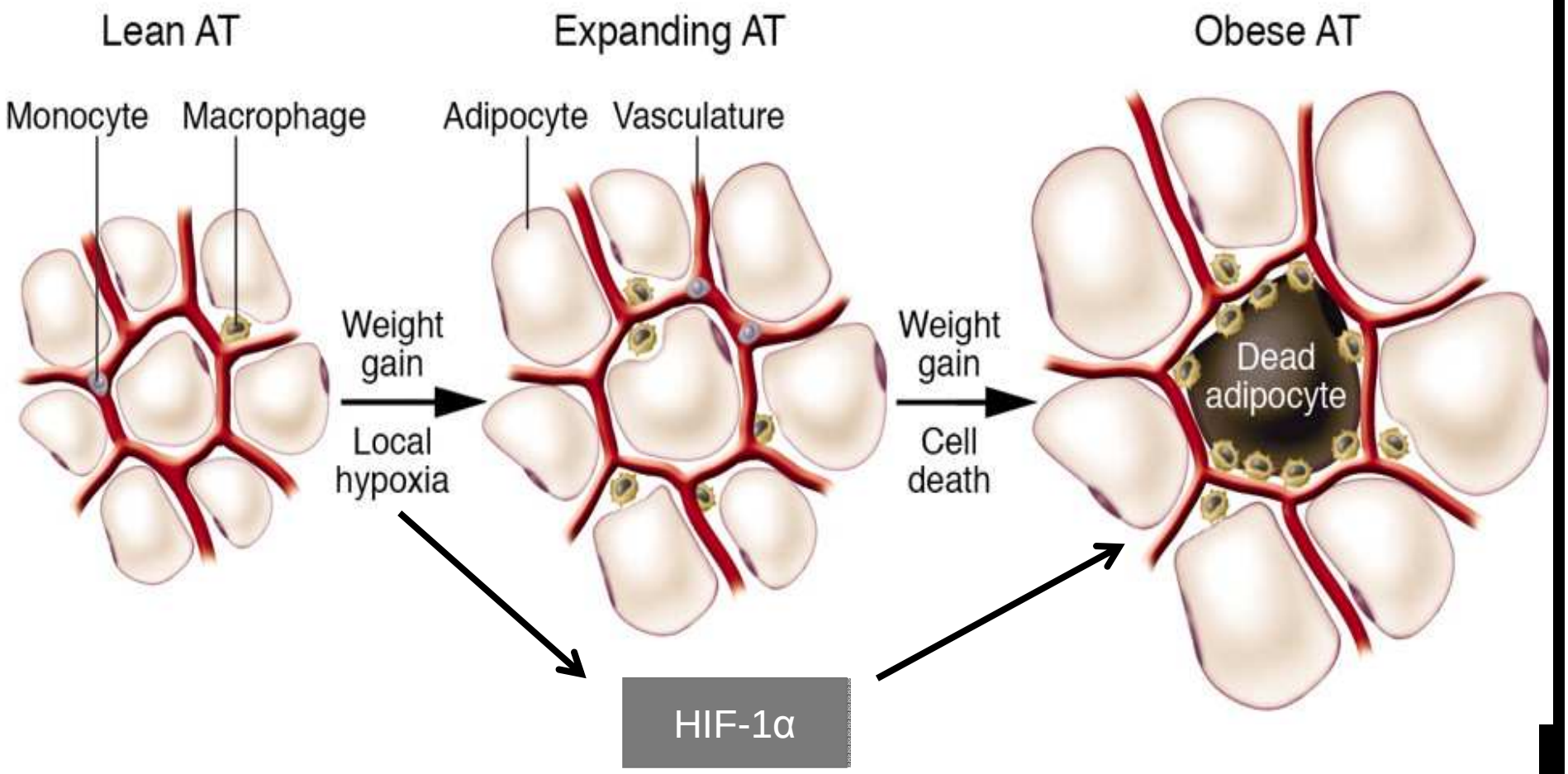
High TG
Low HDL-C
Small, dense LDL particles

Cell types in white adipose tissue (WAT)

- **adipocytes** (lipid-filled cells) 30%
- **preadipocytes and fibroblasts**
- matrix of collagen fibres
- blood vessels (**capillaries/endothelial cells**)
- **immune cells** (monocytes/macrophages, lymphocytes)



