Chemistry of Medicine I

医用化学第一

Lecture II

1.4 Mechanism to control BGL

血糖値の調節機構

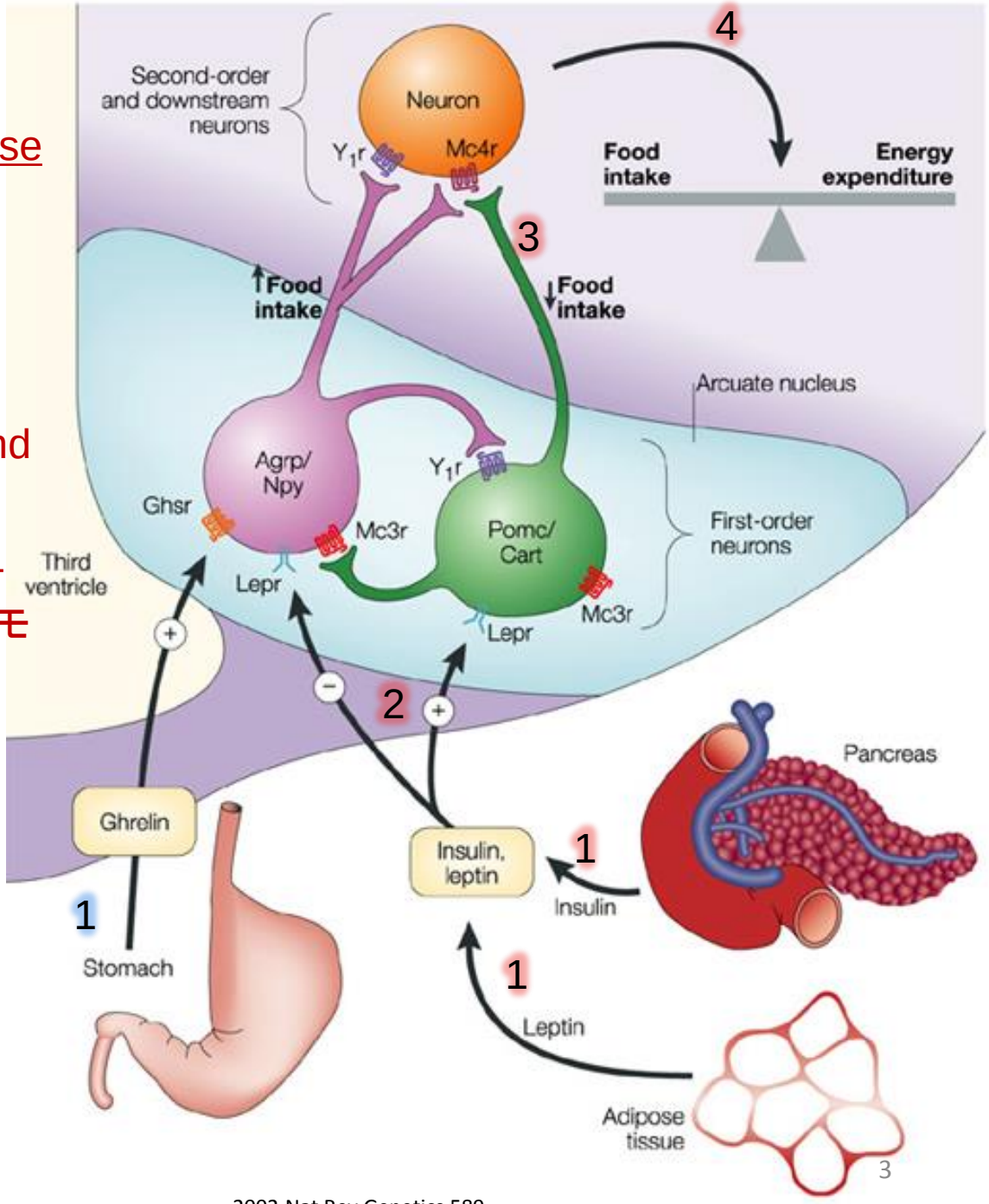
Appetite 食欲

Mechanism of satiety (満腹) response

1. Satiety hormones (leptin from adipose, and insulin from pancreas) reaches to brain (arcuate nucleus, 弓状核).
2. Activating Pomc/Cart neuron, and suppressing Agrp/Npy neuron.
3. Pomc/Cart neuron releases Mc4 (neurotransmitter, 神経伝達ホルモン) to activate downstream neurons.
4. Energy expenditure response.

