学術俯瞰講義

奥深さと美しさによる全体像

可能性が生まれる

発生生物学からみた
生命科学
浅島　誠
東京大学大学院総合文化研究科 教授

分子モーターから観た
生命科学
廣川　信隆
東京大学大学院医学系研究科長

ウイルスからみた
生命科学
野本　明男
東京大学大学院医学系研究科 教授

ゲノムから見た
生命科学
黒岩　常祥
東京大学名誉教授

主題科目／テーマ講義

生命の科学

構造と機能の調和

10月16日→1月29日

月曜日 5時限
駒場キャンパス

16時20分▶17時50分
18号館ホール

Global Focus on Knowledge Lecture Series

2006 Winter Semester: “Science of Life”

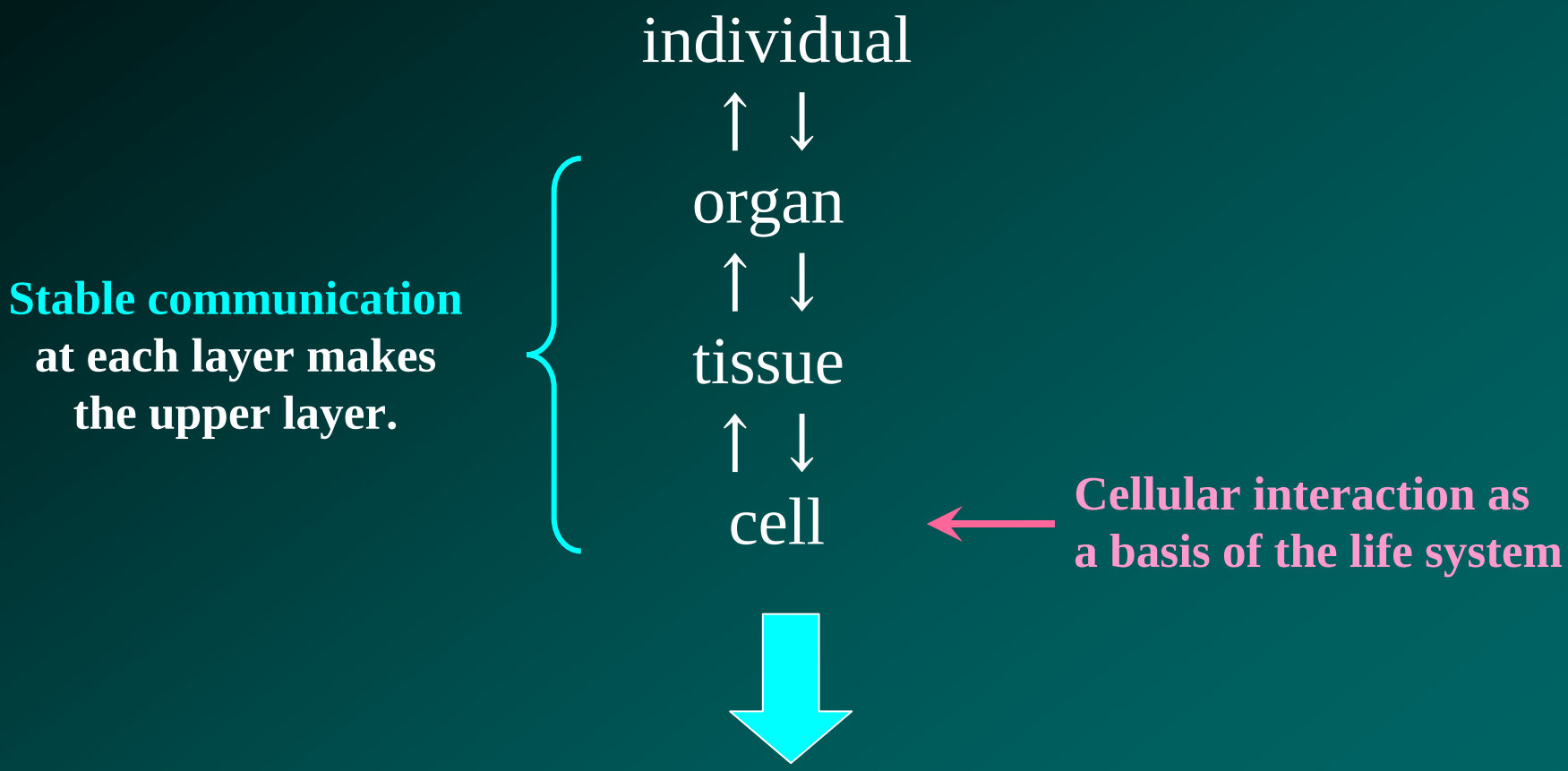
Life Science: from the Perspective of Developmental Biology

The 2nd Lecture　Oct.23（Mon）

Biological information system and networking

Professor Makoto Asashima
Graduate School of Arts and Sciences, University of Tokyo

The layered system of a multicellular organism



Signal transduction network within or between layers

= the system to maintain homeostasis

A biological signal transduction system

Scale of signal transmission

"far"

"close"

macro

micro

① **"Far range" communication by nerve system and endocrine system**

（input from sensory organ・modulation of blood glucose level by insulin, etc.）

② **"Close range" communication by intercellular secretary factor and changes of membrane potential**

（signal transduction between nerve cells and modulation of muscle contraction）

③ **Intercellular** communication・inner cell or outer cell signal transduction

（modulation of mitosis, differentiation, apotosis）

（outer signal via receptor and mechanism of cell response）

④ Signal transduction **inside cell**

（transcriptional regulation of genome, regulation of protein synthesis and degradation, etc.）

For example… **Human is multi-cellular organism made of 60 trillion cells.**

The system is maintained by appropriate responses and interactions between cells.

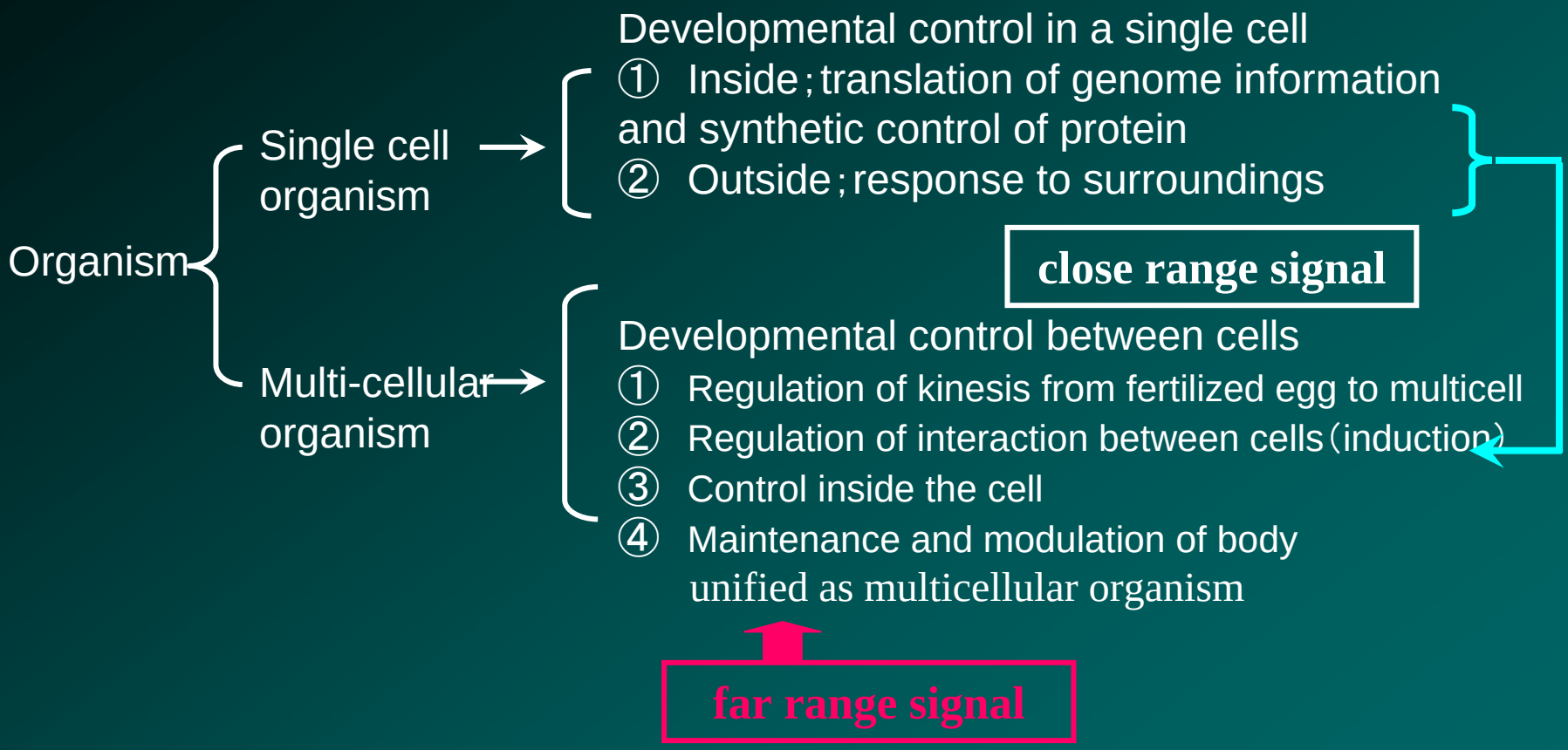
To consider biological development synthetically

Key points

① In development of an organism, signal transduction network changes itself actively.

② "Far range" communication can be reduced into cell level response

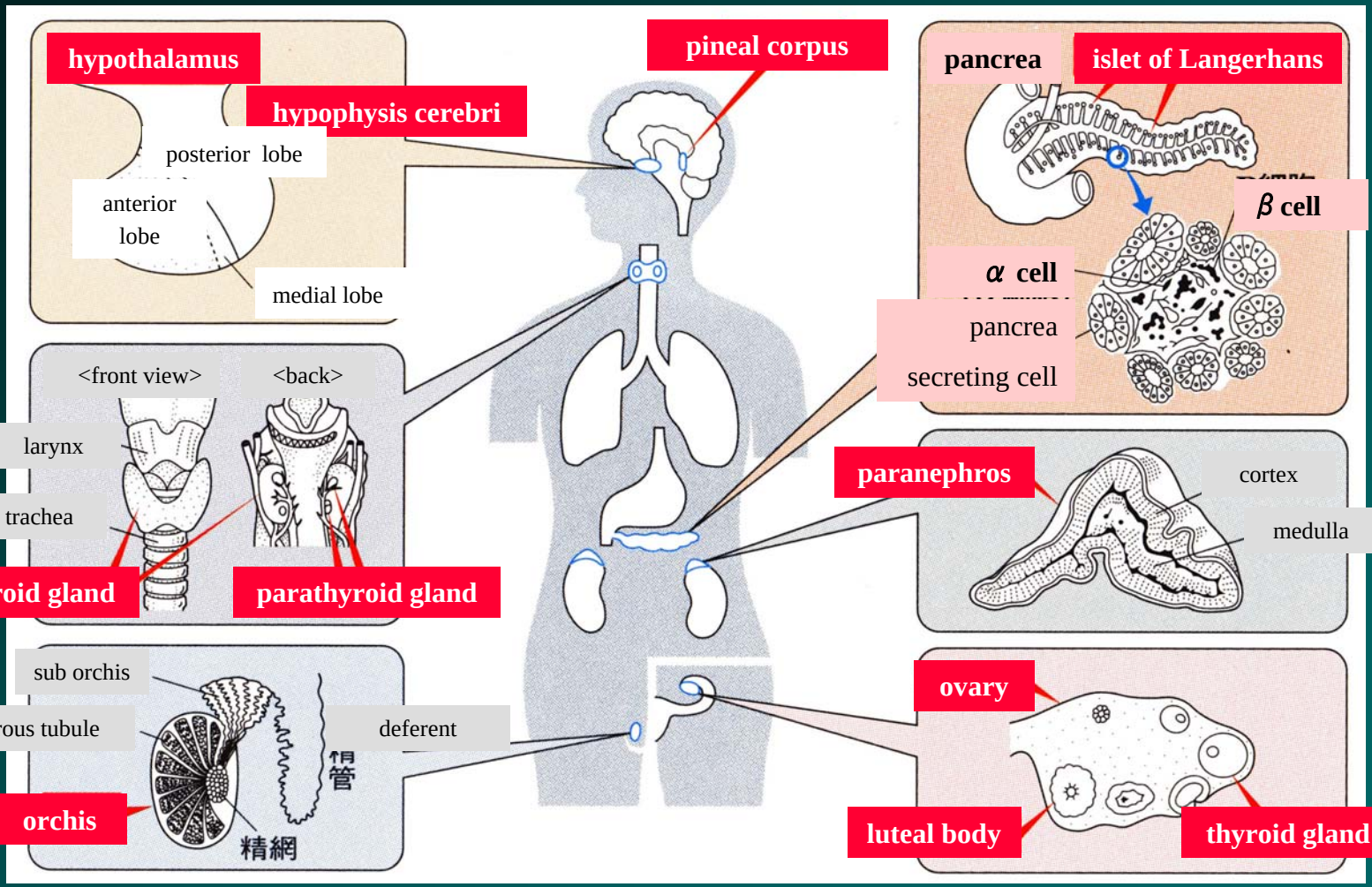
Vision of signal transduction during biological development



It is important to know each stage of the signal transduction system synthetically in order to know biological development.