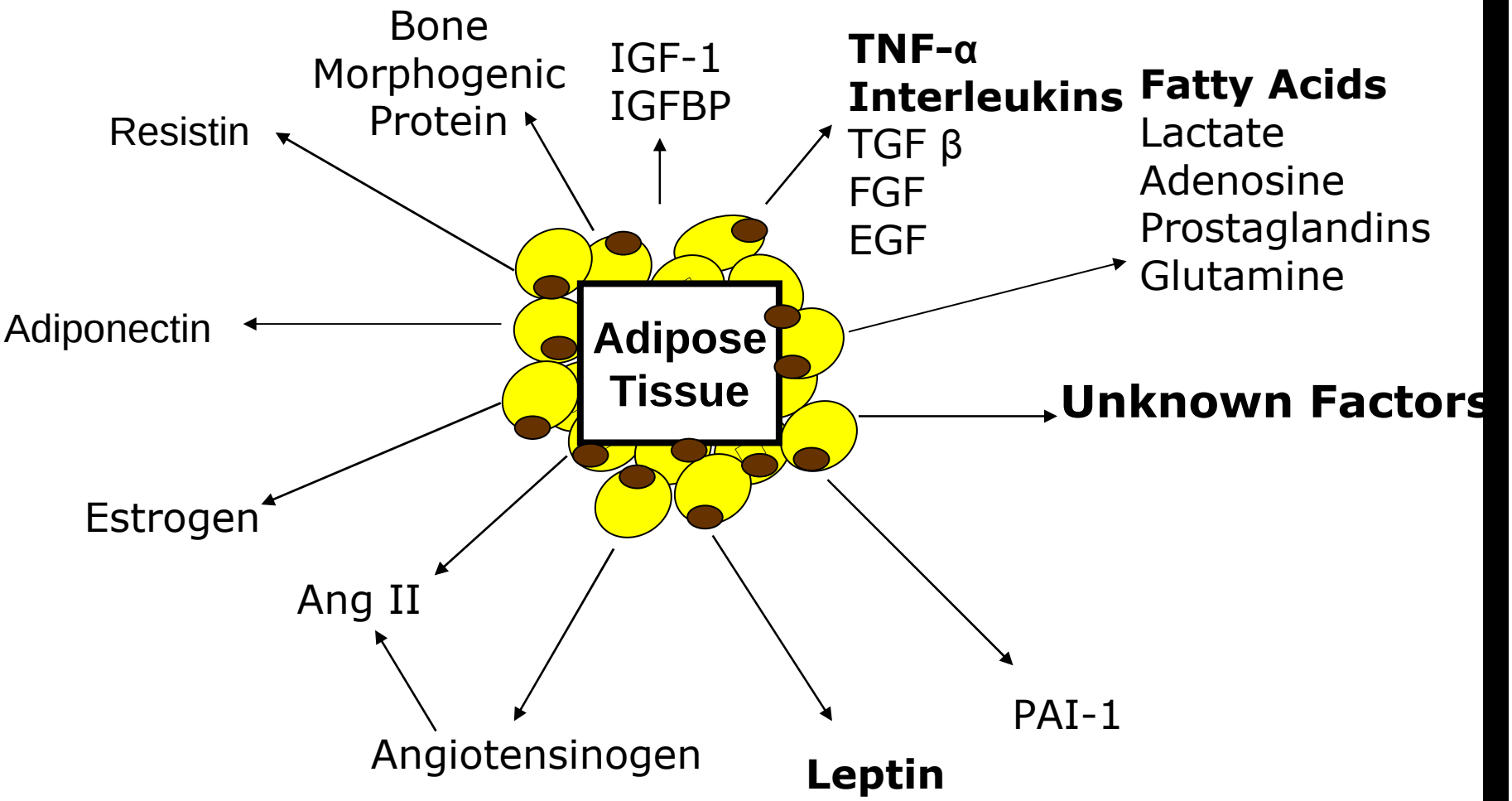
Adipose tissue infiltration by macrophages in obesity: the new concept of ADIPOSOPATHY