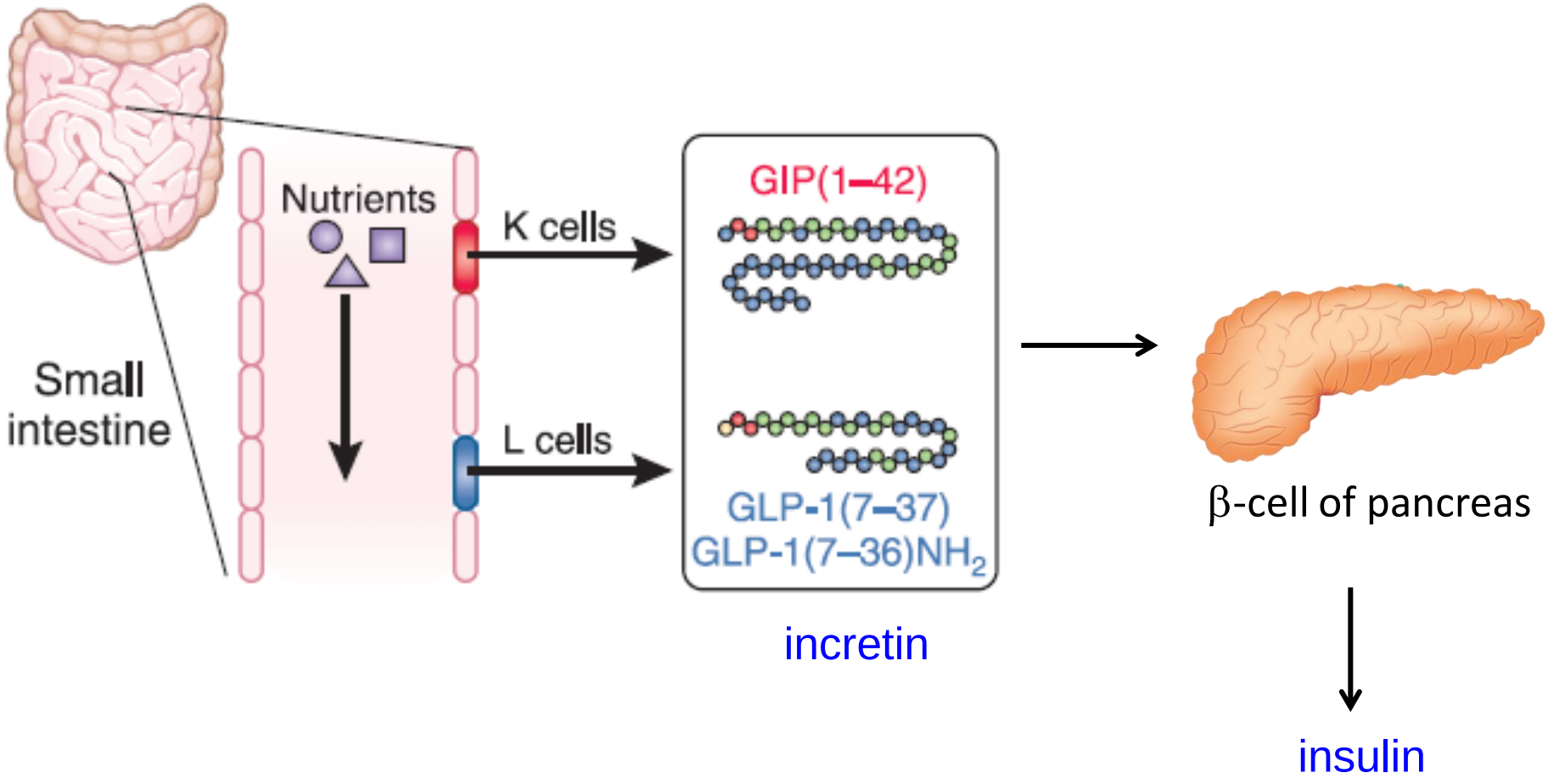
Mechanism of hunger response

1. Huger hormone (ghrelin from stomach) induce opposite response with satiety response.

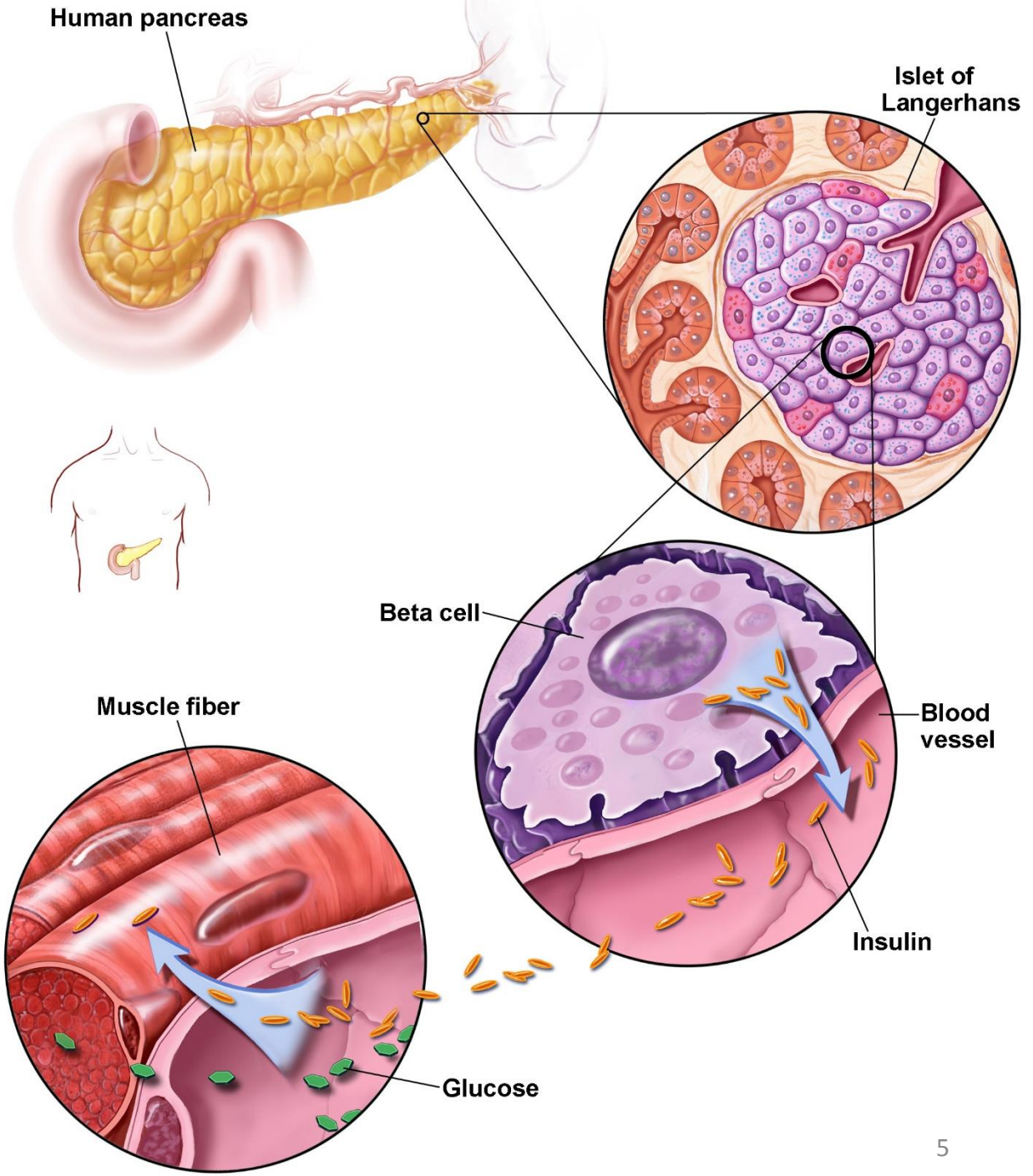


2002 Nat Rev Genetics 589

Glucose intake -> incretin -> insulin -> reduction of BGL

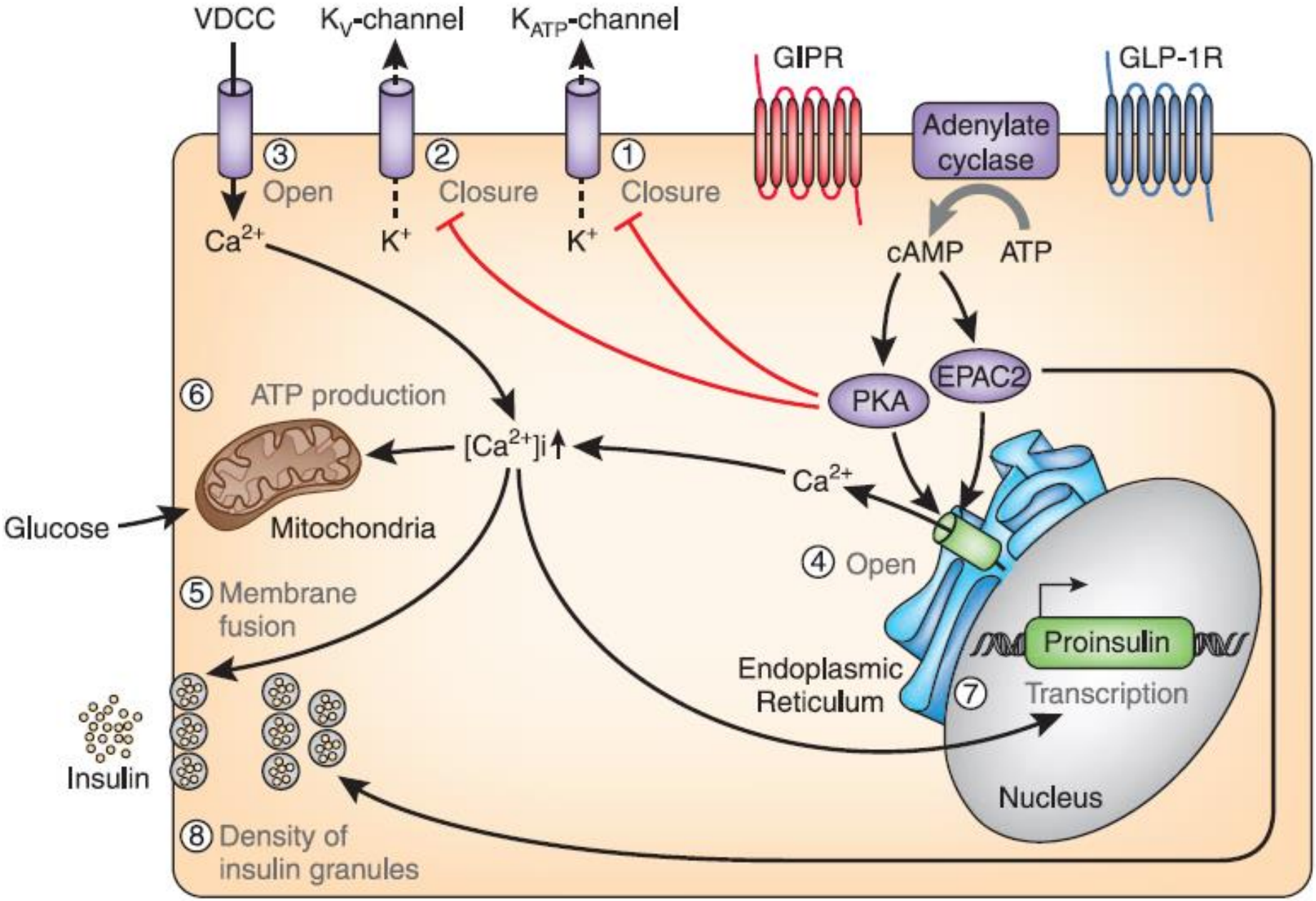


Insulin release from β cell

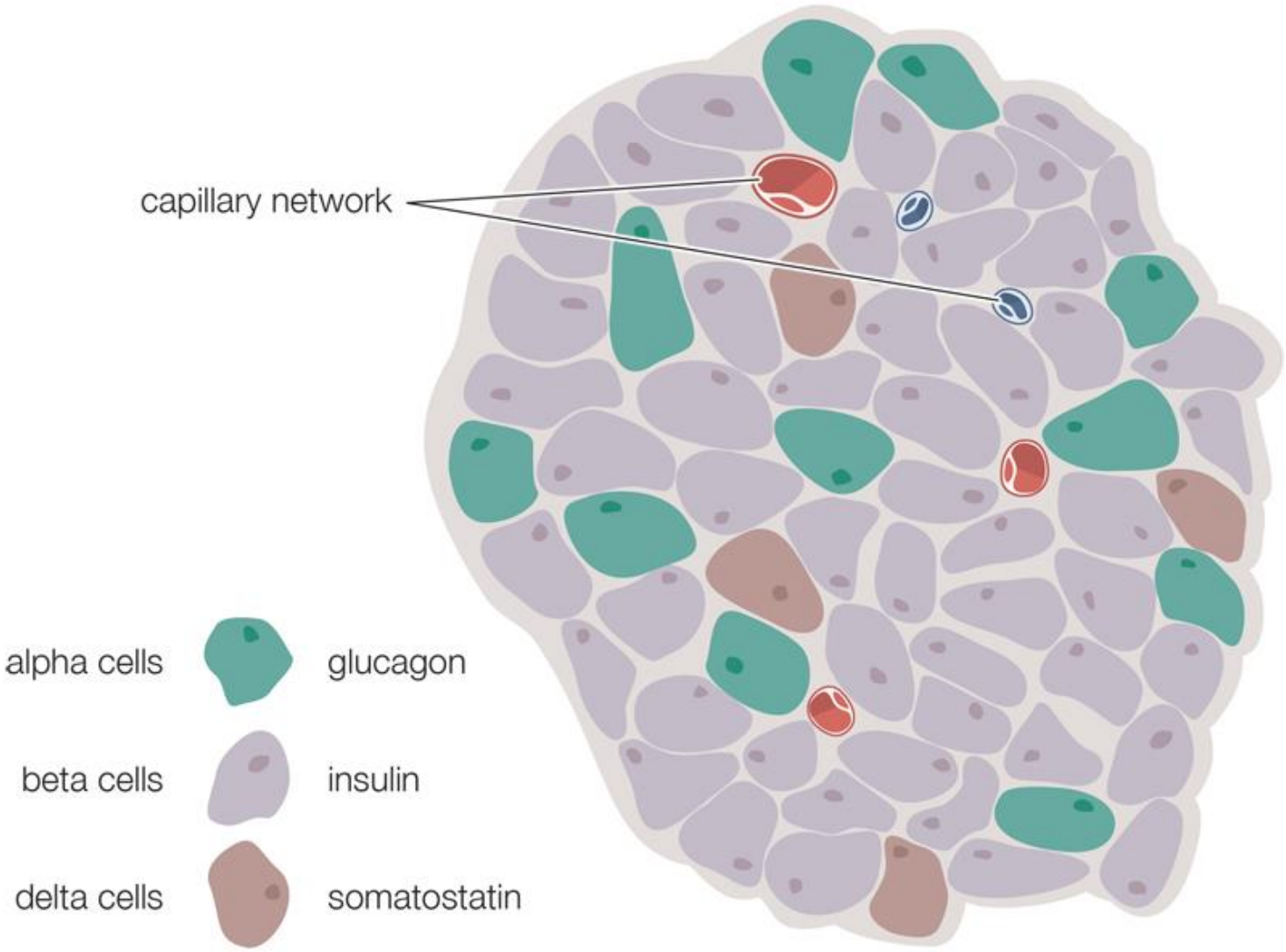


GIP & GLP-1-responsive insulin release of β cell

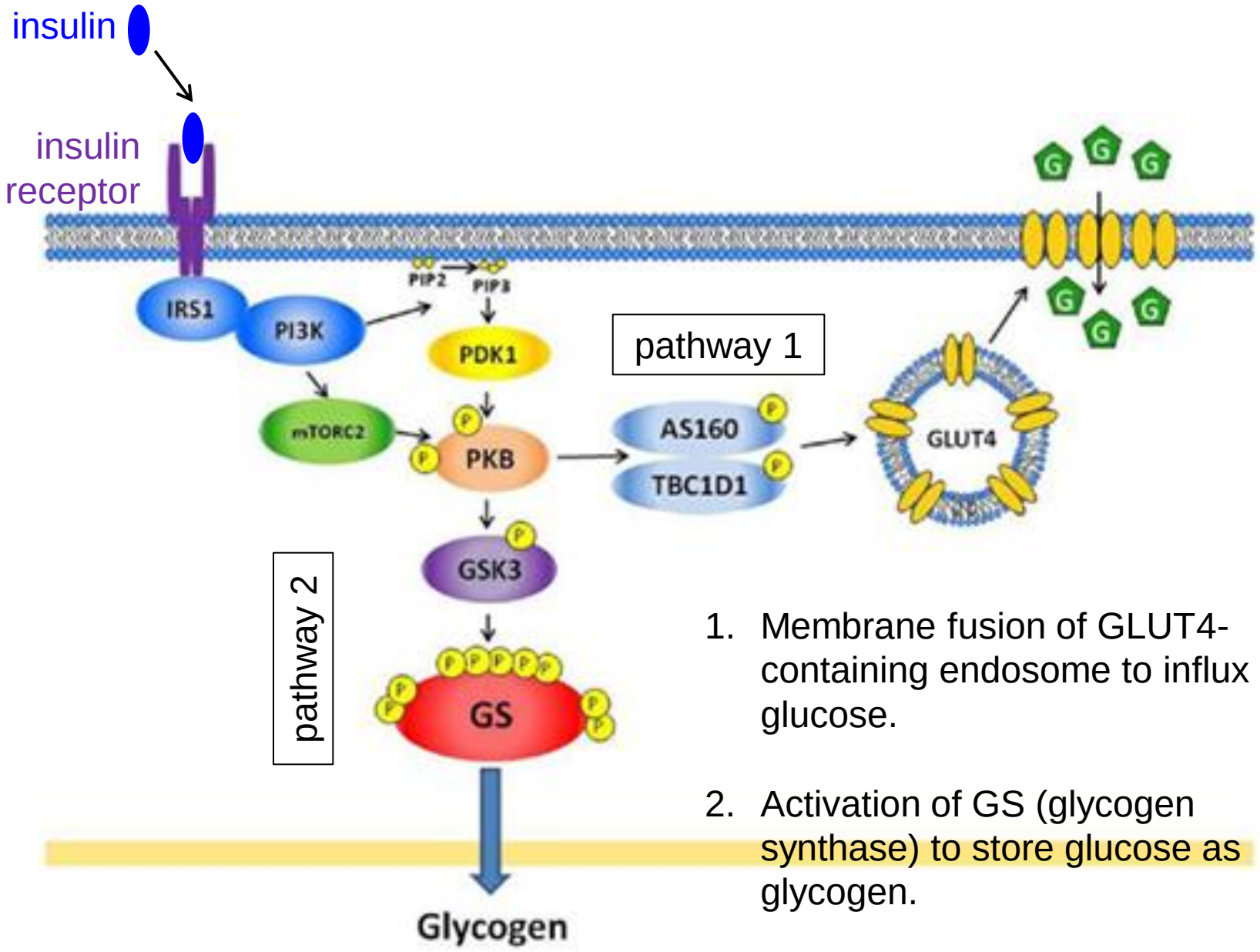
2010 J. Diabetes Invest 8



Islet of Langerhans



Insulin-responsive glucose storage in liver and muscle

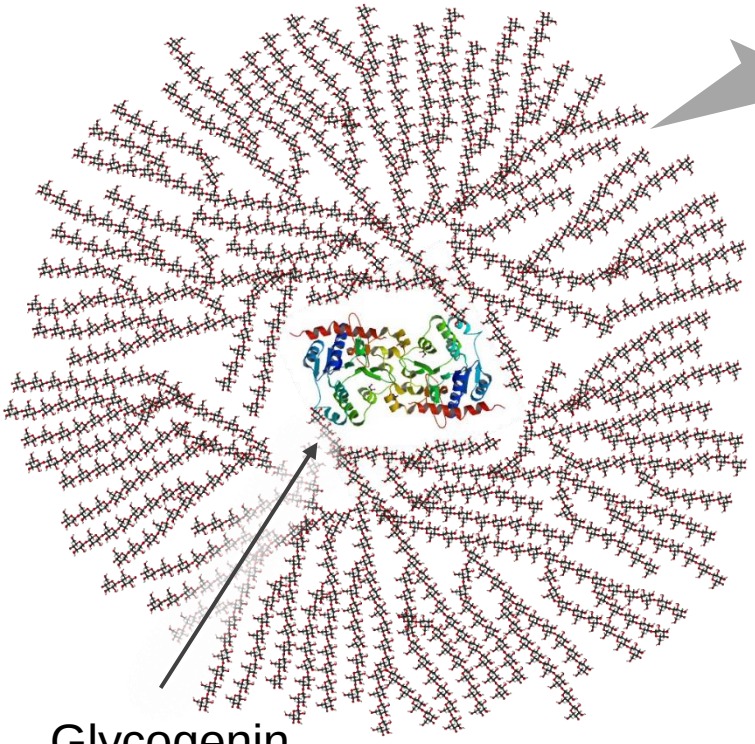


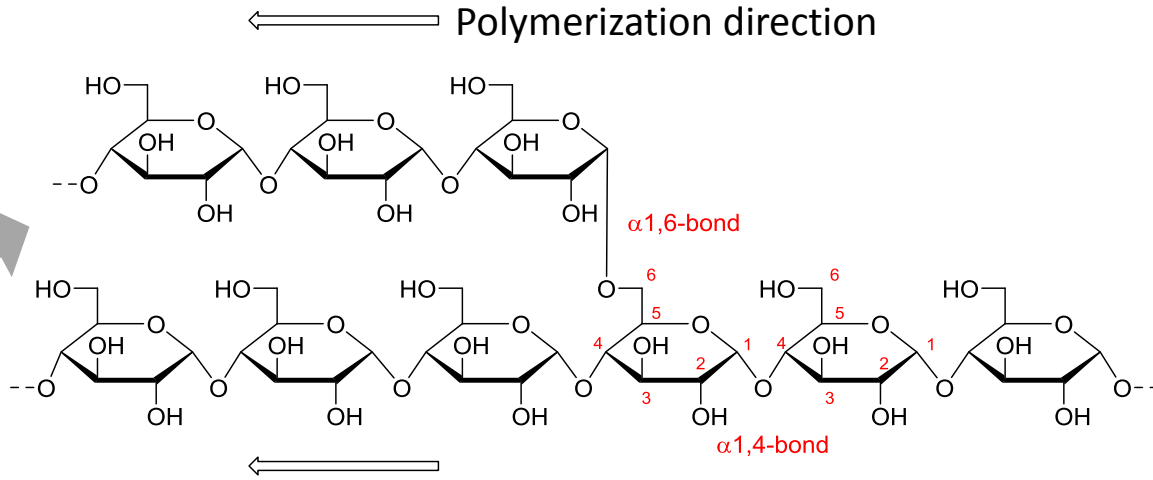
1. Membrane fusion of GLUT4-containing endosome to influx glucose.

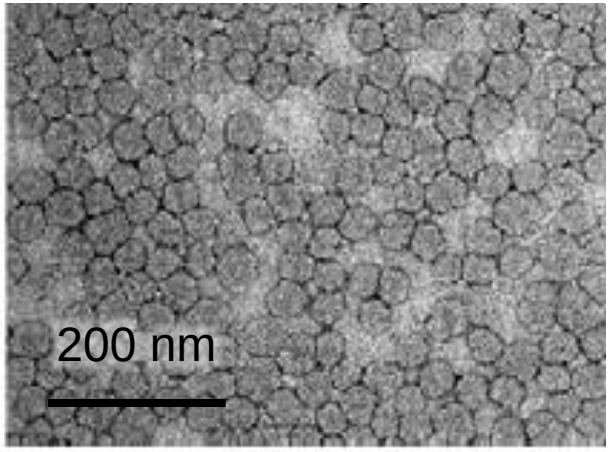
2. Activation of GS (glycogen synthase) to store glucose as glycogen.

Glycogen

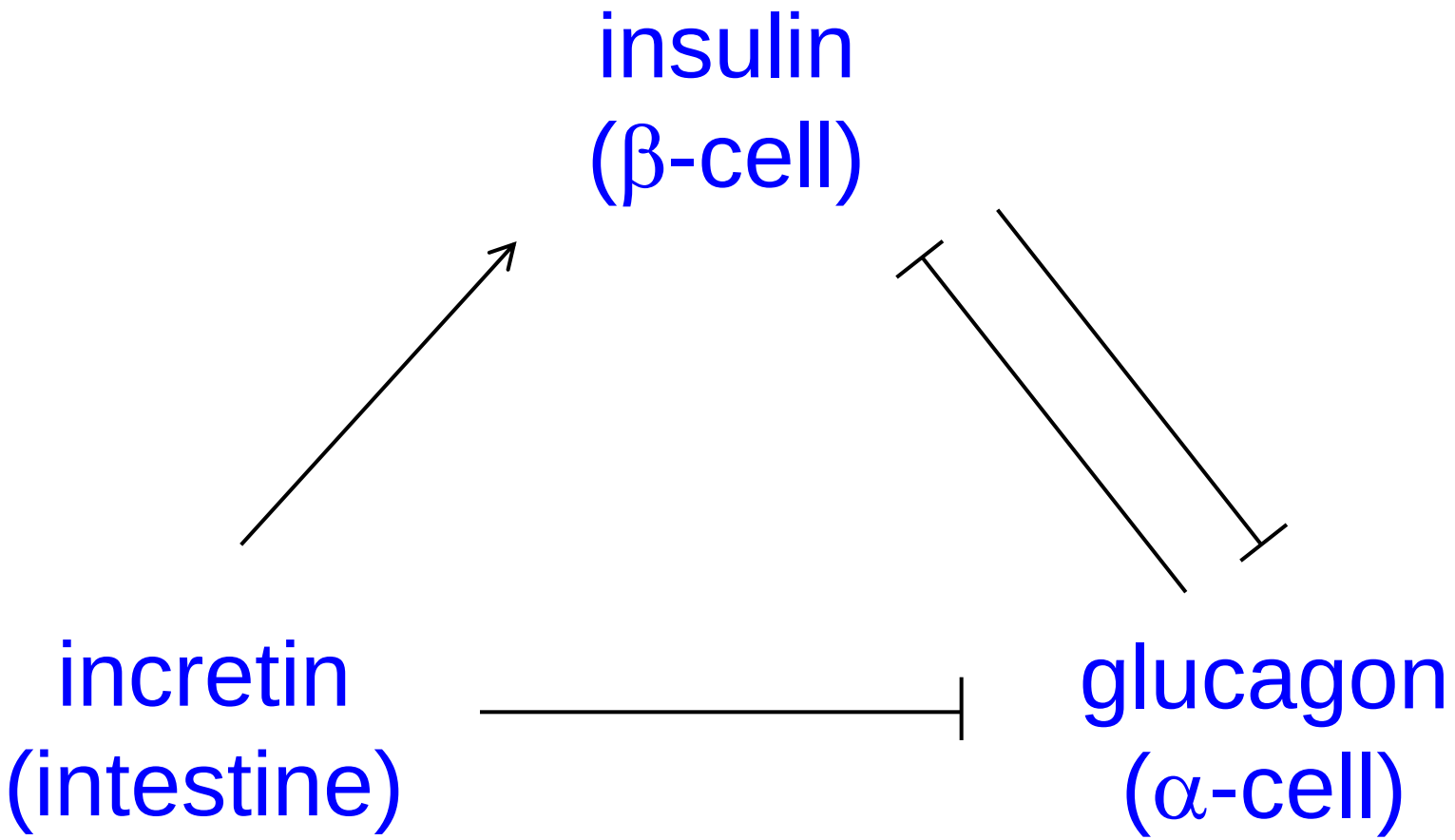
- Size: 20-50 nm.
- composed of 3,000 glucose. 240 branches and 480 termini (3,000x~8%; 2009 Int J Biol Macrmol 478).
- Polymerized by α-1,4 bond and branched at about every 8 to 12 residue by α-1,6-bond.
- hyper-branched structure enables rapid polymerization (energy storage) and degradation (energy consumption) from many termini.
- Glycogenin is a primer of polymerization.