The network of a far range signal①

Hormonal signaling is transmitted by the blood vessel system

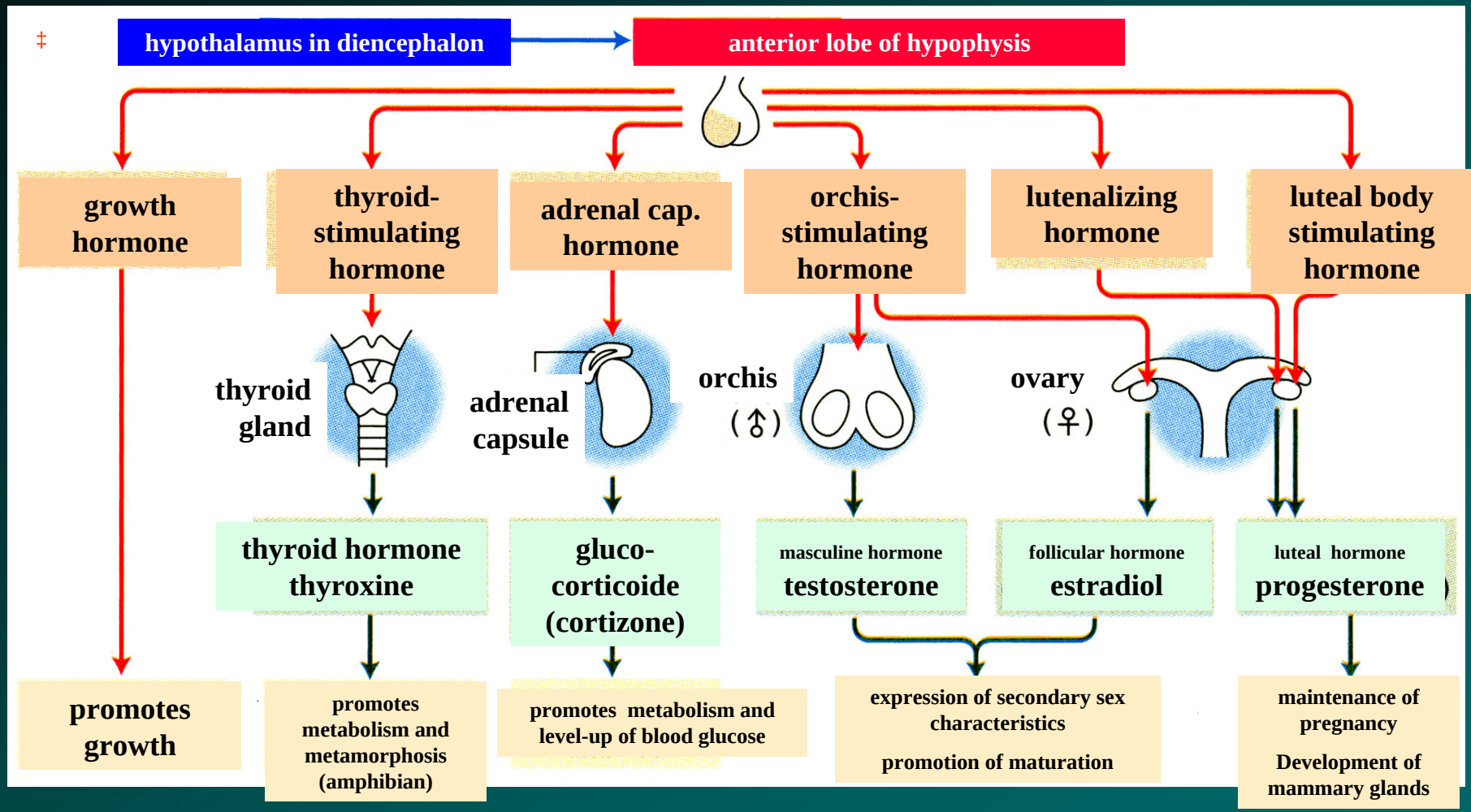


Examples of endocrine glands in an adult body

Buneido 2004

The network of a far range signal①

Hormonal signaling is transmitted by the blood vessel system



Examples of hormone function in an adult body Buneido 2004

The function of hormones in development①

① Development of endocrine glands（differs by glands）

example：development of hypophysis cerebri

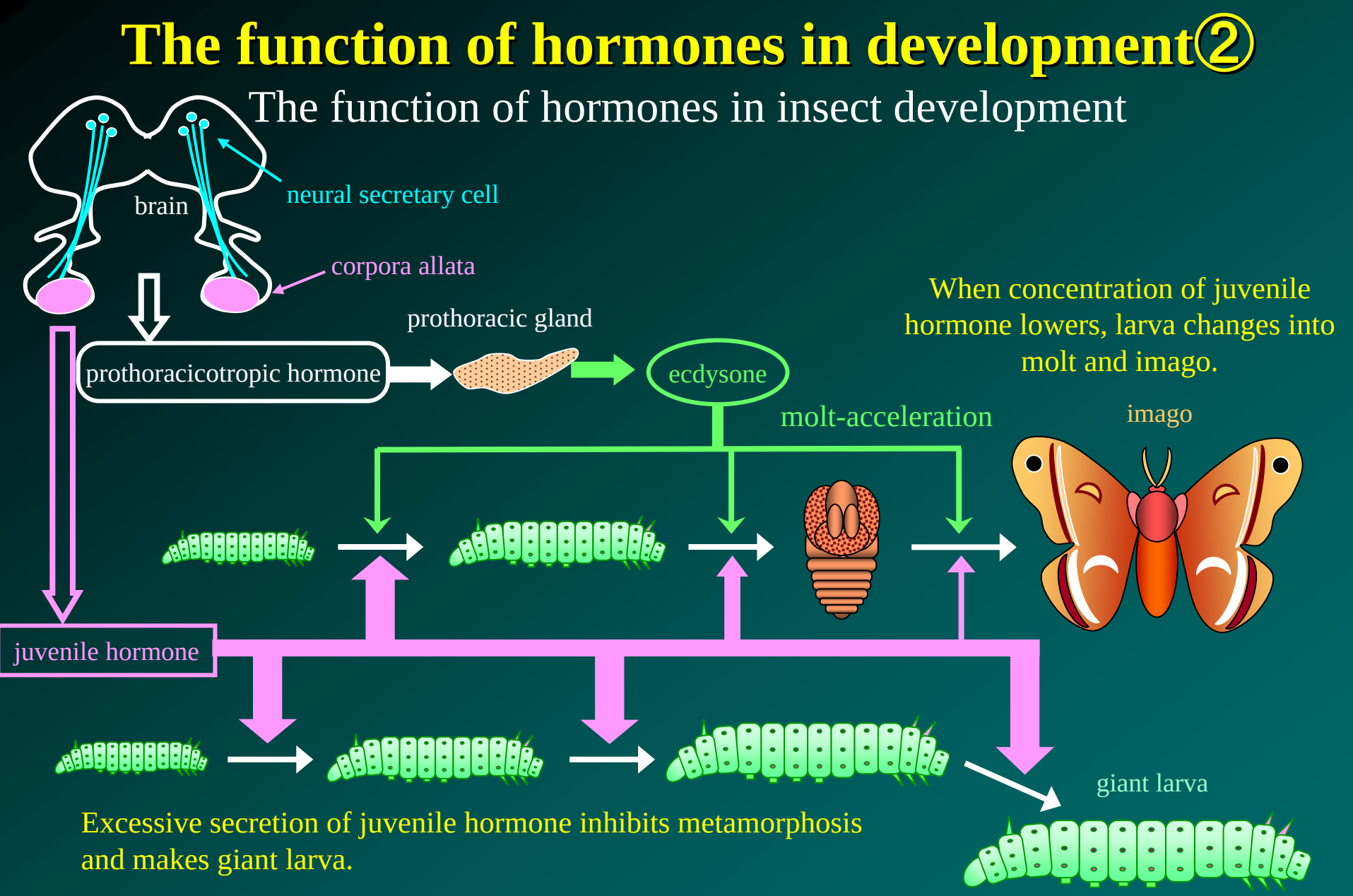
Hypophysis cerebri
- Anterior lobe:glandular hypophysis（pharyngeal mucosa invaginetes）
- Posterior lobe：neural hypophysis （hypothalamus extends）

② Effect of hormone during development

Androgen shower

→ androgenization of brain by signal transduction via blood flow

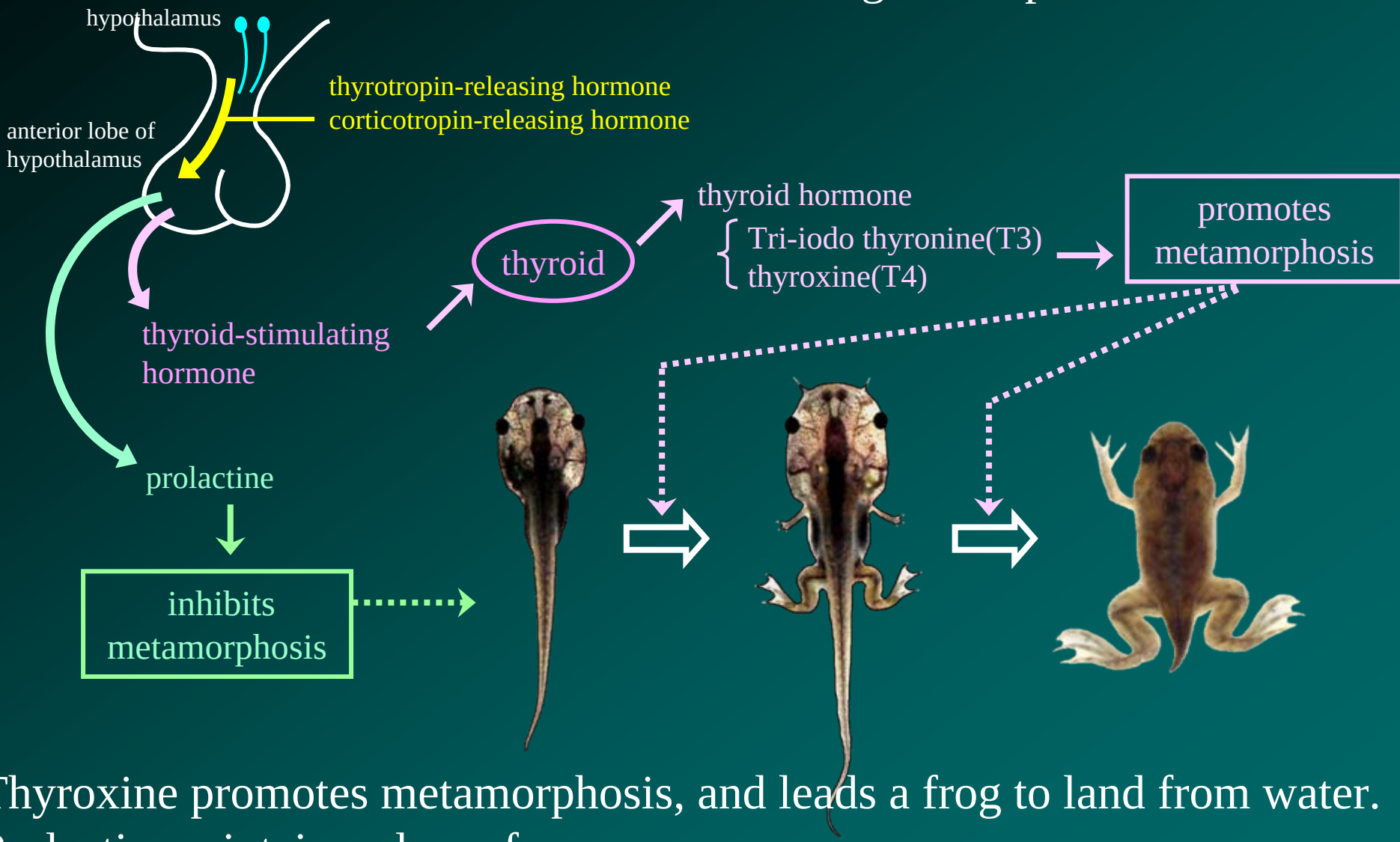
The function of hormones in development②



Juvenile hormone and ecdysone regulate the system of metamorphosis.

The function of hormones in development③

The function of hormones in frog development

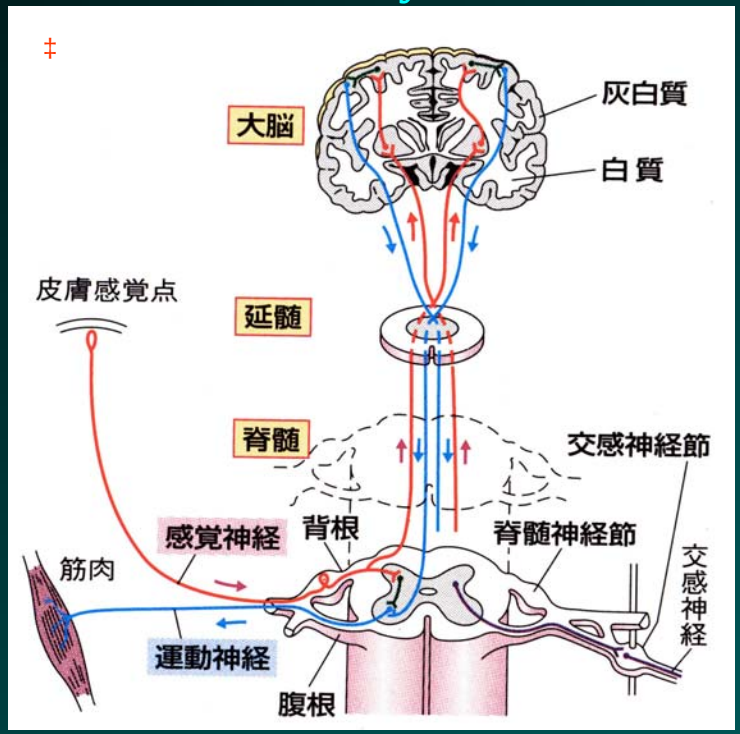


Thyroxine promotes metamorphosis, and leads a frog to land from water.
Prolactin maintains a larva form.
The antagonism of two hormones mobilize the system of metamorphosis.