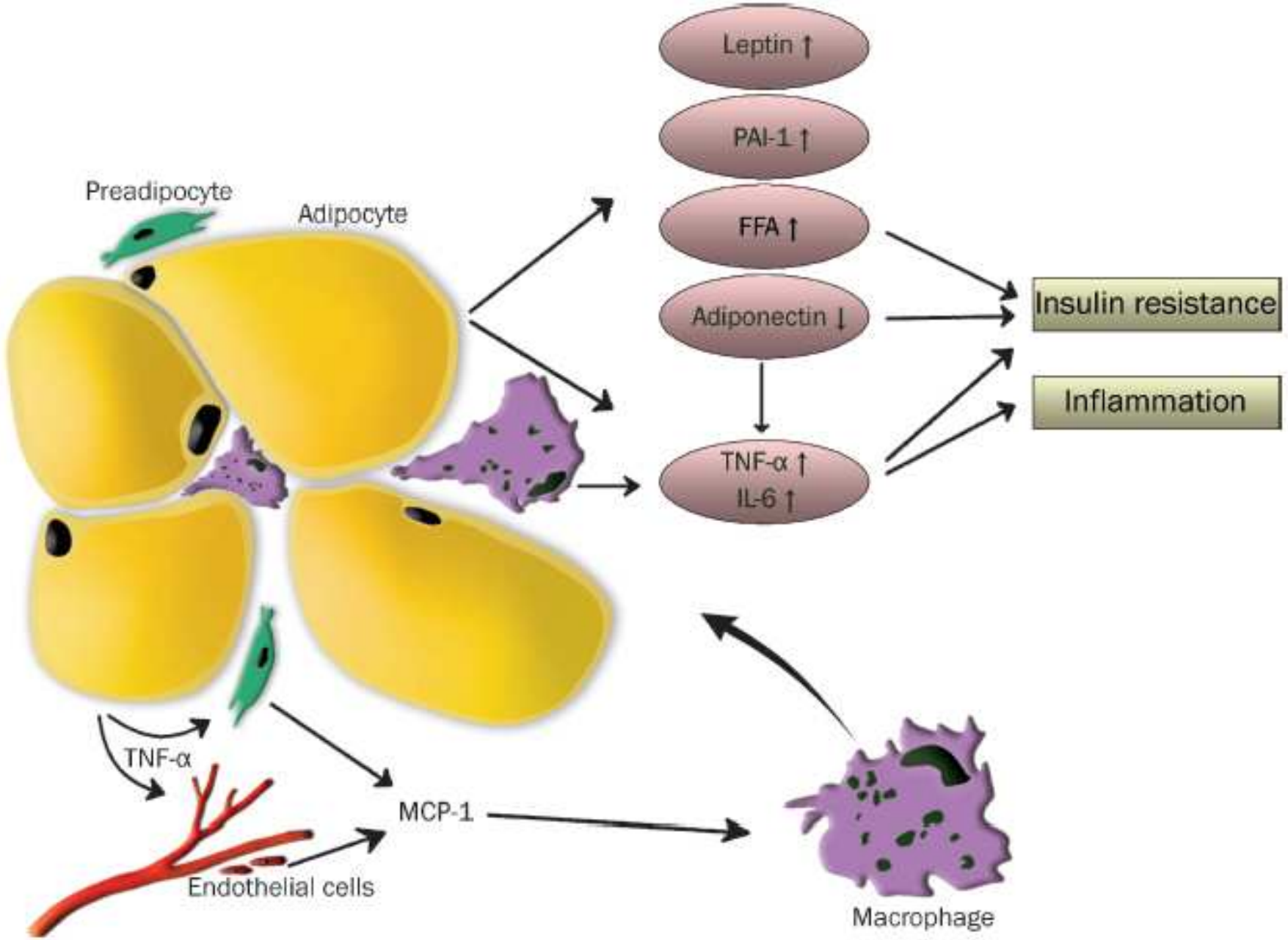


J. Clin. Invest. 2006;116:33-35
J. Intern. Med. 2007;262:422-430

Hipoxia-inducible factor 1-alpha

SECRETORY PRODUCTS OF ADIPOSE TISSUE




Leptin ↑
PAI-1 ↑
FFA ↑
Adiponectin ↓
Insulin resistance
Inflammation
TNF-α ↑
IL-6 ↑
Preadipocyte
Adipocyte
TNF-α
MCP-1
Endothelial cells
Macrophage

