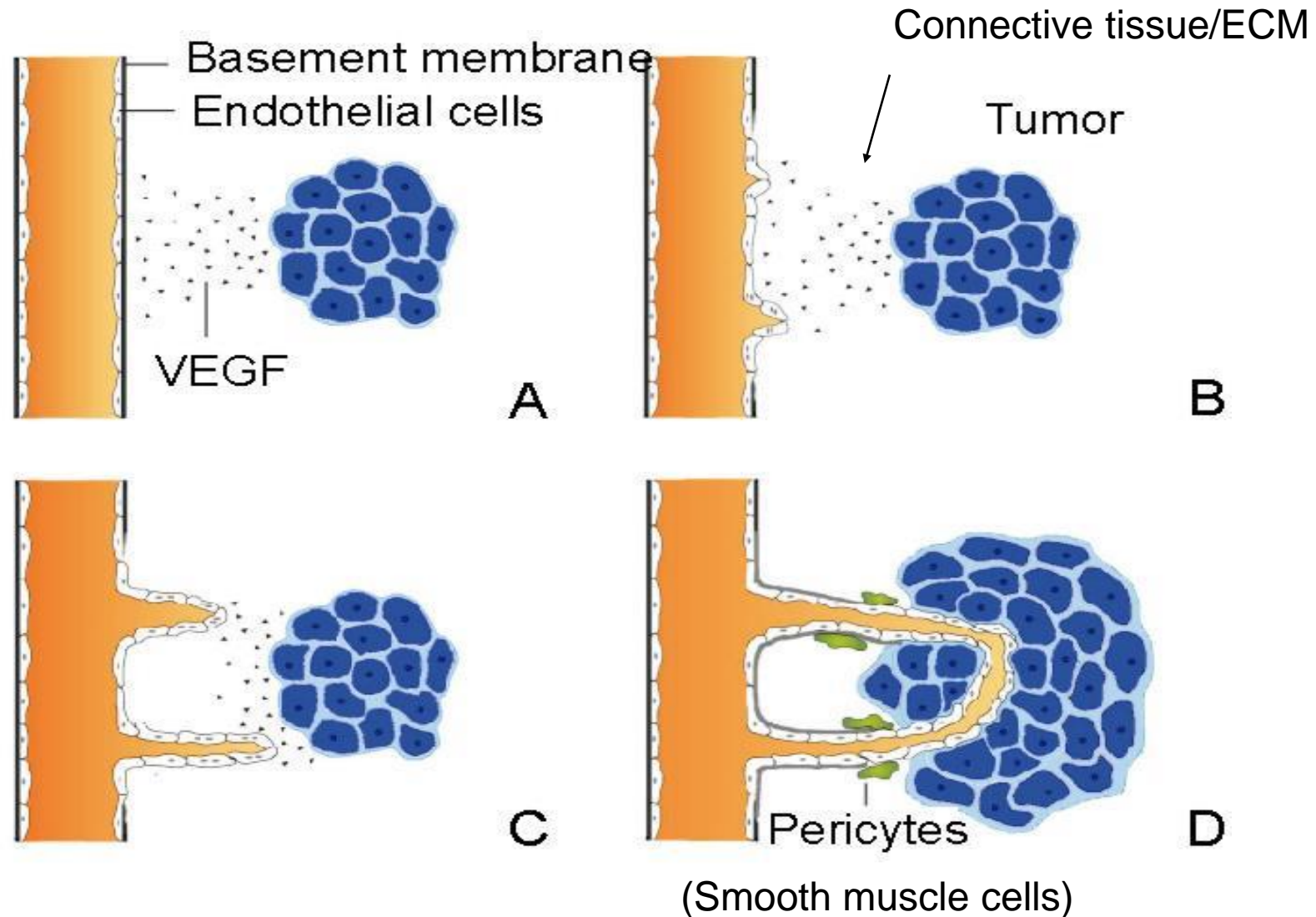


Questions for angiogenesis

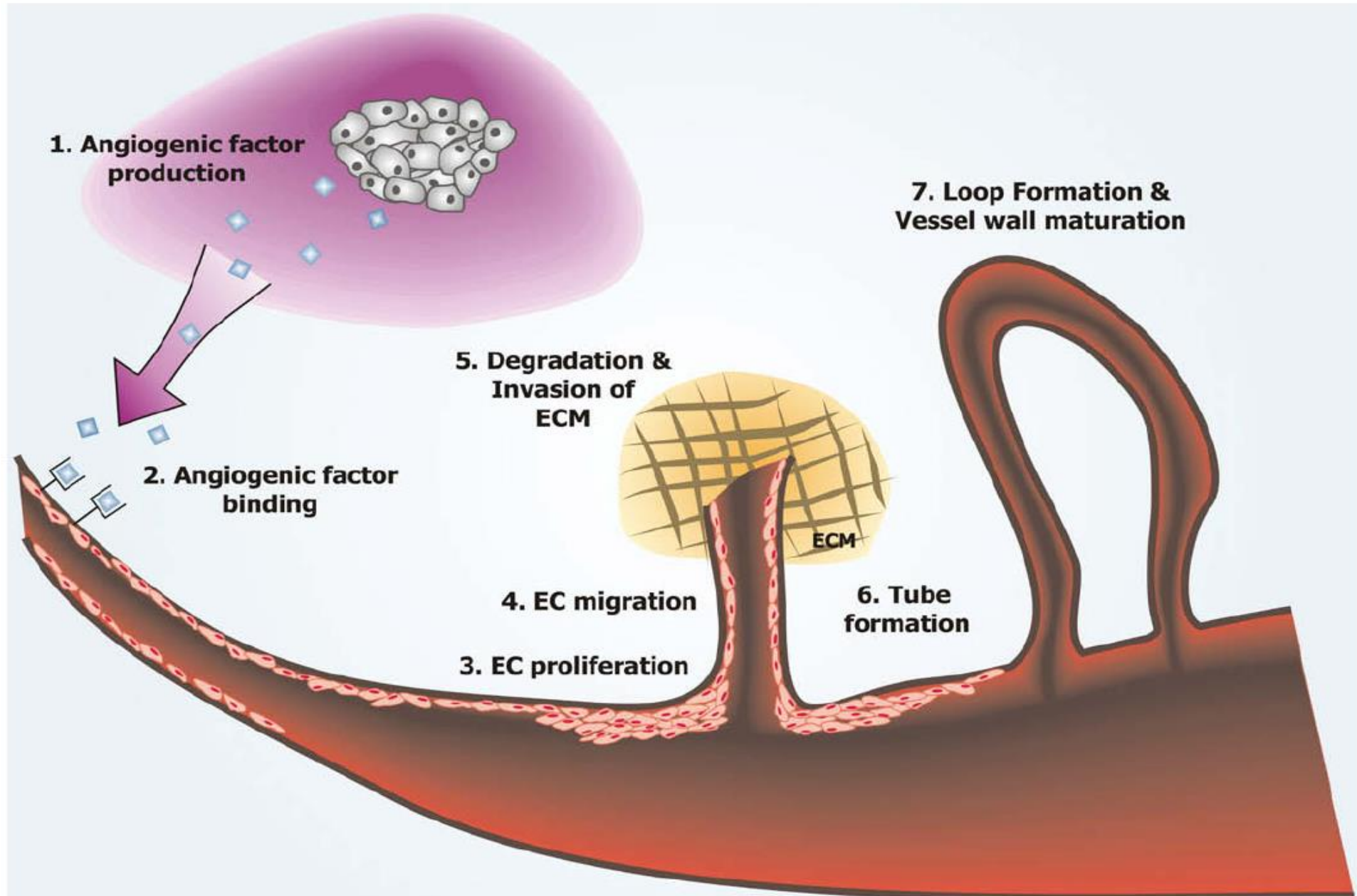
- 1. What is angiogenesis?
- 2. What are the functions of endothelial cells during angiogenesis?
- 3. Which cells can induce angiogenesis?
- 4. What is tumor angiogenesis and what are its consequences?
- 5. Steps and cell processes for tumor angiogenesis?
- 6. Name pro-angiogenic factors
- 7. Transcription factors of angiogenesis, regulation of transcription factors via UPS,
- 8. Which types of angiogenesis do exist in human body?

Tumor angiogenesis

Process of tumor angiogenesis, the formation of tubes from preexisting vessels



Tumor Angiogenesis



Factors necessary for angiogenesis

1. Which factors are involved?

Pro-angiogenic factors

- FGF = fibroblast growth factor
 - **VEGF = vascular endothelial growth factor**
 - EGF = epithelial growth factor
 - TNF α = tumor necrosis factor α
 - Interleukins and prostaglandins
 - **HIF-1 α**
 - β -catenin
 - NF- κ B
 - c-Jun
- } transcription factors

2. Which cells are involved?

- Endothelial cells
- Smooth muscle cells (Pericytes)
- Fibroblasts (cells of the ECM)

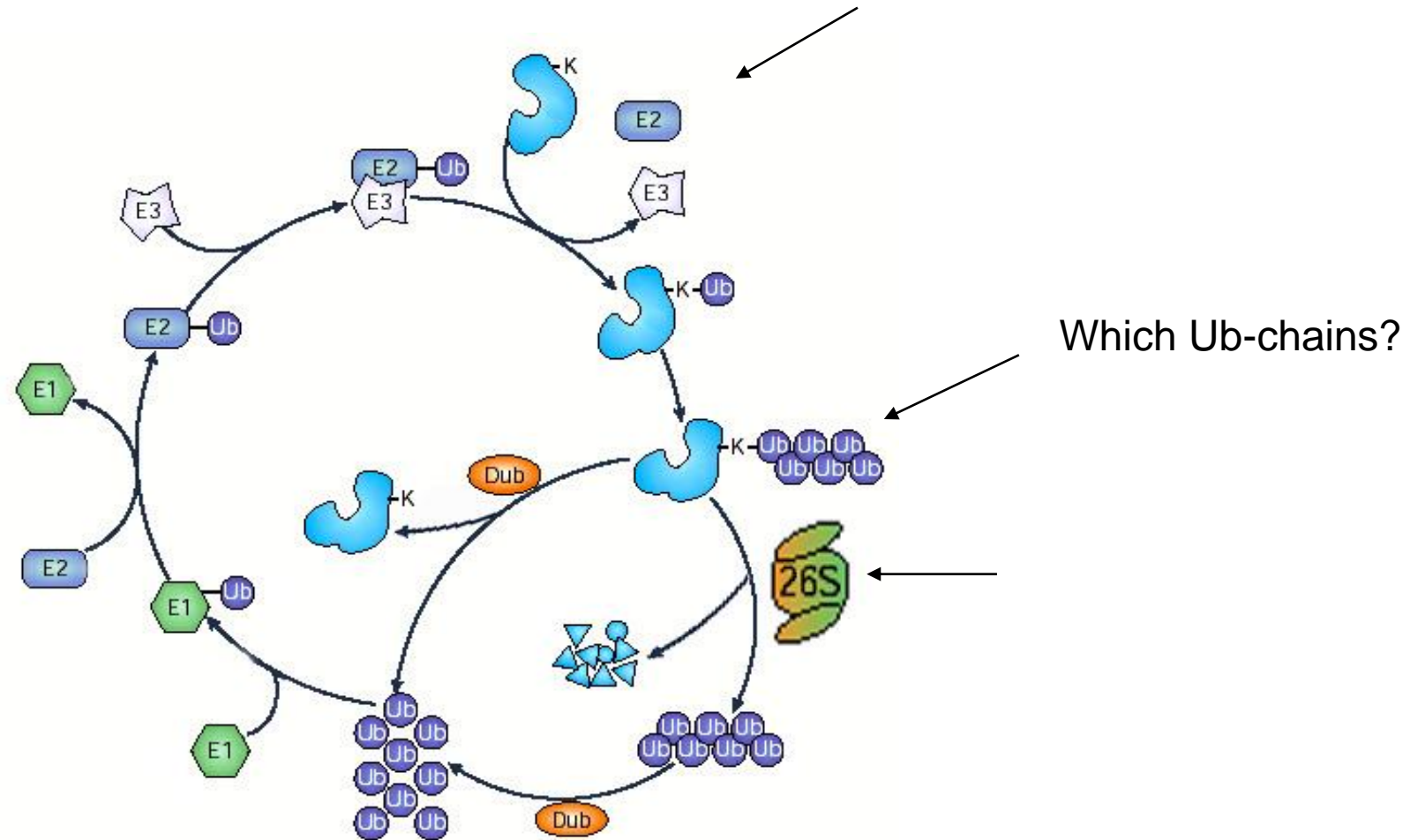
Which cells are involved?

- Endothelial cells (Proliferation, migration, angiogenesis stimulation)
- Visceral smooth muscle cells (Pericytes: vitality of tubes)
- Fibroblasts (ECM remodeling, angiogenesis stimulation)
- **By inflammation**: immune cells (ECM remodeling, angiogenesis stimulation)
- **By tumor angiogenesis**: tumor cells (angiogenesis stimulation)
- **By obesity**: adipocytes, immune cells (angiogenesis stimulation)

Stabilization of transcription factors for angiogenesis:

- **HIF-1 α**
- β -catenin
- NF- κ B
- c-Jun

Regulation of substrate binding to their own E3 Ub Ligases via post-translational modifications e.g hydroxylation, phosphorylation....?

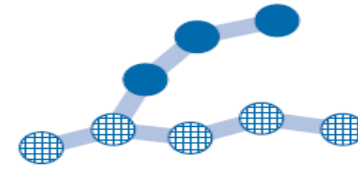


The diversity of possible Ub chains

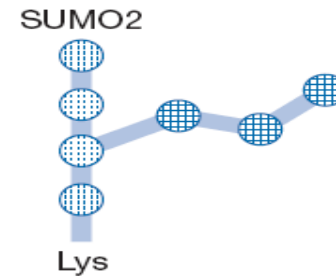
A Homotypic



B Mixed chain



C Heterologous



D Multiple monoubiquitylation



Institut für Experimentelle Innere Medizin
Medizinische Fakultät
Otto-von-Guericke-Universität Magdeburg

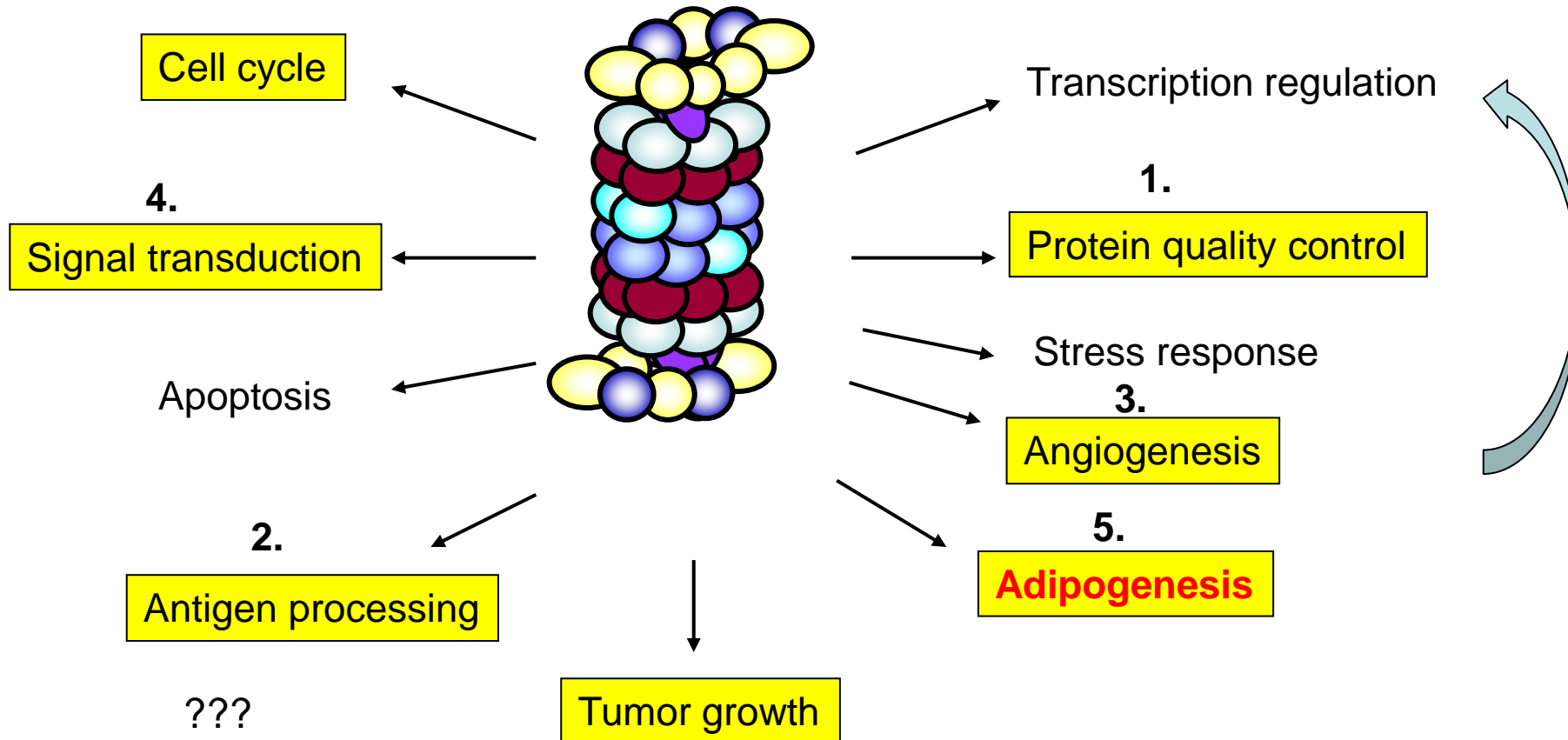


VL 4 (Dr. Dawadschargal Dubiel)

Adipogenesis/Adipogenese

Functions of the ubiquitin proteasome system (UPS) in cells

26S proteasome



Outlines:

- Definition of obesity/adipositas
- Human adipose tissues
- Adipocytes types
- White adipose tissue (WAT) is connected with obesity
- Causes for obesity

Components of the WAT

-Processes in the WAT (Adipogenesis, Angiogenesis, Apoptosis, Infiltration of immune cells)

-Expansion of the WAT:

-Hyperplasia and hypertrophy of adipocytes

-Adipogenesis: Definition

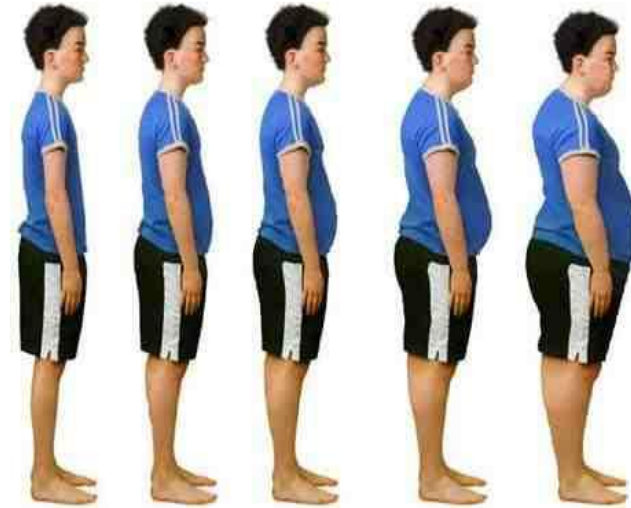
Inducers

Features of white adipocytes: Secretion of adipokines
(Adipokines, mechanism)
Accumulation of lipid droplets
(Formation, expansion and degradation of LDs)

- Obesity-associated diseases:
- Treatments of obesity

Obesity - Adipositas

- **Adipositas**, from latin *adeps* „Fat“
- Obesity is abnormal or excessive fat accumulation that may impair health (WHO).
- Obesity is defined as excess of fat with a body mass index (BMI) of 30 kg/m² or greater



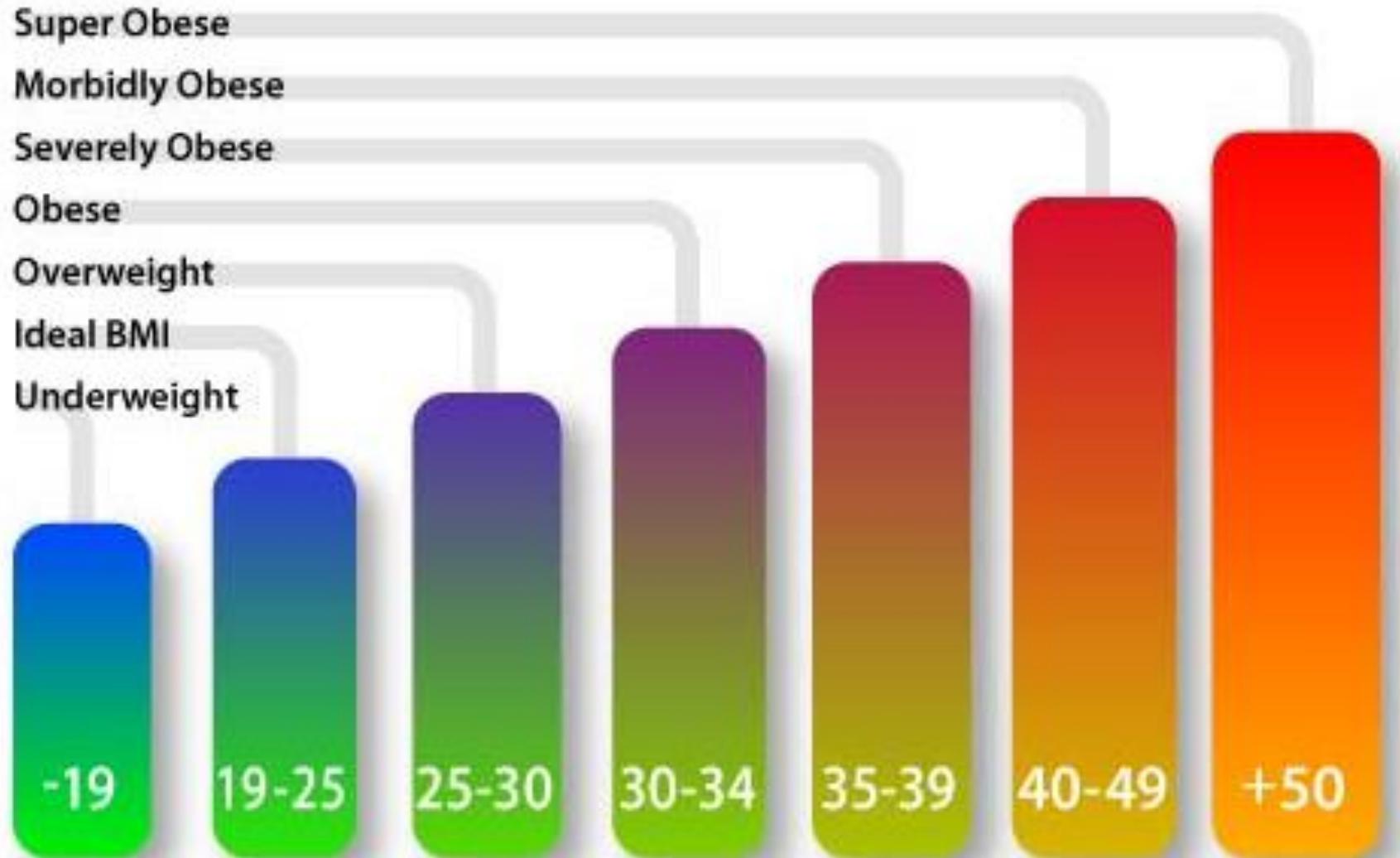
CALCULATE YOUR

$$\text{BMI} = \frac{\text{WEIGHT (kg)}}{\text{HEIGHT X HEIGHT (Metre)}}$$

- waist circumferences
(Bauchumfang)



BMI Classification



A worldwide epidemic...

- 1997: WHO formally recognized obesity as a global epidemic
- Currently more than 500 million obese people worldwide
- Obesity and overweight are linked to many co-morbidities:
 - Atherosclerosis
 - Diabetes type 2
 - Heart disease
 - Cancer, high risk
 - High risk for COVID19

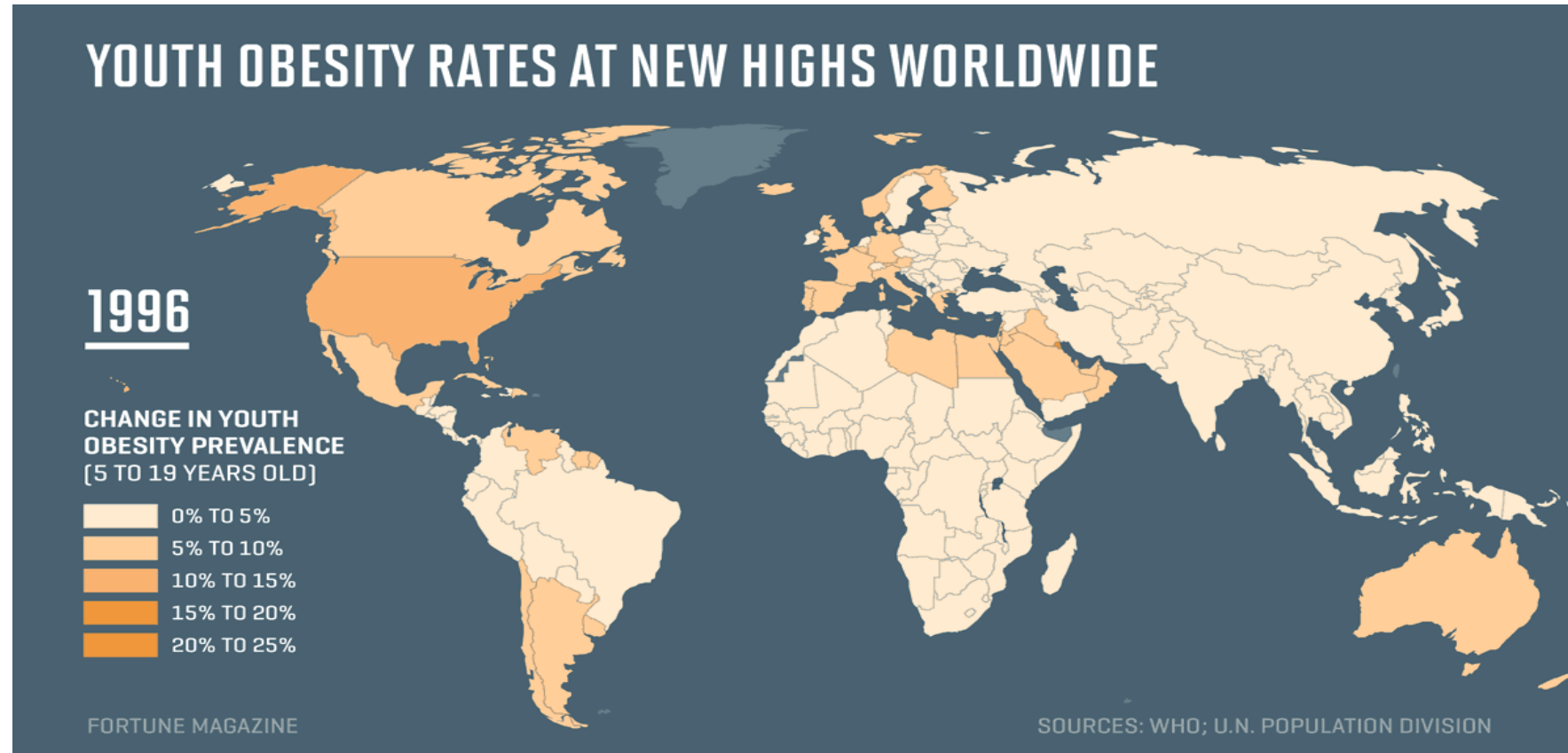
A worldwide epidemic...

WHO: 9 June 2021

Data of 2016

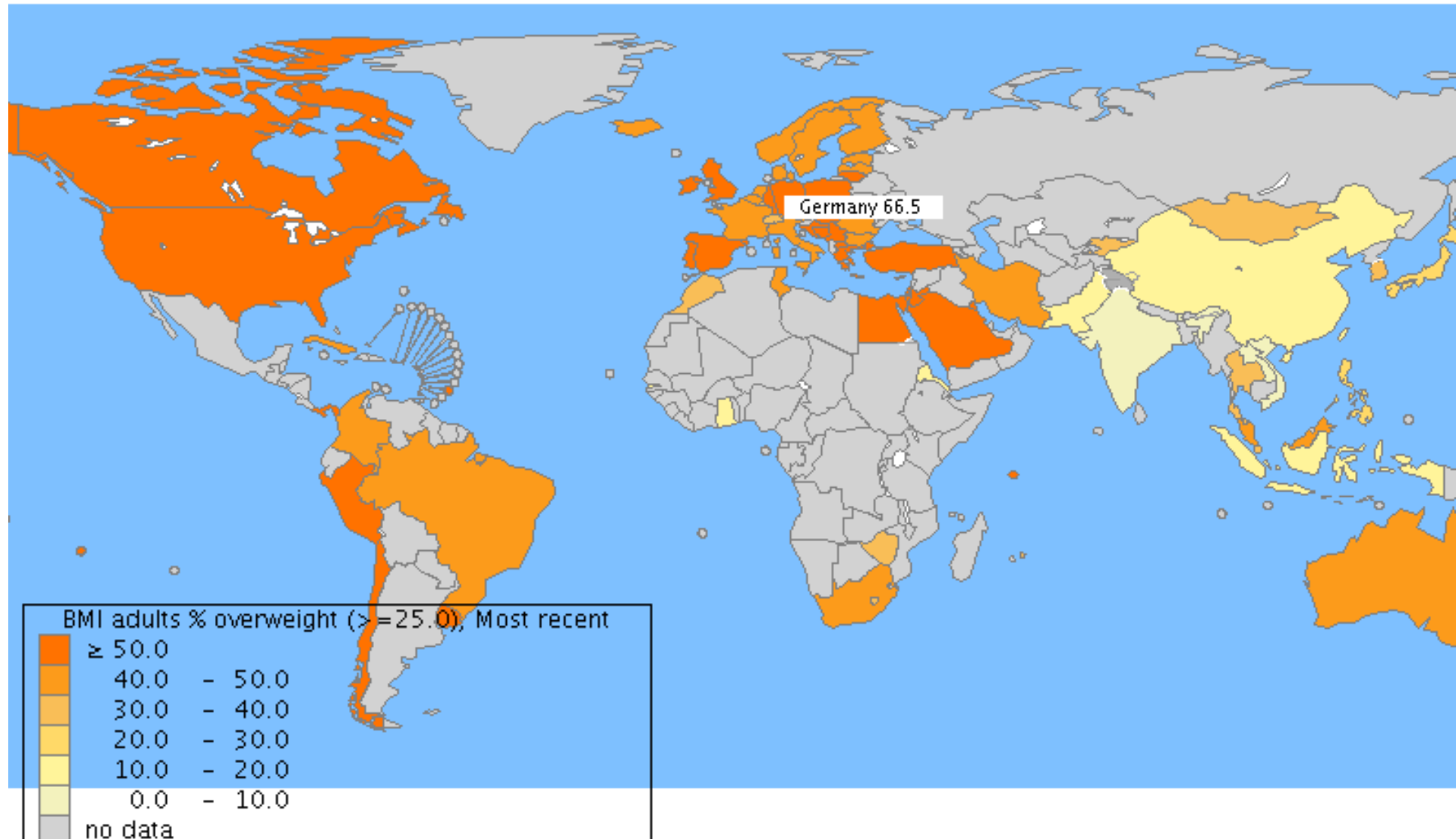
- **Worldwide obesity has nearly tripled since 1975.**
- **In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese:**
- **39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.**
- **39 million children under the age of 5 were overweight or obese in 2020.**
- **Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016.**
- **Obesity is preventable?**

A worldwide epidemic...



1. High-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in Asia and Africa .
2. In Africa, the number of overweight children under 5 has increased by nearly 24% percent since 2000. Almost half of the children under 5 who were overweight or obese in 2019 lived in Asia.

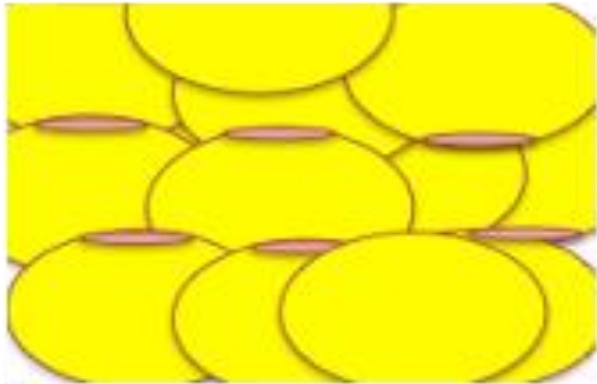
A worldwide epidemic...



Types of adipose tissue

- Which fat tissue do occur in human body?

White adipose tissue (WAT)



Throughout the body

Unilocular lipid droplets

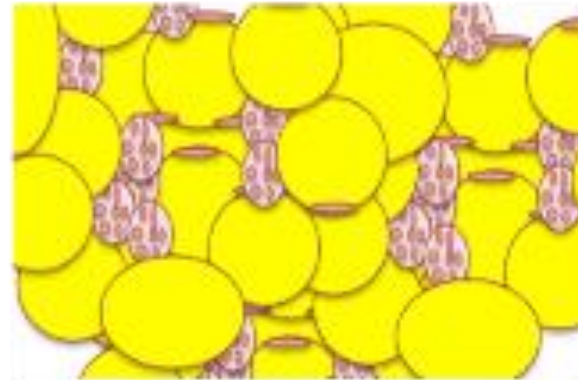
Sparse mitochondria

Storage site of energy surplus

Energy storage

Thermogenesis???

Beige adipose tissue (BAT???)



Infiltrated in WAT

Multilocular lipid droplets

infiltrated in WAT, vascularized,
and innervated

Mitochondria dense

Energy produced in the form of
heat

Recruited by cold and
pharmacological stimuli

Thermogenesis

Brown adipose tissue (BAT)



Mostly interscapular

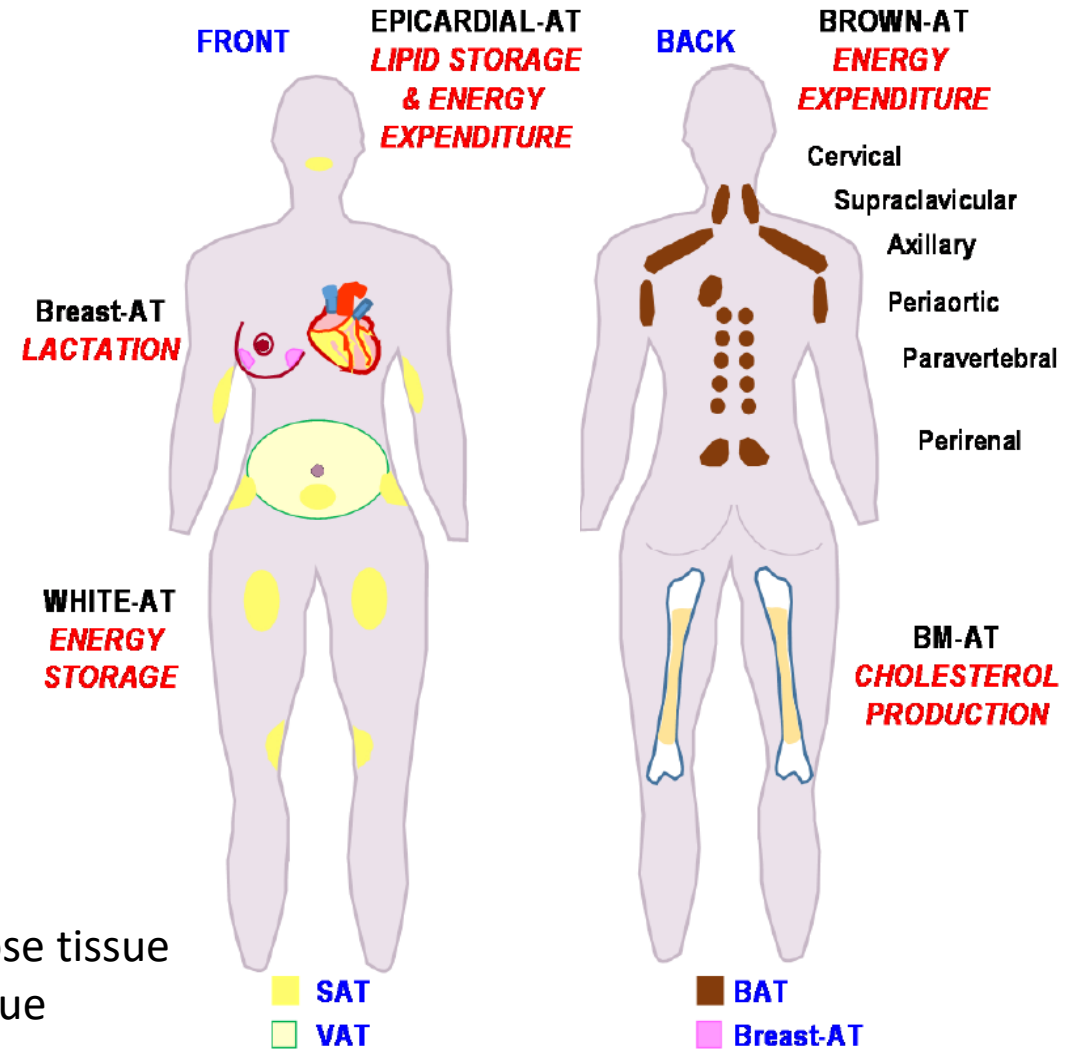
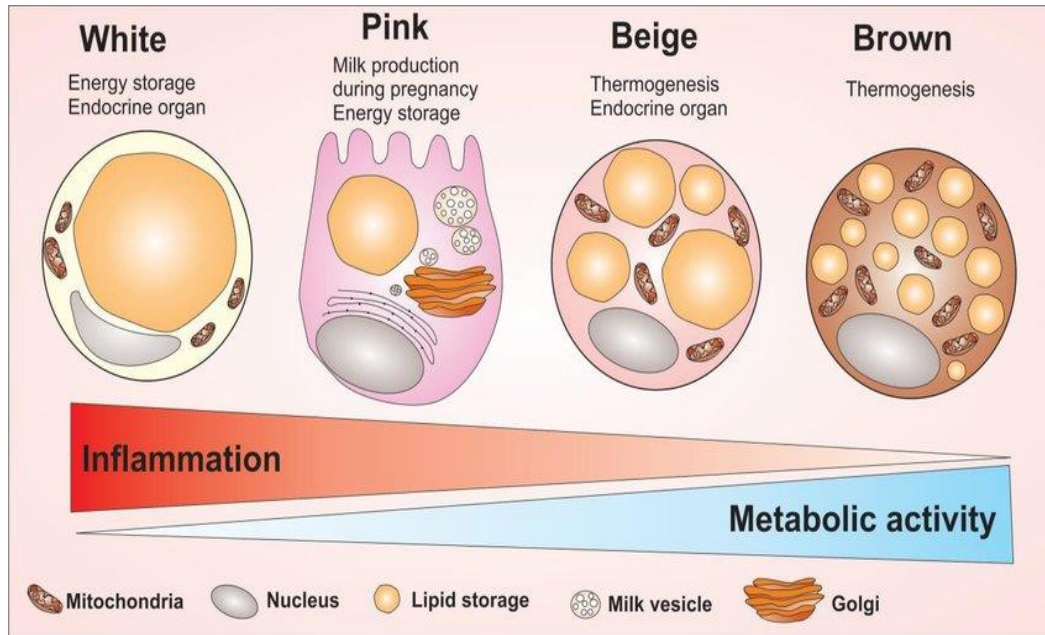
Multilocular lipid droplets

Highly vascularized and
innervated

Mitochondria dense

Energy produced in the form of
heat

Location of adipose tissues on human body



Secretion of adipokines different!