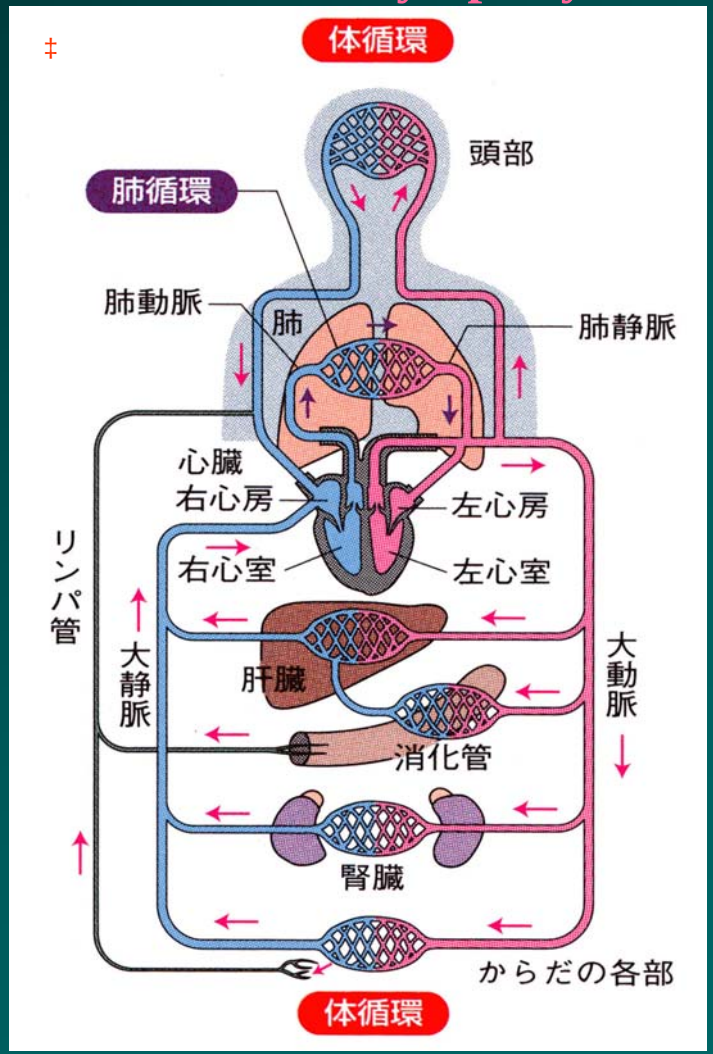
The network of a far range system②

Nervous and vascular system as a base for signal transduction

Adult neural system



Adult blood and lymph system



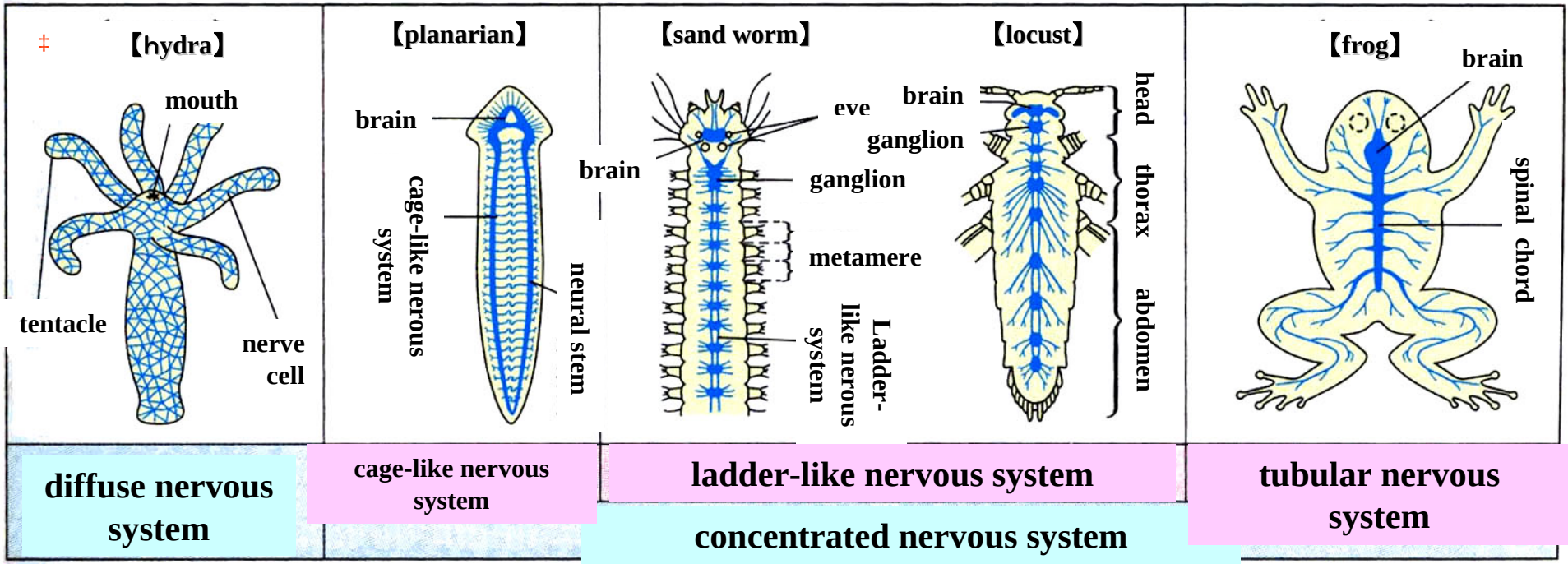
Focus on

・development of nervous and vascular system

・effect on organ development

Buneido 2004

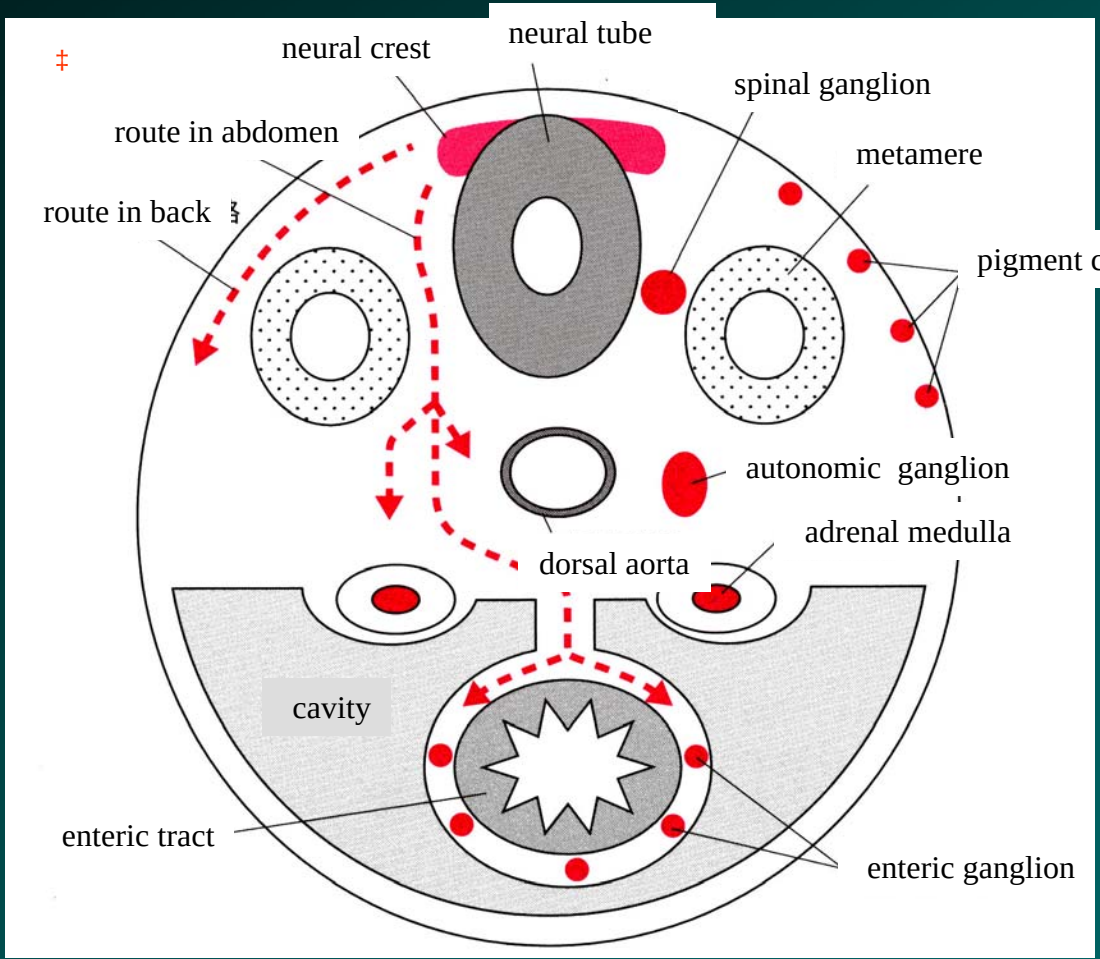
The structure of the nervous systems in animals



Buneido 2004

An example of neural network development①

Diagram of neural crest cells in vertebrate development



Shokabo 2004

Surrounding cells direct neural crest cells to appropriate parts of the body, and construct a neural network.

Neural crest cells differentiate into various cells（pigment cell, etc.）

An example of neural network development②

Movement of neural crest cell in chicken development

anterior neural crest　　posterior neural crest

“The pictures of chicken neural crest”

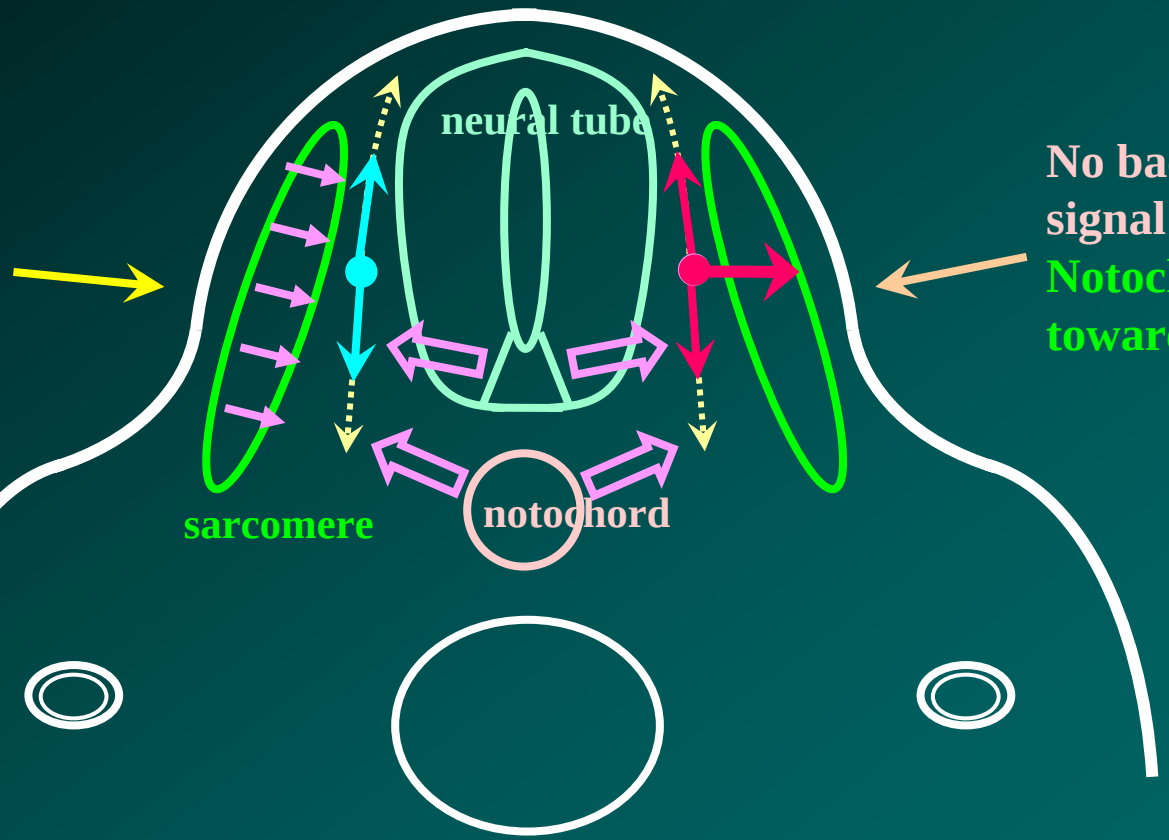
inserted here were omitted according to copyright issue.

green：stained by HNK-1（neural crest cell-specific marker）antibody

Migration of neural crest cells are regulated differently by polarity of the surrounding environment.

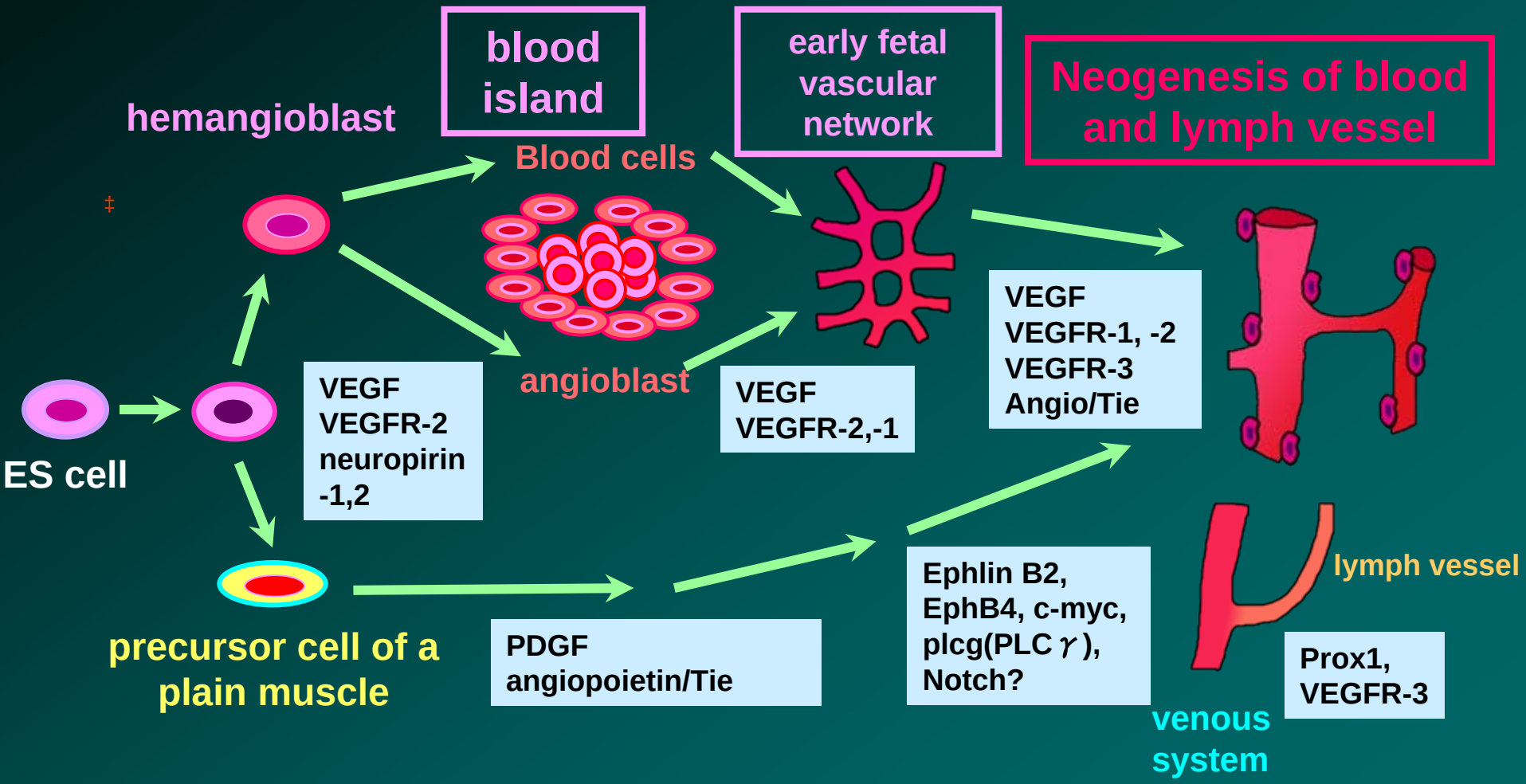
An example of neural network development③

Guidance to sensory nerve axon from spinal ganglion in body trunk



The spinal ganglion decides the direction of sensory nerve axon's growth by backlash signals from sarcomere, neural tube, and notochord.

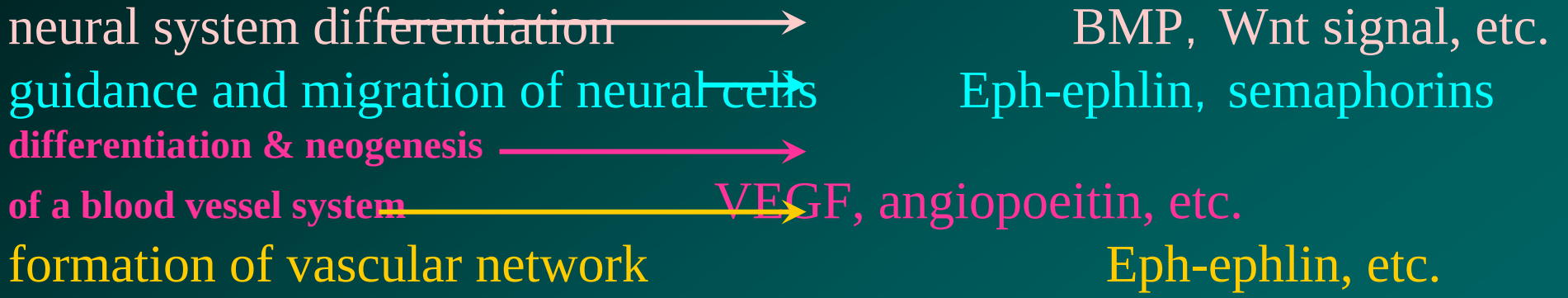
Development mechanism in blood & lymph vessels



Issues in development of a neural/vascular network

What kind of molecular mechanism
constitutes the network structure?

A typical example:



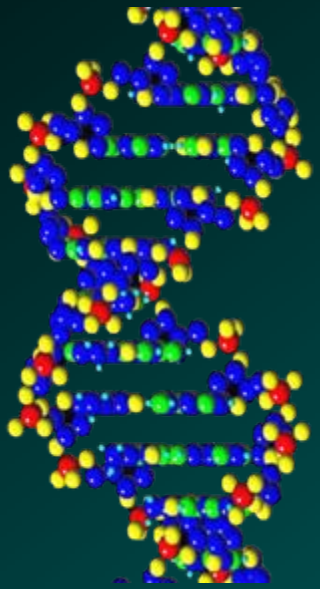
Elucidation of these signal transmission systems and the interaction between them is needed to clarify the developmental mechanism.

A network of close range signals

- a structure of cell and signal transduction into & out of a cell

1953 Watson & Crick discover the double-helix structure

Their model explained various insights into heredity by showing very clearly how genetic codes are preserved and inherited.



DNA double helix structure model

Rapid development of research in the late 20th century

- Discovery of a translation mechanism of gene information
- Decoding genetic codes（DNA sequence and corresponding amino acid）
- Invention of various methods to decode the DNA sequence
- Discovery of the “restriction enzyme” by microbiologists, discovery of genetic engineering using bacteria.
- Invention of PCR

An approach to an essential understanding of life, even human, became possible

Discovery of signal transduction mechanism in a cell

（era of genetic engineering・life engineering）

Genome

Cell = the basic unit of every life form

Nucleus= inside the cell, modifies the cell

Genome = inside nucleus, made of all the DNA that constitute an organism. DNA strands record all the genetic codes.

↓

" to decode a genome" is
" to read the blueprint of life"

↓

A need for comprehension of the functions of numerous proteins.

2003 Apr.14 Decoding of the human genome completed.

30 billion base pairs were decoded by USA, Japan, UK, Germany, China, France in 15 years.

- **"Exon"were less then 5% of the whole human genome**
- Total number of human genes were only **32000.**
  Only twice that of the fly.
- Difference between human genome and chimpanzee genome is only 1.2%。
- Beginning of a new "RNA world"

↓

Everything cannot be explained by genome decoding.

↓

- A large number of proteins and glucides also need to be analyzed.
- What explains the differences between the fly, chimpanzee, and man?
- What is the meaning of "intron" ?