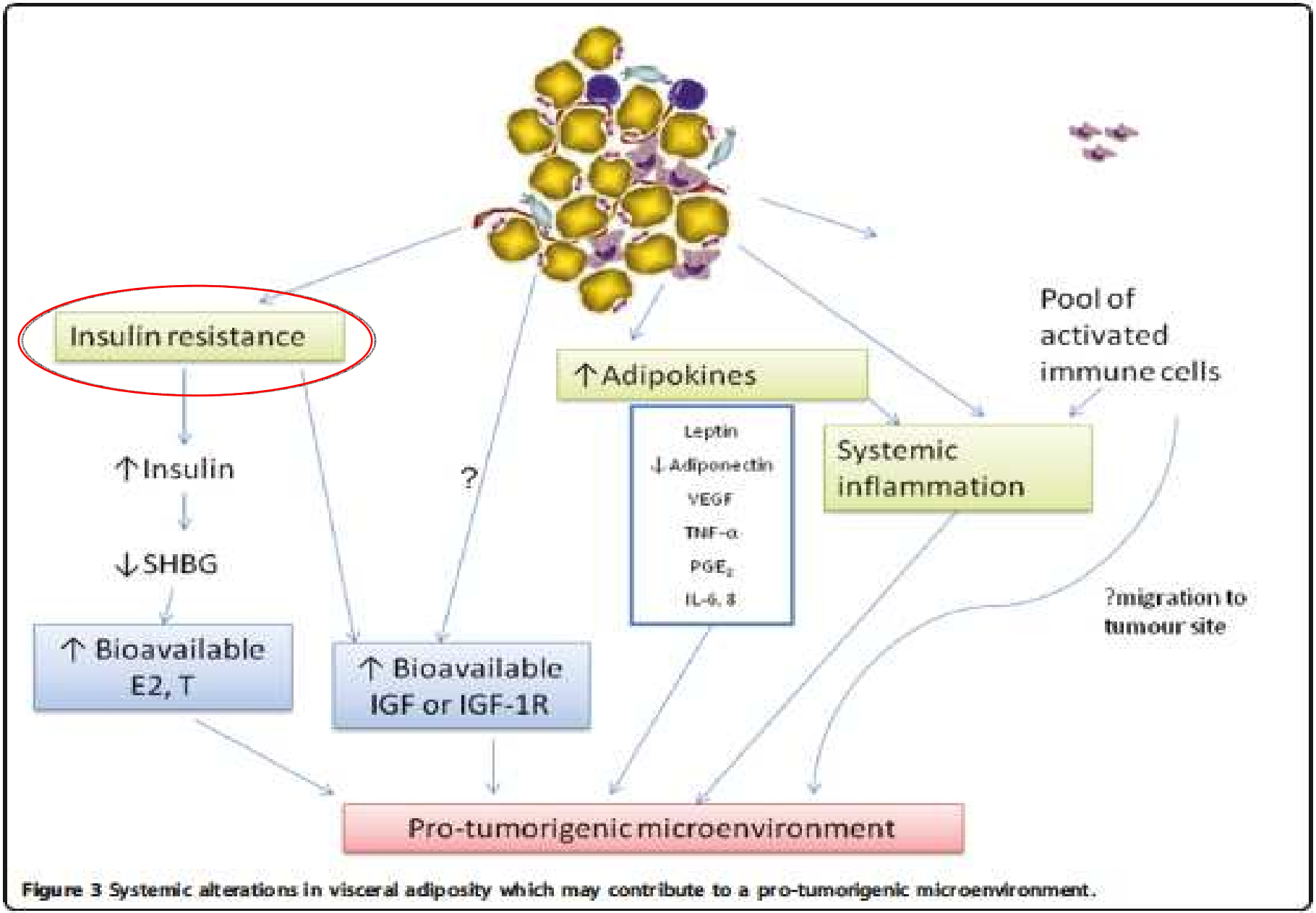


Figure 3 Systemic alterations in visceral adiposity which may contribute to a pro-tumorigenic microenvironment.

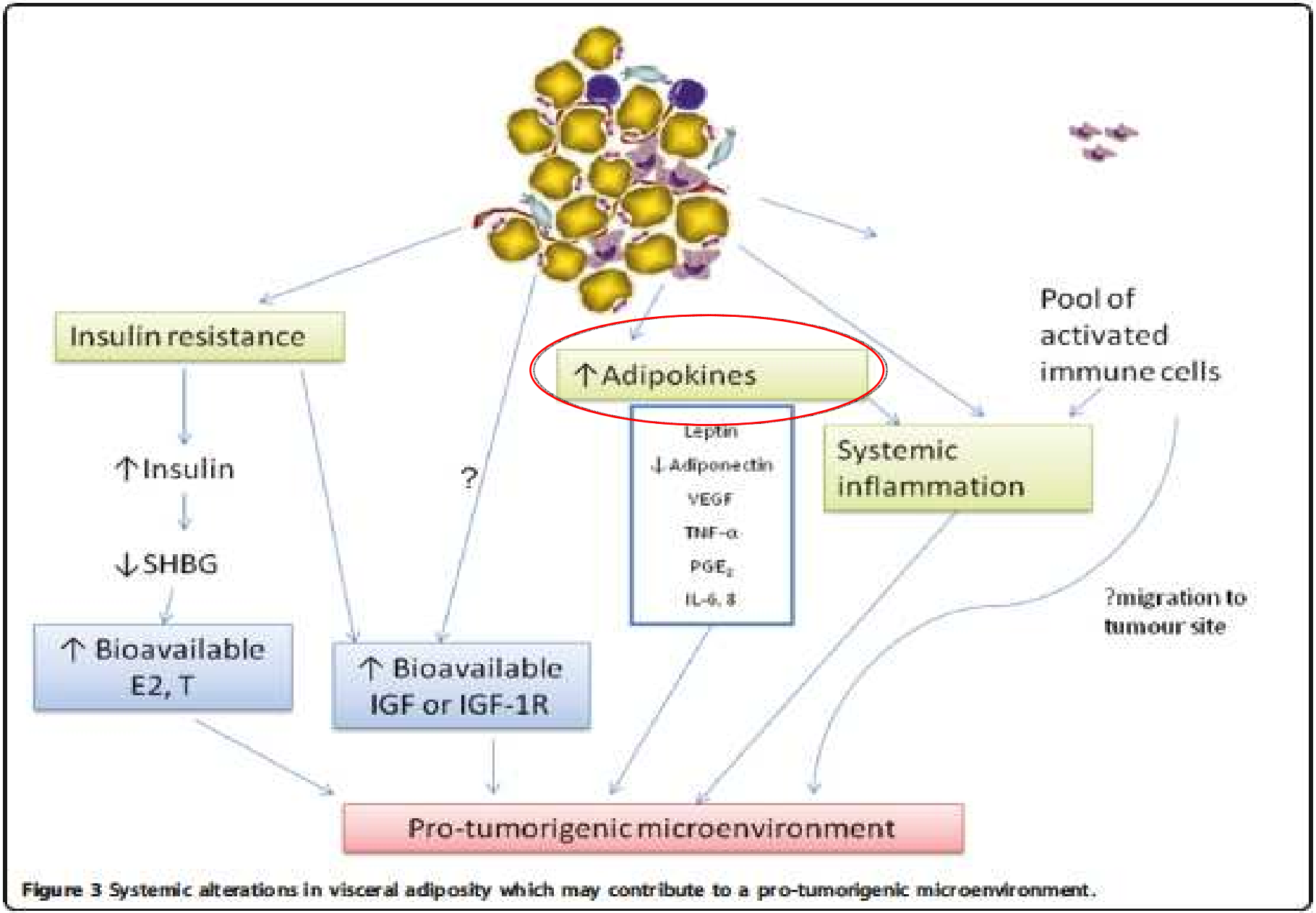


Figure 3 Systemic alterations in visceral adiposity which may contribute to a pro-tumorigenic microenvironment.