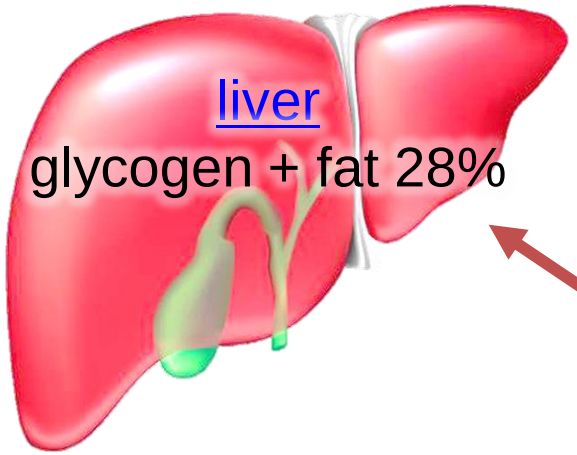


BGL control mechanism



Usage of intake glucose

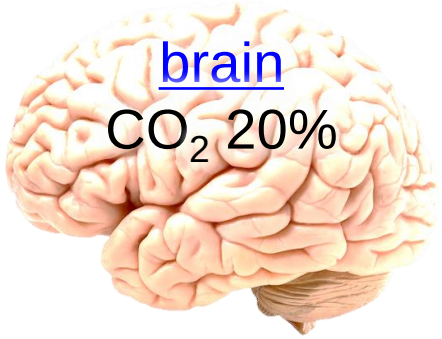
*5-hours after eating of 68 g glucose



liver
glycogen + fat 28%

29%

23%



brain
CO_2 20%

blood glucose

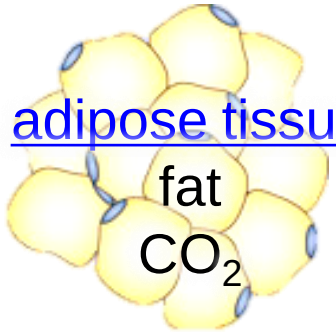
26%

muscle
glycogen 9%
CO_2 13%
glycolysis metabolites 4%

100%

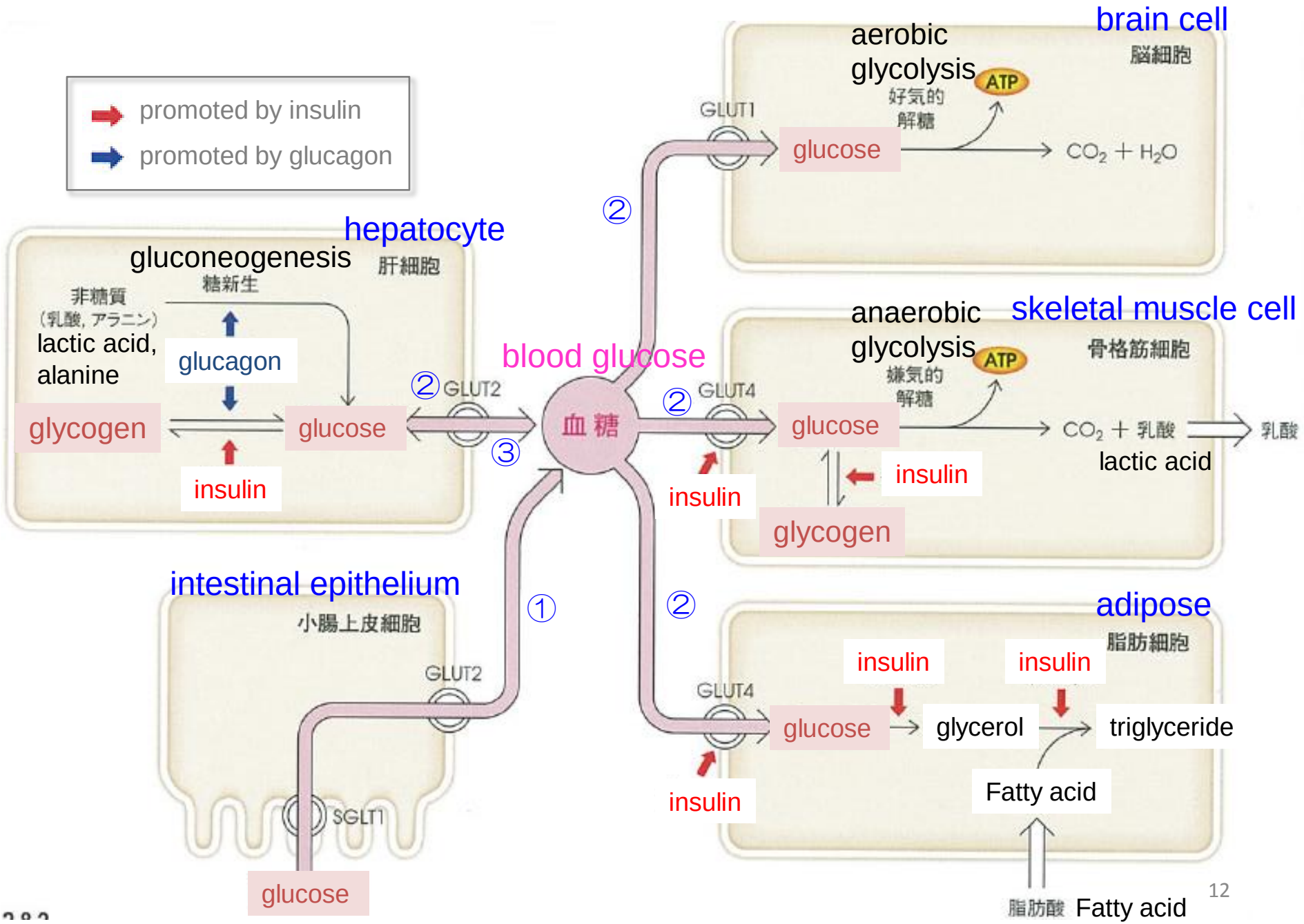
intestine

3%



adipose tissue
fat
CO_2

Glucose metabolism



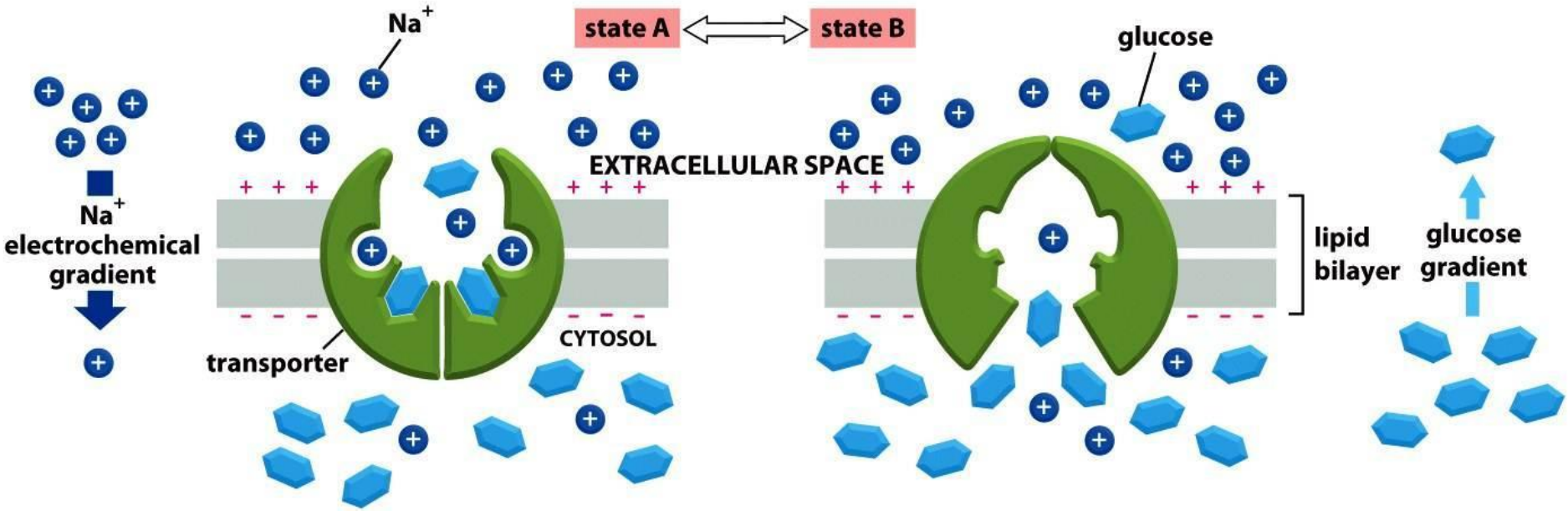
Glucose transporter

GLUT

Passive transporter (no need of ATP energy). Bidirectional transport.

SGLT (sodium-glucose transporter)

Active transporter utilizing Na^+ ion-gradient. One-directional transport.



1. 5 Cause of DM　糖尿病の原因：

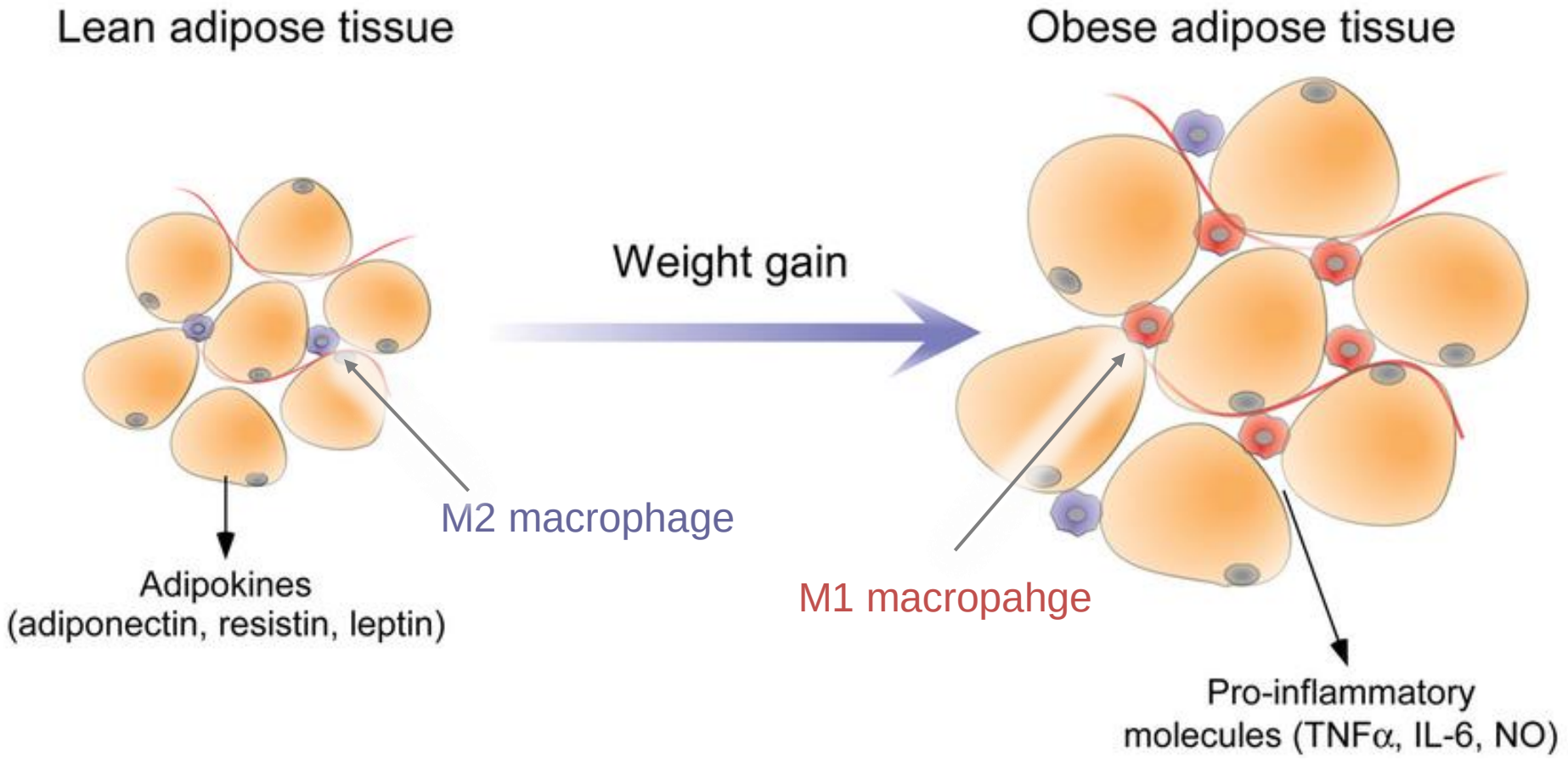
insulin resistance　インスリン抵抗性

inflammation　炎症

glucose addiction　グルコース依存症

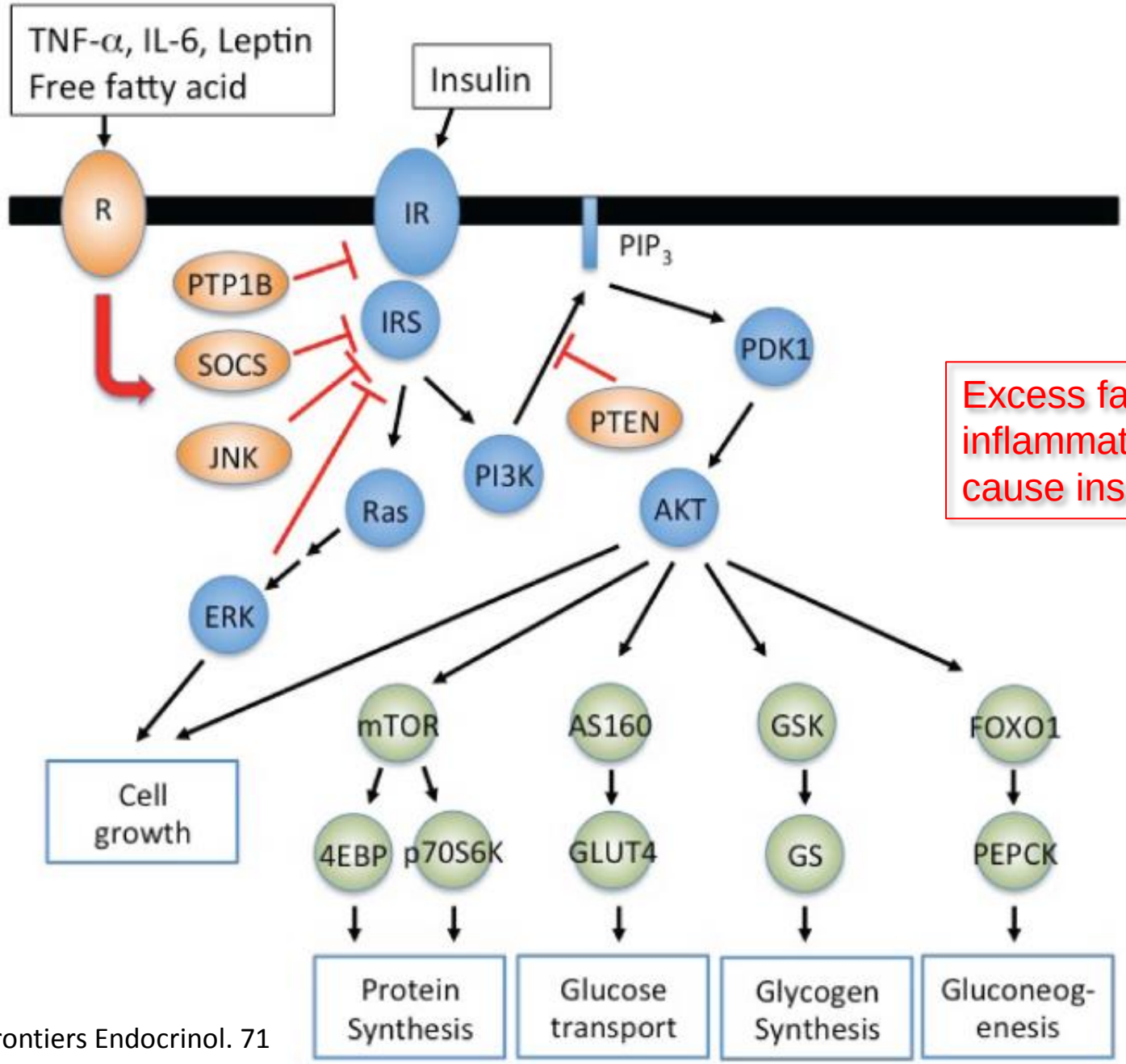
autoimmunity (type 1)　自己免疫疾患（一型）

Obese adipose cause inflammation



2011 Annu Rev Pathol Mech Dis 275

Insulin resistance インスリン抵抗性

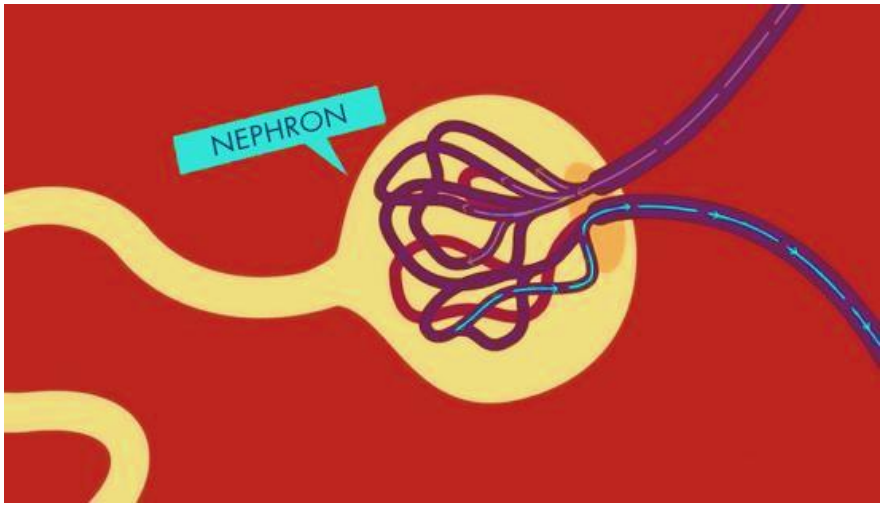


Excess fatty acid and inflammatory cytokines cause insulin resistance.