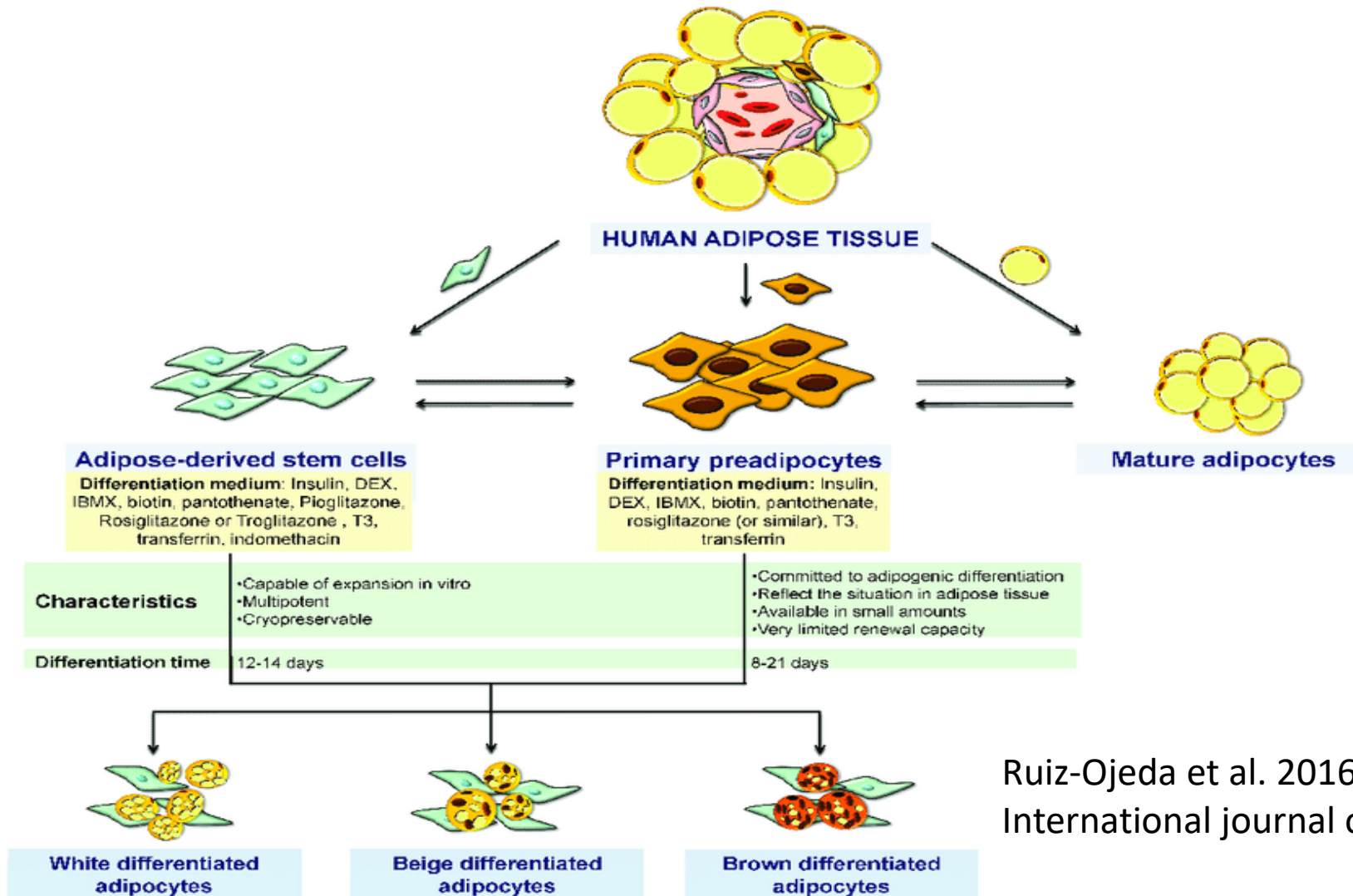
Ladoux et al. 2021, Biomedicines

SAT: subcutaneous adipose tissue
VAT: visceral adipose tissue

Occurrence of different adipose tissues

- White adipose tissues (WAT): by adults and children (e.g. subcutaneous, visceral)
- Brown adipose tissues (BAT): by babies, very rare by adults and by most of winter sleeping animals
- Beige adipose tissue: Inducible by cold and pharmacological agents by adults, location almost exclusively in subcutaneous (SAT) depots in humans
- Pink adipose tissue: women
- Blue adipose tissue: adults in liver???

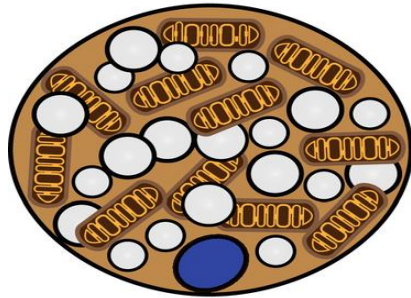
Adipocytes types in human adipose tissue



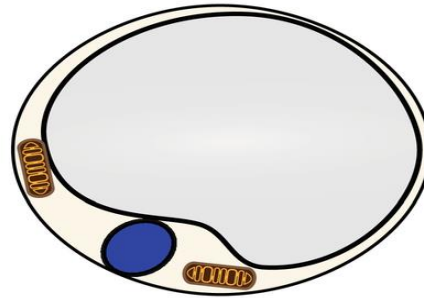
Ruiz-Ojeda et al. 2016
 International journal of molecular sciences

Adipocytes types

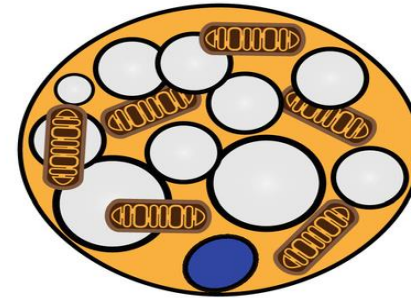
Brown Adipocyte



White Adipocyte



Brite (or Beige) Adipocyte



 Mitochondria
  Nucleus
  Lipid droplet

	<i>Brown</i>	<i>White</i>	<i>Brite/beige</i>
UCP1 Expression	Positive	Negative	Positive
Mitochondrial Density	High	Low	Medium
LD Morphology	Multi-locular	Uni-locular	Multi-locular
Primary Function	Thermogenesis Endocrine	Energy storage Endocrine	Thermogenesis? Endocrine?



Functions of white adipose tissue

- Energy storage
- Protect some inner organs
- Normal glucose homeostases
- Dermal white adipose tissue: protect from pathogen, activation of immune system during inflammation and wound healing, wound healing
- Regulation of hormones → more functions: regulation of appetite, glucose metabolism etc.

**Abnormal and excessive accumulation of the
white adipose tissue**

(WAT)



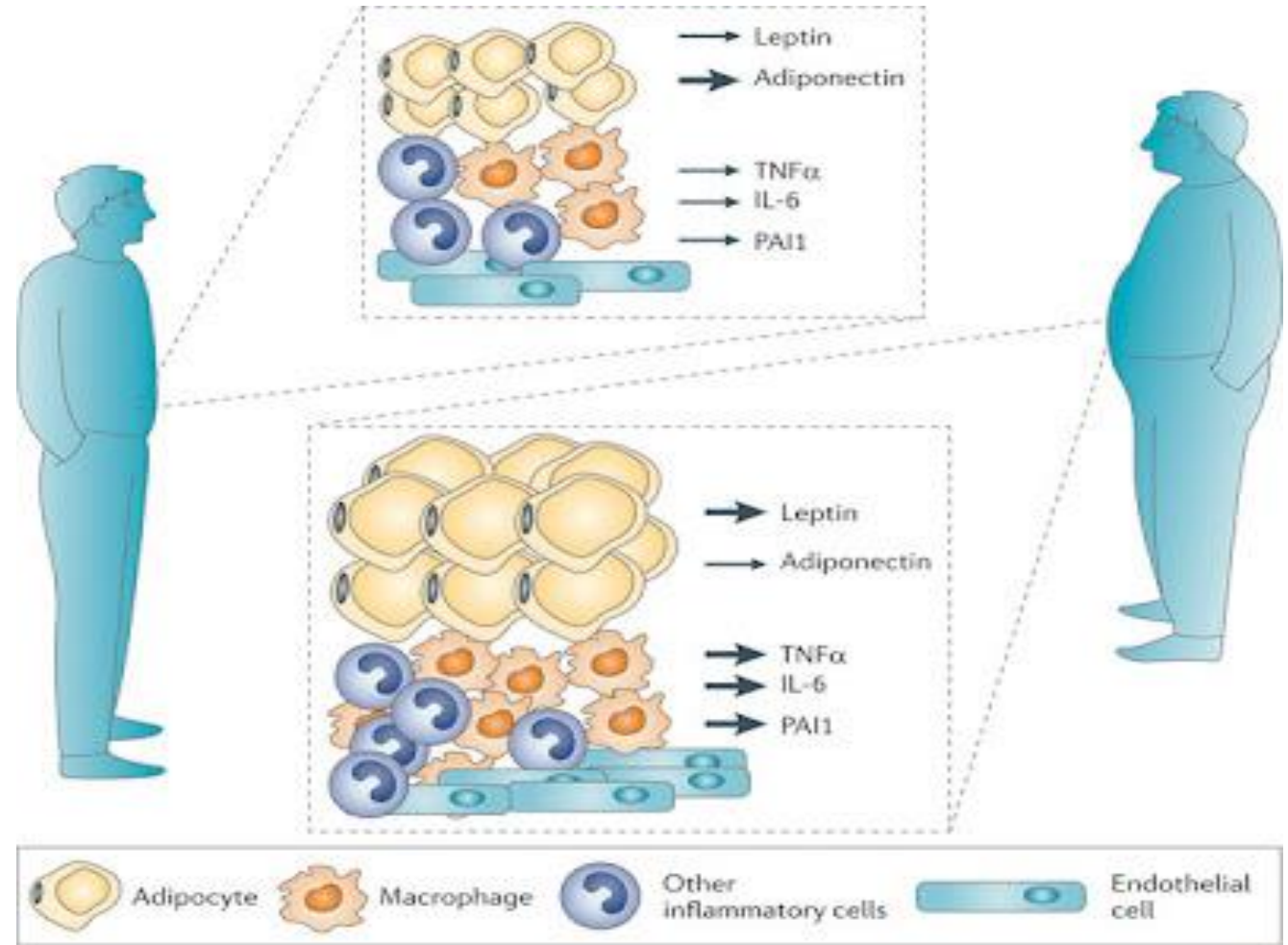
Obesity

Causes for obesity

- A combination of excessive food intake (fast food), lack of physical activities
- Genetical reason: very limited
- Medications: e.g. hormones
- Virus (infection???)

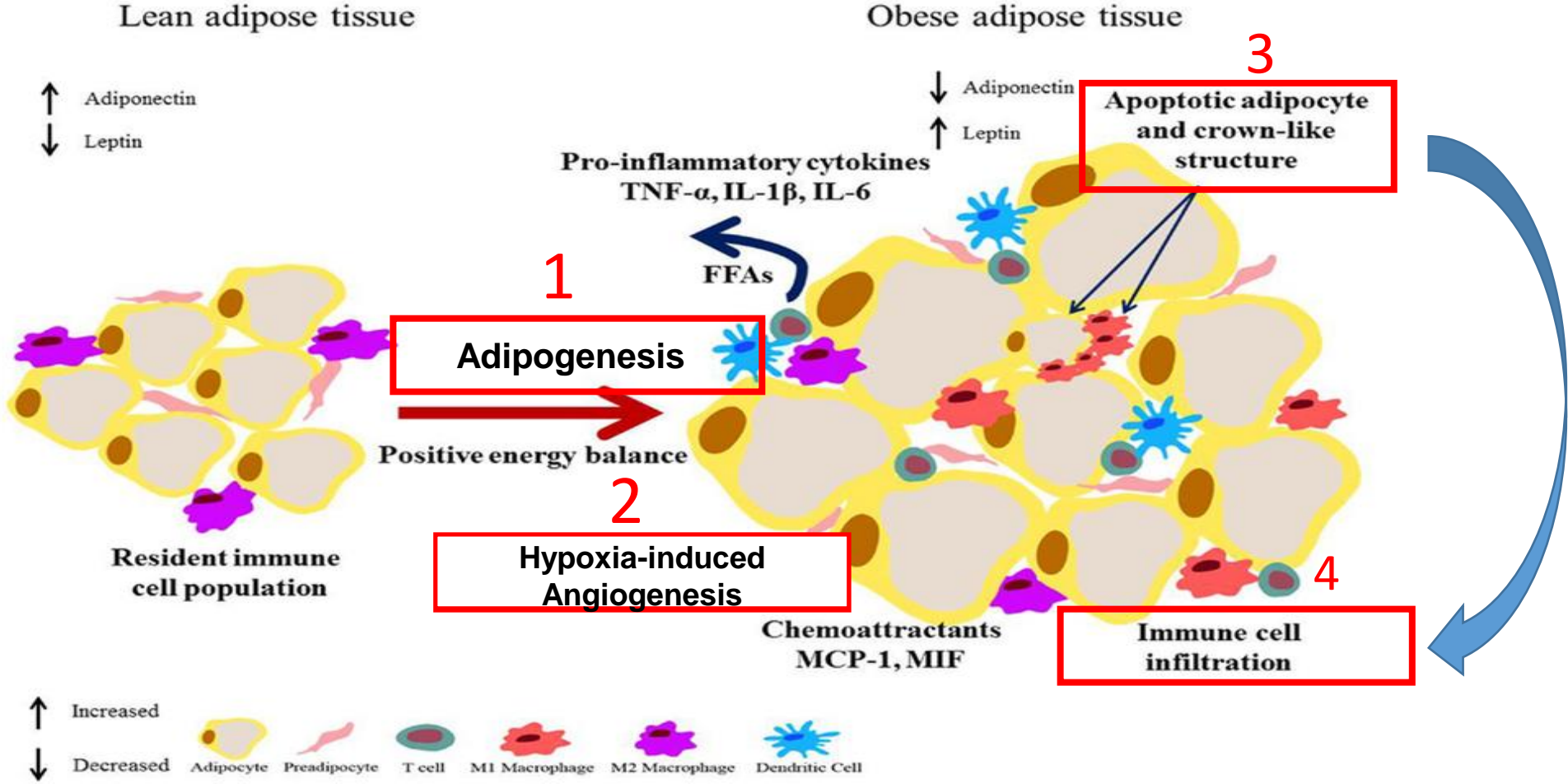
Components of the white adipose tissue (WAT)

- Mature adipocytes
- Preadipocytes
- Immune cells
- Endothelial cells
- Nerves



Nature Reviews | Cancer

Cellular processes which are active in the white adipose tissue (WAT)



Cell processes which are active in adipose tissues:

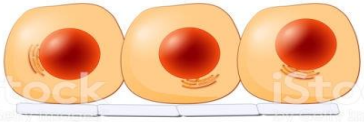
- Adipogenesis (for expansion of WAT): **mesenchymal stem cells (MSCs)**, preadipocytes, adipocytes
- Angiogenesis (for expansion of WAT): endothelial cells
- Apoptosis (for immune cell infiltration)
- Infiltration of immune cells: immune cells

How does expand the white adipose tissue?