Local production of:

- •Inflammatory cytokines
- •Adipokines
- •Growth factors
- •Hypoxic environment

May regulate tumoral:

- •Cell communication
- •Apoptosis
- •Immune response
- •Growth
- •Intracellular signalling

Figure 2 Paracrine mechanisms linking adipose tissue and cancer development

ADIPOKINES

Vascular Disease Related

- Angiotensinogen
- PAI-1

Insulin Resistance Related

- ASP (Acylation-stimulating protein)
- TNFα
- IL-6
- Resistin
- Leptin
- Adiponectin

ANGIOTENSINOGEN (AGE)

Links obesity with hypertension

Positive correlation of blood pressure with AGE levels

Primarily produced in liver, but also by WAT

Deficiency partially protects against diet-induced obesity

PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI-1)

Impairment of fibrinolytic system contributes to cardiovascular complications of obesity

WAT is main tissue source of PAI-1

Produced by pre-adipocytes, primarily in visceral WAT

Acts to inhibit fibrinolysis (is pro-thrombotic)

Also influences cell migration and angiogenesis

Could impair pre-adipocyte migration leading to WAT growth

TNF-A

Proinflammatory cytokine

Produced by adipocytes and macrophages in WAT

Over-expressed in obesity

Link between TNFα and insulin resistance

Alters insulin signaling and MAPK pathways *in vitro* and *in vivo*

IL-6

10-30% of circulating IL-6 is from WAT

Highly correlated with body mass and inversely related to insulin sensitivity

Alters insulin signaling in the liver

IL-6 KO mice develop mature-onset obesity and glucose intolerance

RESISTIN

Discovered in 2001

Expressed in adipocytes in mice and in macrophages in humans

Increased in obesity

Recombinant resistin

- Promotes insulin resistance in mice
- Decreased insulin stimulated glucose uptake in WAT

VISFATIN

- Discovered in 2004
- Specifically expressed in visceral fat as opposed to subcutaneous fat
- Binds to insulin receptor on an allosteric site to insulin
- Can mimic insulin in down-stream insulin signaling pathways

LEPTIN

Secreted by adipocytes

Regulates food intake – satiety factor

Leptin receptor is expressed in hypothalamus

OB/OB AND DB/DB MOUSE MODELS

Spontaneous mutations first noted in 1950

Morbid obesity (3x normal weight)

Hyperinsulinemia (50-fold increase)

Hyperglycemia

Infertile

Slightly increased cholesterol

LEPTIN AND LEPTIN RECEPTOR

Both ob/ob and db/db mice originally developed from spontaneous mutations

The genes mutated in these mice were later identified as leptin and its receptor

ob/ob and db/db mice are obese, hyperphagic, hyperglycemic, and hyperinsulinemic and are commonly used models for studies of diabetes

ob/ob **littermate**

POSSIBLE PHYSIOLOGIC ROLES OF LEPTIN

Obesity

Anorexia

Diabetes

Reproduction

Bone Mass

Immune System

Glomerulosclerosis

Hematopoeisis

Aging

Sweet-sensing modulator

Angiogenic activity

Hypertension

ADIPONECTIN

Discovered in mid-1990's

Protein highly expressed in adipocytes and circulates at high concentrations

Plasma concentrations are reduced in obesity and insulin resistance

TNFα and IL-6 inhibit adiponectin expression

Administration of recombinant adiponectin ameliorates IR in obese and lipodystrophic mice

Adiponectin is anti-atherogenic

L’obesità e le malattie correlate sembrano avere una evoluzione epidemica.

Ma le epidemie sono malattie trasmissibili batteriche o virali.

QUINDI……

E’ un “virus”?

Ed è trattabile?? Vaccinabile??

HABITAT IDEALE DEL “VIRUS”: SOCIETÀ MECCANIZZATA

HABITAT IDEALE DEL “VIRUS”: AMBIENTE

HABITAT IDEALE DEL “VIRUS”: SCAFFALI, BANCONI, CARRELLI STRACOLMI DI CIBO

HABITAT IDEALE DEL “VIRUS”: LUOGHI DELLA TENTAZIONE FUGACE

HABITAT IDEALE DEL “VIRUS”: SENZA LIMITI

VEICOLI CLASSICI DEL “VIRUS”