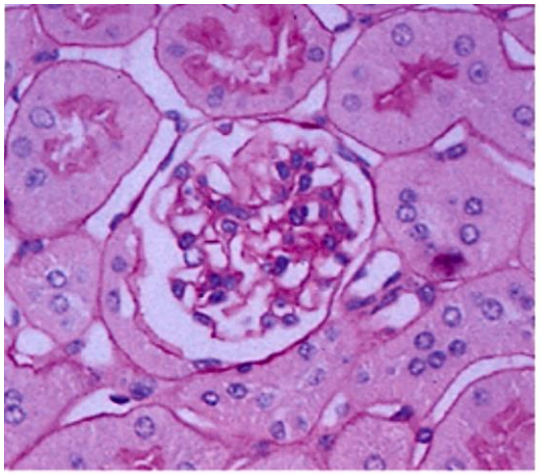
2013 Frontiers Endocrinol. 71

RAGE induces damaging of tissue

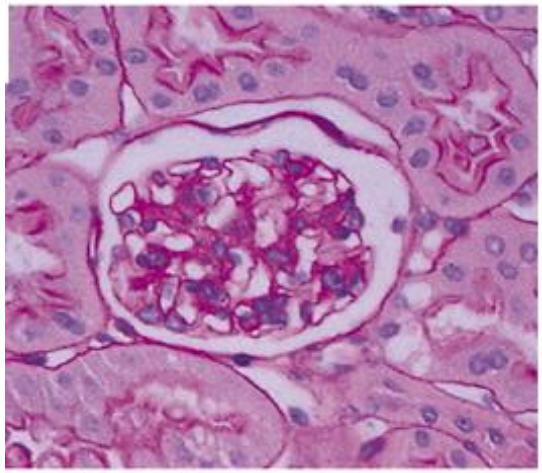
(case of nephron in mouse)



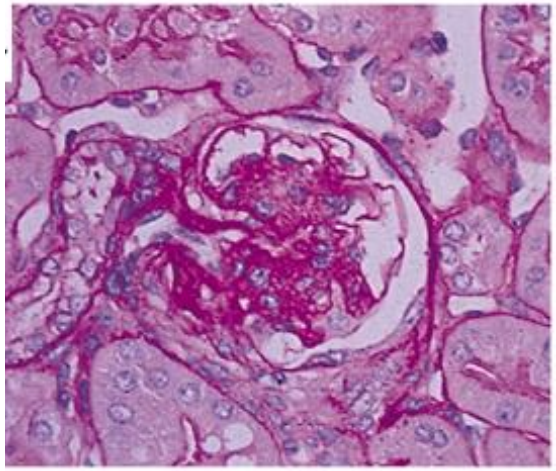
normal



DM



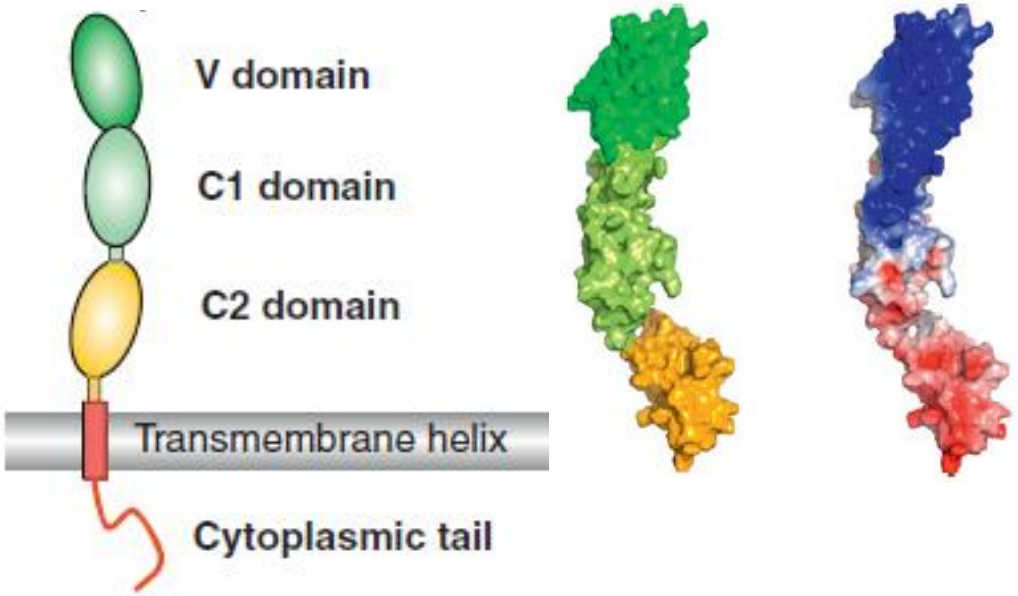
DM
RAGE transgenic

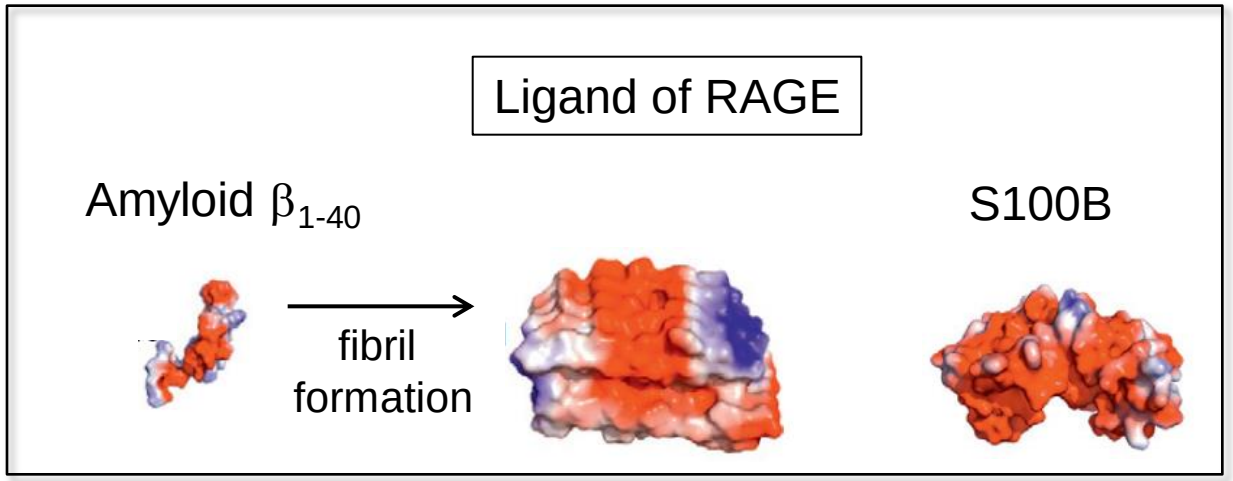


2001 J. Clin. Invest. 261

Receptors for AGE (RAGE)

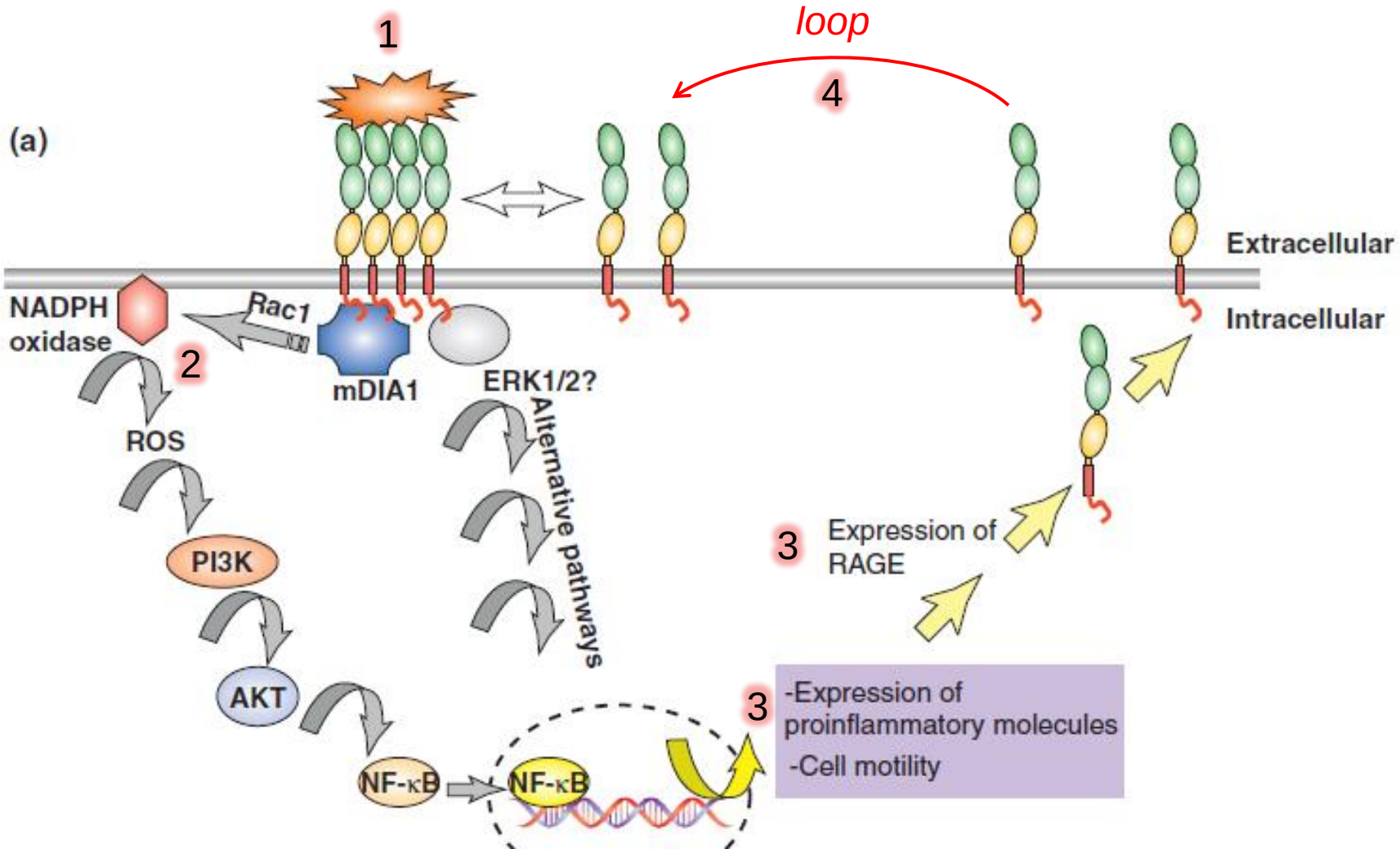
- Expressed in many organs especially in endothelium and lymphocytes.
- Removing AGE from blood.
- Inducing chronic inflammation and being related to many diseases (diabetes, Alzheimer's disease, atherosclerosis, cancer)
- Receptor not only for AGE but also for other negatively charged proteins.



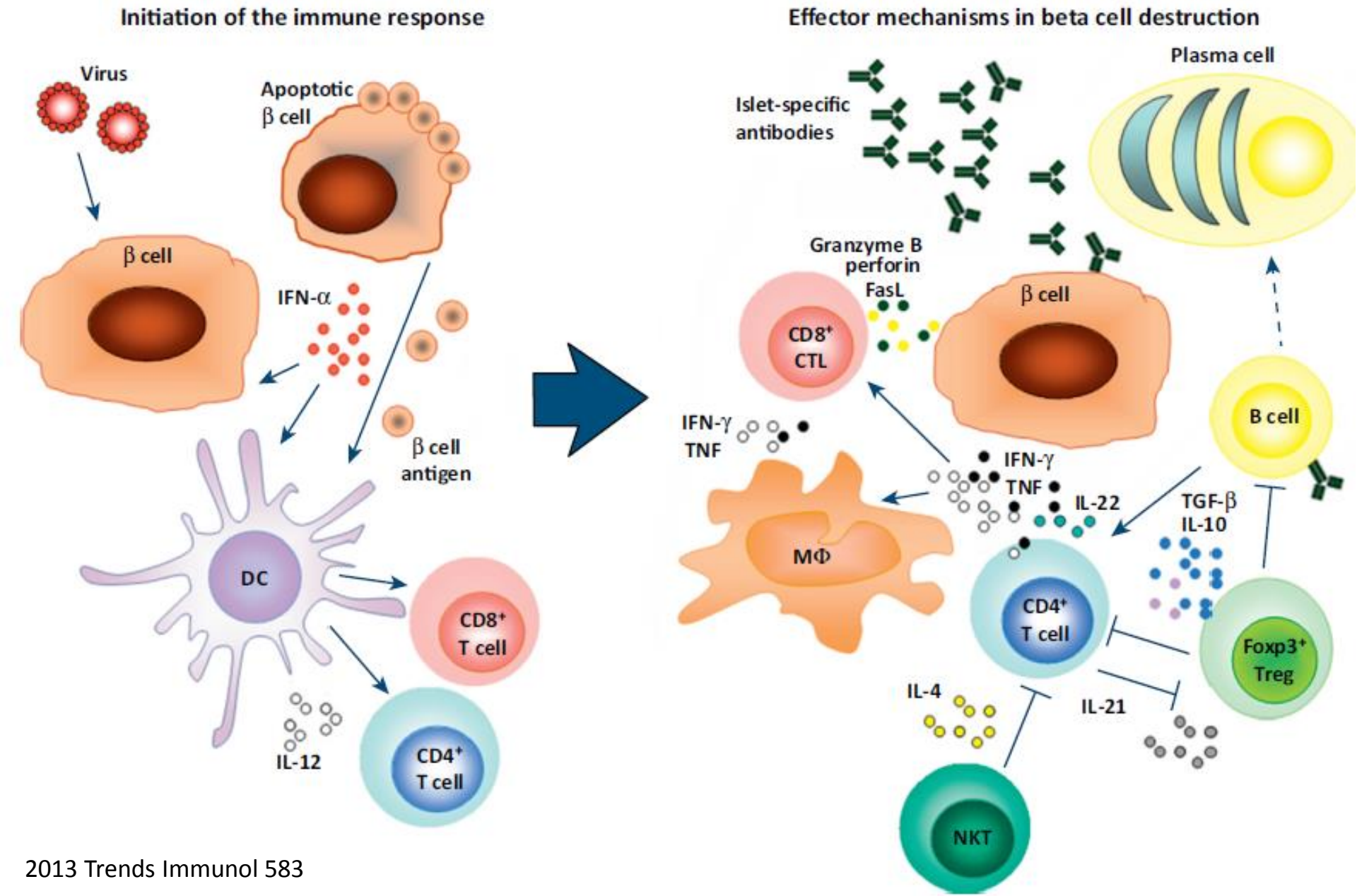


Cell singling of RAGE

1. AGE binds to RAGE to induce intracellular signaling.
2. NADPH oxidase produces ROS to activate NF-kB (transcription factor).
3. NF-kB expresses more RAGE and proinflammatory cytokines.
4. Repeating this process to cause chronic inflammation. 慢性炎症