(Hyperplasia & Hypertrophy from adipocytes)

Cell hyperplasia and hypertrophy:

Healthy cell



Hypertrophy



Increase in cell size

Hyperplasia



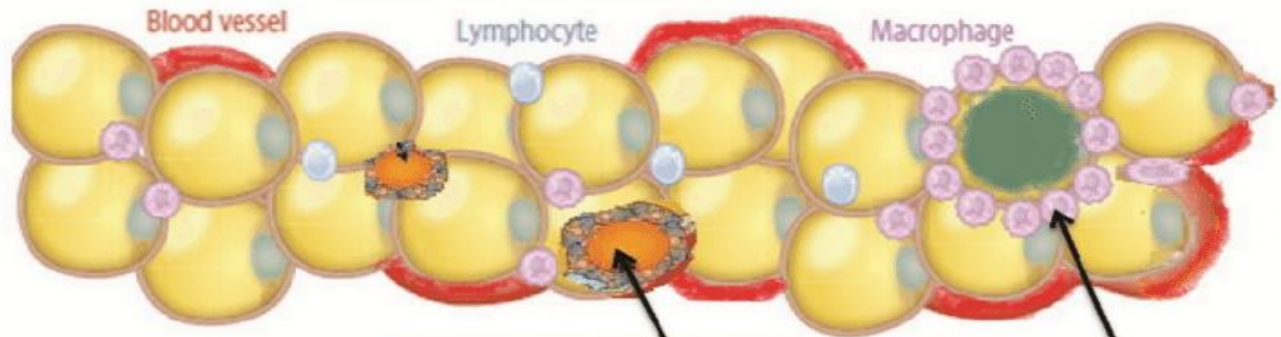
Increase in cell number

Lean adipose tissue



Obesity

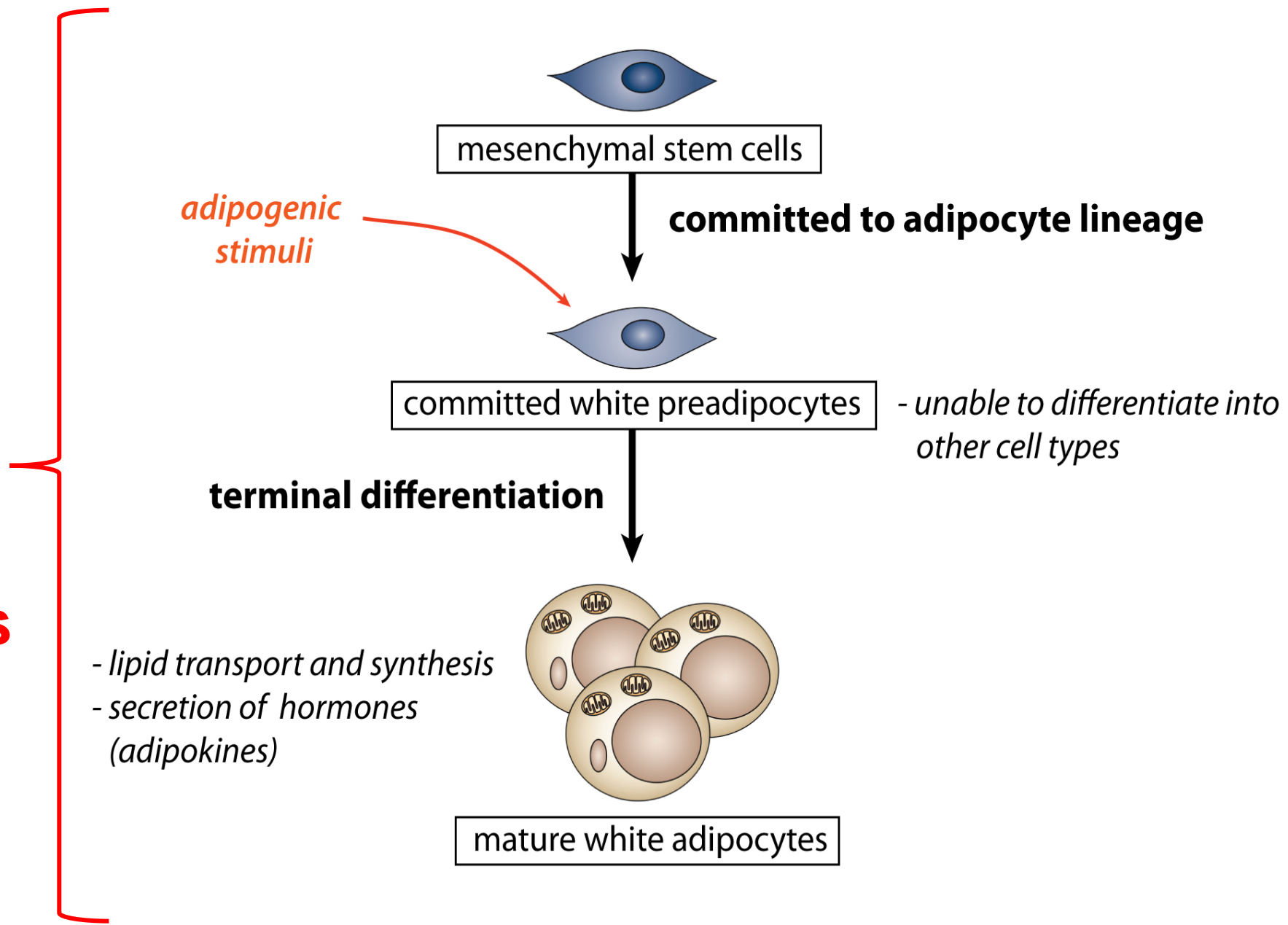
Hyperplasia and hypertrophy



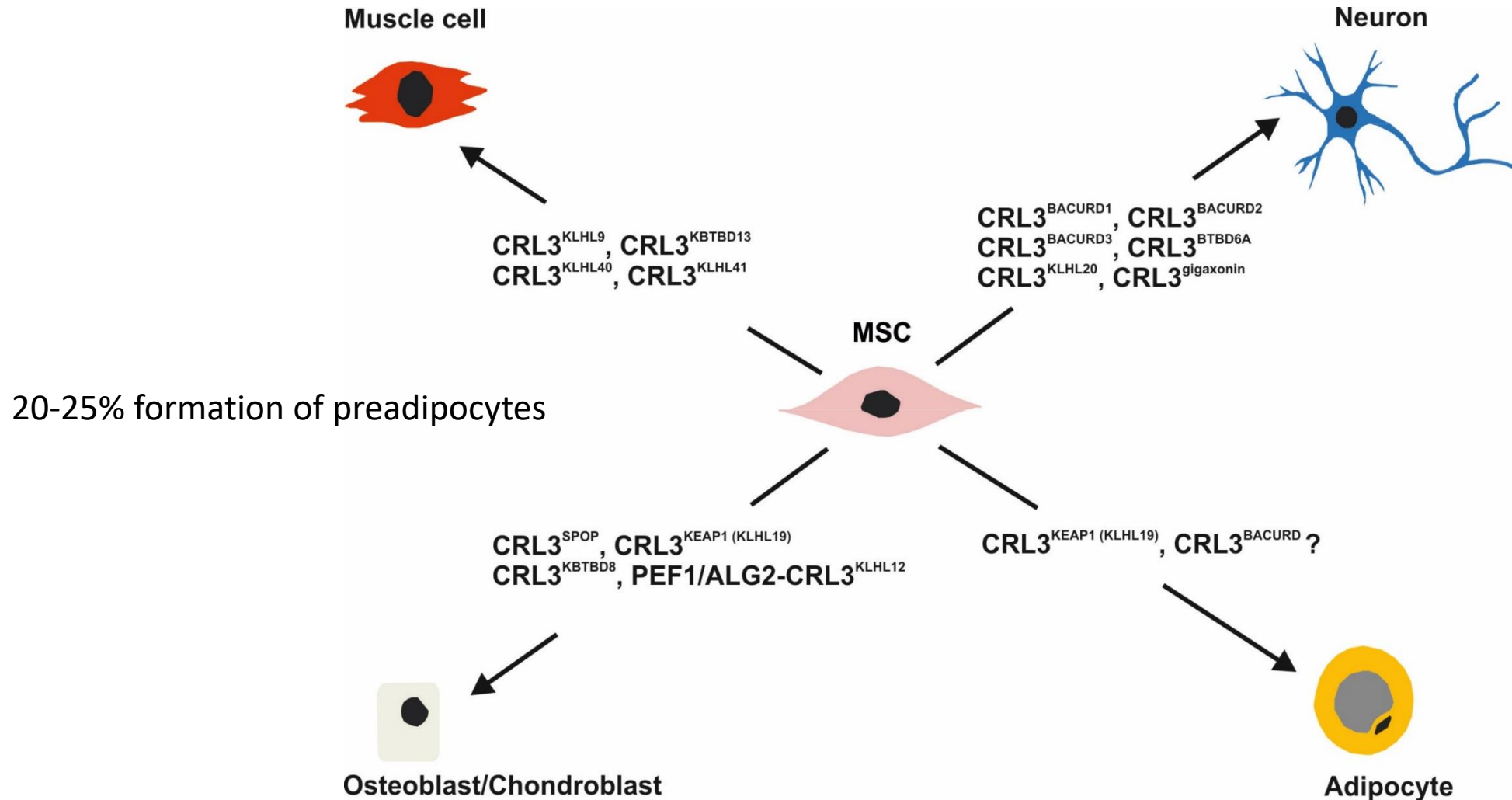
Group of adipo-angiogenic cells (angiogenesis and adipoangiogenesis)

Crown structure (died adipocytes and macrophages M1)

1. Adipogenesis



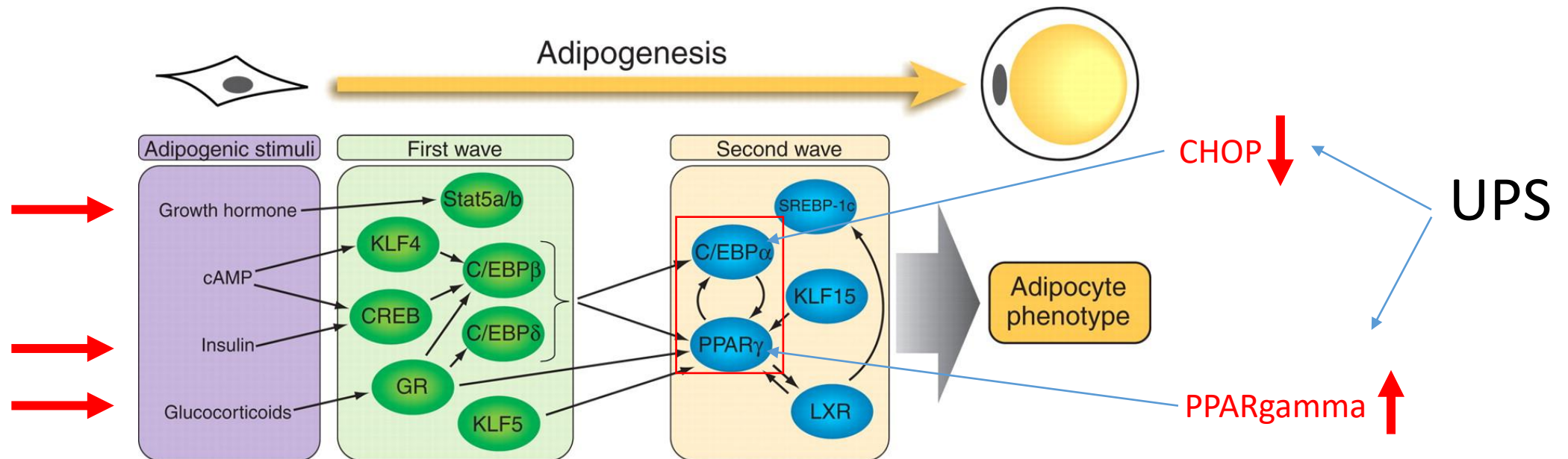
Multilineage differentiation programs of mesenchymal stem cells (MSCs)



Dubiel, W., Dubiel, D., Wolf, D.A., and Naumann, M. (2018). Cullin 3-Based Ubiquitin Ligases as Master Regulators of Mammalian Cell Differentiation. *Trends Biochem Sci* 43, 95-107.

Inducers of adipogenesis

- adipocyte differentiation from fibroblast-like preadipocytes to lipid-loaded adipocytes.

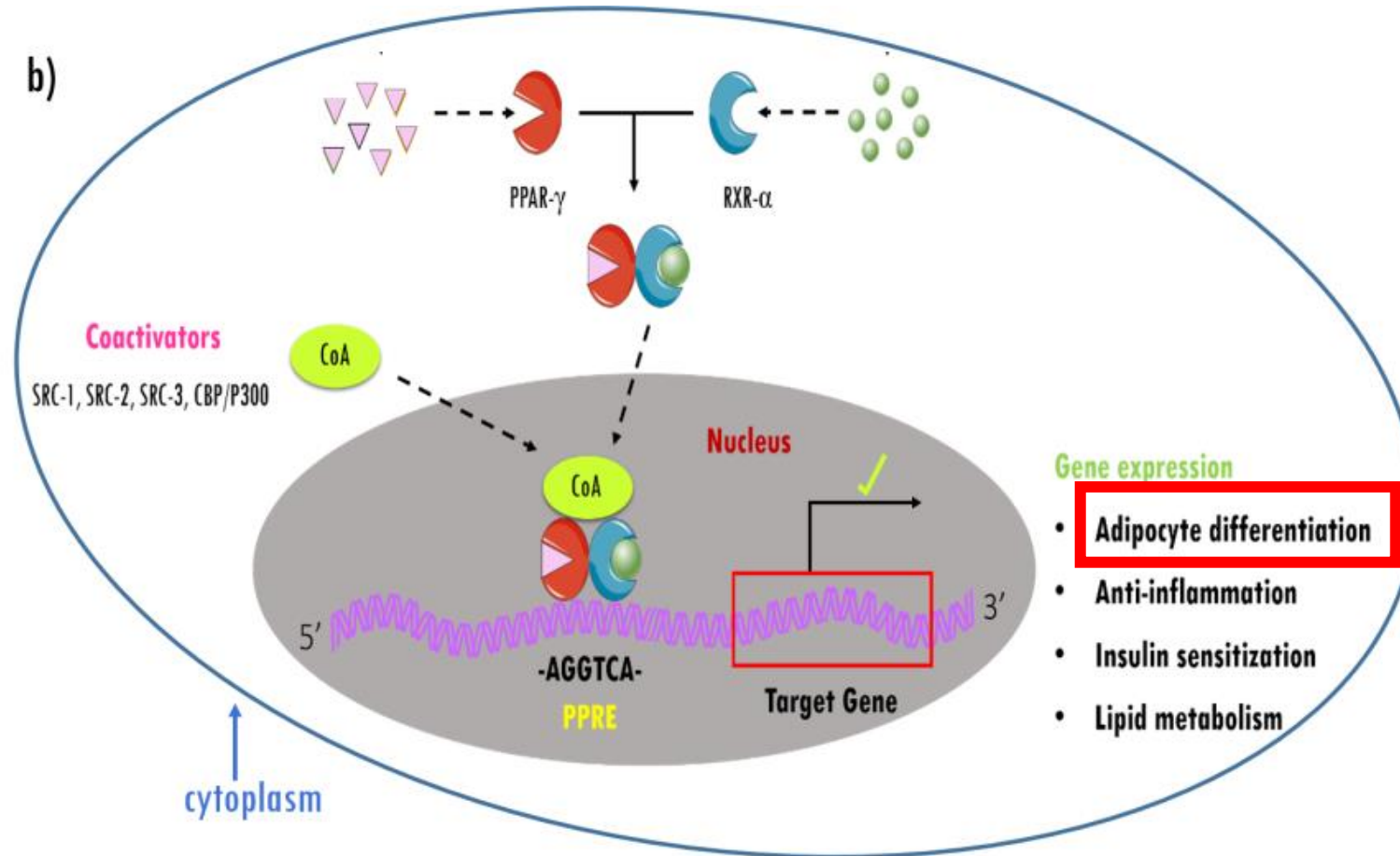


Transcriptional Networks Controlling Adipocyte Differentiation.

R. SIERSBÆK AND S. MANDRUP. Cold Spring Harbor Symposia on Quantitative Biology.

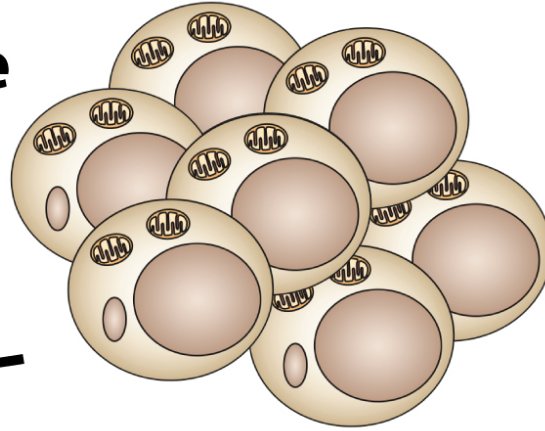
Dysfunction of adipogenesis is a hallmark of obesity.

PPAR- γ inducible genes



Why study adipogenesis?

White Adipose Tissue (WAT)



functions



- energy storage
- endocrine organ
 - **leptin** regulating metabolism
 - **adiponectin** regulating insulin sensitivity
- ...

diseases



- Lipodystrophy
 - reduced adipose tissue
 - ectopic lipid storage
- Obesity
 - adipocyte expansion and increased adipogenesis

2. Obesity needs angiogenesis

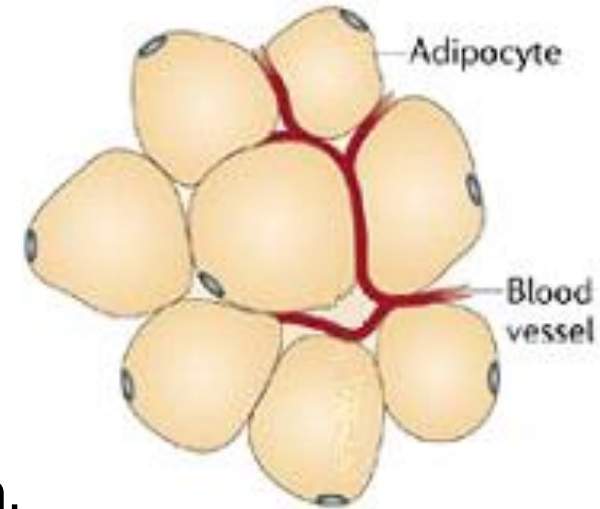
Under which conditions angiogenesis is switched on?