Life sciences method after genome decoding

- Speed up function analysis of proteins, not only genes
- Detect & analyze functions of many factors simultaneously

DNA microarray → detects expressions of more than10 thousand genes simultaneously

Proteome analysis → detects amounts of various protein expressions simultaneously

Discover relations by computer processing of huge amounts of data

- Simulation using a simple mathematical model

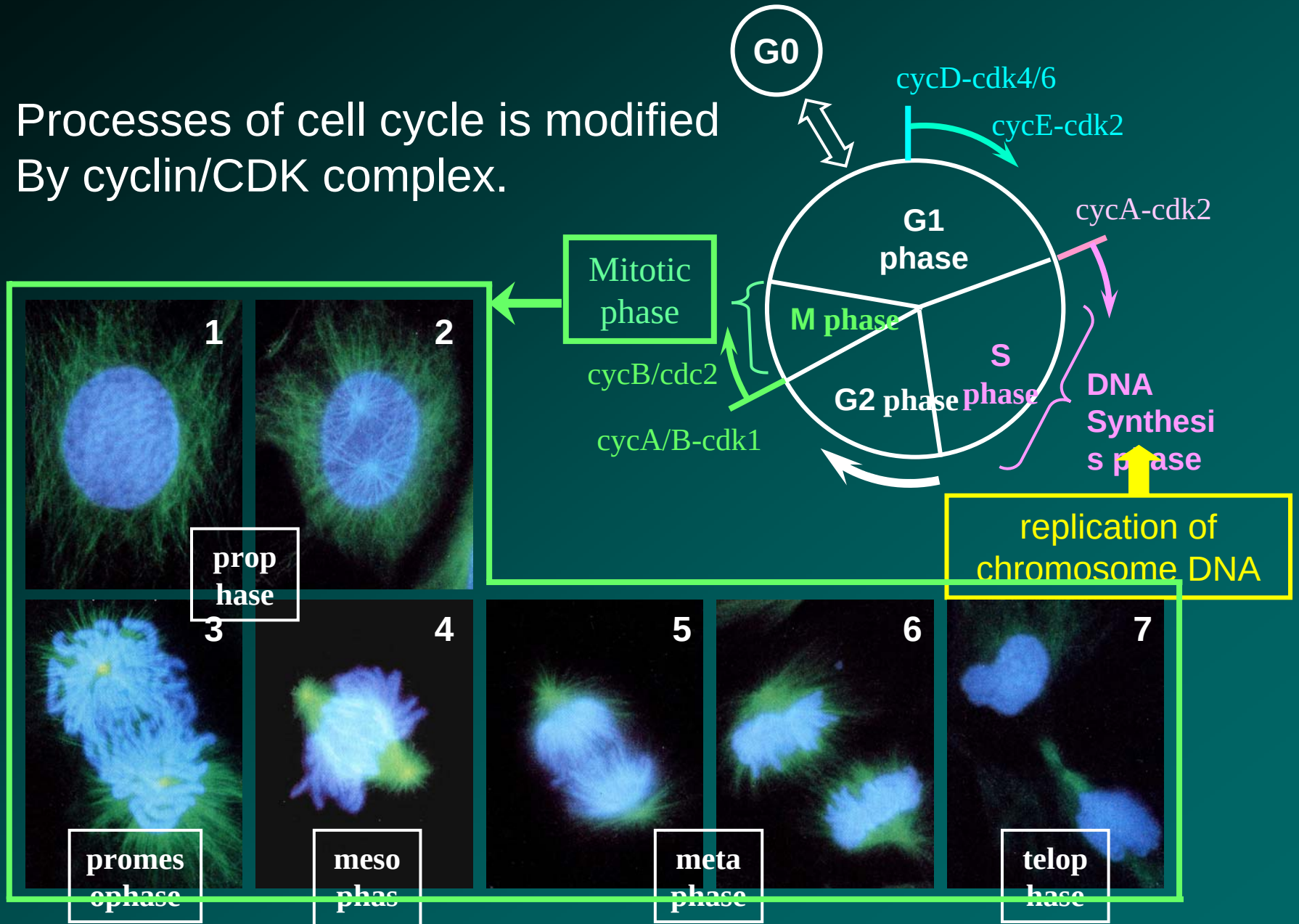
Rise of bioinformatics as a new science

→ **Research of not only one, but a whole system of factors**

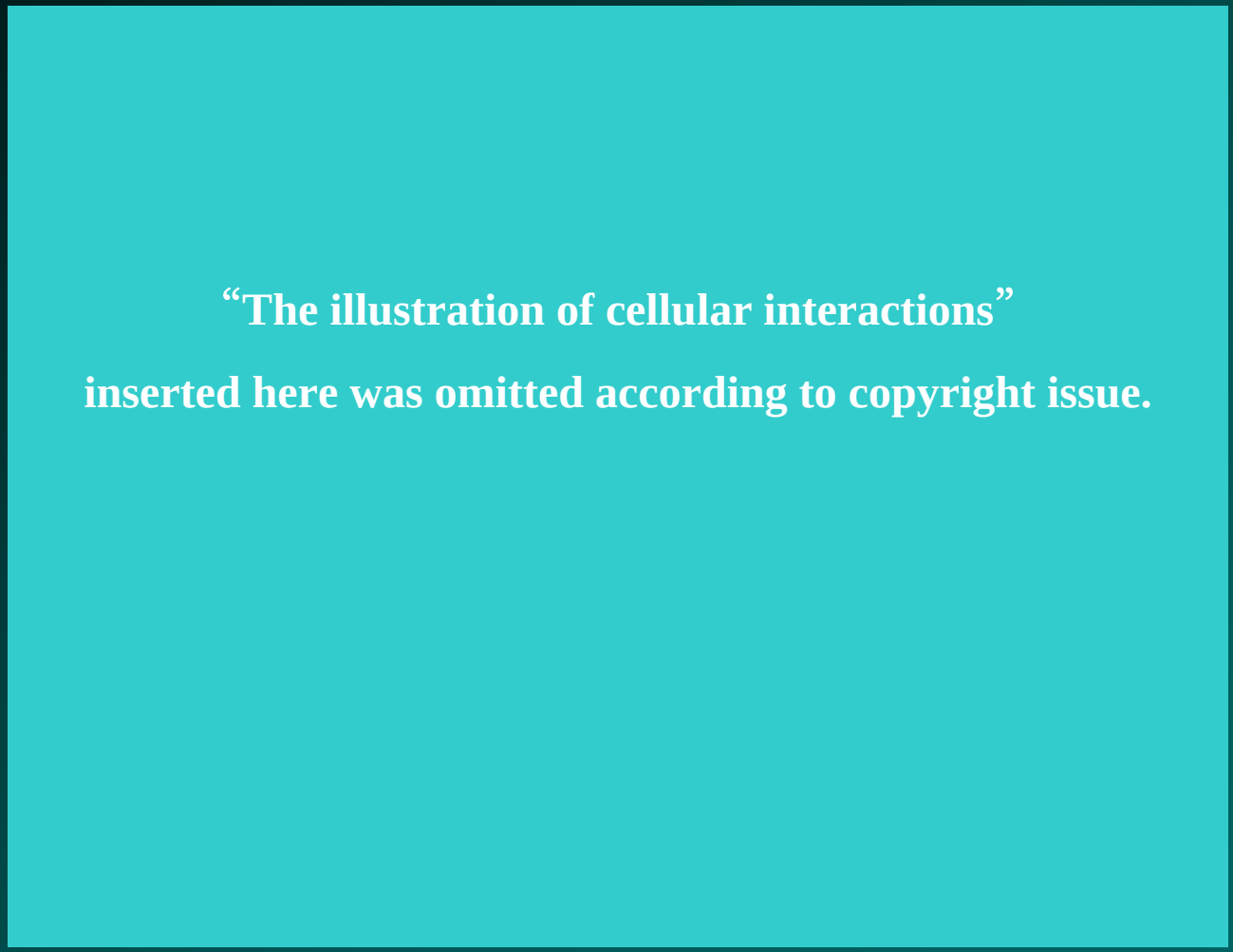
- Comparison with other organisms →"what determines the formation of life forms"
- Analysis of human disease genes
  →beginning of a new drug discovery science in made to order medicine

The regulation mechanism in mitosis and related signal molecules

Processes of cell cycle is modified
By cyclin/CDK complex.



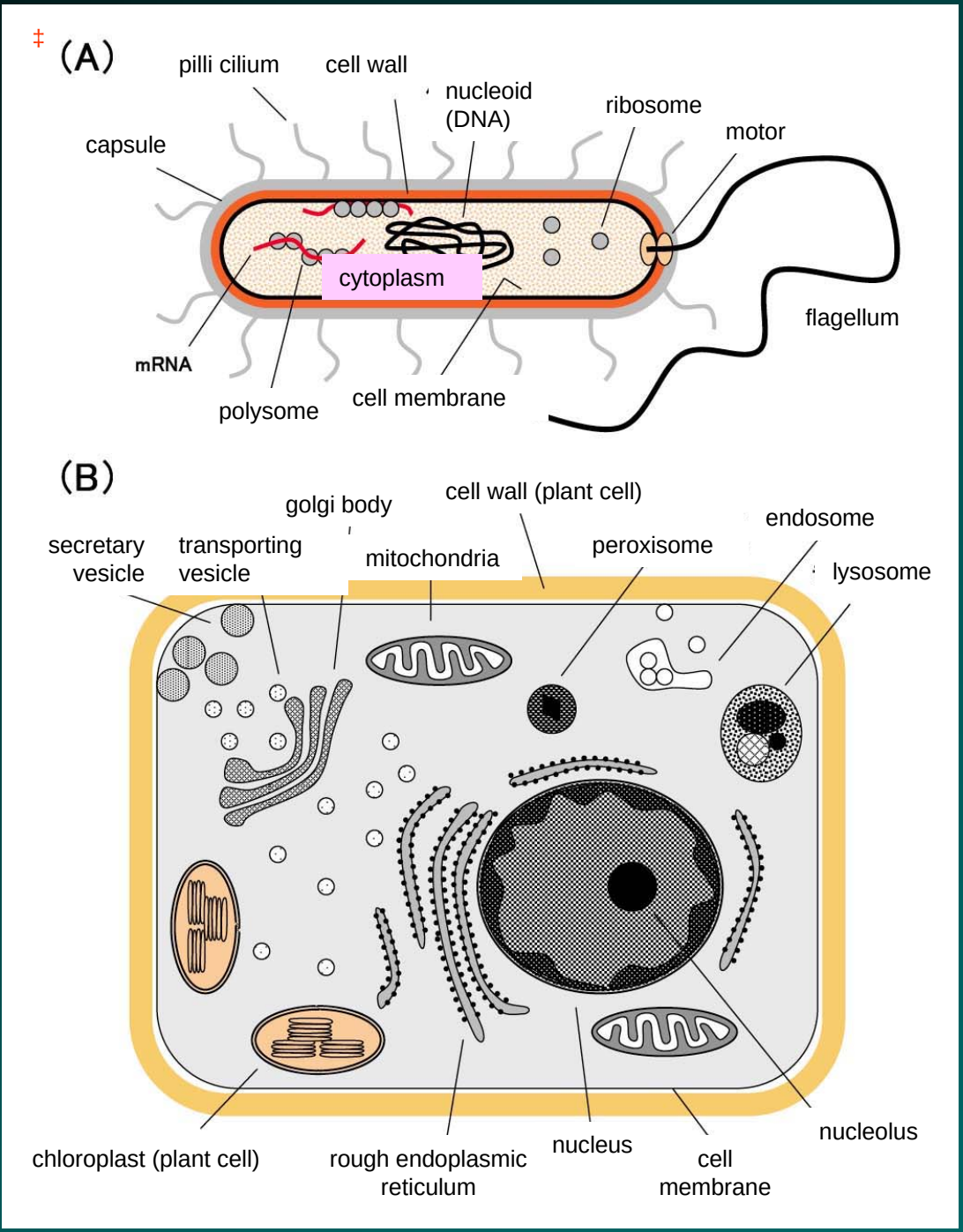
Cellular interaction and cell selection



Each cell contains its information. Cells transmit their signals to neighboring cells.

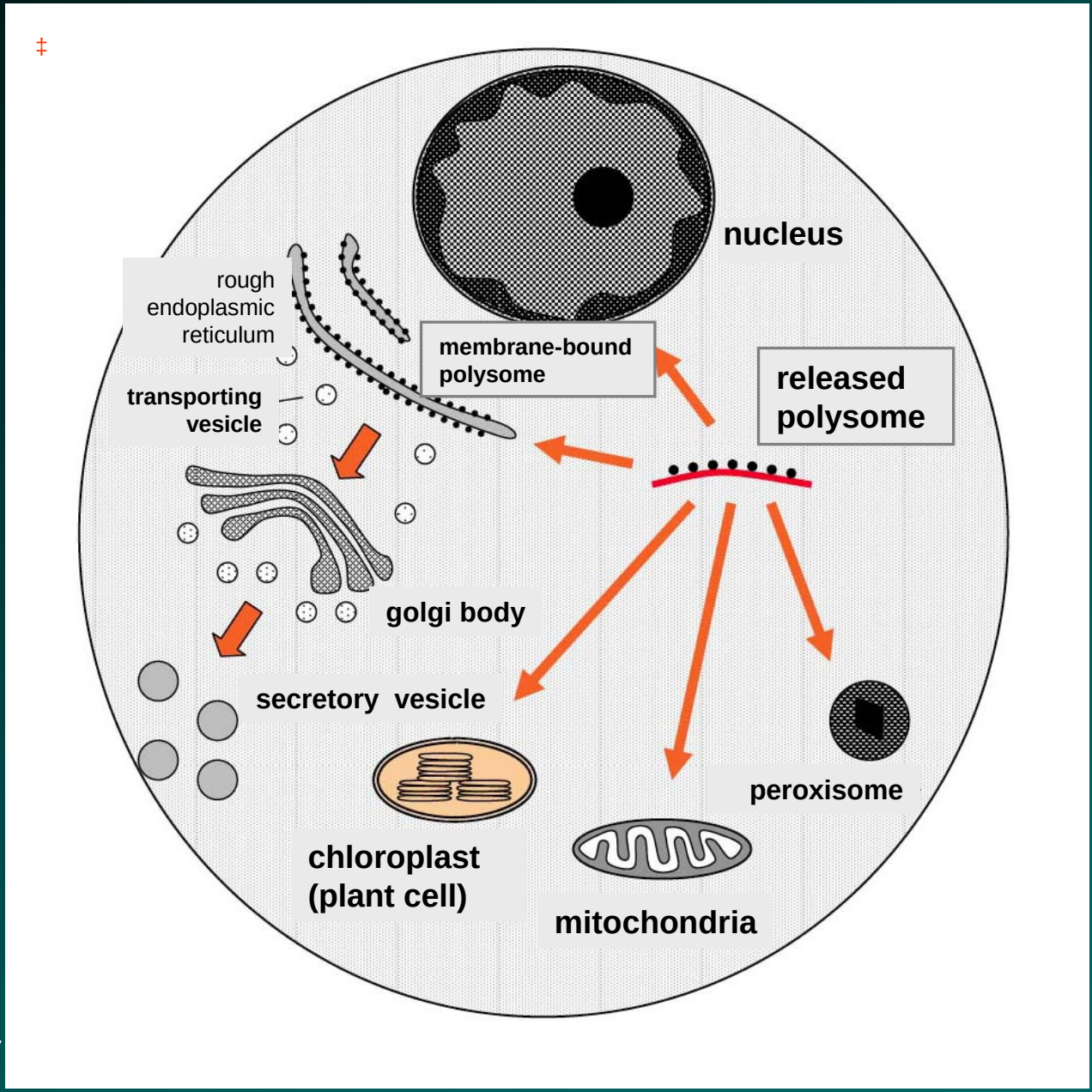
A mechanism of signal transduction into and out of the cell