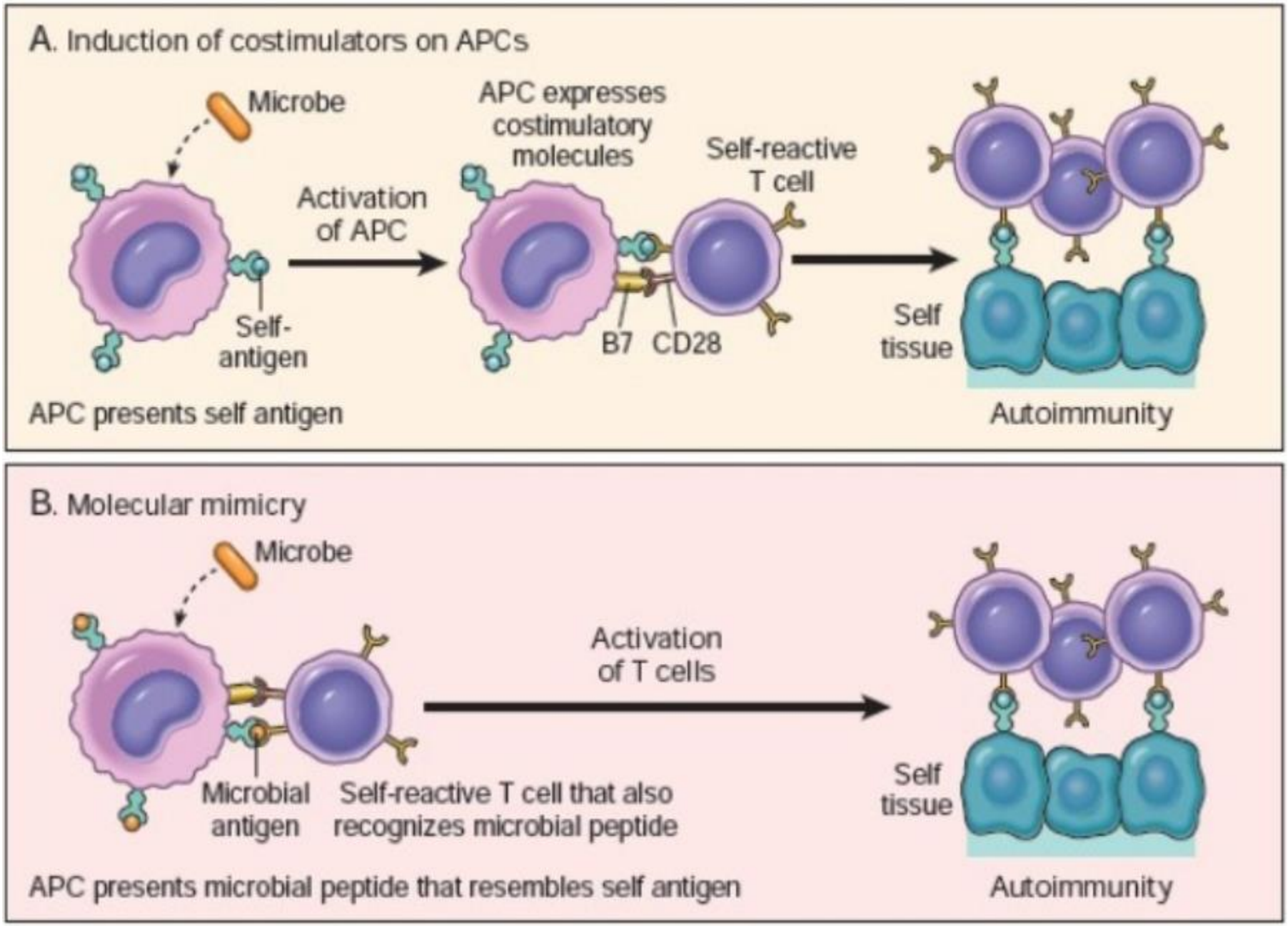


Autoimmunity (Type 1 DM)



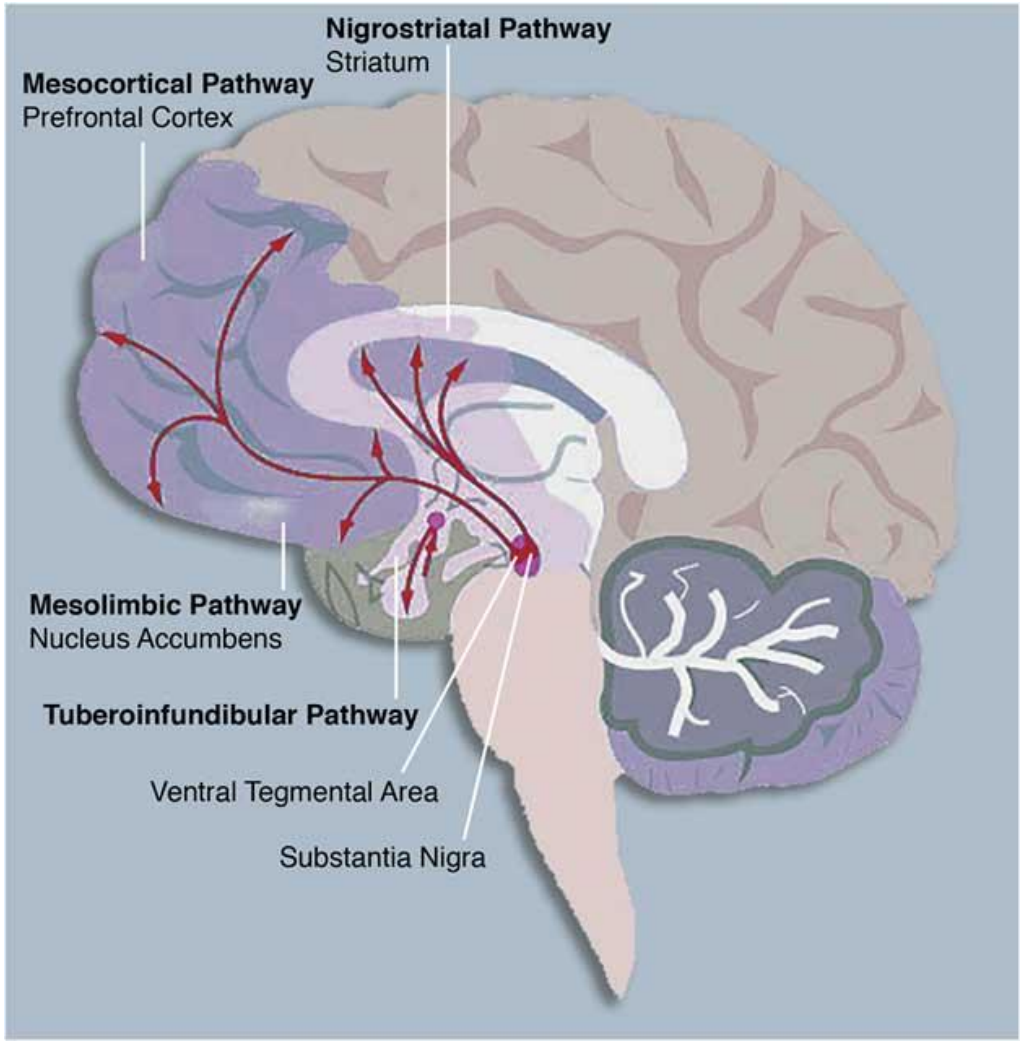
2013 Trends Immunol 583

Misidentification of self-peptides



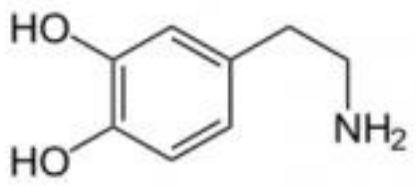
Glucose addiction via reward system
報酬系による糖分依存症