CARICA VIRALE SUPERSIZE

VETTORI DEL VIRUS

VETTORI DEL VIRUS: RACCOLTE PUNTI

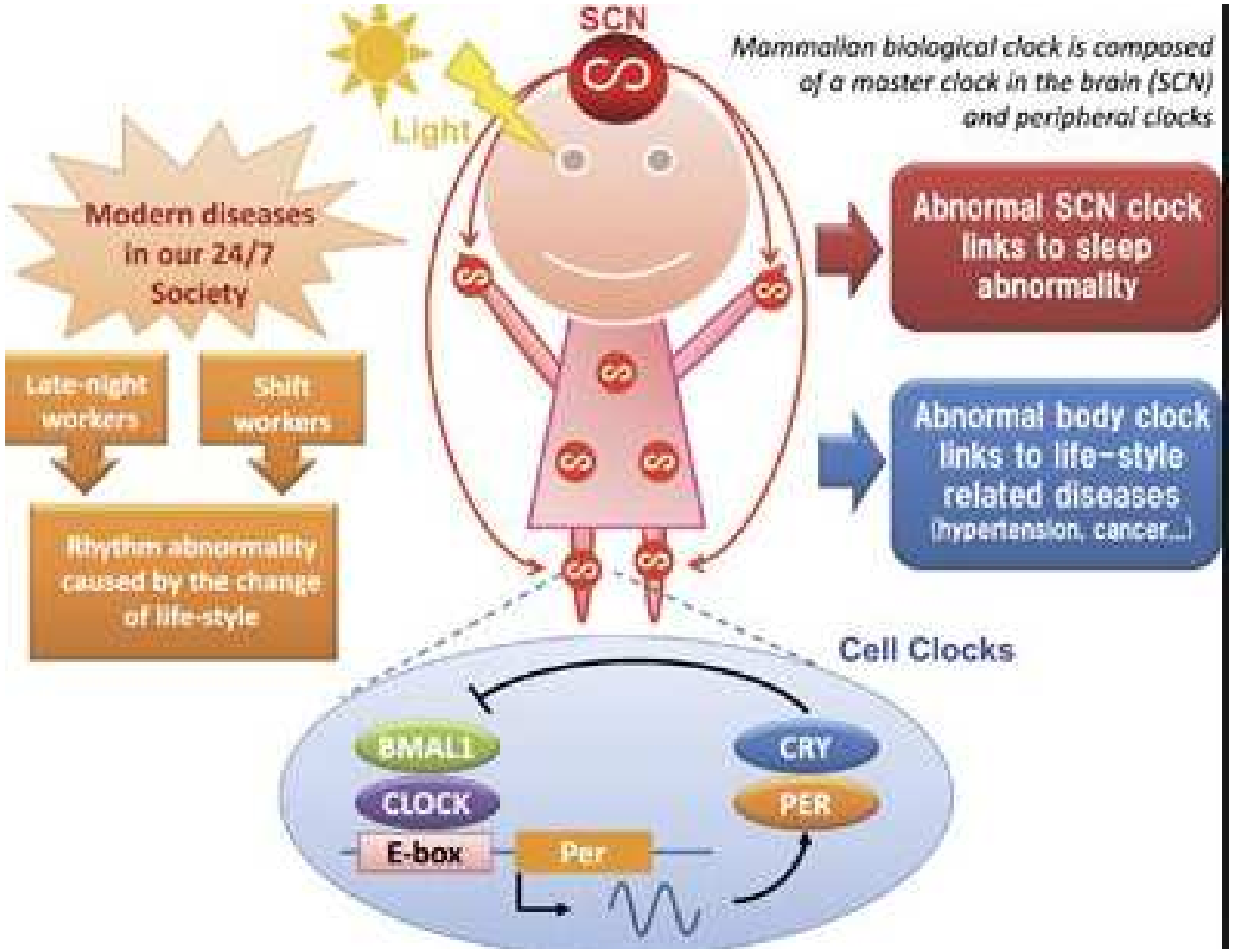
ATTRAZIONE FATALE