Normal angiogenesis:

- 1. Embryogenesis**
- 2. Menstruation**
- 3. Wound healing**
- 4. Obesity, adipose tissue expansion requires vascularization**

2. Obesity needs angiogenesis

- The adipose tissue growth by cell proliferation and differentiation of preadipocytes called adipogenesis
- Differentiating preadipocytes produce proangiogenic factors such as **VEGF**
- ❖ **Adipogenesis needs angiogenesis** to supply growing adipose tissue with nutrients and oxygen, vasculature responds by increasing the number and/or size of blood vessels.
- **Inhibition of angiogenesis reduces obesity?**

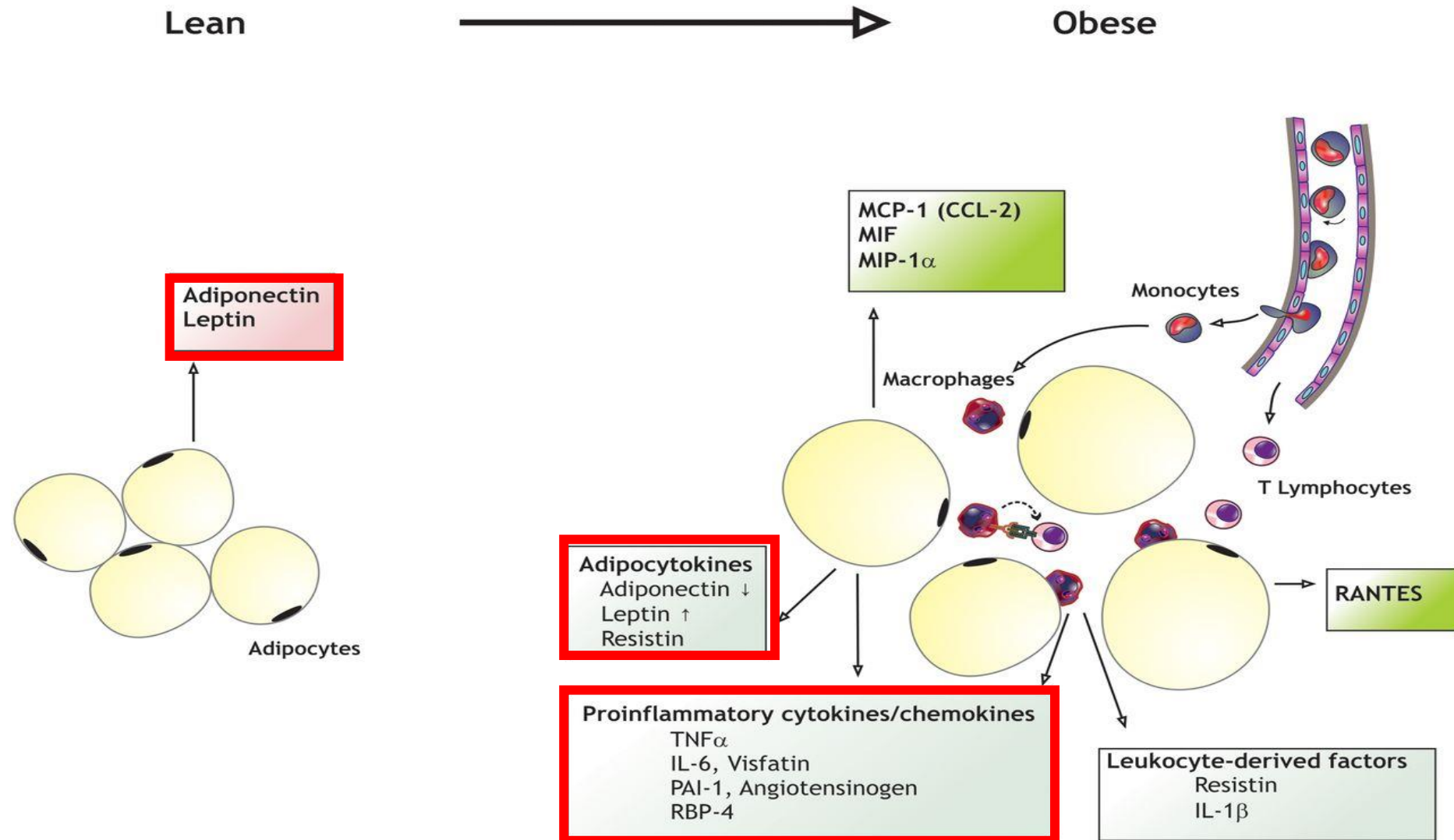


3. Apoptosis

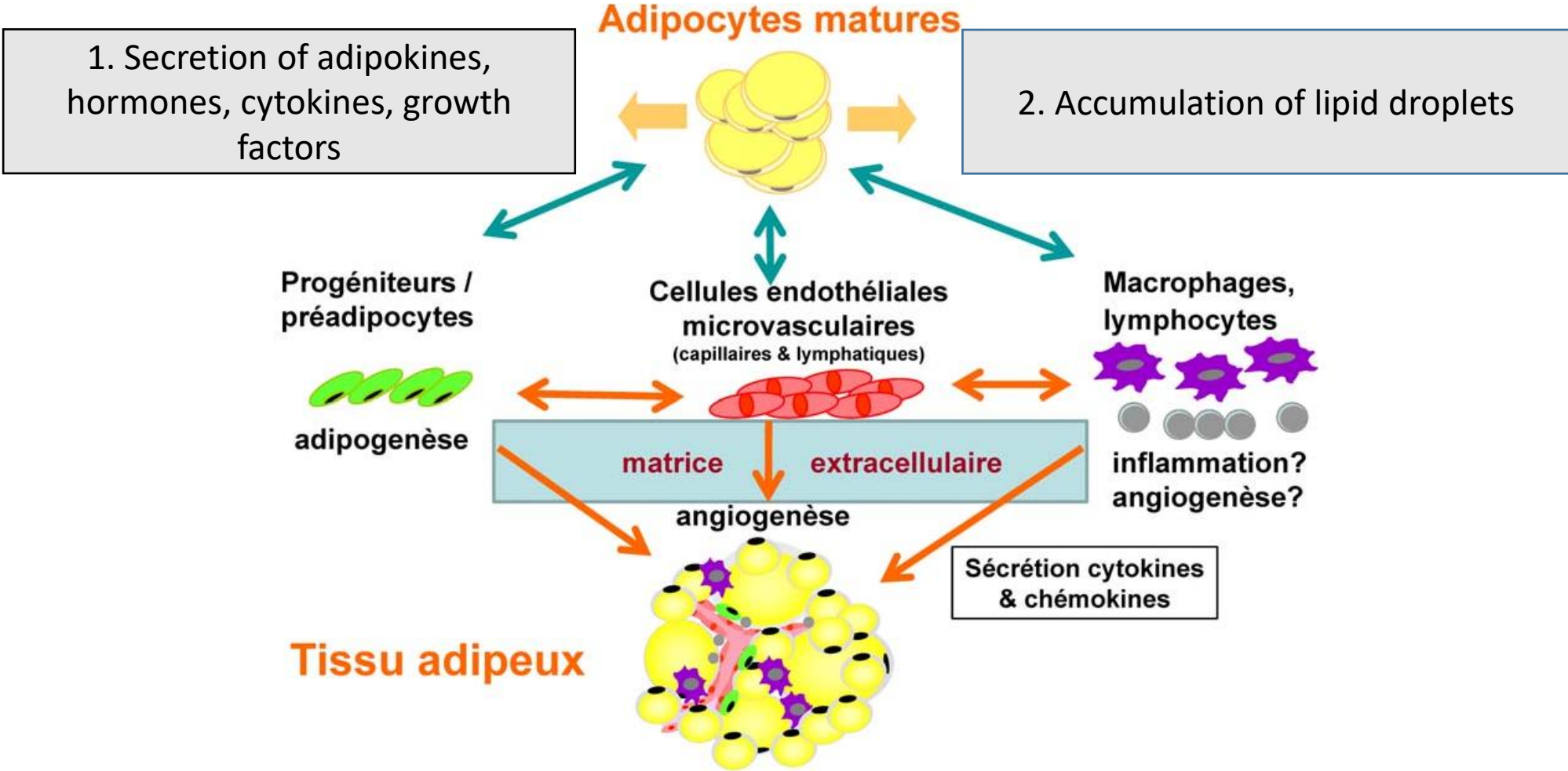
**Obese tissues contain apoptotic
adipocytes**

→ immune cell infiltration

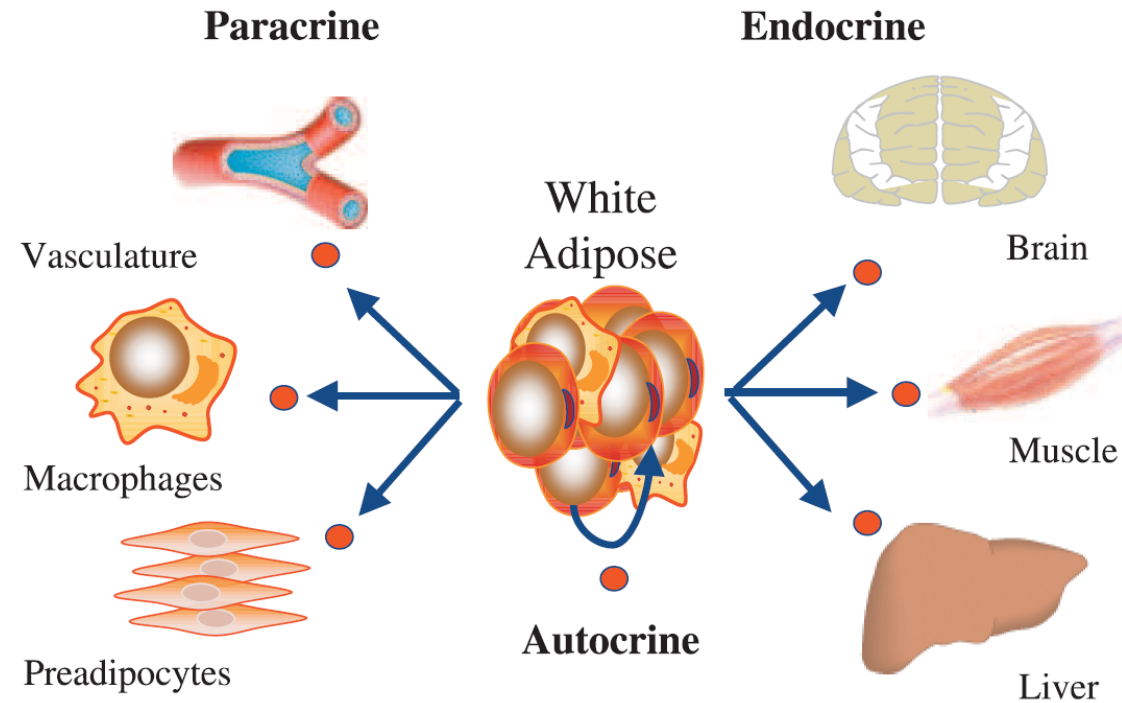
4. Obesity induces immune cell infiltration



Features of adipocytes



1. WAT is an endocrine organ, which influence itself and other organs



Adipokines with demonstrated autocrine, paracrine, and/or endocrine effects:

Cytokines and Cytokine-Like Proteins:

Leptin, TNF α , IL-6

Complement-Related Proteins:

Adiponectin, Adipsin, and ASP

Fibrinolytic Proteins:

PAI-1

Proteins of the Renin–Angiotensin System:

Angiotensin II

Others:

Resistin, Visfatin, RBP-4, Adrenomedullin

Secretion products of adipose tissues

- Adipose tissue secretion products

- Adipokines e. g. leptin, adiponectin

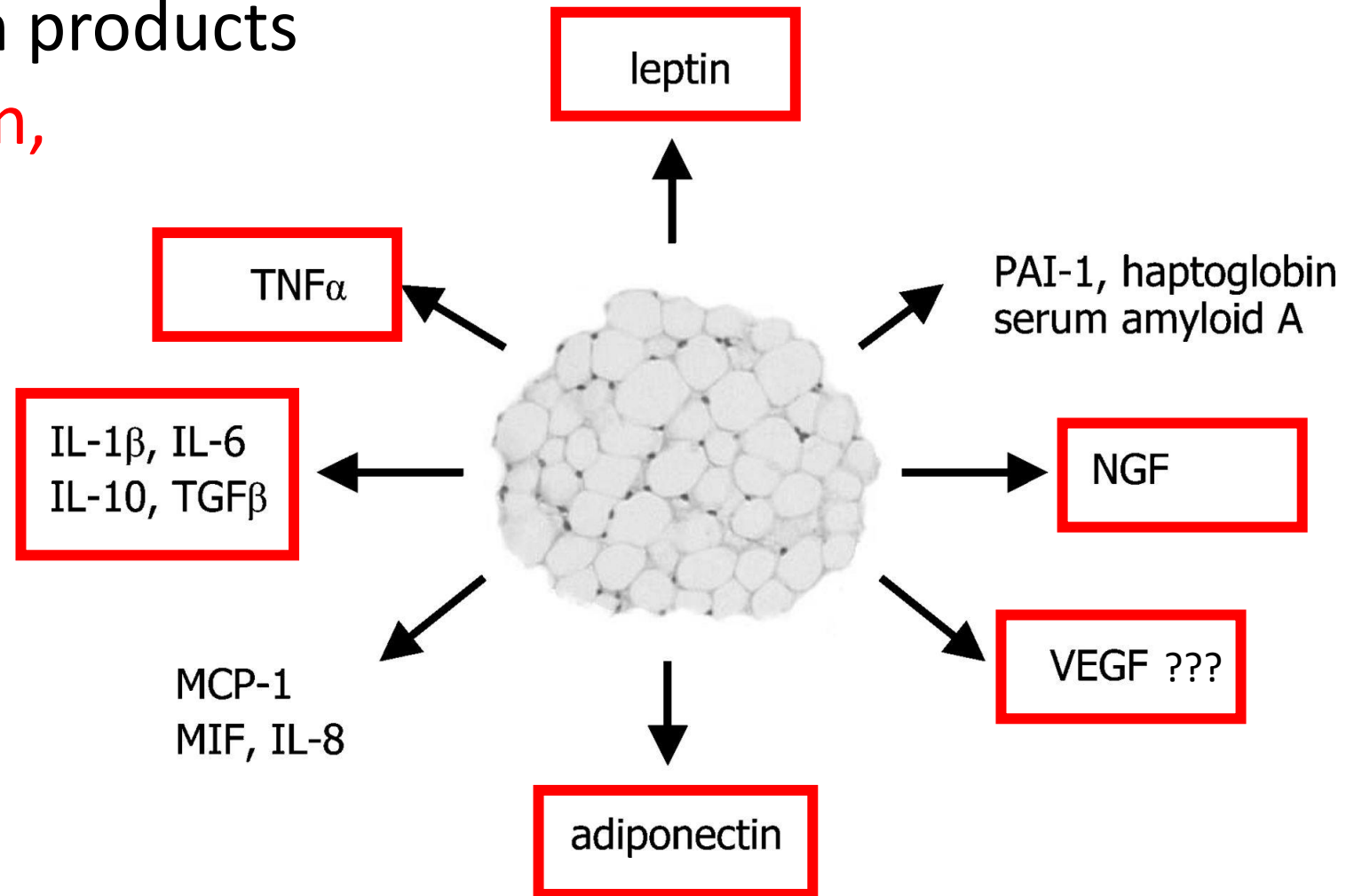
- Other hormones

- Growth Factors

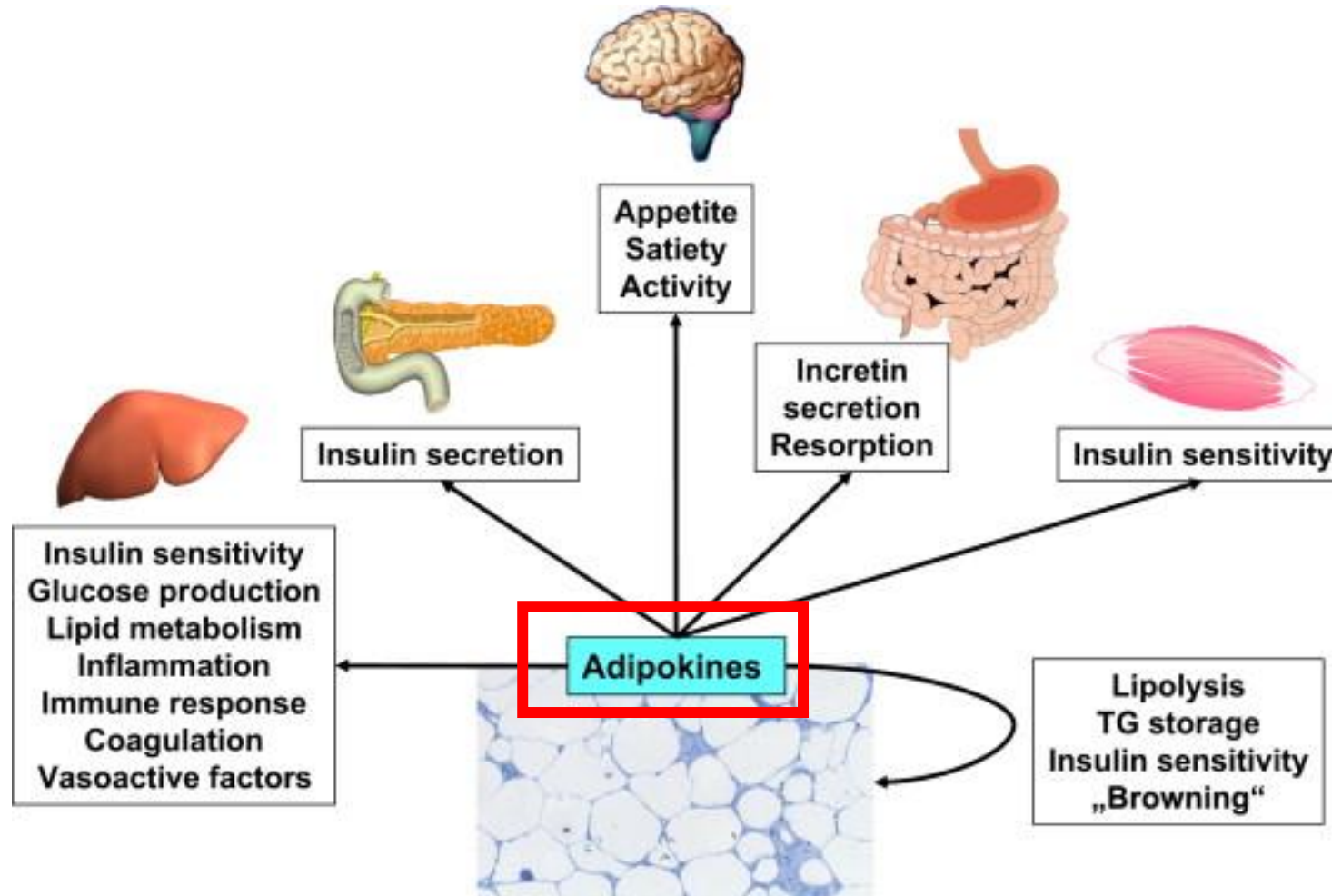
- Cytokines

- VEGF

- Chemokines



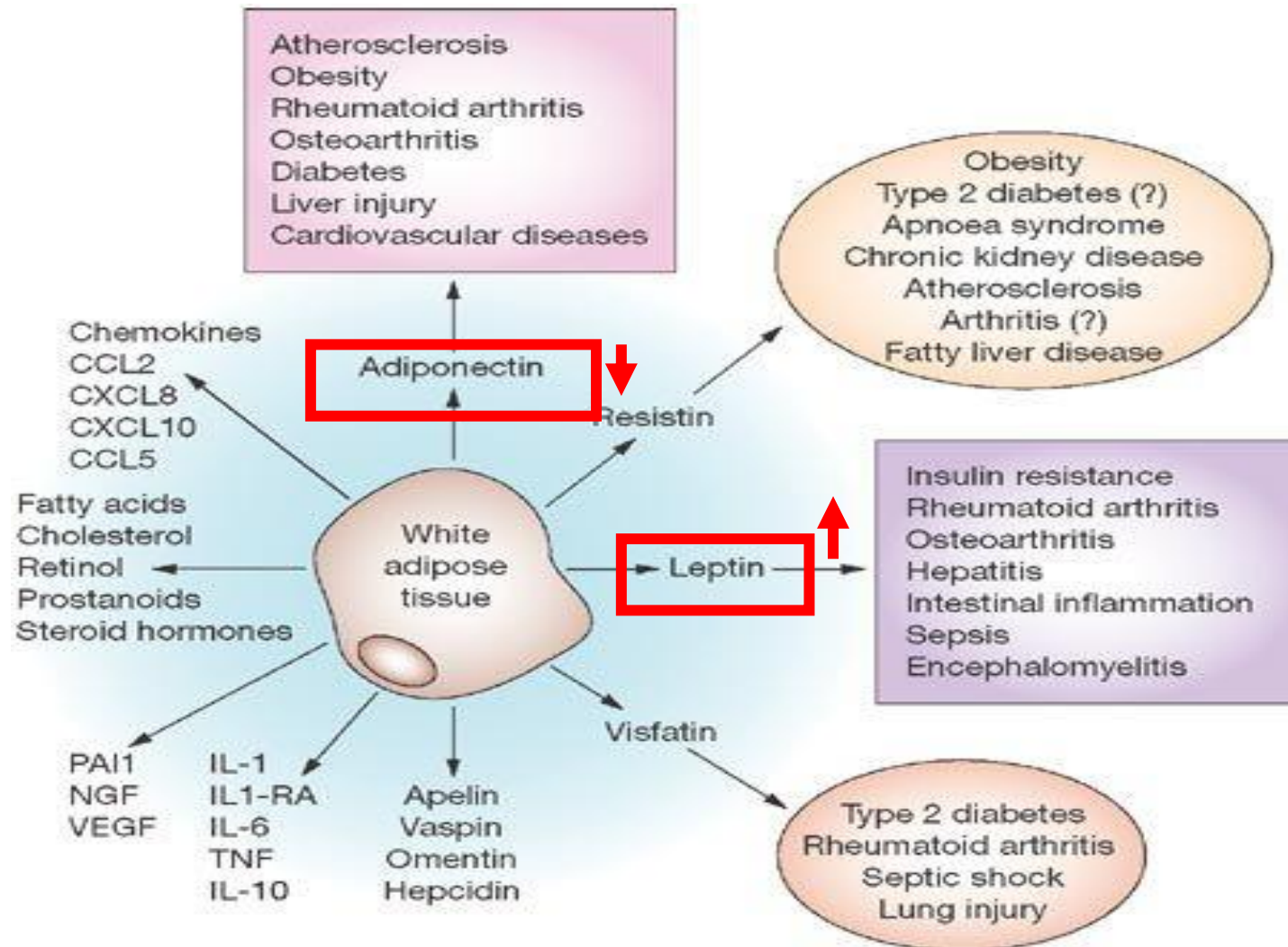
Adipokines influence other organs



Adipokines

- **adipokines**, or **adipocytokines** (Greek *adipo-*, fat; *cytos-*, cell; and *-kinos*, movement) are cytokines (cell signaling proteins) secreted by adipose tissue
- e.g. Leptin (energy balance by inhibiting hunger)
- Adiponectin (glucose regulation and fatty acid oxidation)
- Resistin (from immune cells metabolism cholesterol: LDL)
- Ghrelin (from stomach: stimulate hunger)

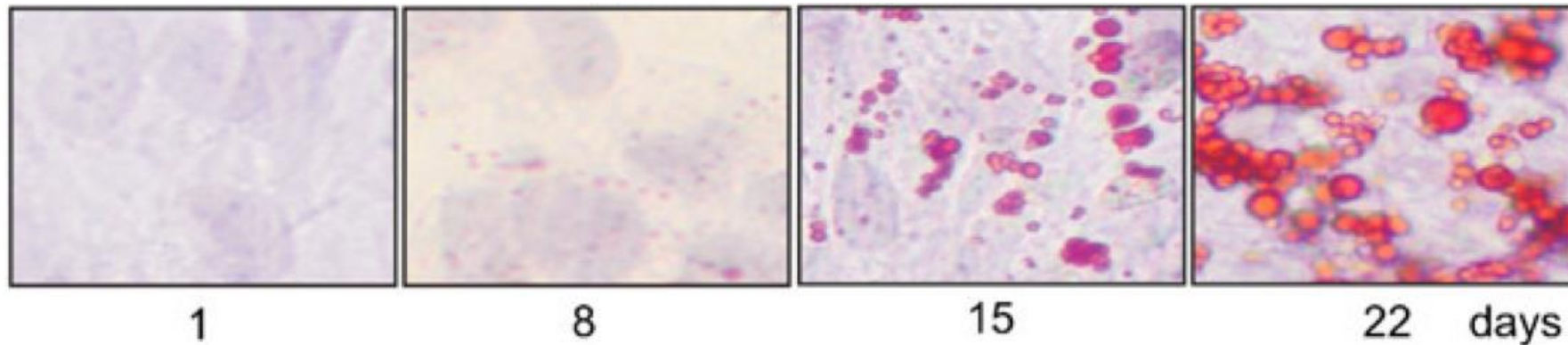
Secretion products of adipose tissues induce some diseases



2. Features of adipocytes

LiSa-2: accumulation of lipid droplets

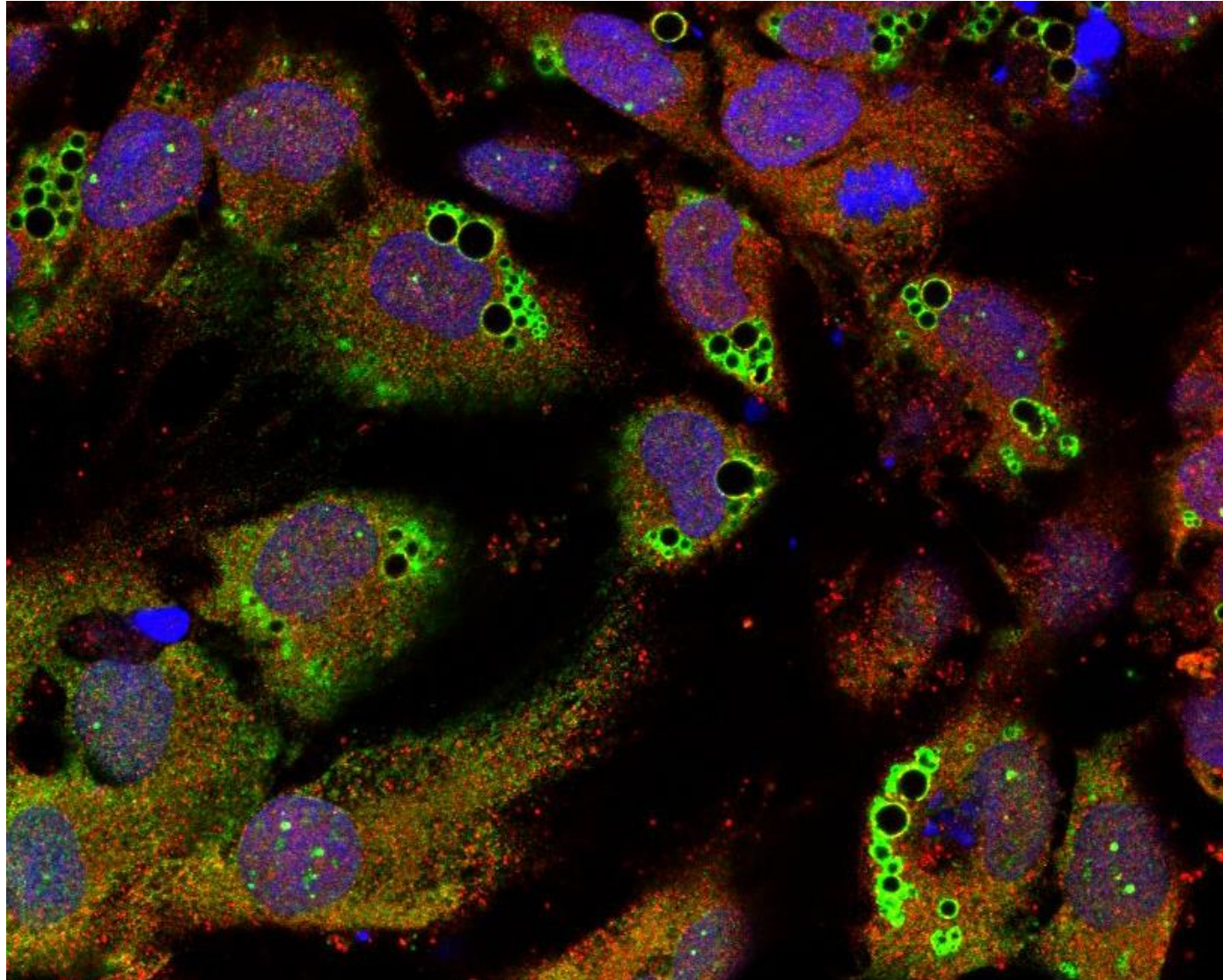
Differentiating LiSa-2 cells, lipid formation visualized by ORO staining



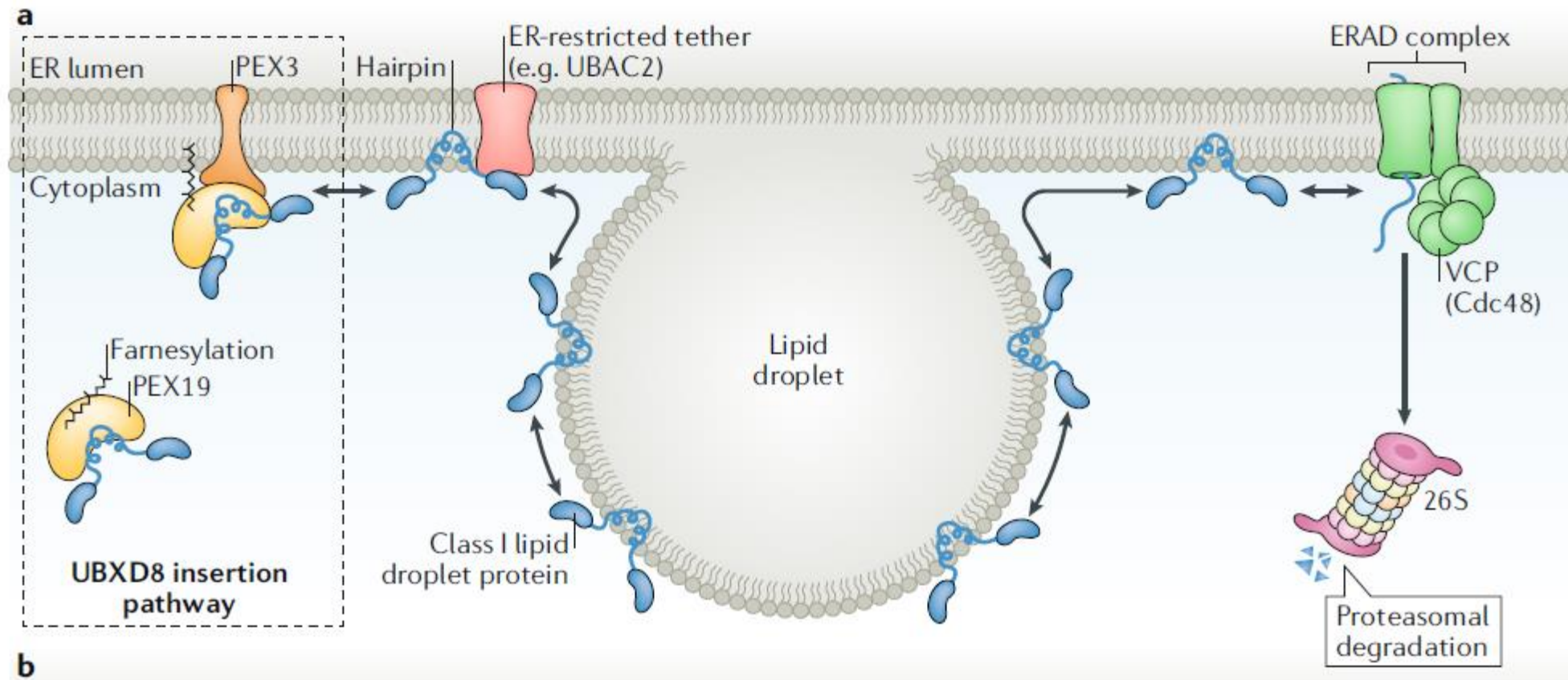
adapted from Huang et al., 2012

2. Features of adipocytes

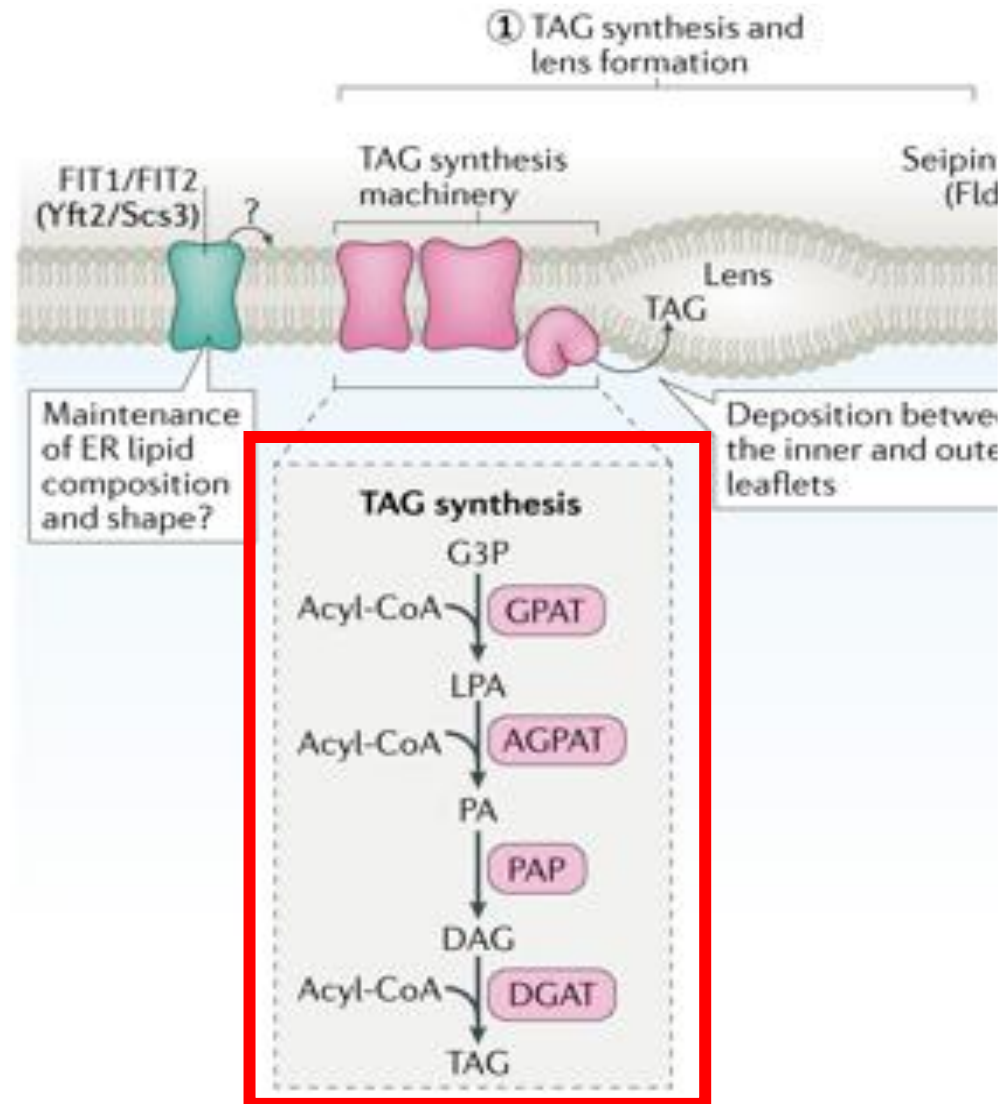
LDs are stained with Cullin3 and Rab18 antibodies



Formation of lipid droplets

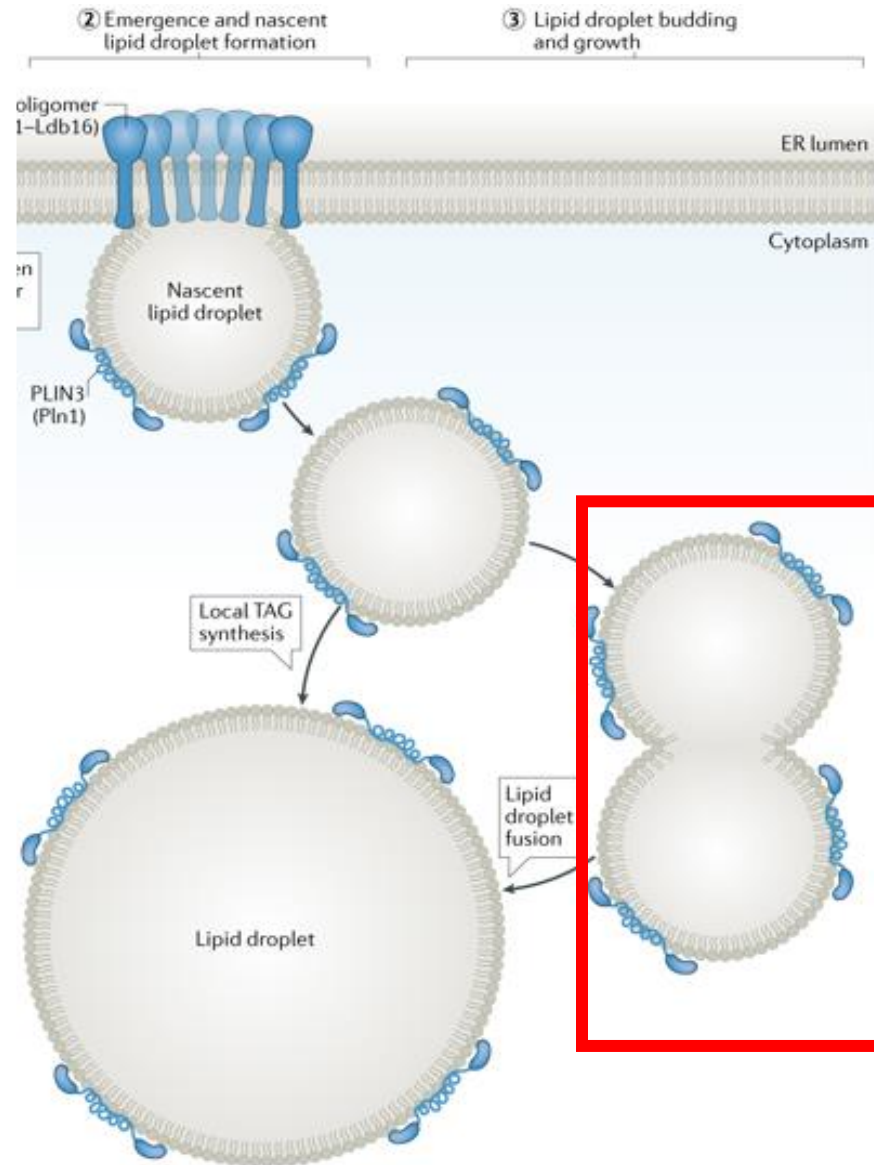


Content of lipid droplets (synthesis of TAG)