Reward system



Reaction to sugar imaged by PET scan

Neurotransmitter for reward system



Dopamine ドーパミン

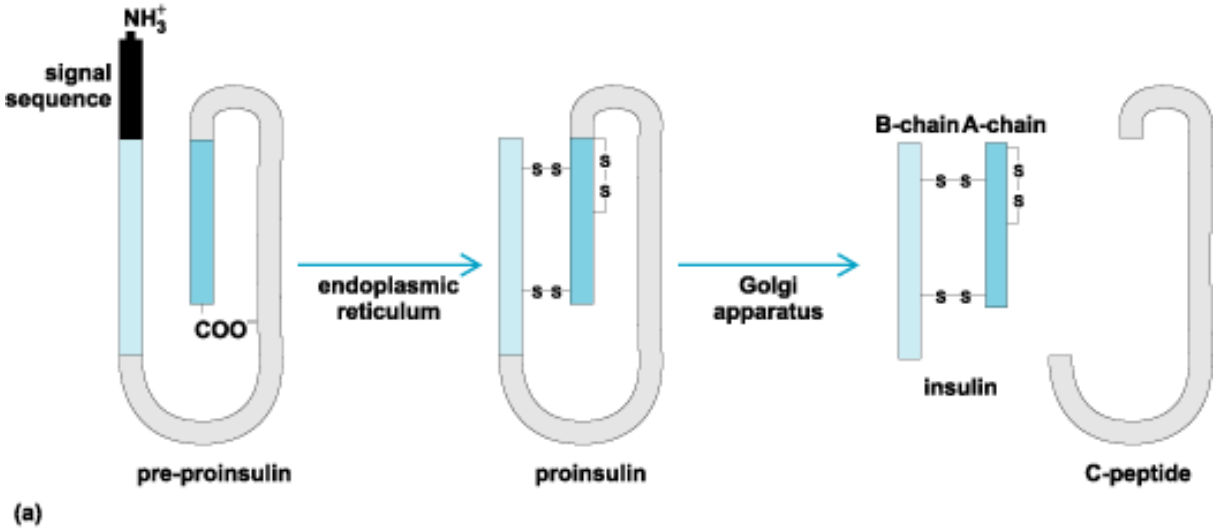
1. 6 Therapy of DM 糖尿病の治療：

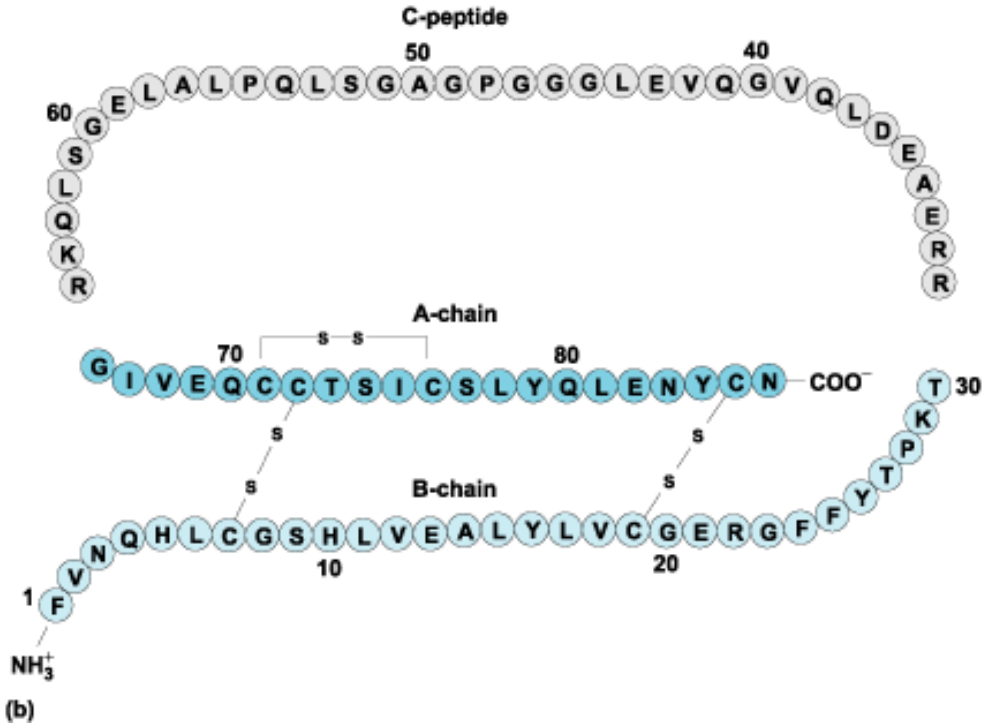
Insulin, GLP-1 インシュリン、GLP-1

Medication 薬物治療

Implantation of pancreas 膵臓移植

Insulin

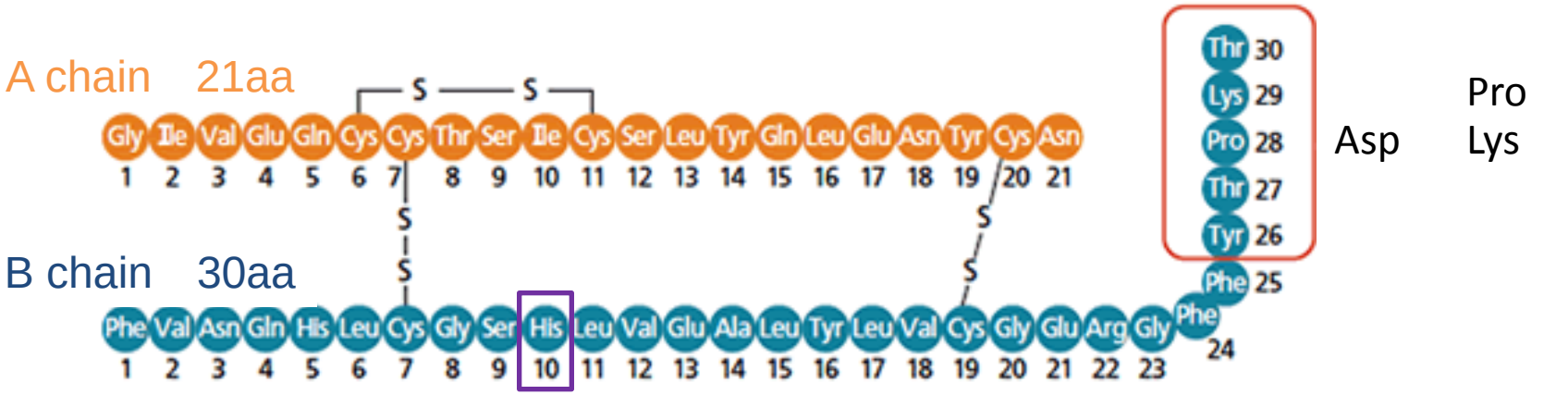


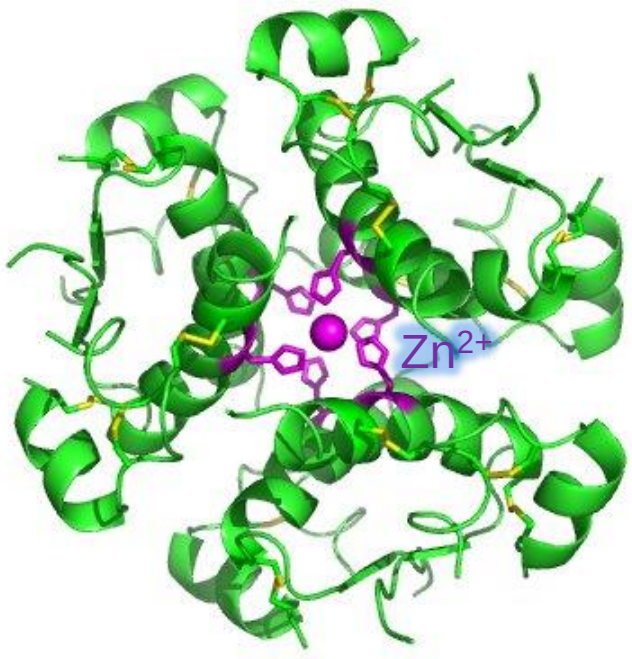


C-peptide also secreted with insulin from β cell

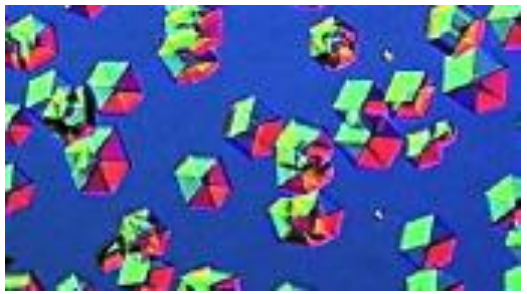
Insulin

aspart lispro





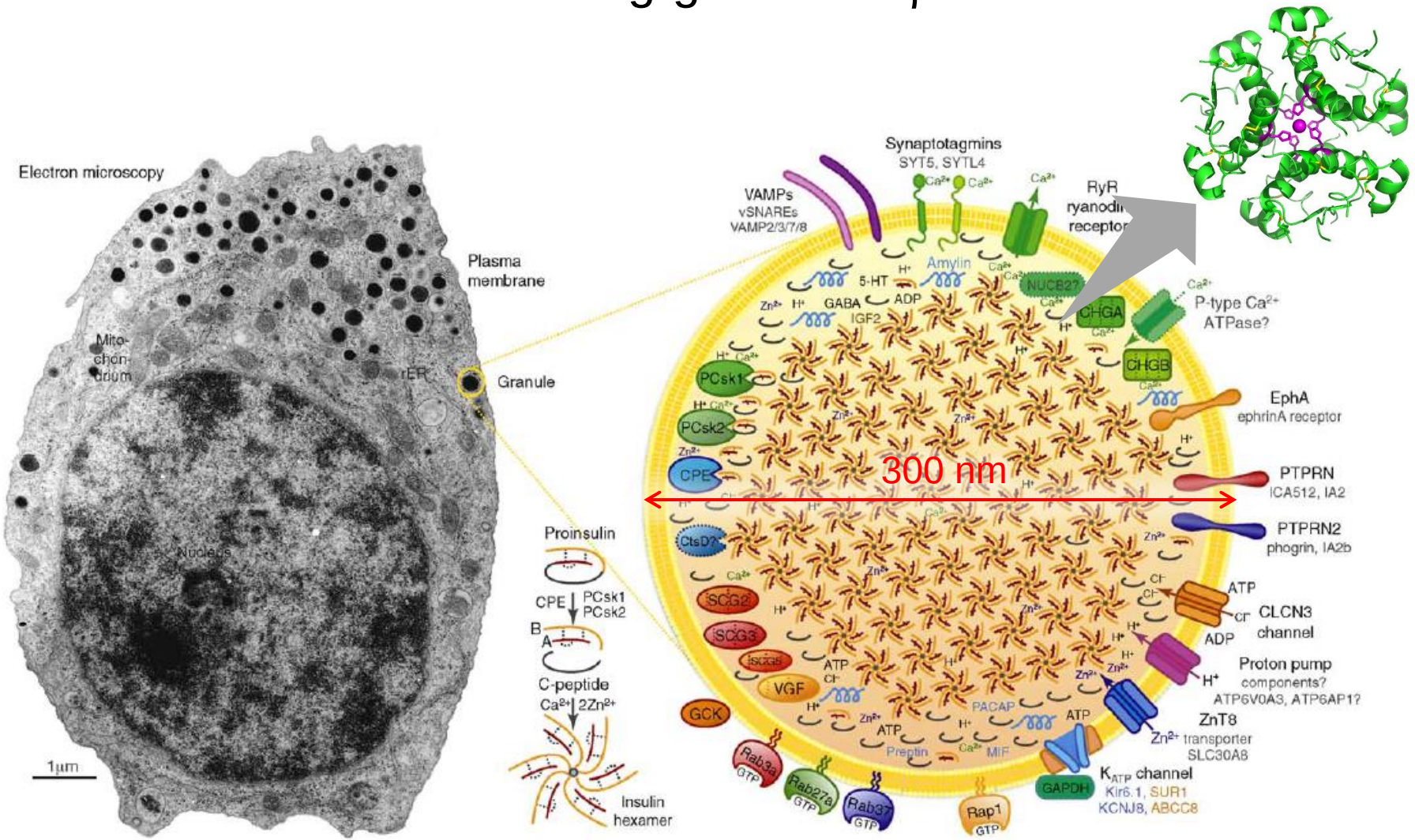
hexamer (top view)



hexagonal crystal

hexamer exist as crystal in β-cell.

Insulin-containing granule in β-cell

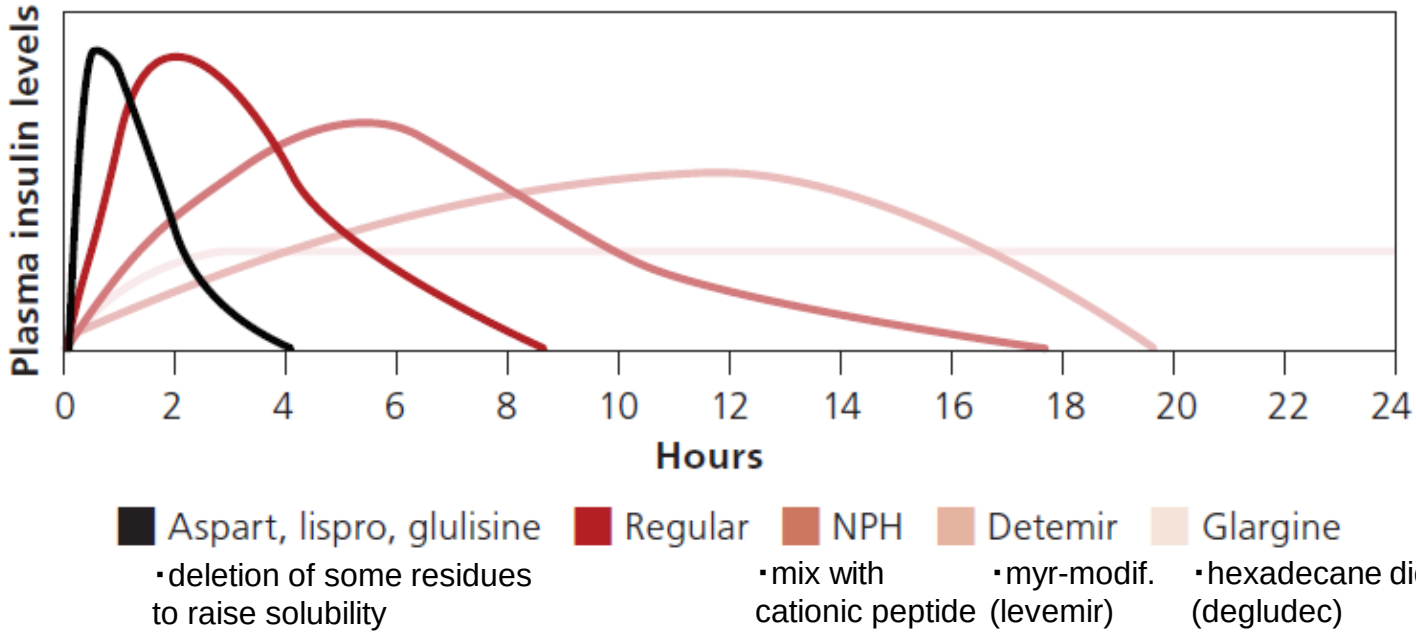


10^4 granules/β–cell

$2x10^5$ insulins/granule

$2x10^9$ insulins/β–cell

Engineered insulins for rapid or sustained release

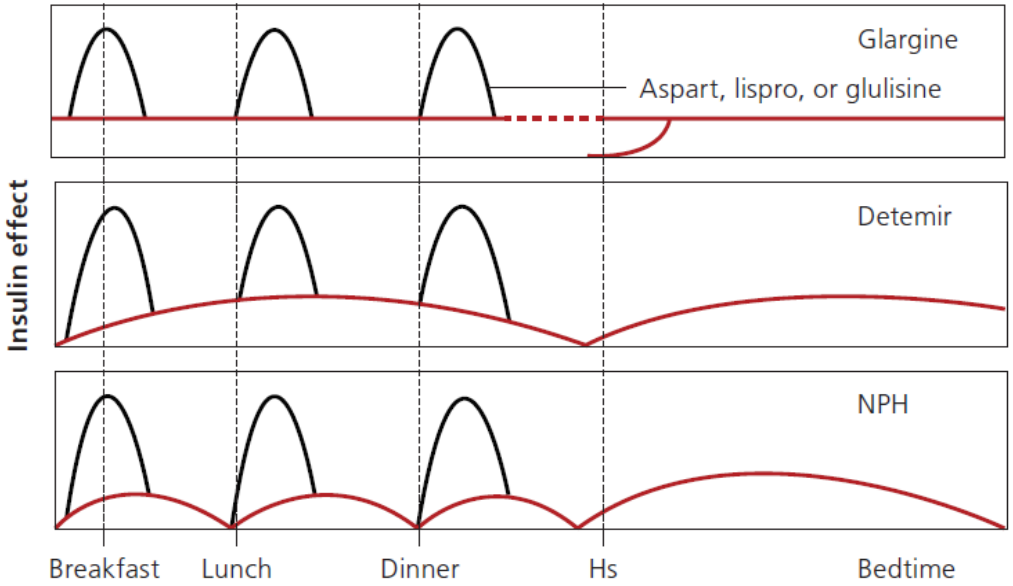


- deletion of some residues to raise solubility
- mix with cationic peptide
- myr-modif. (levemir)
- hexadecane dioicacid-modif. (degludec)

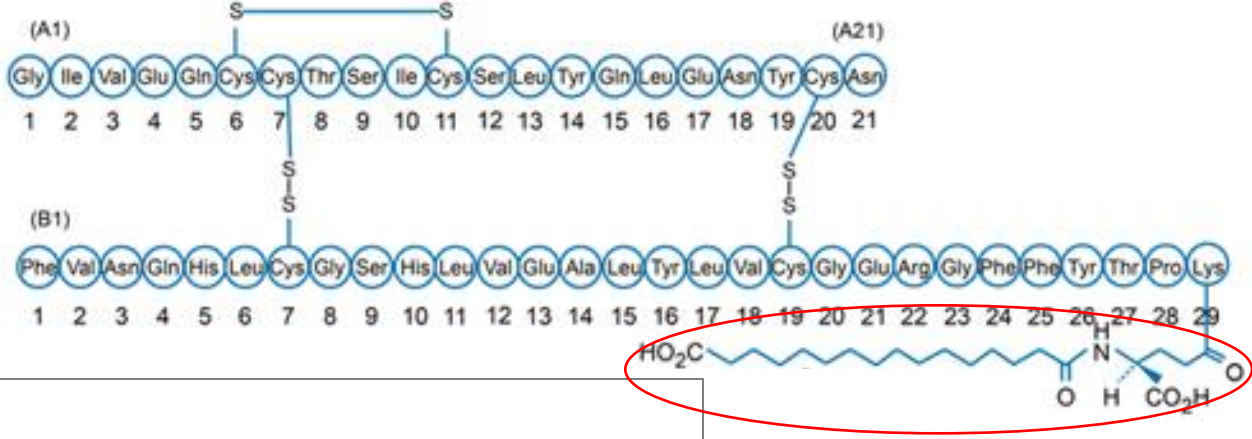
<u>Combination of rapid and sustained insulin</u>