Cell structure



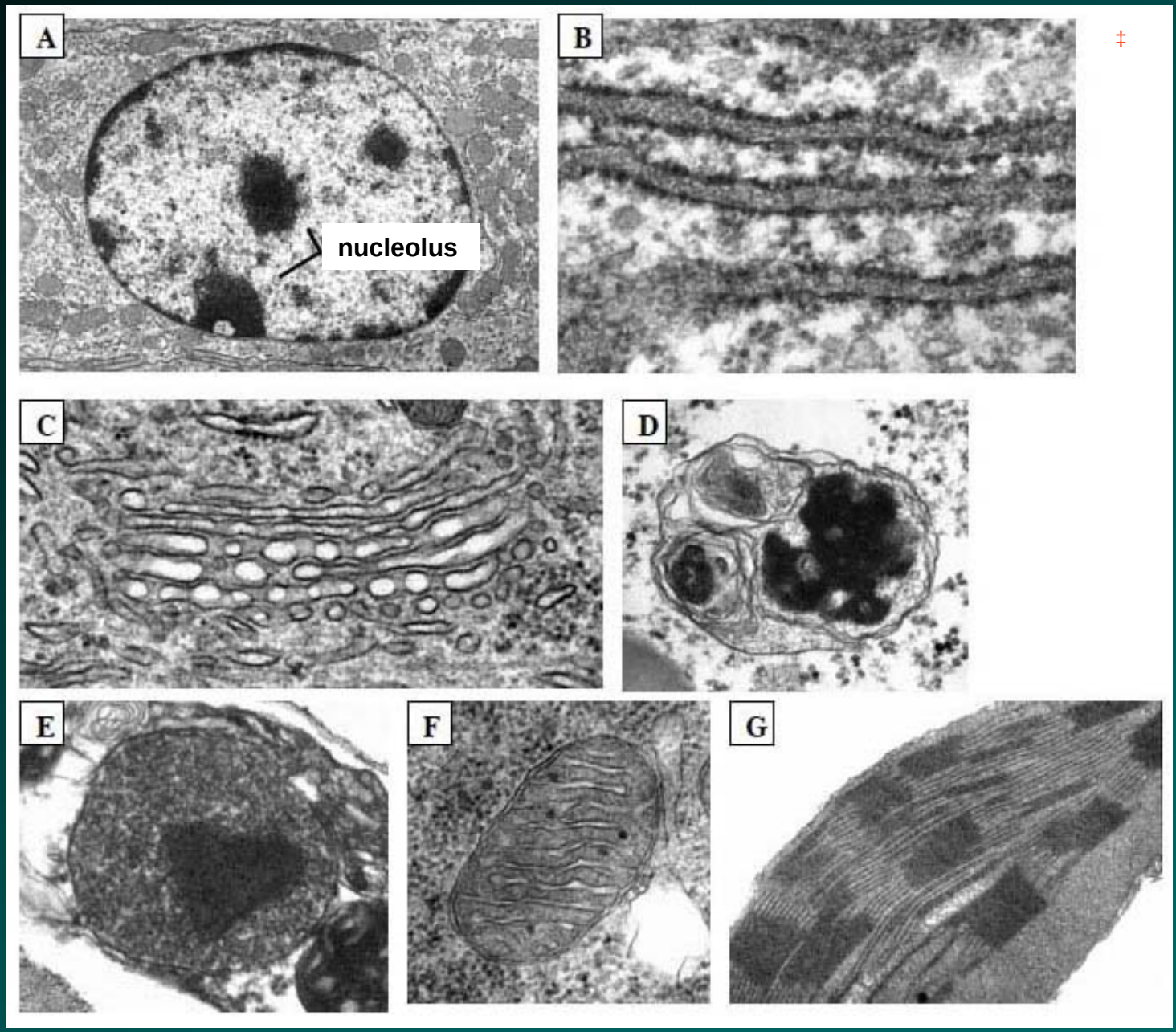
Yodosha, 2007

The flow of protein inside a cell



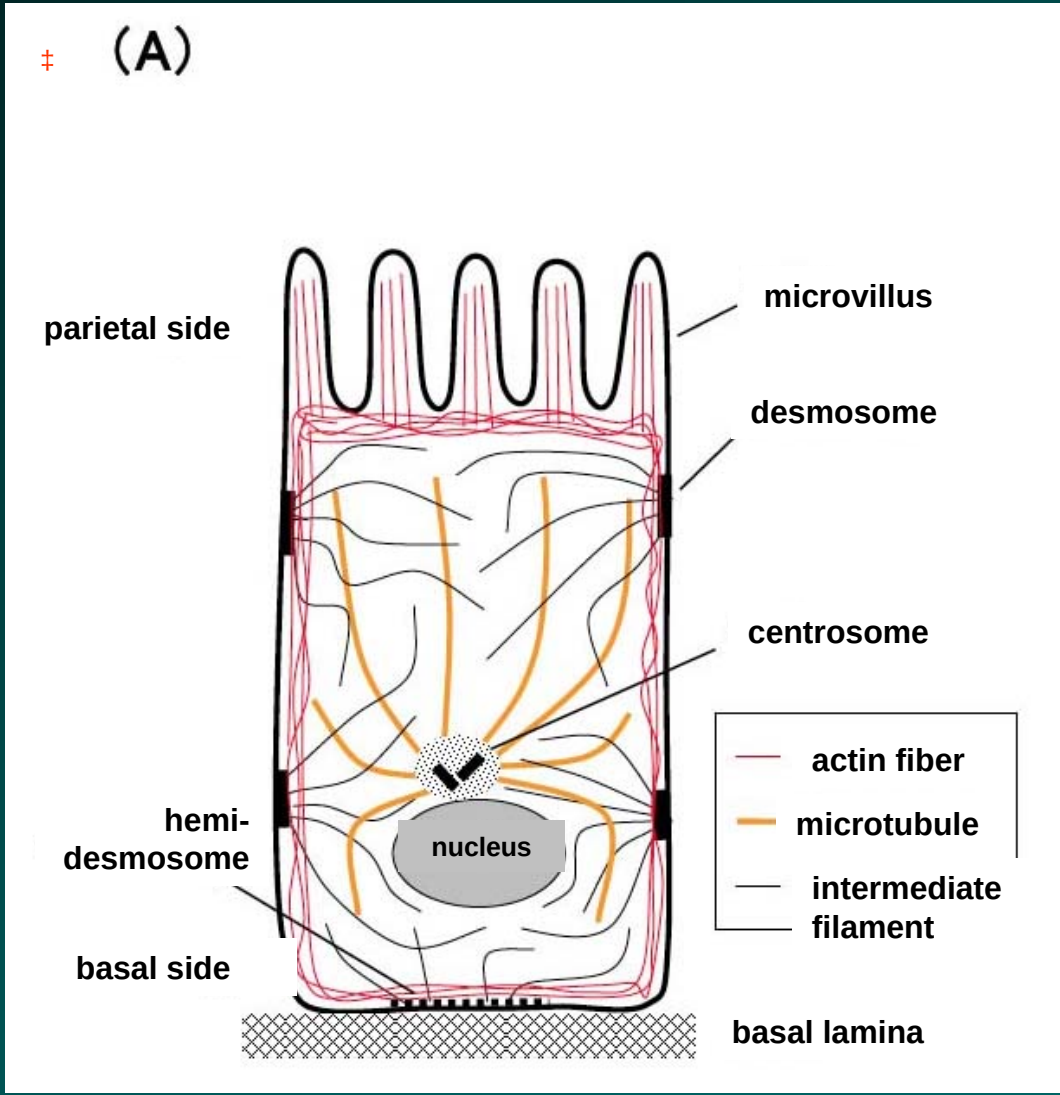
Yodosha, 2007

Structure of a sub-cellular organelle



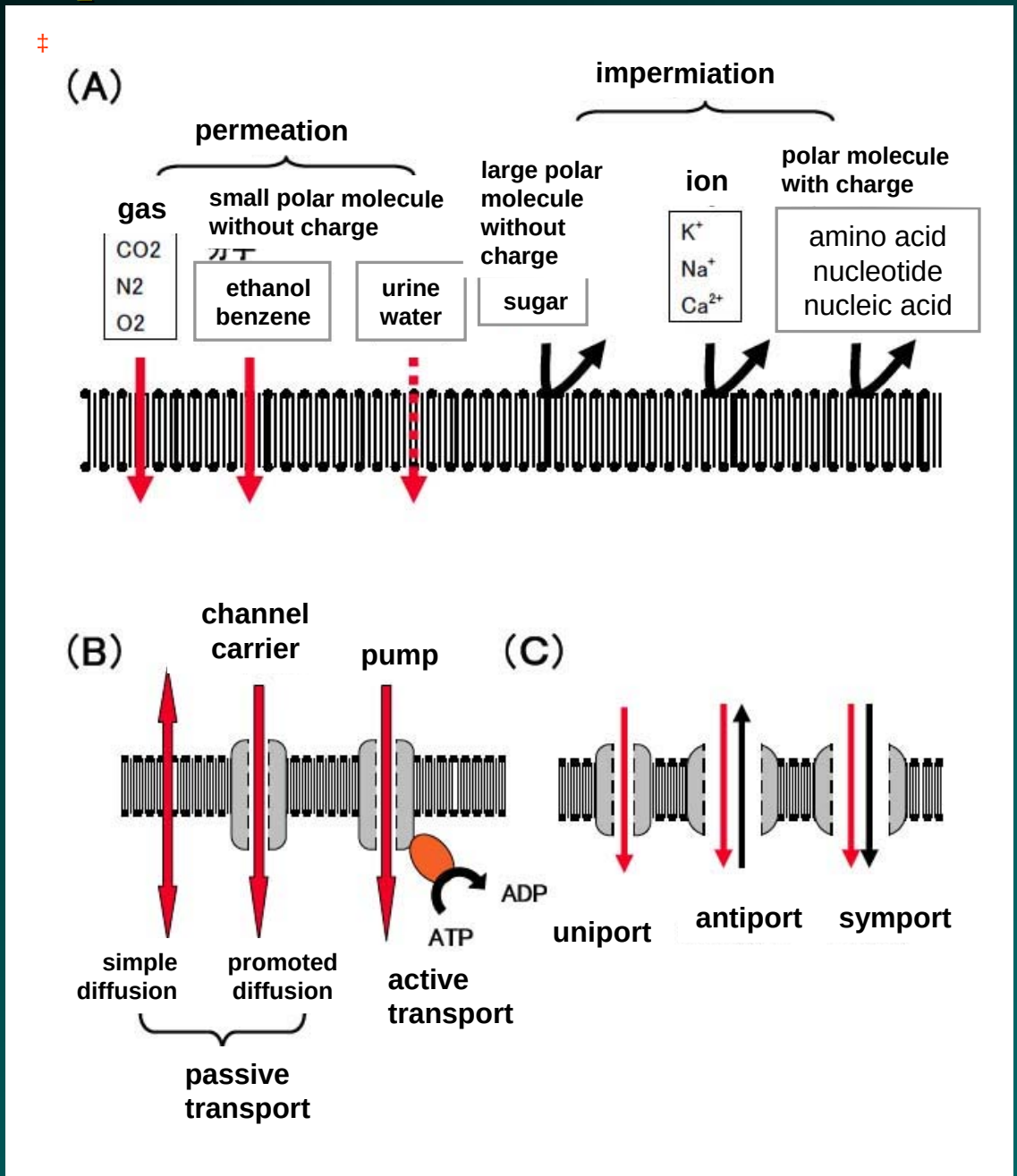
Yodosha, 2007

Each cell has polarity.
Inhomogeneous locations of substances construct the system.