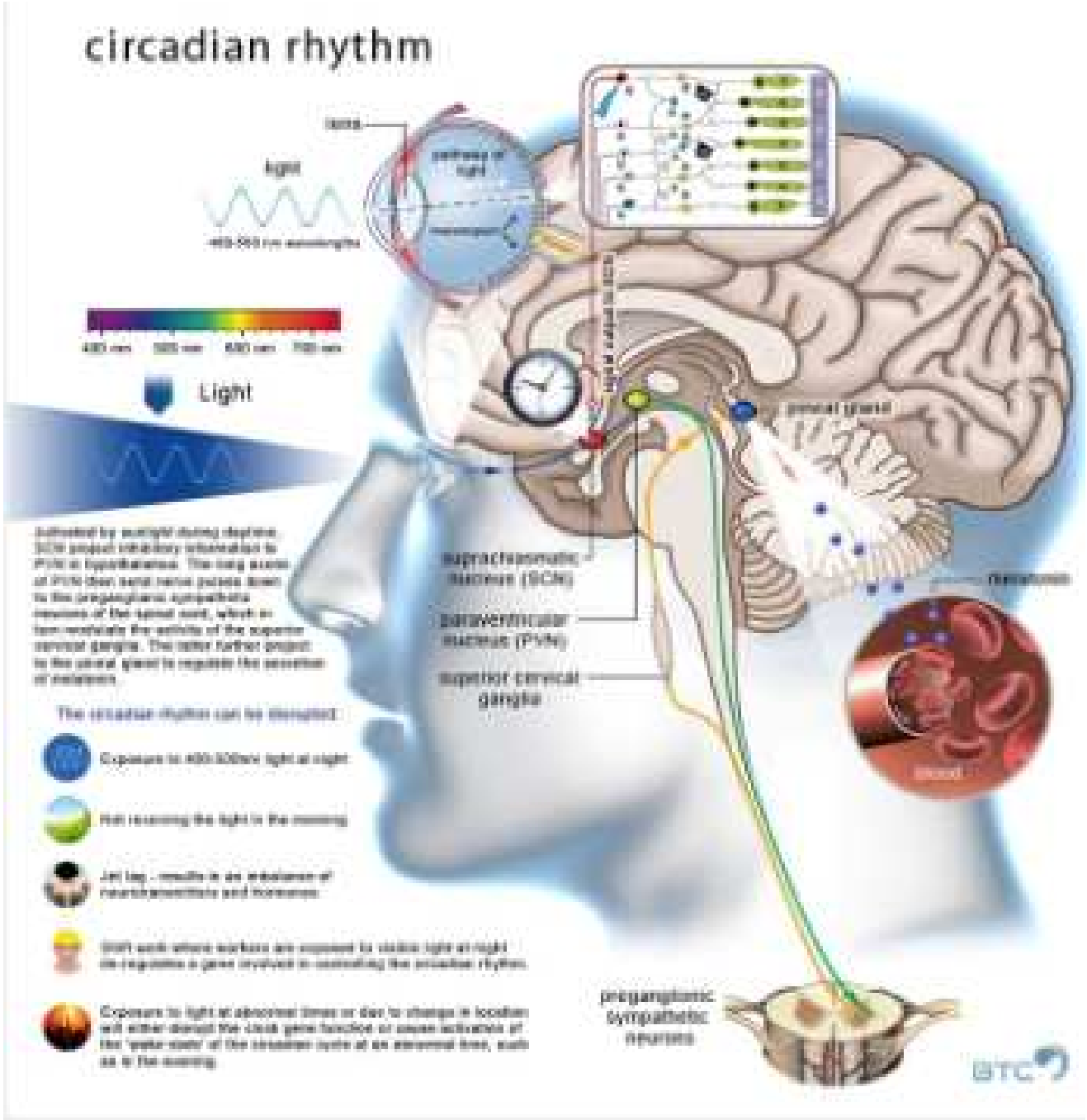
UNTORI TELEVISIVI

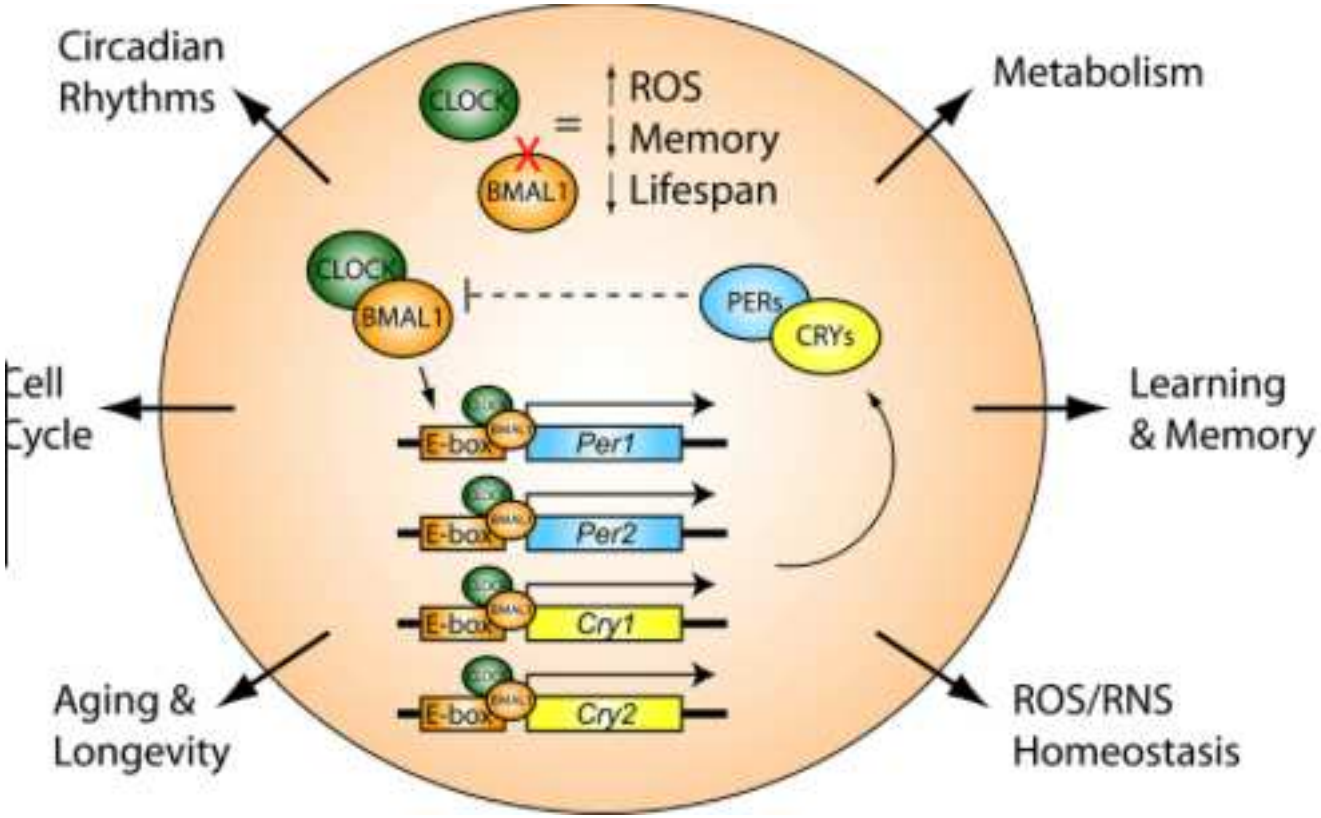
CONTAGIO INFANTILE (+ AMBIENTE)