Rapid insulin: for abrupt increase of BGL after meal

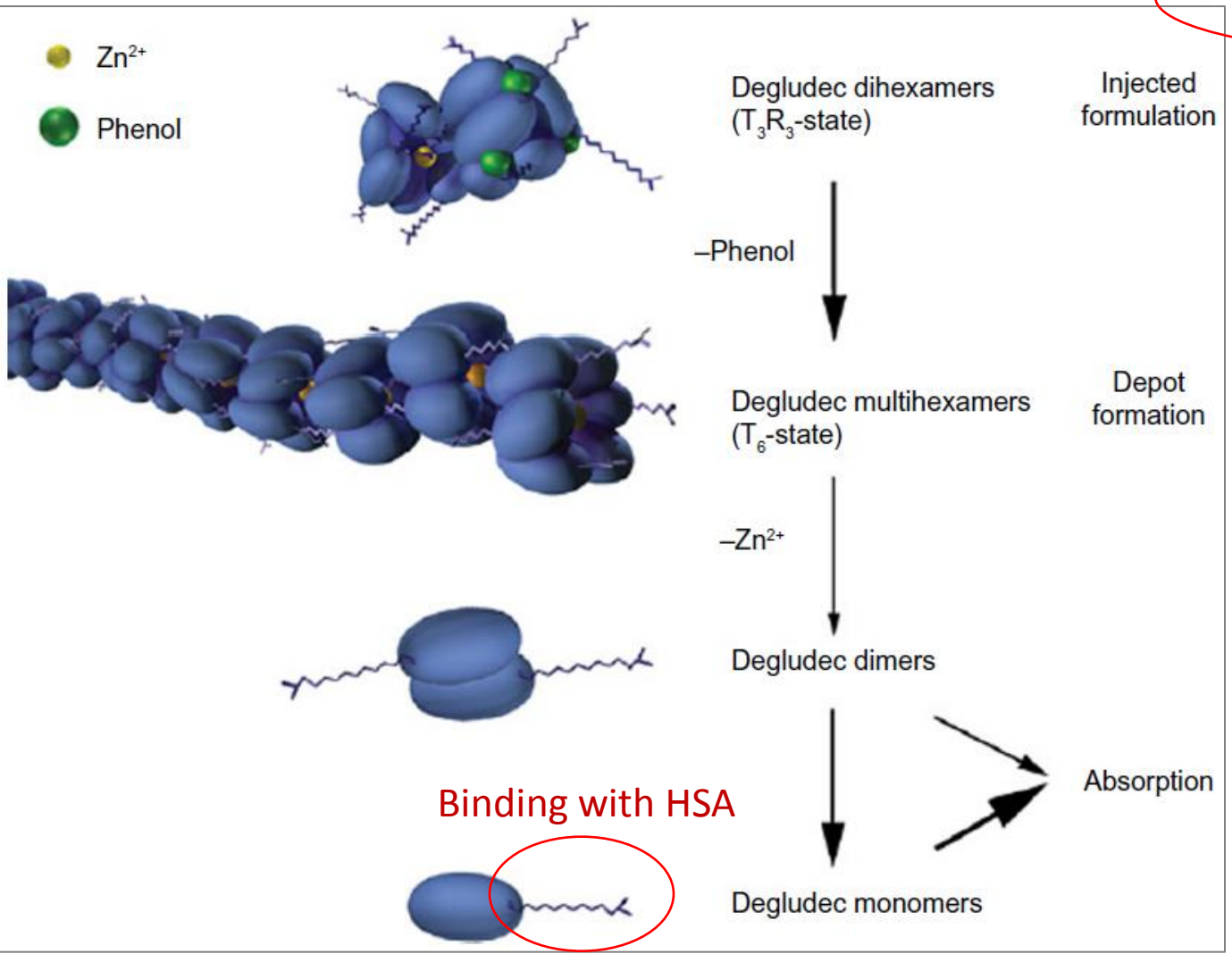
Sustained insulin: basal BGL reduction



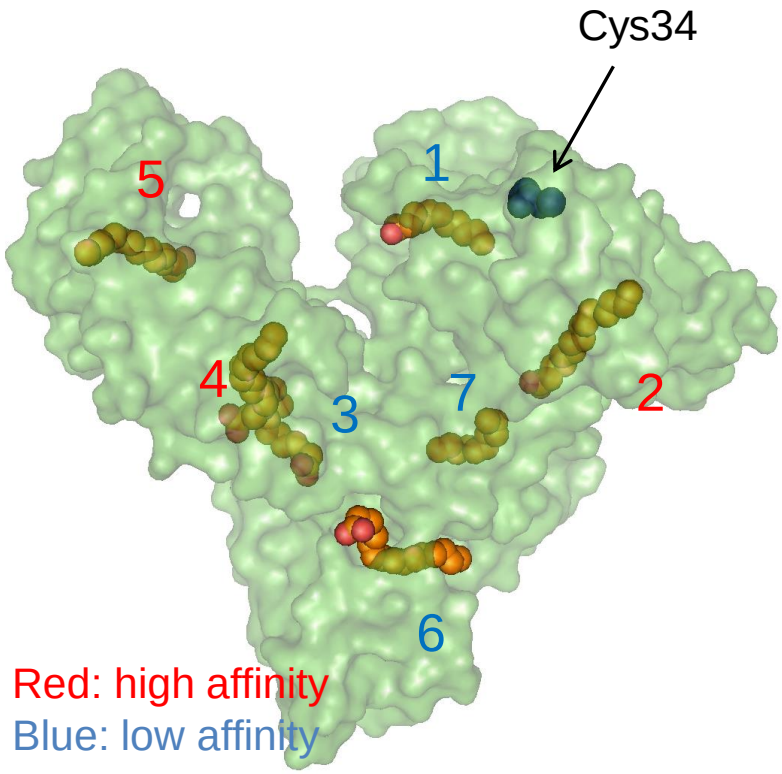
Degludec



Binding with HSA for long blood half-life



Human serum protein (HSA): a suitable drug carrier



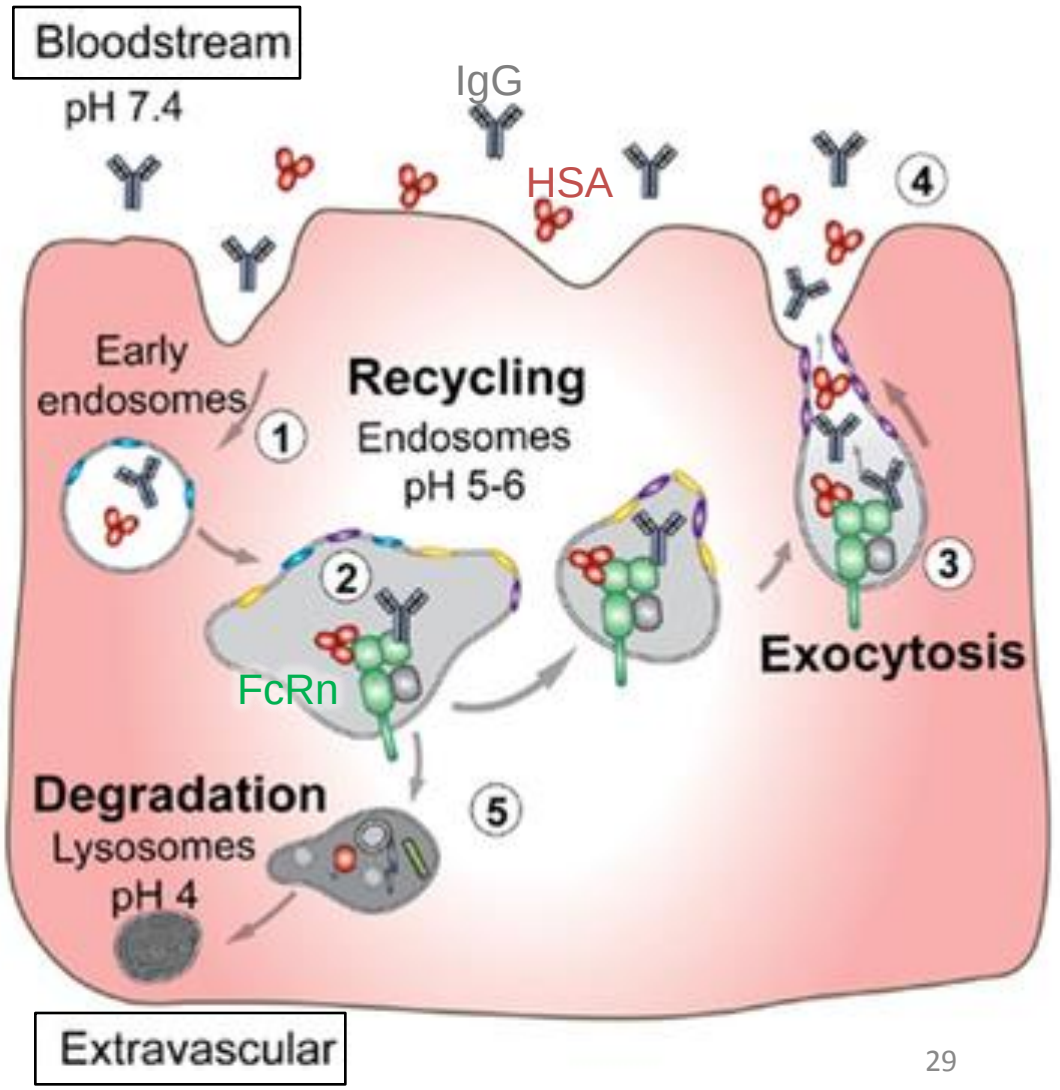
Red: high affinity
Blue: low affinity

Long blood half life: 3 weeks

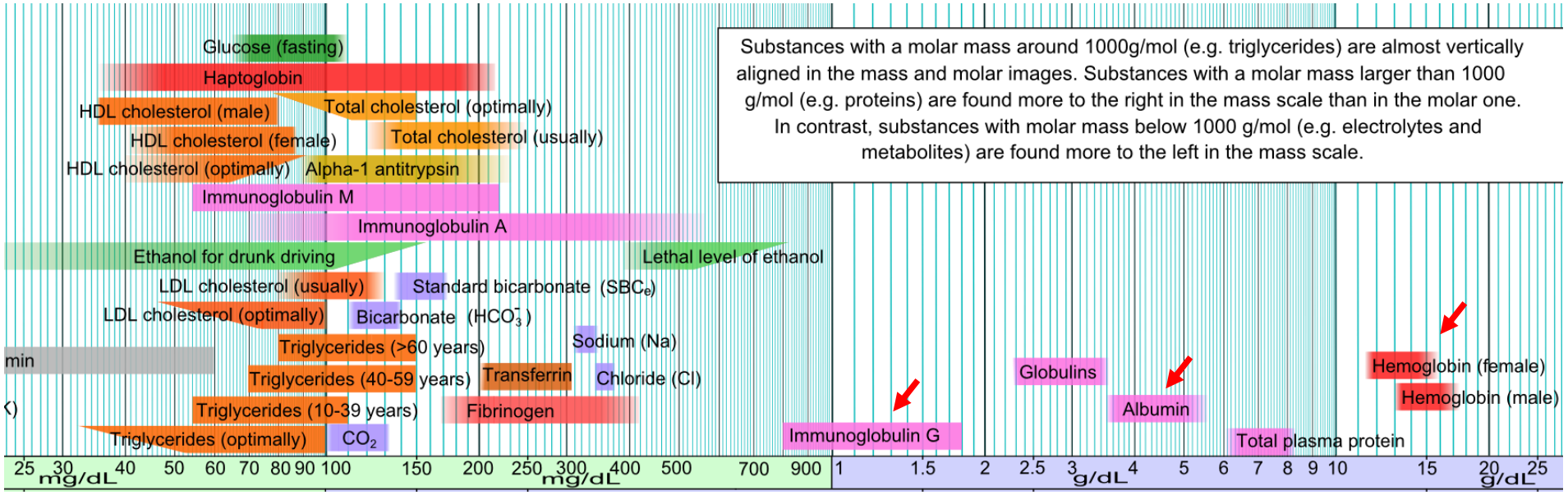
High blood conc.: 50 g/L

Carrier of fatty acid: Kd ~ 10^{-7} M

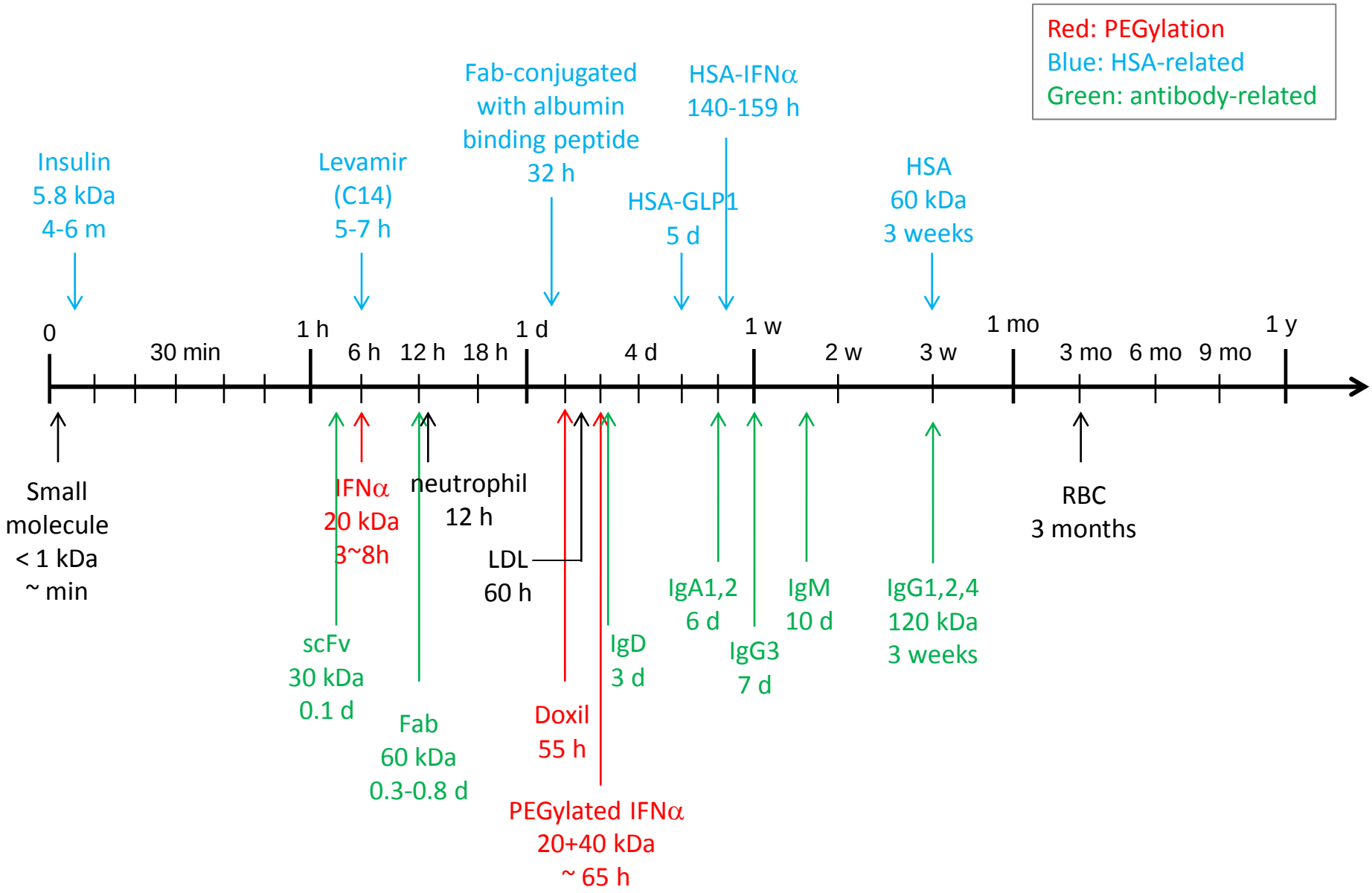
HSA and IgG can recycle back to blood by FcRn.



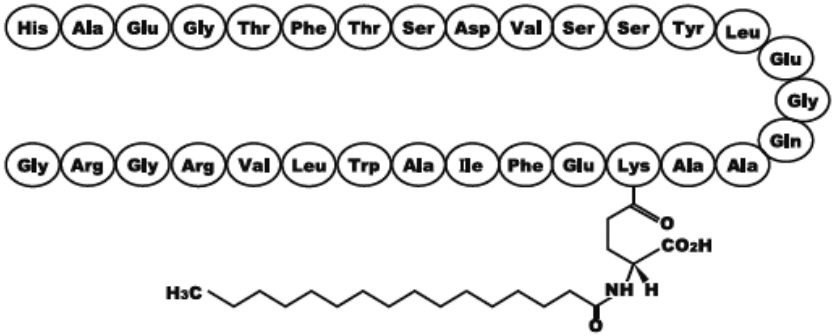
Conc. of proteins in blood

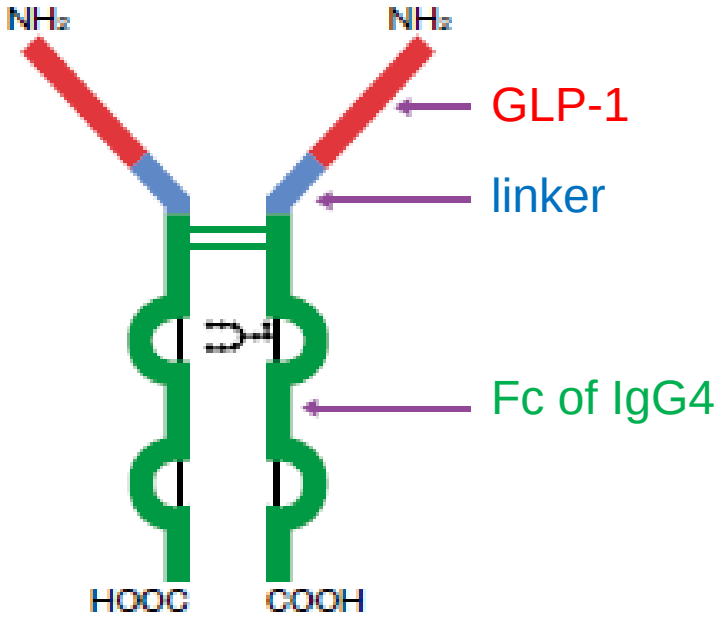


Blood half-life



Engineered GLP-1 for long blood half-life





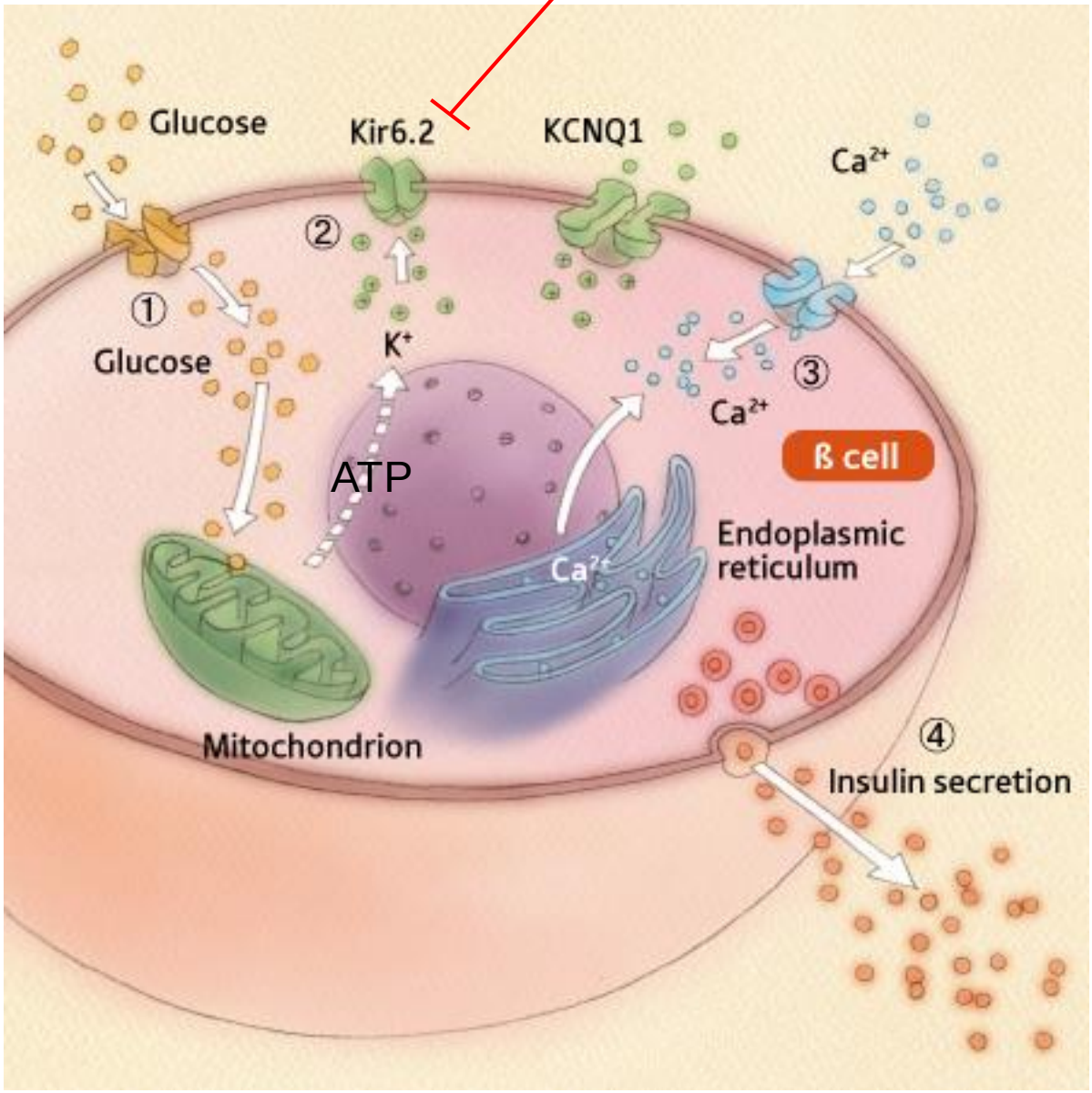
Liraglutide

- Long blood half-life due to the high affinity to HSA.
- Once in a day (subcutaneous injection).