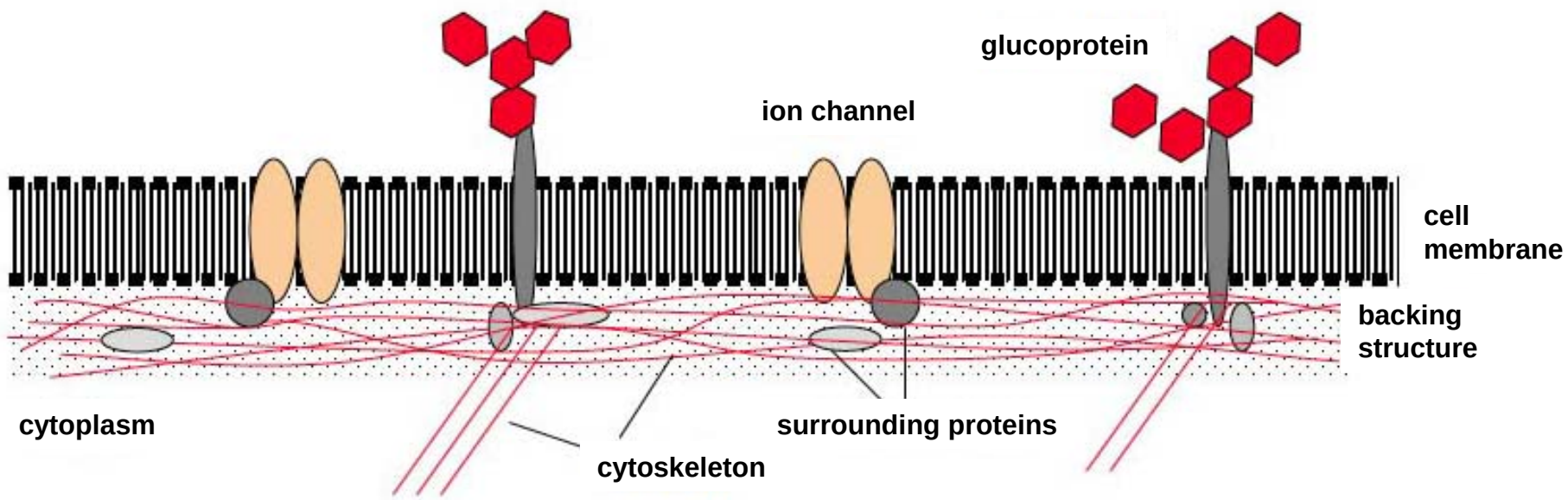
Yodosha, 2007

Close relationship between structure and function of cell membrane



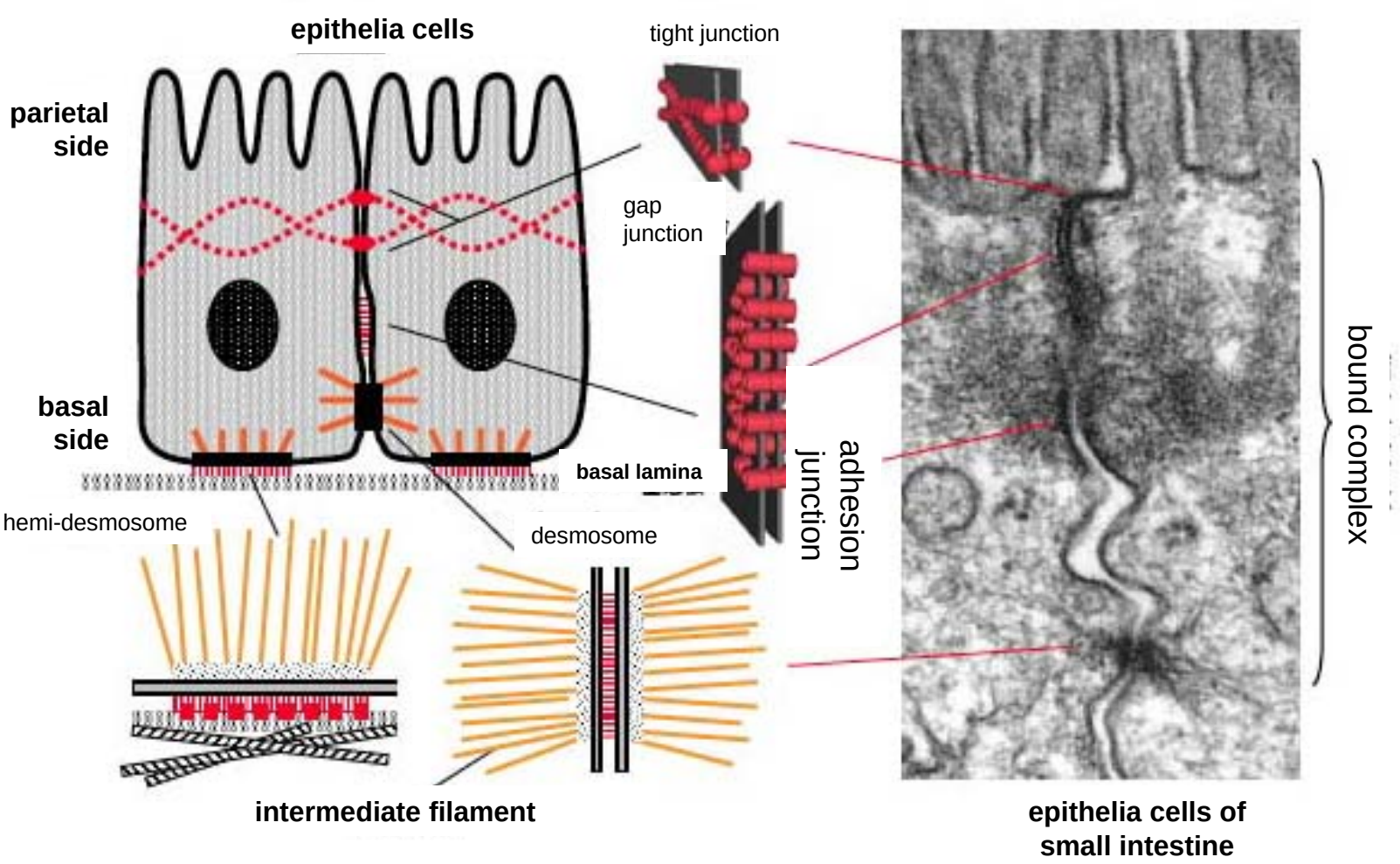
Yodosha, 2007

Signal transduction through cell membranes



Yodosha, 2007

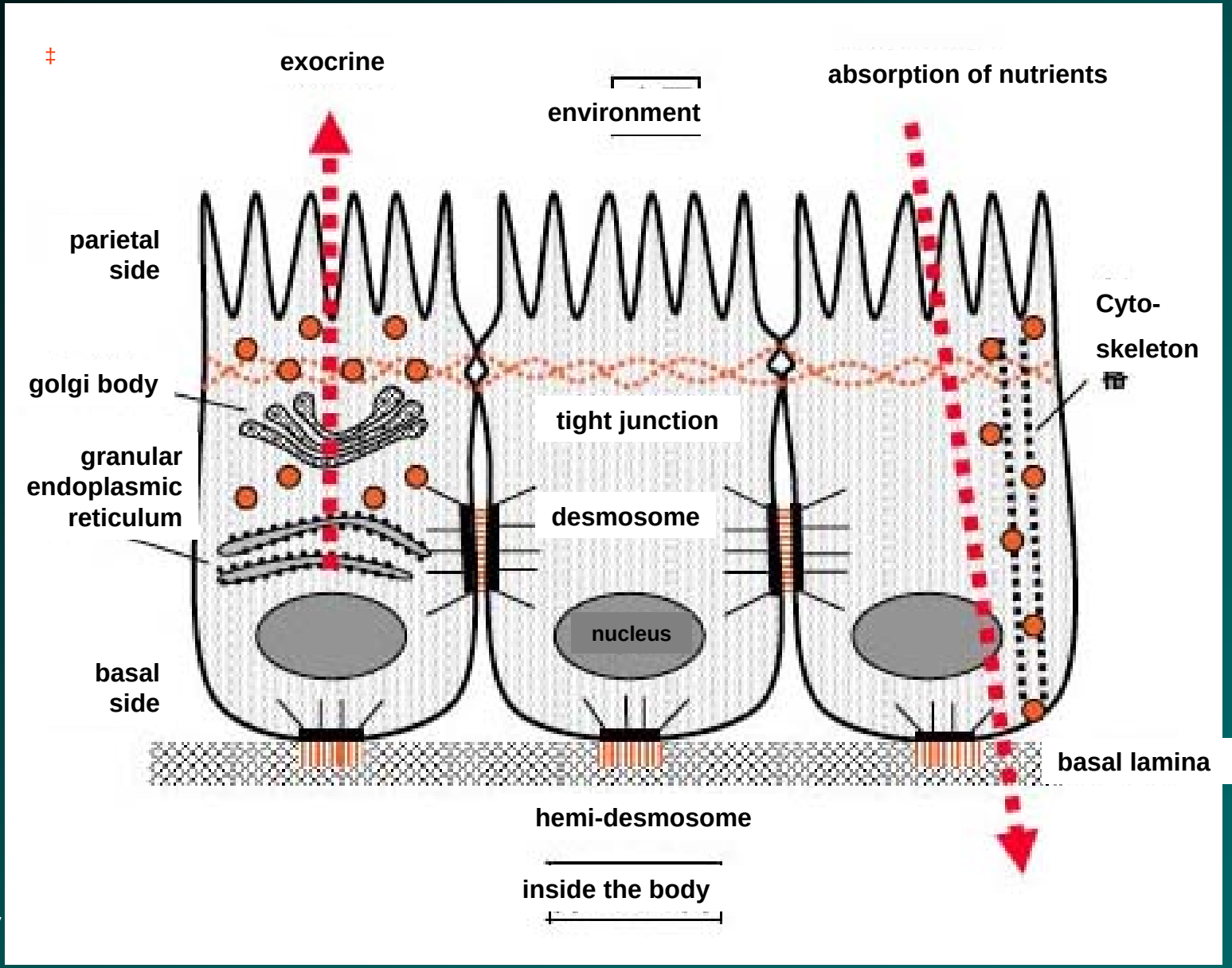
Adhesion between cells



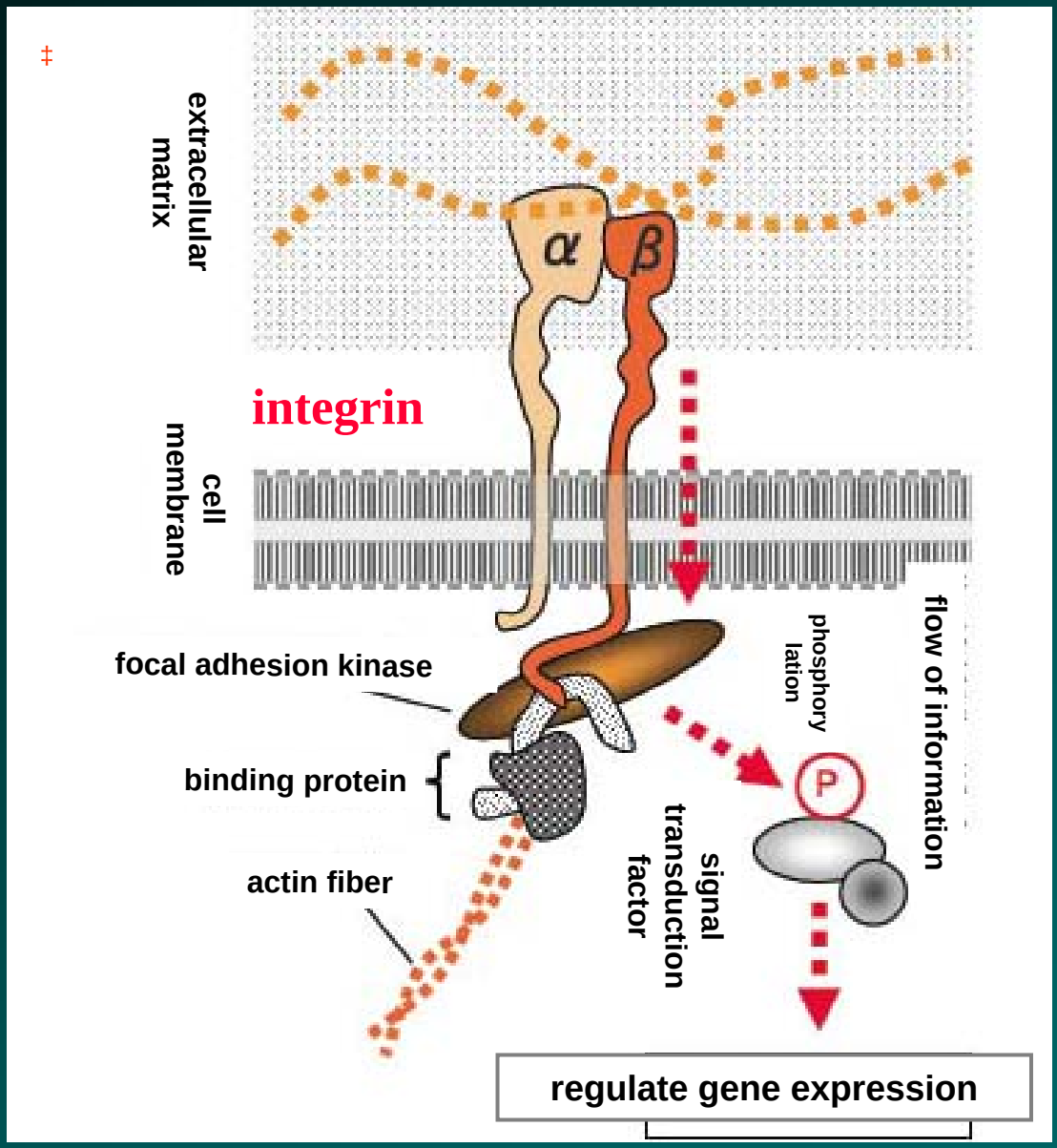
Yodosha, 2007

The signals are transmitted between cells through these structures.

The importing of molecules to the body



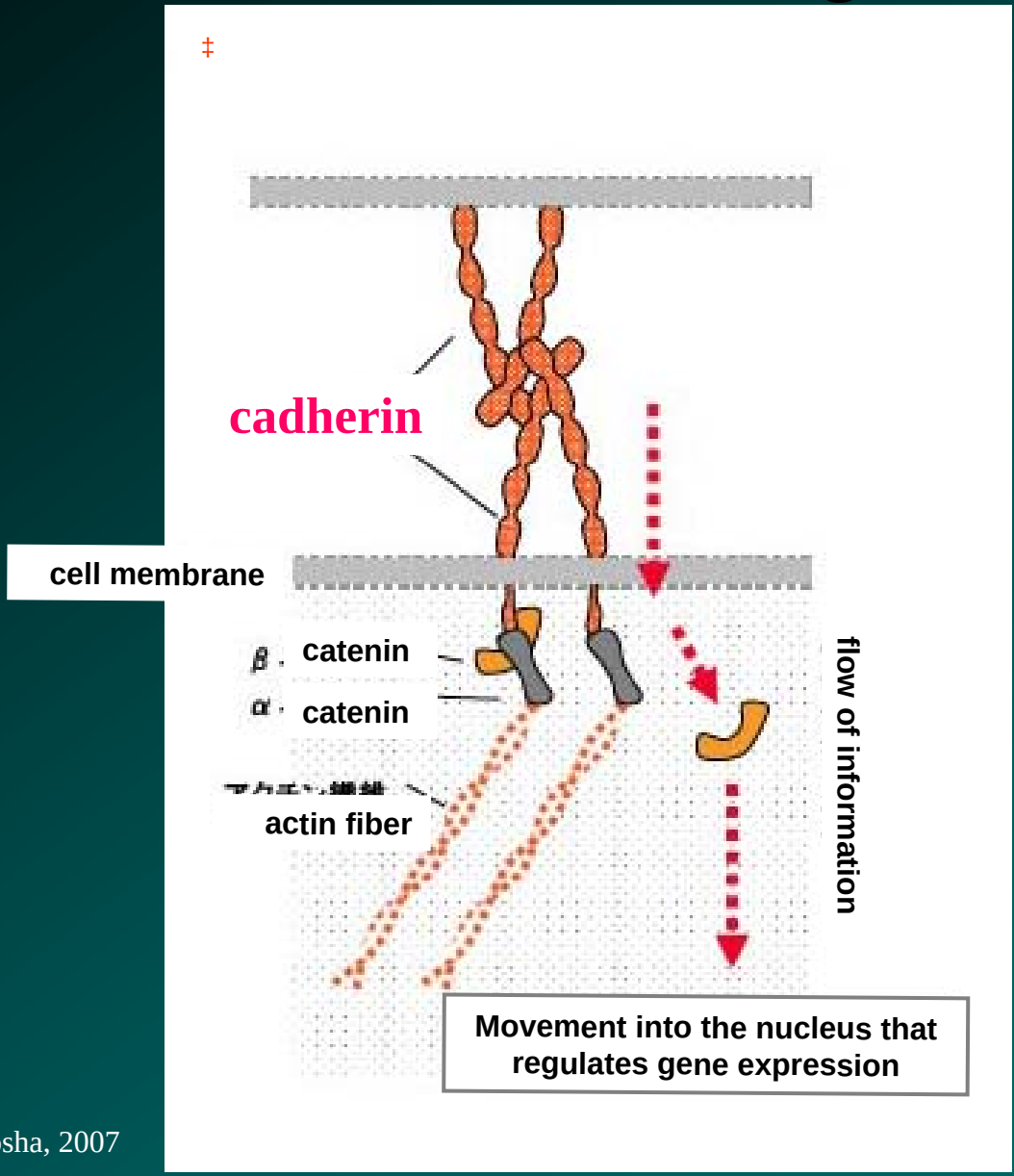
Signal transduction from an extra-cellular matrix



Yodosha, 2007

The signals from an extra-cellular matrix are transmitted through integrin.

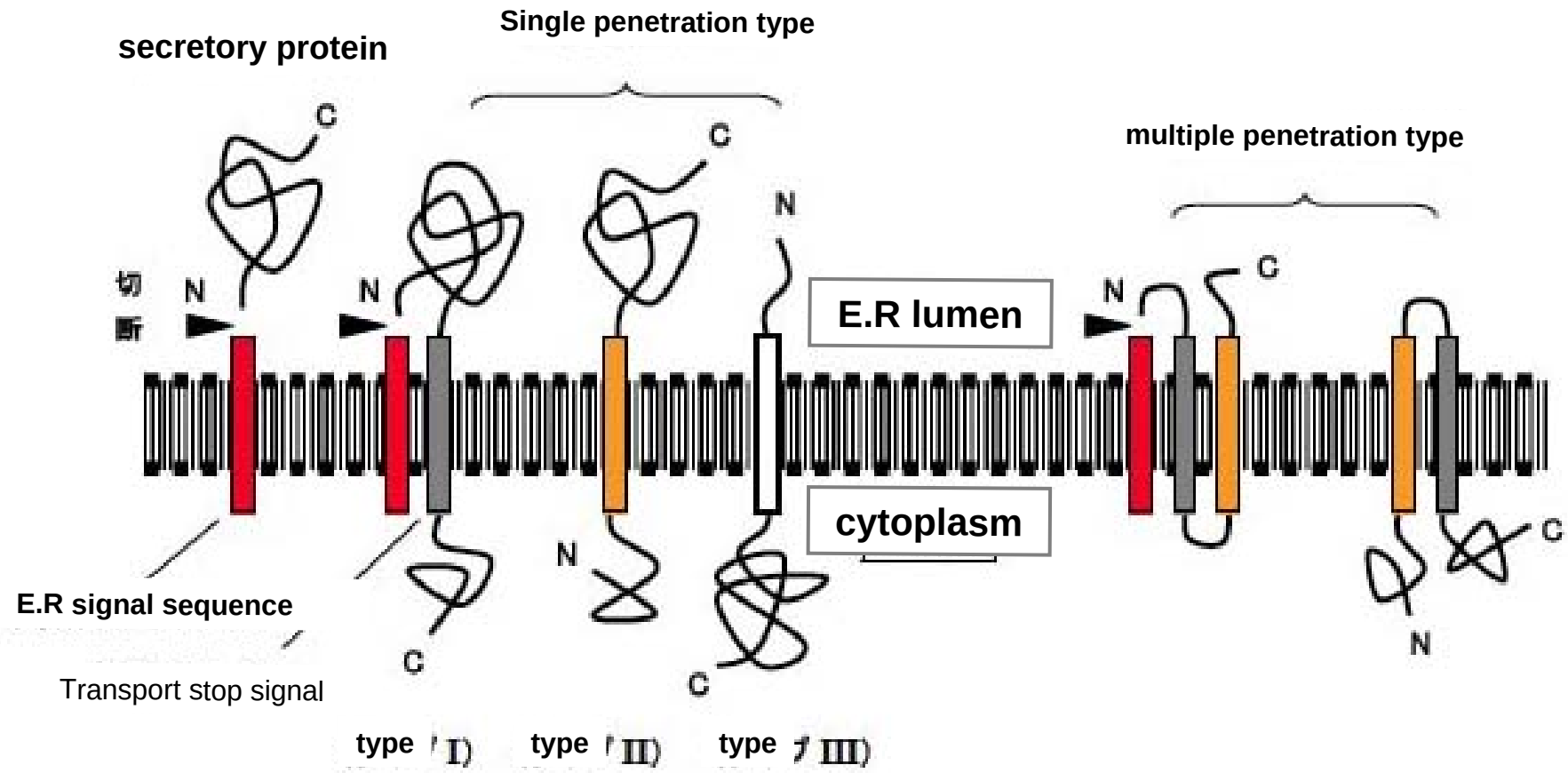
Signal transduction into the cell through a cellular junction