CONTAGIO AMBIENTALE-SOCIALE

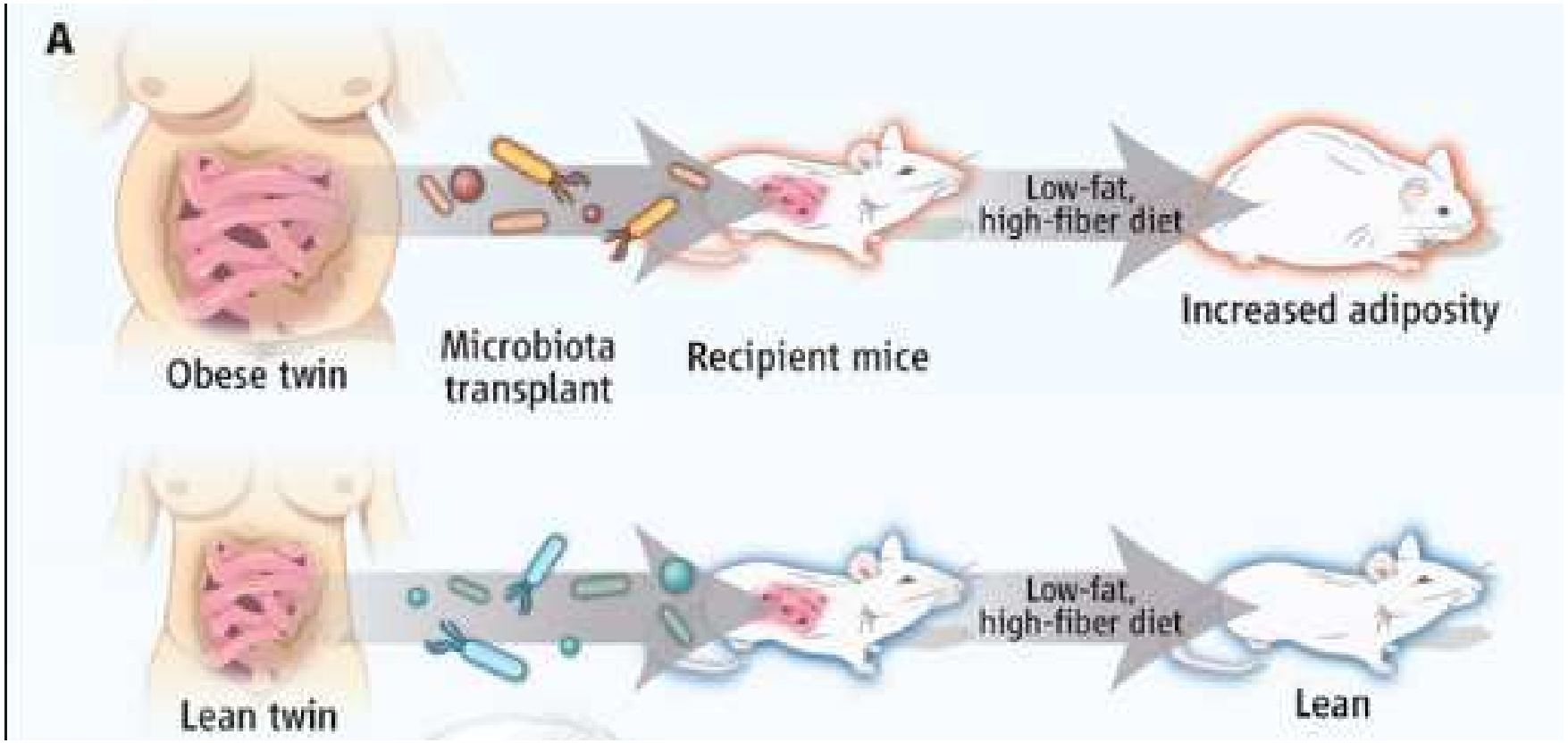
CLOCK GENES


SCN
Light
Mammalian biological clock is composed of a master clock in the brain (SCN) and peripheral clocks
Modern diseases in our 24/7 Society
Late-night workers
Shift workers
Rhythm abnormality caused by the change of life-style
Abnormal SCN clock links to sleep abnormality
Abnormal body clock links to life-style related diseases (hypertension, cancer...)
Cell Clocks
BMAL1
CLOCK
E-box
Per
CRY
PER


circadian rhythm
light
Light
suprachiasmatic nucleus (SCN)
paraventricular nucleus (PVN)
superior cervical ganglia
preganglionic sympathetic neurons
BTC


Circadian Rhythms
CLOCK
BMAL1
=
↑ ROS
↓ Memory
↓ Lifespan
Metabolism
CLOCK
BMAL1
PERs
CRYs
Cell Cycle
E-box
Per1
E-box
Per2
E-box
Cry1
E-box
Cry2
Learning & Memory
Aging & Longevity
ROS/RNS Homeostasis

MICROBIOTA


A
Obese twin
Microbiota transplant
Recipient mice
Low-fat, high-fiber diet
Increased adiposity
Lean twin
Low-fat, high-fiber diet
Lean

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Cell Metabolism

Time-Restricted Feeding Prevents Obesity