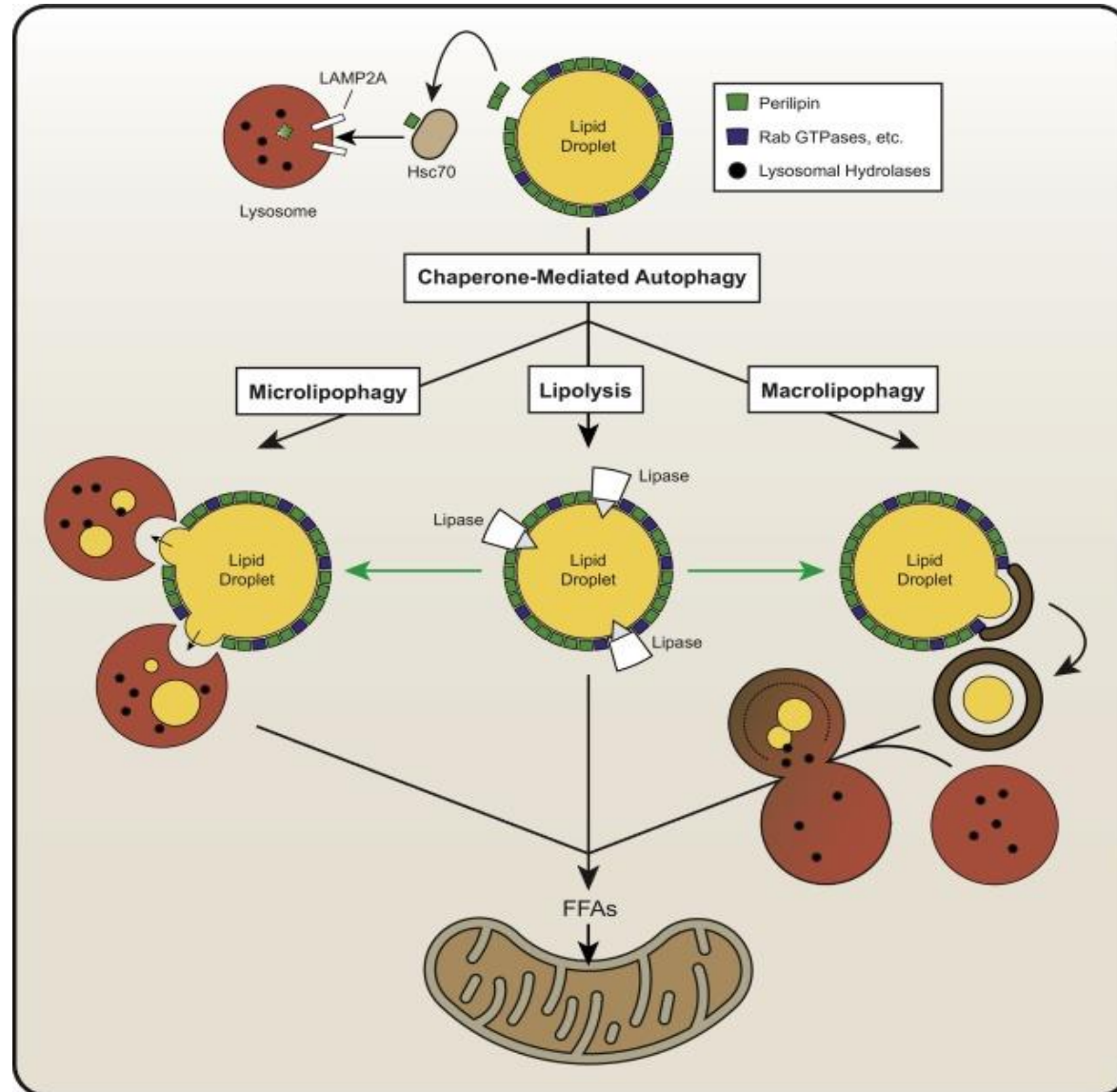


James A. Olzmann & Pedro Carvalho,
Nature reviews | Molecular cell Biology, 2019

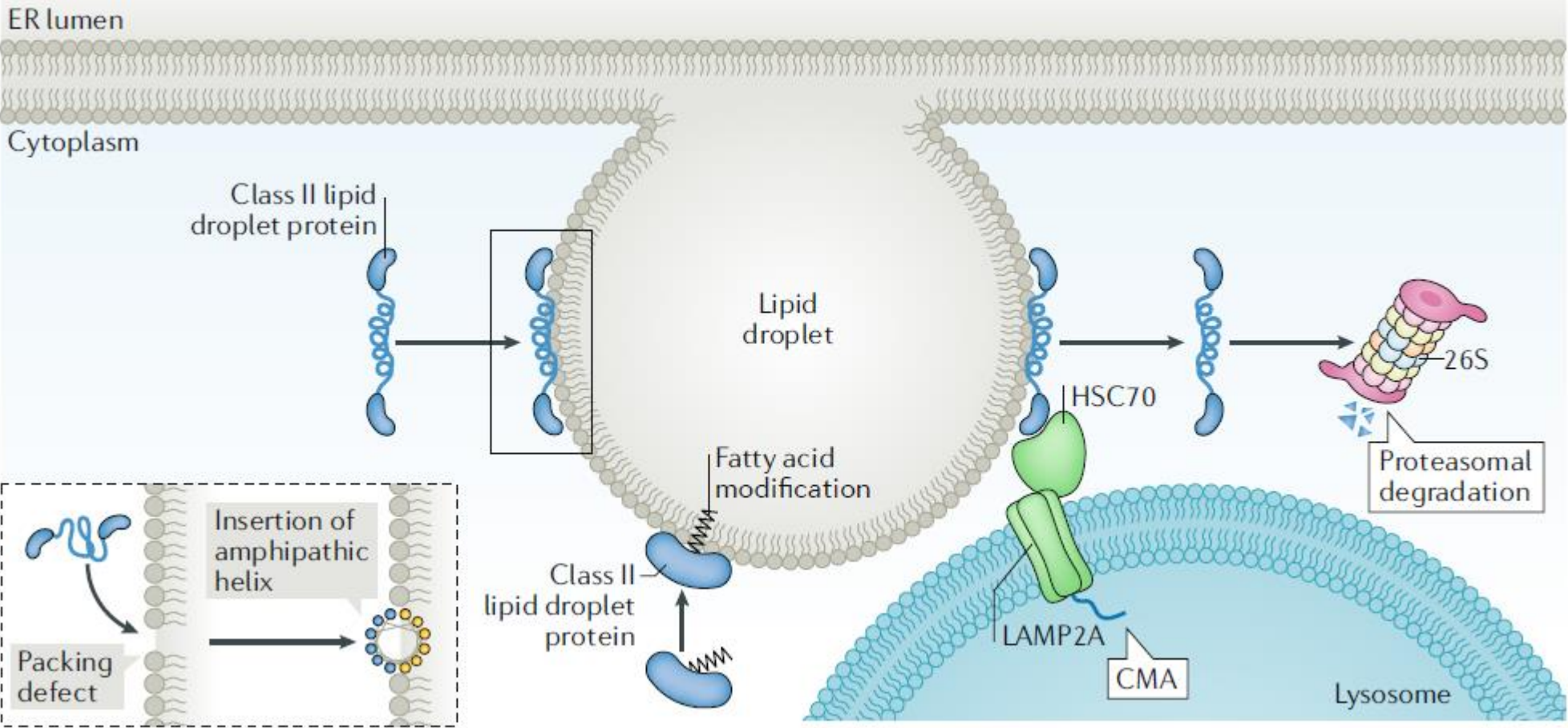
Expansion/growth of lipid droplets



Degradation pathways of Lipid Droplets



Degradation of Lipid Droplets by lysosome (lipophagy)



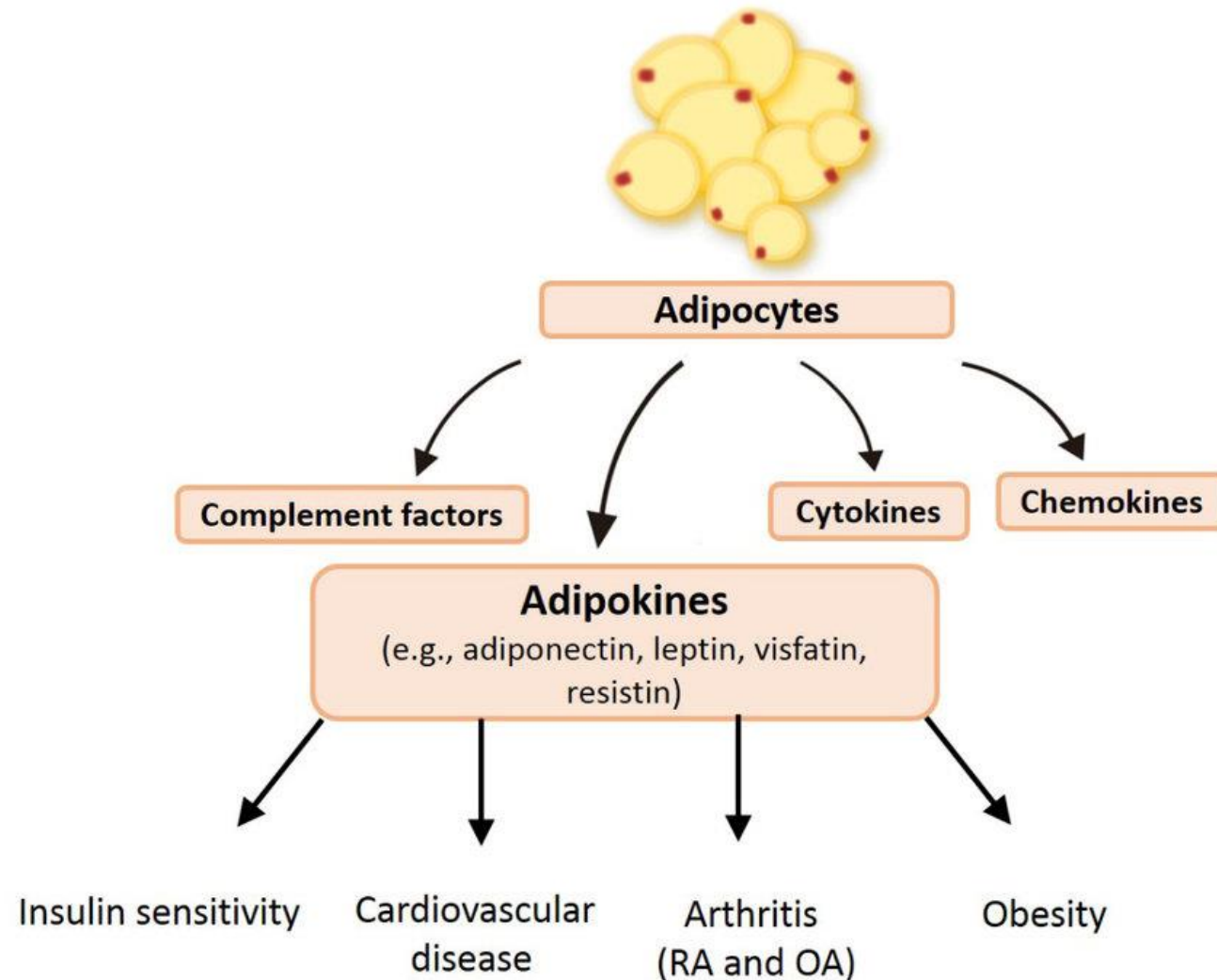
Obesity is associated with other diseases:

- Obesity and overweight are linked to many co-morbidities:
 - Diabetes type 2
 - Cardiovascular disease
 - Osteoarthritis
 - Non-alcoholic fatty liver disease
 - **Cancer** (endometrial, breast, colon), **high risk**

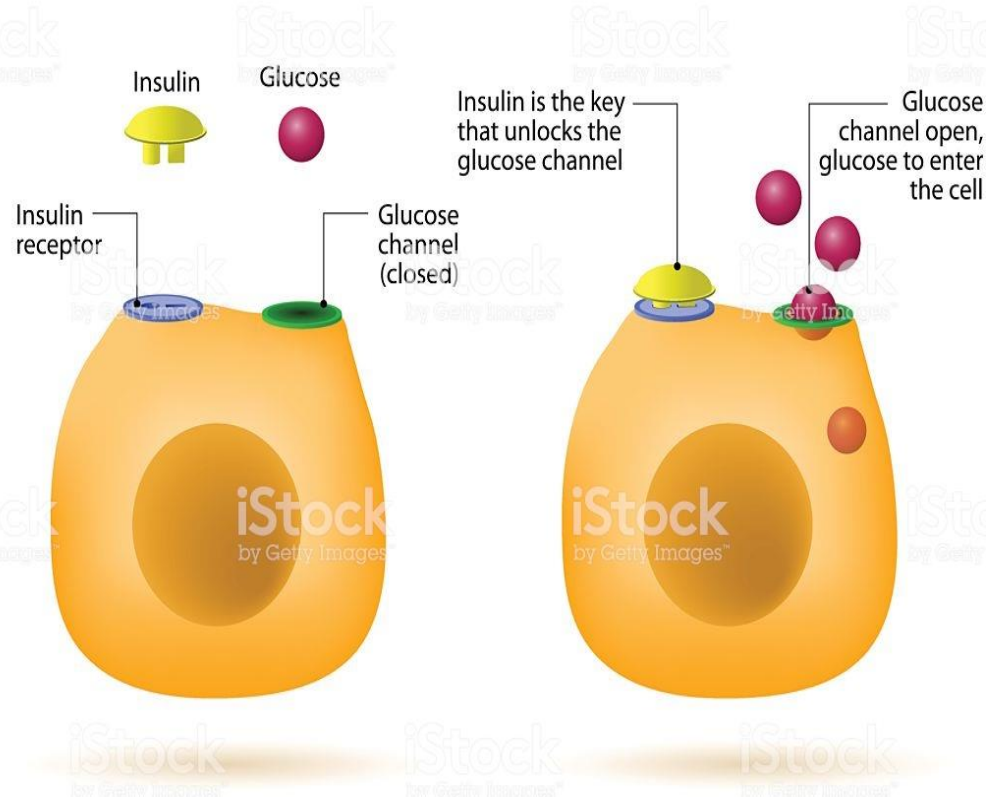
National Institutes of Health-AARP Diet and Health Study report a *positive association between BMI and mortality*.

2.8 million adults die each year as a result of being obese
(WHO).

Adipokines and other secretion products from WAT induce diseases

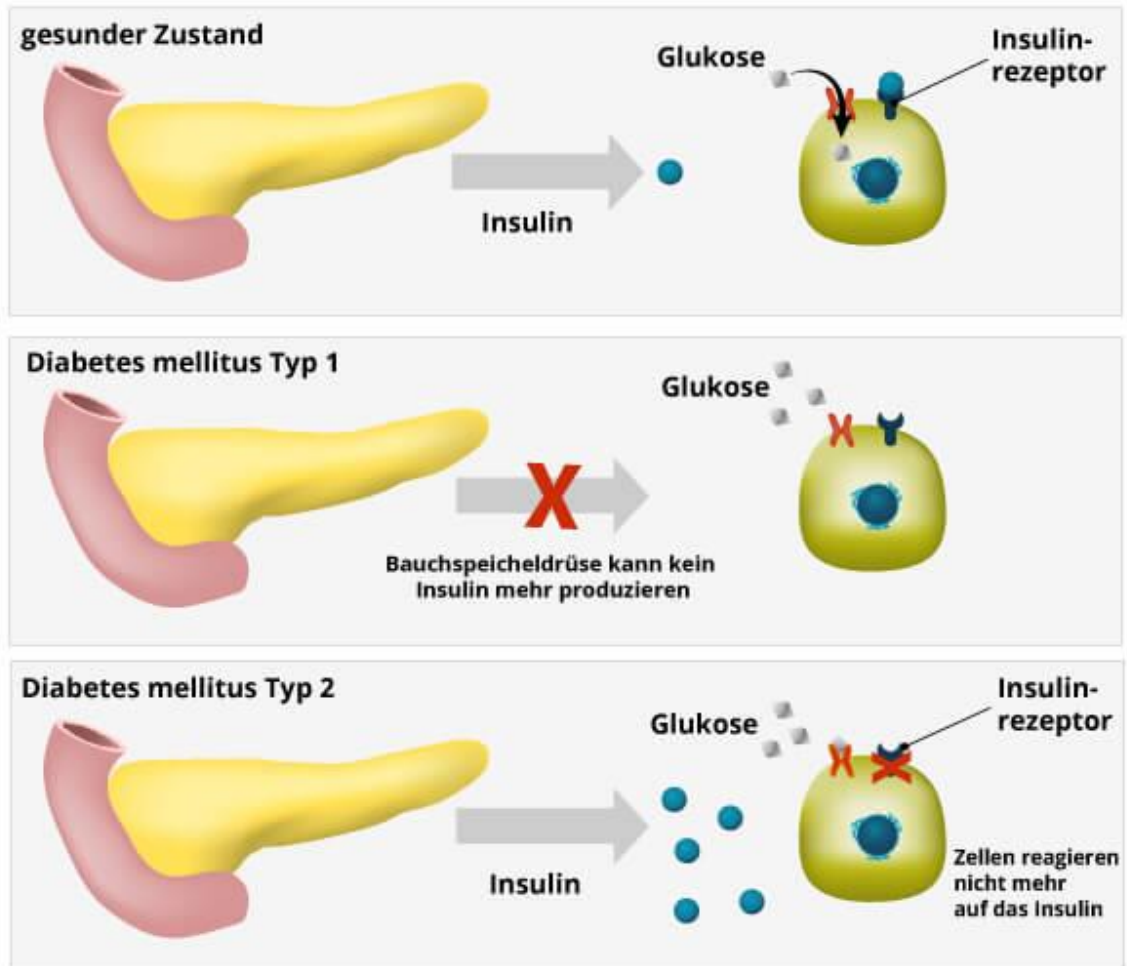


HOW DOES INSULIN WORK?