Yodosha, 2007

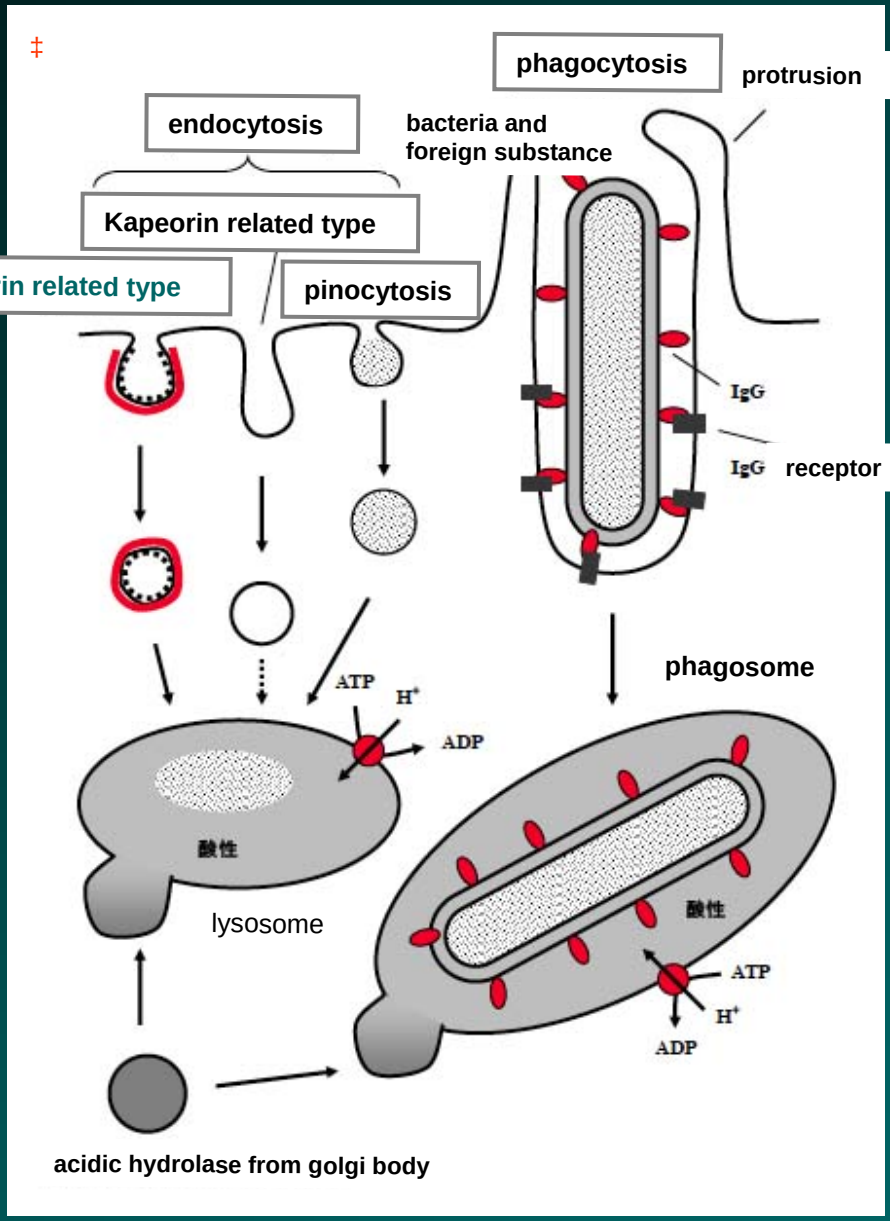
The signals are transmitted between cells through cadherin.

The Membrane-localized structure of proteins



These proteins are strongly related to cell functions.

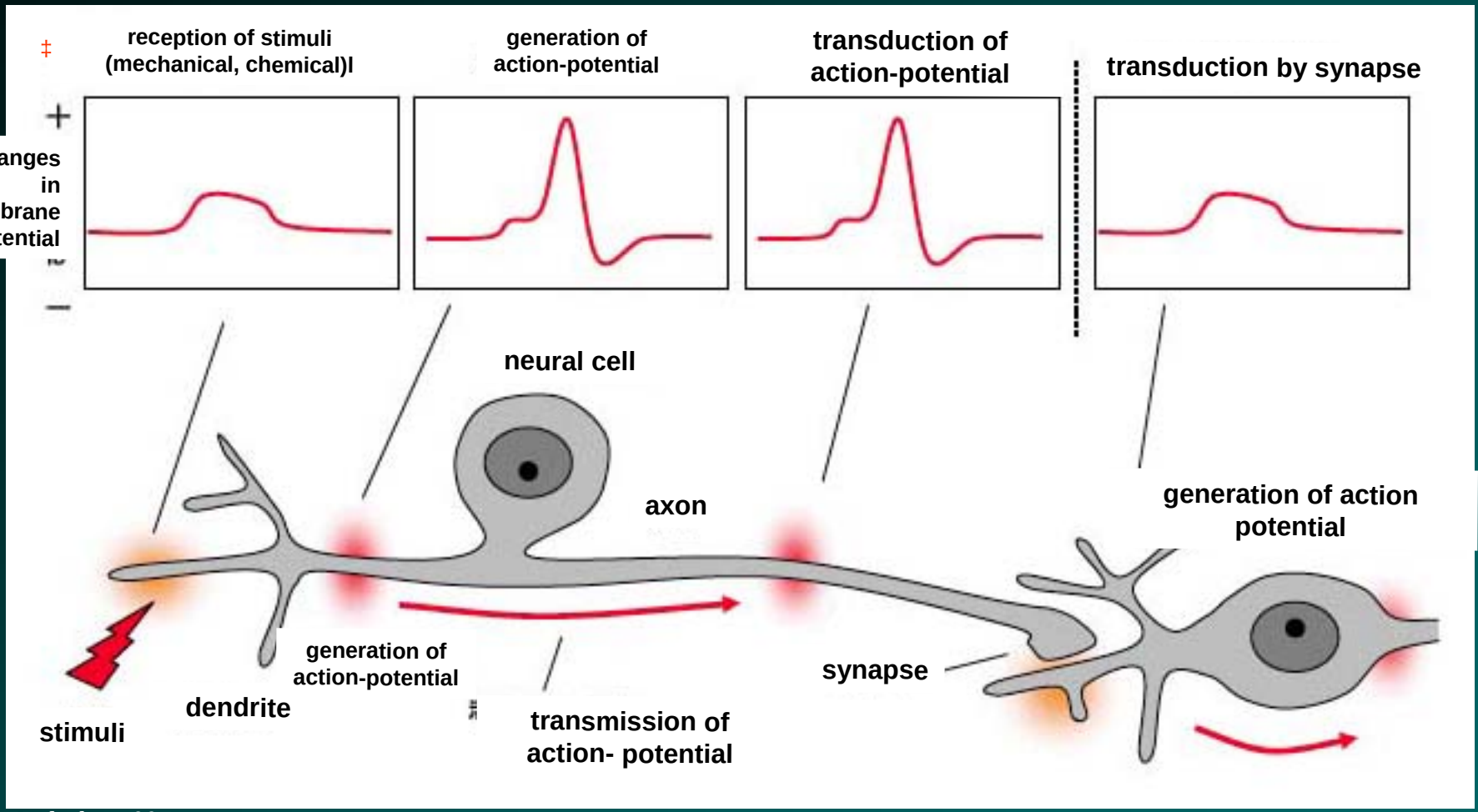
Trans-cellular importation and intracellular degradation



Yodosha, 2007

Cells destroy inner proteins systematically.

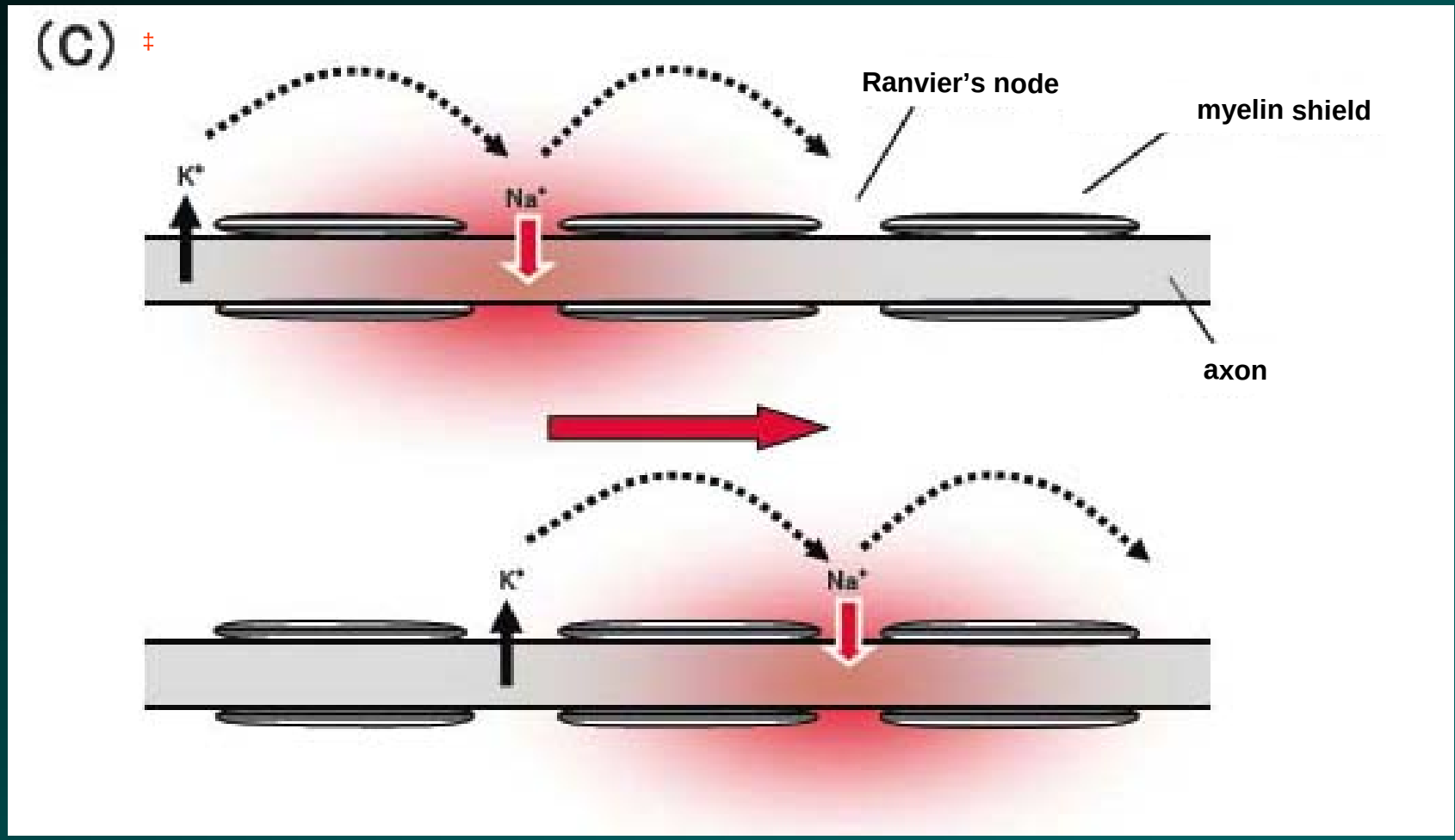
The mechanism of nerve cell signal transduction①



Yodosha, 2007

Action-potential is transmitted along an axon, and the signal is transmitted to the next neural cell by secretion of a signal molecule from the synapse.

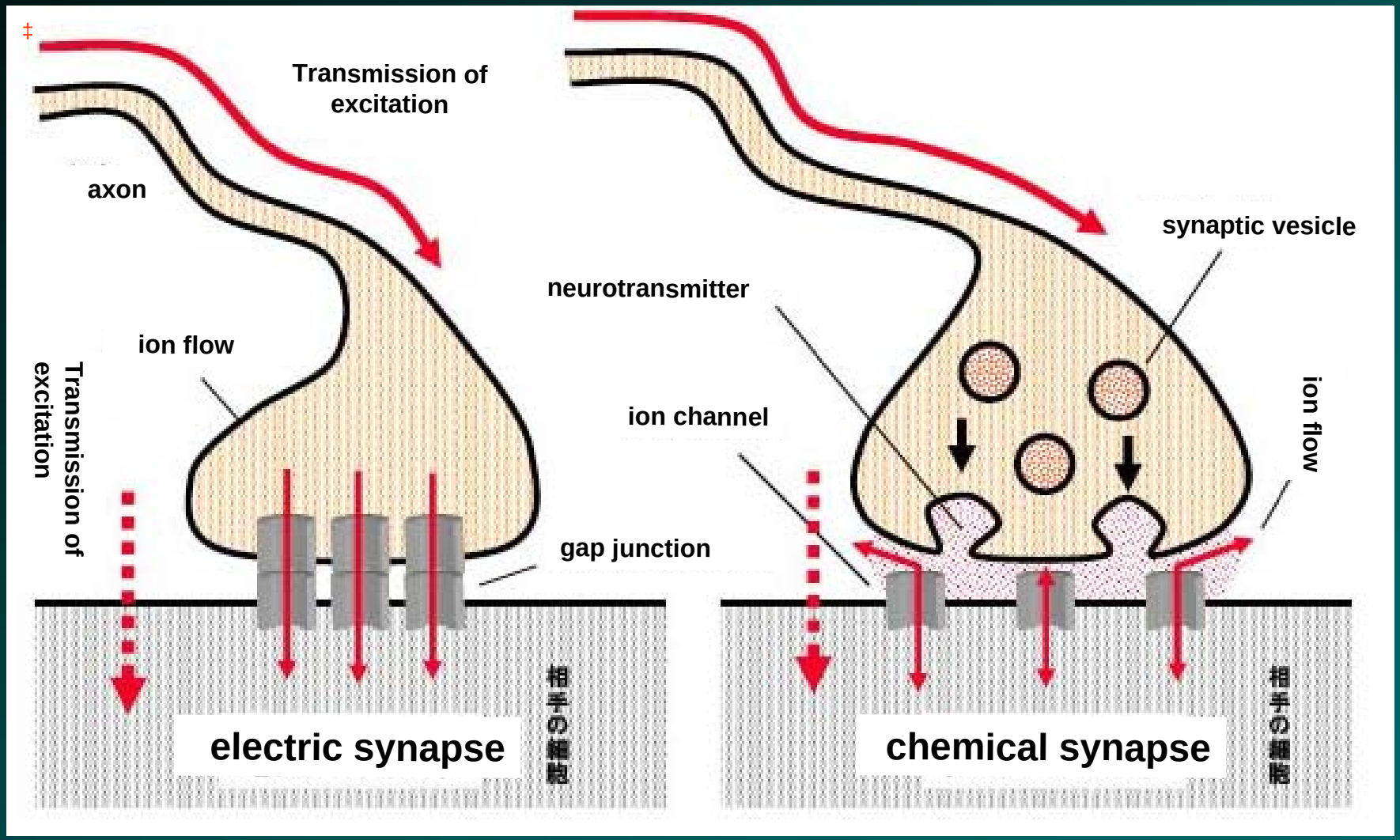
The mechanism of nerve cell transduction②



Yodosha, 2007

Action-potential is transmitted at high speed by myelin shiild on the neural axon.