Dulaglutide

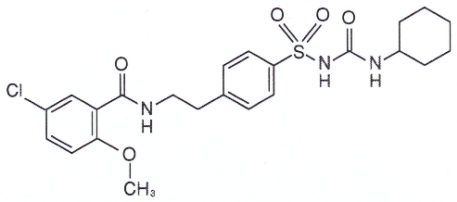
- Long blood half-life due to the fusion with Fc.
- Once in a week (subcutaneous injection).

Sulfonyl urea: activation of insulin release



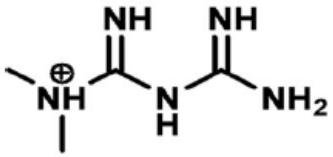
1. Glucose raises ATP conc.
2. Closing of K^+ channel
3. Opening of Ca^{2+} channel
4. Membrane fusion of granule to release insulin

Sulfonyl urea compounds close K+ channel to release insulin.

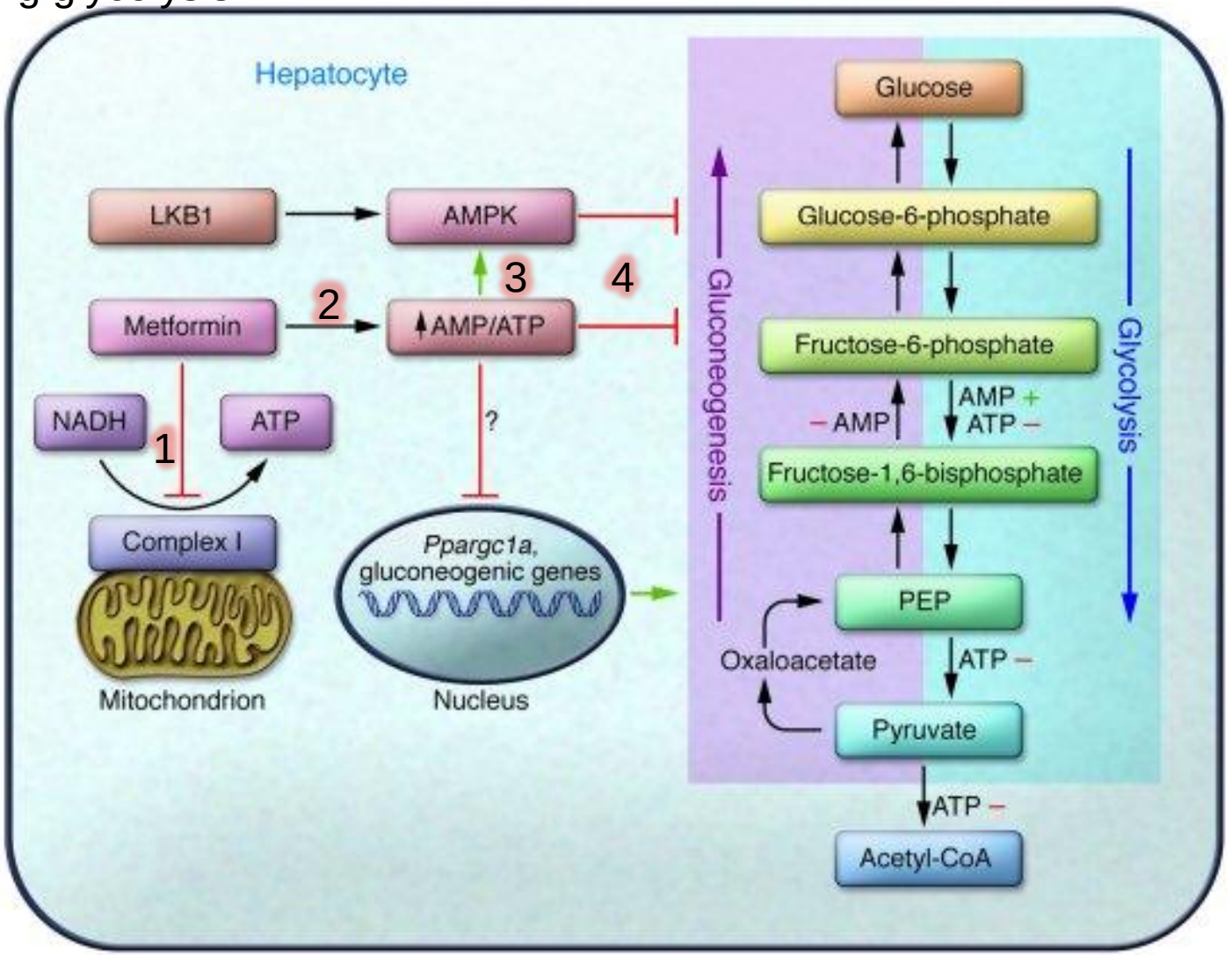


Metformin: raising AMP/ATP ratio to accelerate glycolysis in liver

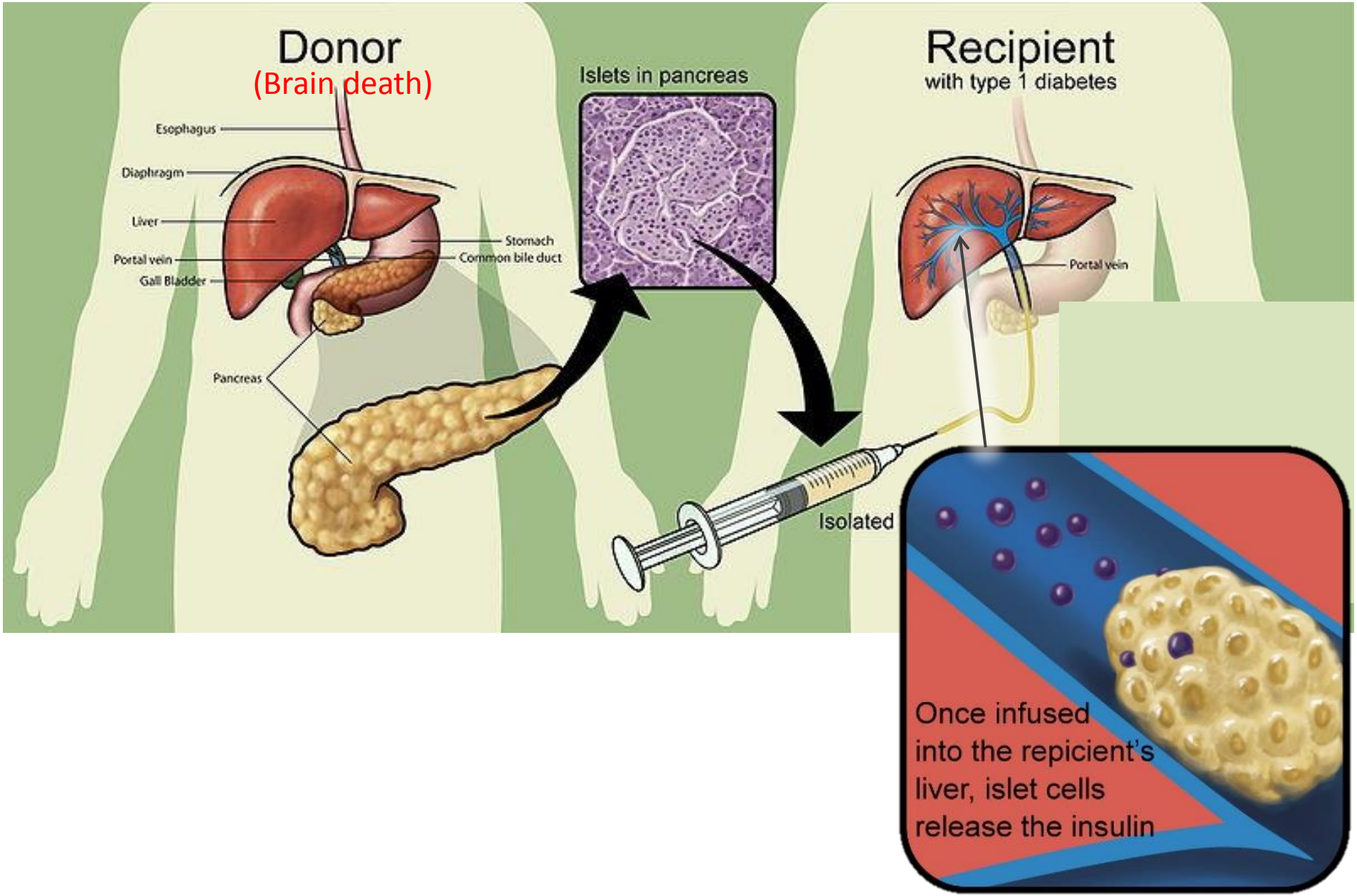
1. Binding to mito. membrane to disturb ATP synthesis
2. Increase of AMP/ATP (lacking of energy)
3. Activation of AMPK (transcription factor)
4. Accelerating glycolysis



metformin



Islet graft for type I-DM （一型DMへの膵島移植）



Islet graft for type I-DM （一型DMへの膵島移植）

1. Pre-transplantation
- anti-thymocyte globulin (killing lymphocytes)
- Immunosuppressant

2. Transplantation

3. Post-transplantation
- Anti-IL-2R antibody (killing T cell) on post transpl. day 4.
- Immunosuppressant (twice a day)

- Patients who did not need insulin injection were 10% (after 5 years from transplantation). 治療5年後までインスリン注射が不要だった症例は約10%
- Requiring immunosuppressant -> risk of opportunistic infection. 免疫抑制剤が必要。日和見感染のリスク。

Creating human's organ in living animal

- No need of immunosuppressant.
- No need of human donor.

Prof. Hiromitsu Nakauchi
中内啓光教授
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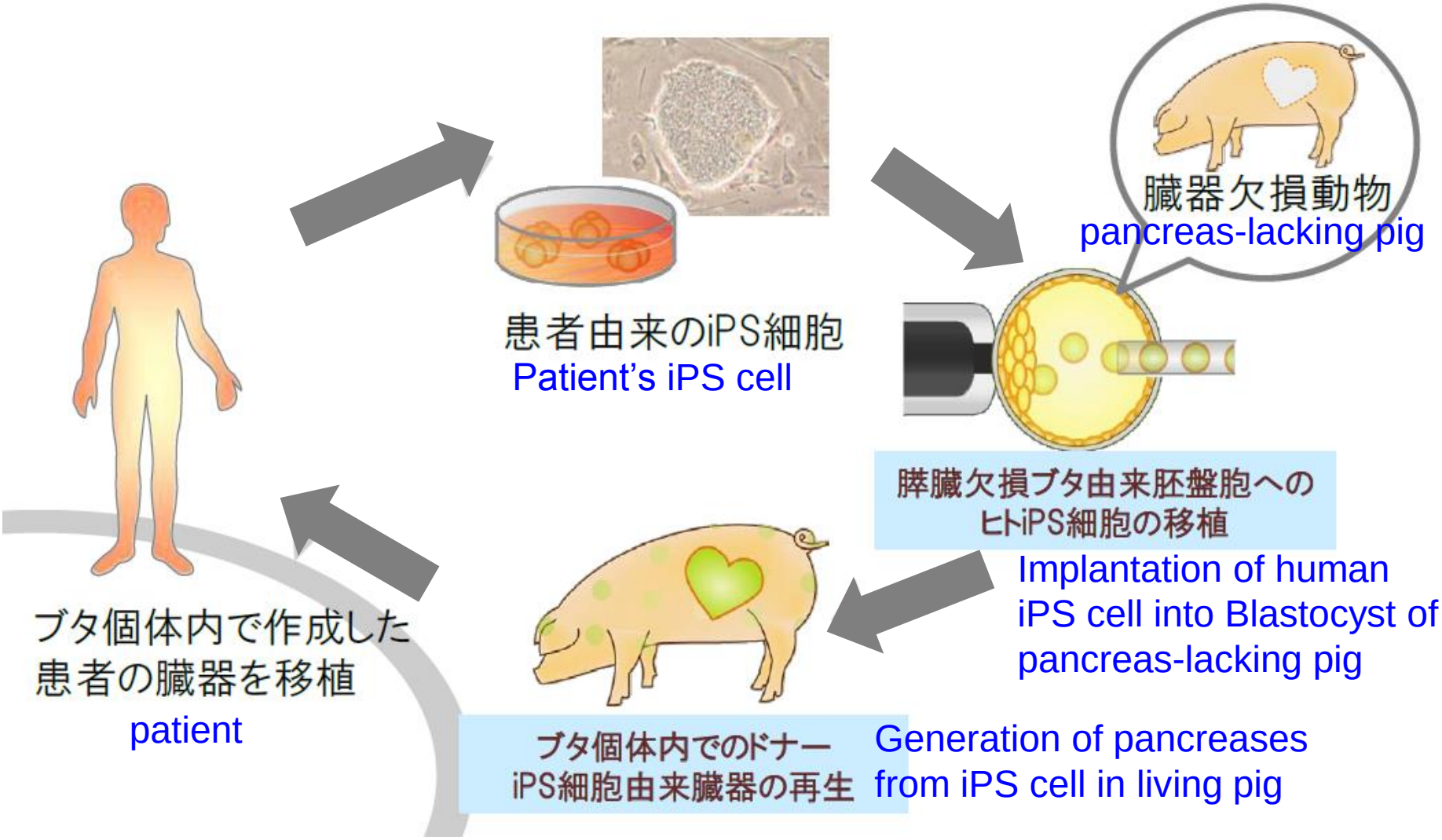

Treg can suppress Th: re-education of immunity to treat autoimmunity

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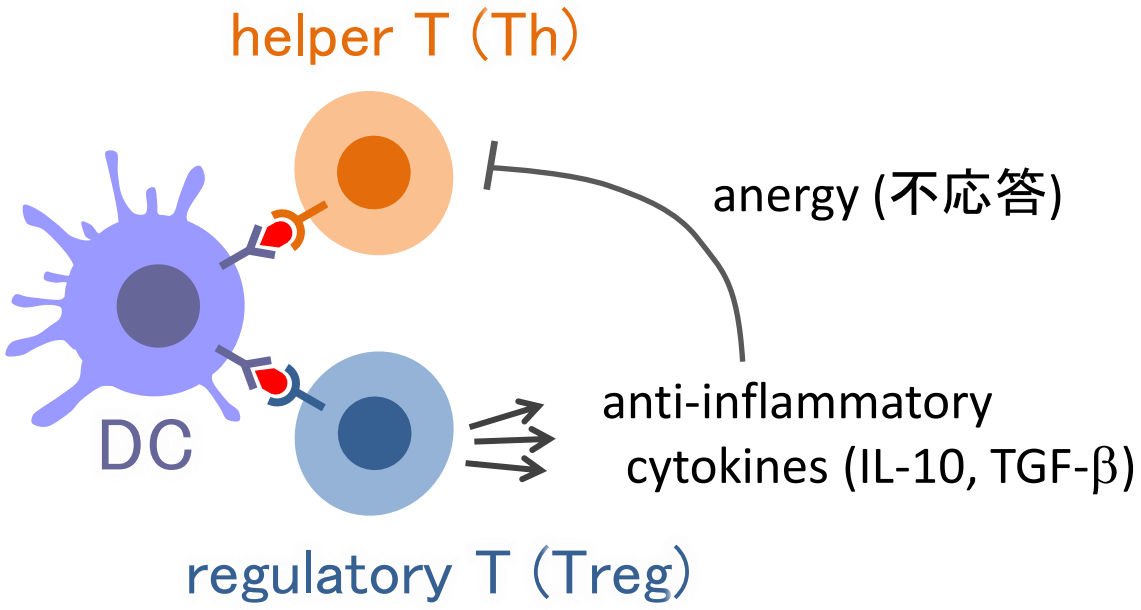

Treg is more activated by DC than Th because of

higher affinity TCR

higher affinity co-receptor (CTLA-4)

higher affinity IL-2R

Quiz 2:

Please deepen your question from the standpoint of evolutionary medicine for DM and suggest your original therapy.

糖尿病に関して、進化医学の立場からした先日の質問をより深めて問題を明らかにし、独自の治療法を提案してください。