Where and in which cells is insulin produced?
 -pancreas
 -Islets of Langerhans

Diabetes mellitus Types



Diabetes mellitus types:

- diabetes mellitus type 1: no insulin production
- diabetes mellitus type 2: lesser insulin production, insulin resistance
- diabetes mellitus type 3 (a-h): reasons are different e.g. inflammation, infection, genetical reason
- diabetes mellitus type 4: pregnancy diabetes

Causes of insulin resistance associated with obesity

- Lesser production of insulins or
 - Unsensibility of insulin receptors
- (hyperinsulinemia: high insulin in the blood)

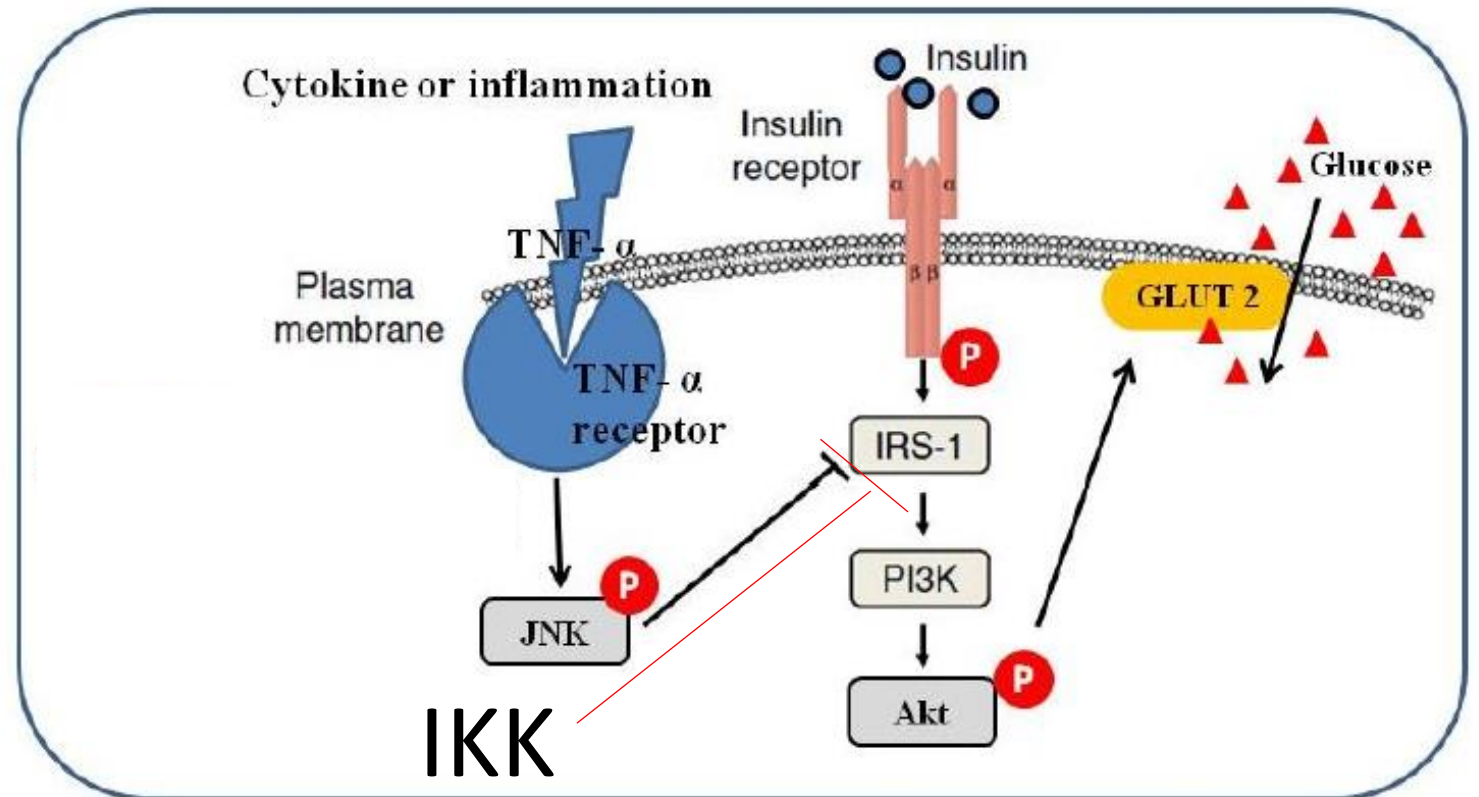
Oversecretion of cytokines causes insulin resistance

ROS production increasement: DNA damage

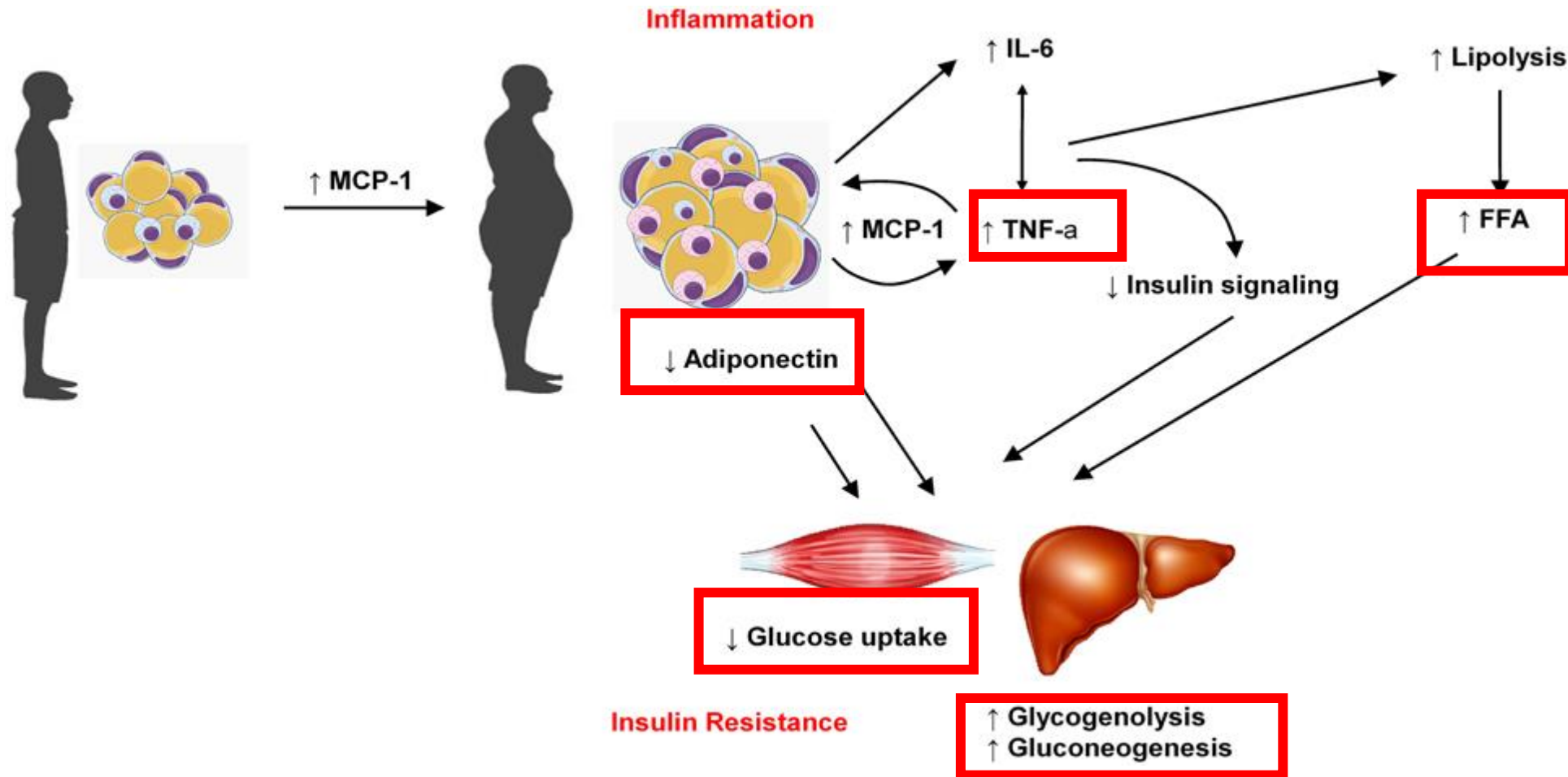
- Secretion of cytokins (TNF α , IL6):

1. Chronic inflammation
2. ROS production:
DNA damage
3. Insulin resistance

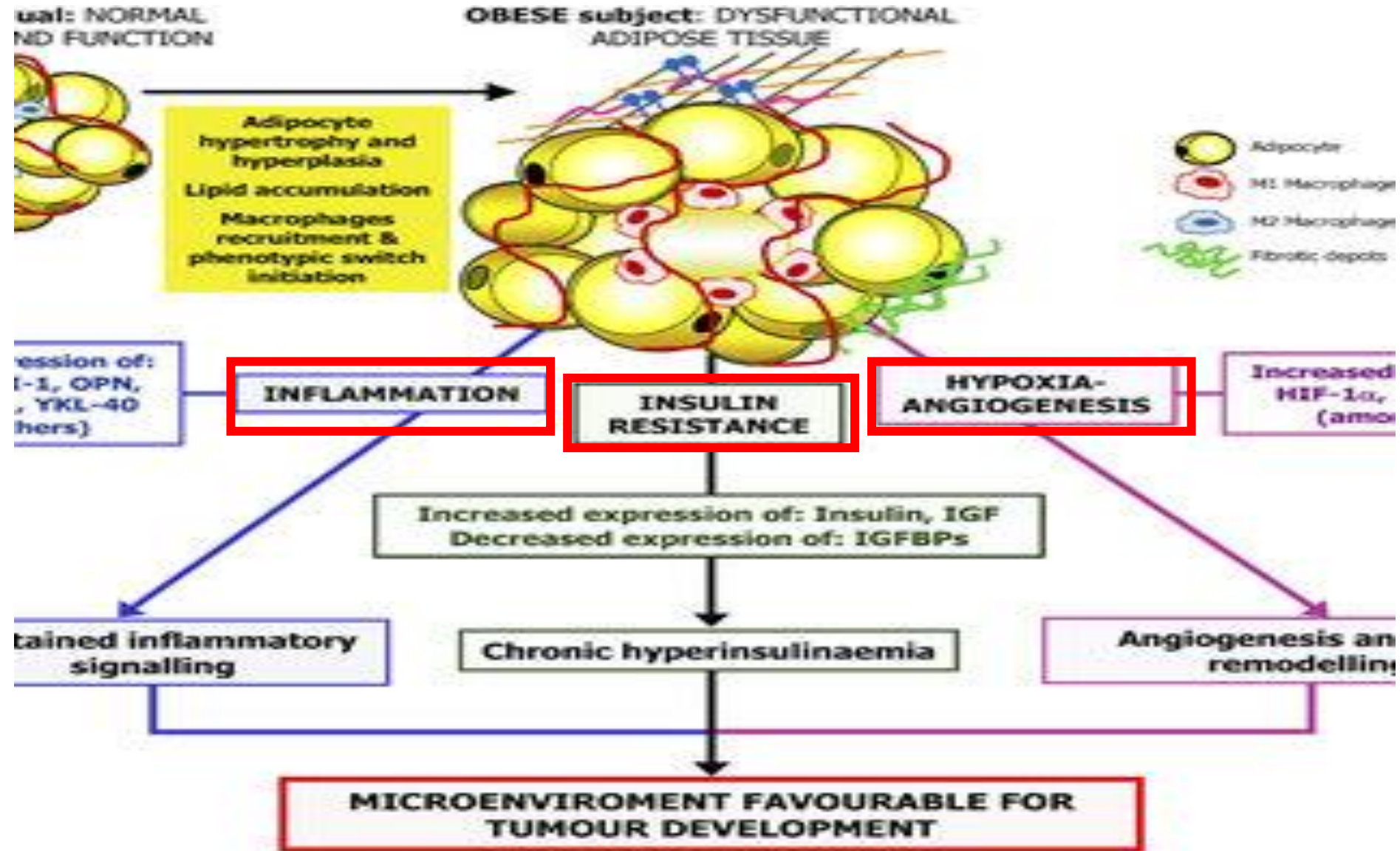
IRS-1: insulin receptor substrate-1



Inflammation and Insulin resistance



Obesity is a high risk for cancer



Obesity is a high risk for cancer

-Chronic inflammation

1. Oversecretion of cytokines and leptins

-Insulin resistance

1. Oversecretion of leptin, decrease of adiponectin

2. Oversecretion of cytokines

-Angiogenesis

1. Secretion of pro-angiogenic factors e.g. VEGF, Growth factors, cytokines

Adipositas ist ein hohes Risiko für schwere Verläufe bei einer COVID-19-Erkrankung

(75 Studien)

Adipositas:

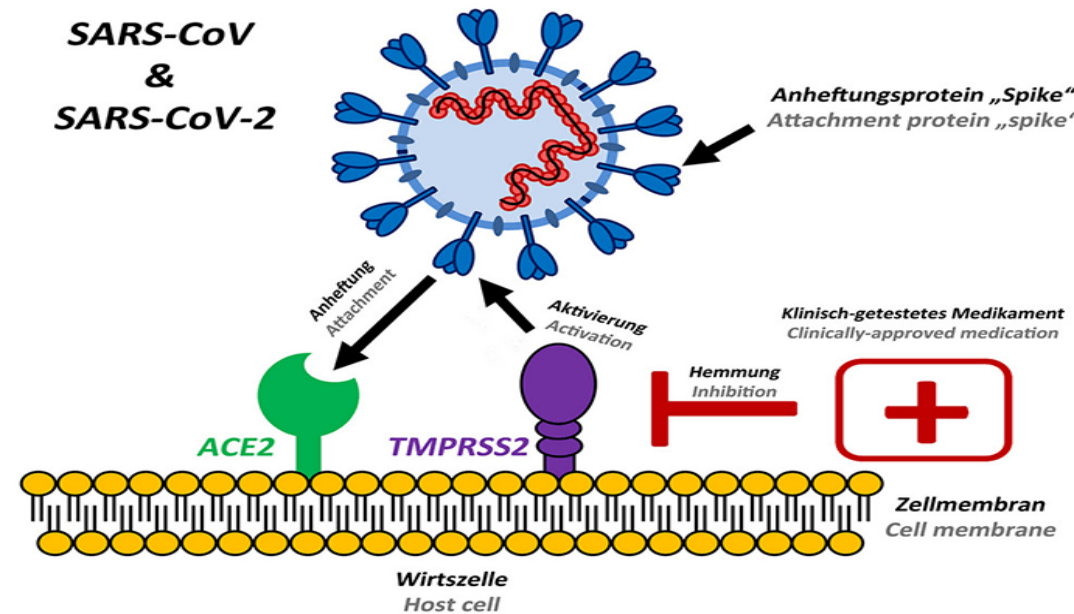
1. erhöhtes Risiko für eine Hospitalisierung bei einer Covid-19-Erkrankung
2. um 74 Prozent erhöhtes Risiko, auf die Intensivstation verlegt zu werden
3. um 48 Prozent erhöhtes Risiko zu sterben

4. das Risiko erhöht sich überhaupt mit dem Erreger zu infizieren?

Metaanalyse : Anstieg um 46 Prozent

Adipositas ist ein hohes Risiko für schwere Verläufe bei einer COVID-19-Erkrankung

Warum???



einige Rezeptoren wie ACE2 (angiotensin-converting enzyme 2) höher exprimiert bei Adipositas: mehr Aufnahme von Viren in Zellen
-erhöhte Sekretion von Adipokinen (Leptin und Zytokinen): Überproduktion von Zytokinen (Zytokinsturm), -> Protease und ROS in nicht spezifischen Immunzellen - > Gewebeschädigung

- Schwächerer Impfschutz bei Adipositas? (Tetanus)

BMI over 27:

Adipositas-Behandlung:

1. Gewichtsverlust durch Diät und Bewegung

2. Medikamente:

Sibutramin, Rimonabant (vom Markt weg!)

(Appetitzügler: unterdrücken das Gefühl "Hunger" im Gehirn)

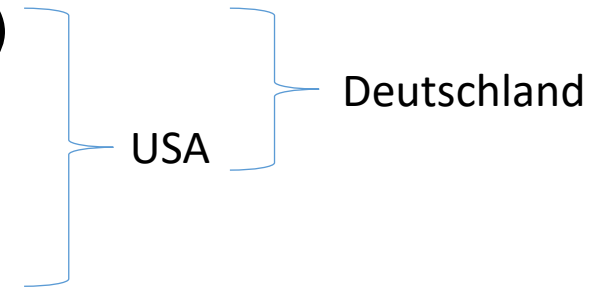
Quellstoffe: fördern das Sättigungsgefühl bereits im Magen.

Orlistat (Fettblocker: verhindern die Aufnahme von Fetten)

Naltrexon-Bupropion, Liraglutid (hemmen den Appetit)

Phentermin/Topiramamat und Lorcaserin

[5-Hydroxytryptophan](#) (5-HTP) Serotonin-Stoffwechsel



Klinische Studie Phase III: **Setmelanotide (Hunger und Sättigungsgefühl): für**

Patienten mit POMC, PCSK1, LEPR, SRC1, und SH2B1 Gendefekten als auch mit Alström syndrome, und Smith-Magenis syndrome ([melanocortin-4 receptor \(MC4R\) pathway](#))

3. Pflanzenextrakte: e.g. **Curcumin** als Zusatzmittel (entzündungshemmend, Apoptose-auslösend in Krebszellen und inhibiert Angiogenese)

Resveratrol (28 neue Studien)

4. Bariatische Chirurgie: **BMI >40 (>35)**, (Magenband, Magenbypass, Schlauchmagen)

Fragen:

- Welche Zellen kommen im weißem Fettgewebe vor?**
- Welche zellulären Prozesse sind aktiv im weißem Fettgewebe?**
- Welche Faktoren werden vom weißen Fettgewebe sekretiert?**
- Nennen Sie 3 Adipositas-assoziierten Krankheiten!**
- Was ist Adipogenese?**
- Welche Hormone und Transkriptionsfaktoren regulieren Adipogenese?**
- Was sind wichtige Merkmale von weißen Fettzellen?**

Warum ist Überernährung ein Risiko für Diabetes Typ II?

- Bei dauerhaft überreicher Ernährung sinken durch das Überangebot an **Glukose** und den damit verbundenen chronisch erhöhten Insulinspiegel Sensibilität und Anzahl der Insulinrezeptoren an den Körperzellen.
- Das freigesetzte Insulin reicht somit nicht mehr aus, um den Glukoseüberschuss abzubauen, weshalb der Körper unter einem relativen Insulinmangel leidet und neues Insulin bilden muss.
- Die Inselzellen der Bauchspeicheldrüse werden über längere Zeit vermehrt beansprucht, was schließlich zu ihrer Erschöpfung führt. Es bildet sich in der Folge ein sogenannter insulinresistenter Diabetes mellitus vom Typ II.