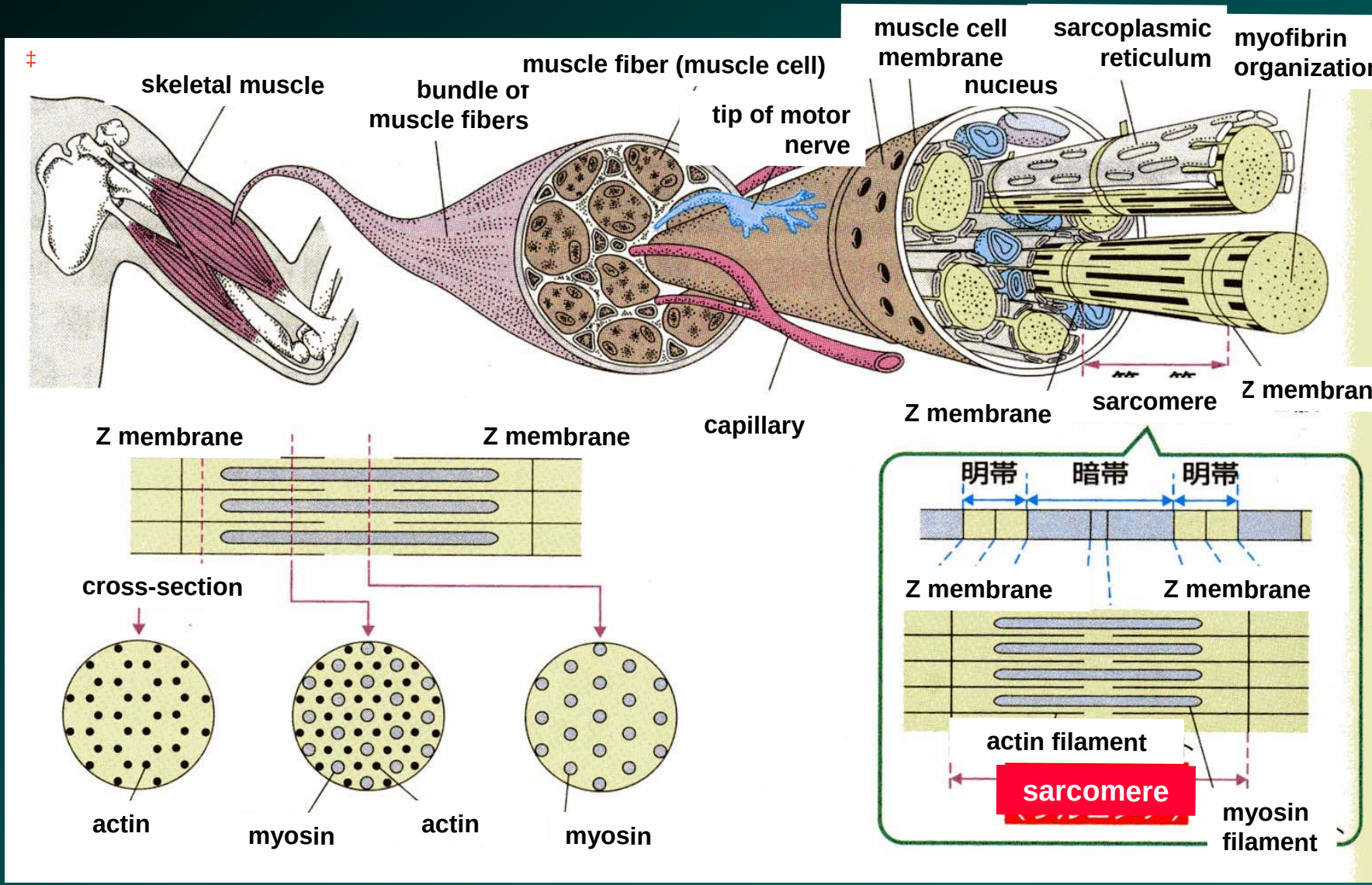
The mechanism of nerve cell signal transduction③



Yodosha, 2006

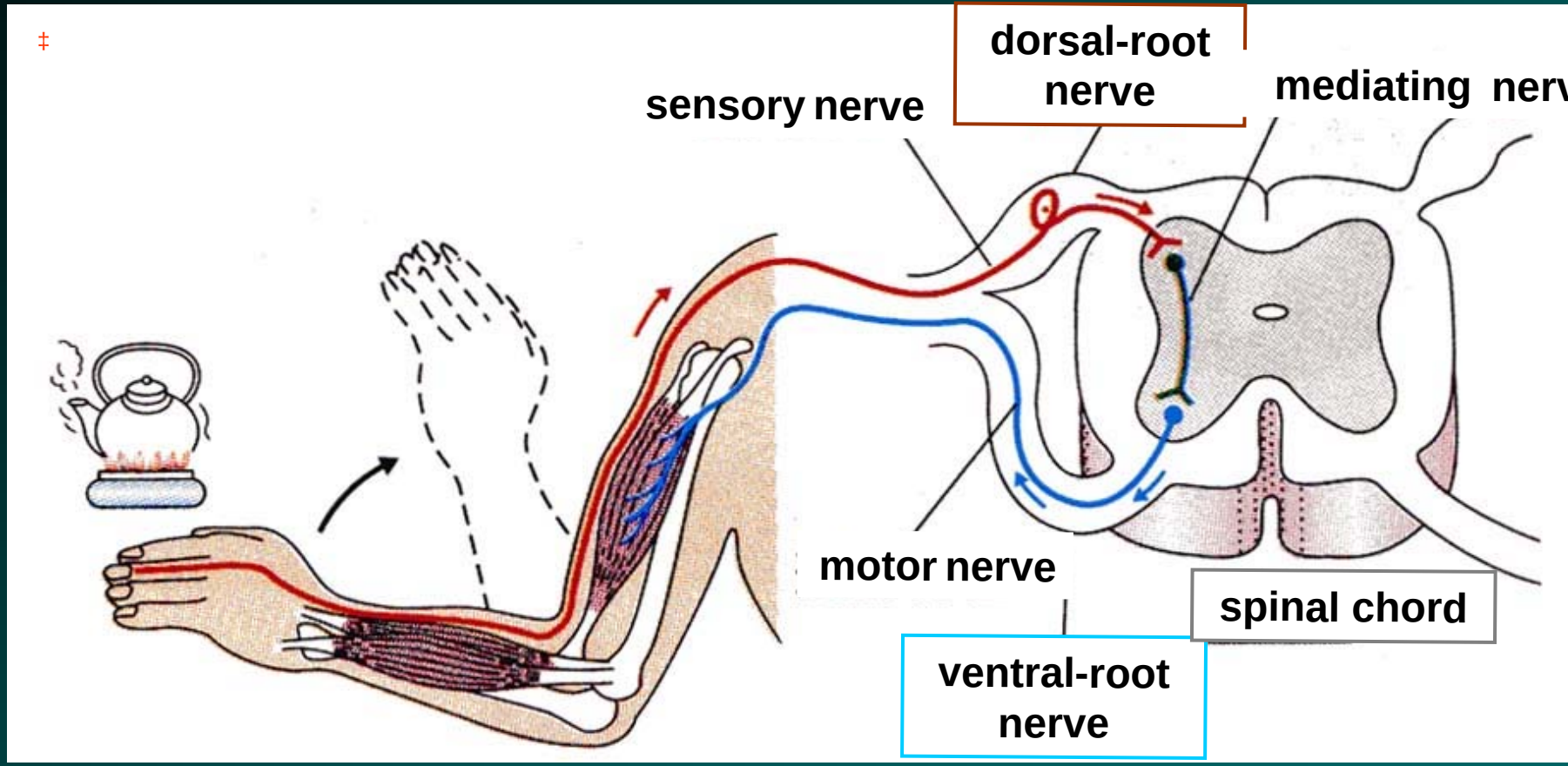
The mechanism of synapse transduction

The structure and functions of the muscles



Buneido, 2004

The relationship between muscle movement and the nervous system



Buneido, 2004

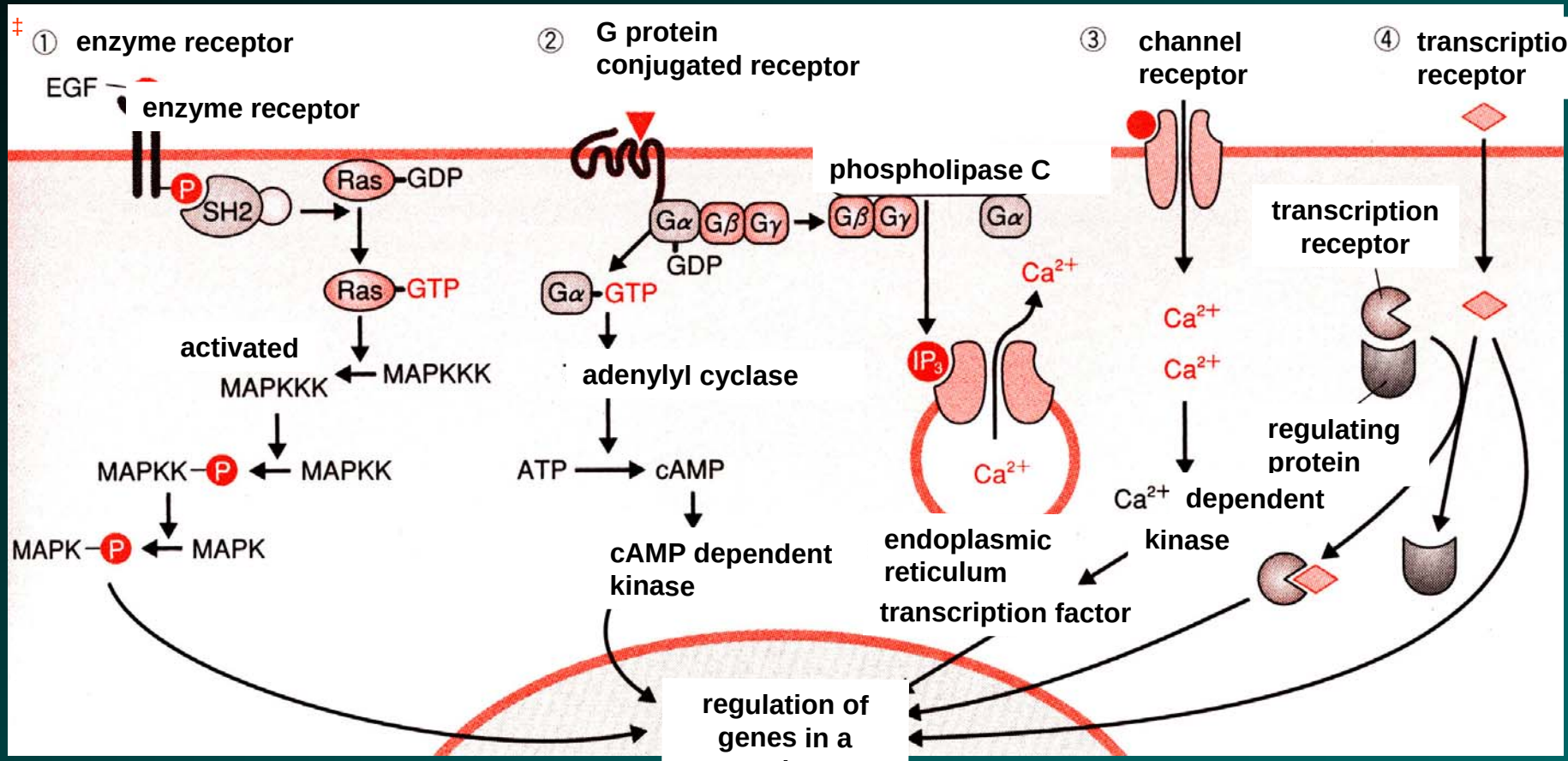
An example of a reflex action

A spinal reflex occurs before the signal reaches the brain.

Mechanisms of signal transduction in a cell

Various signal transduction systems in a cell

Typical receptors in signal transduction into the cell

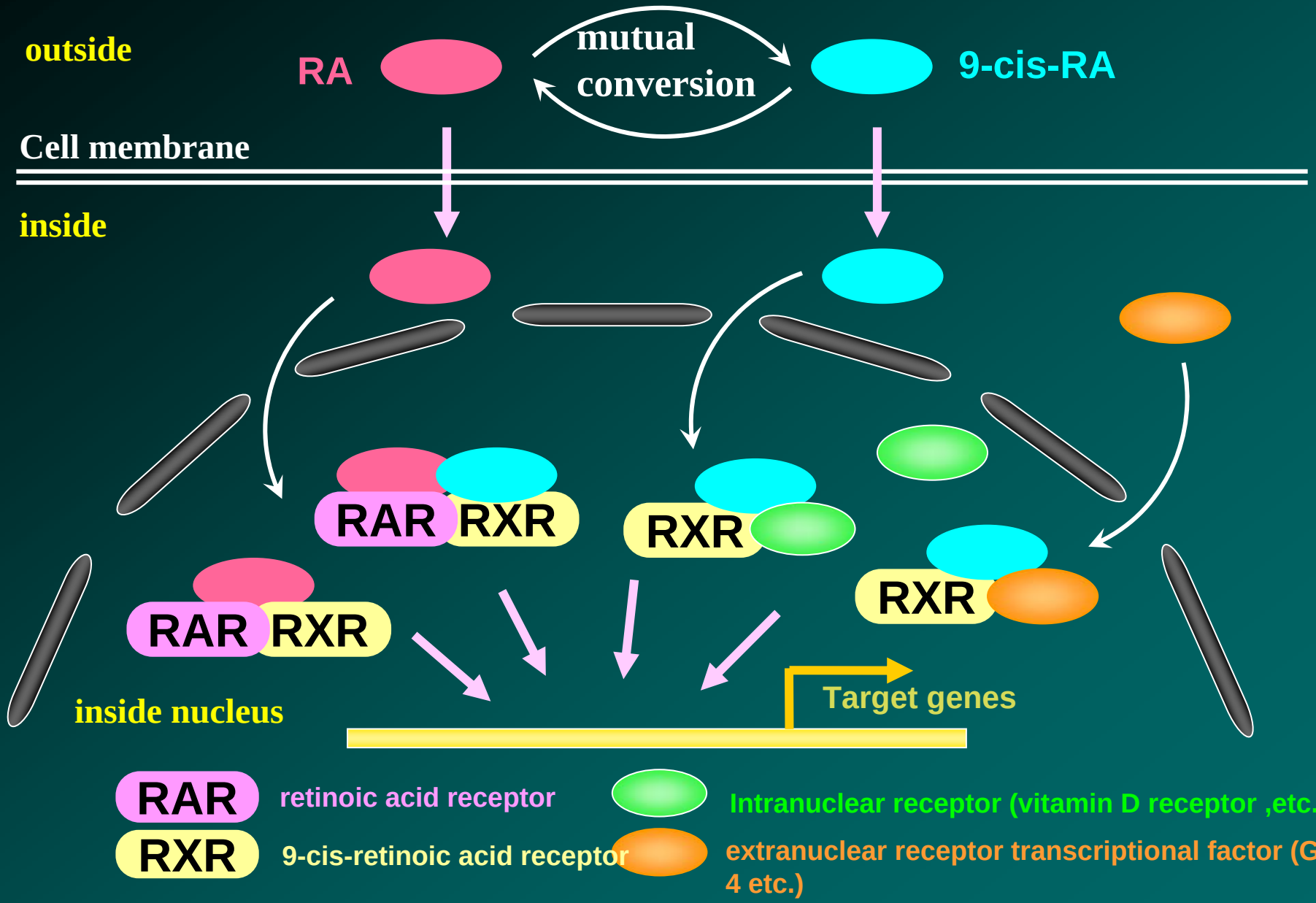


Yodosha, 2006

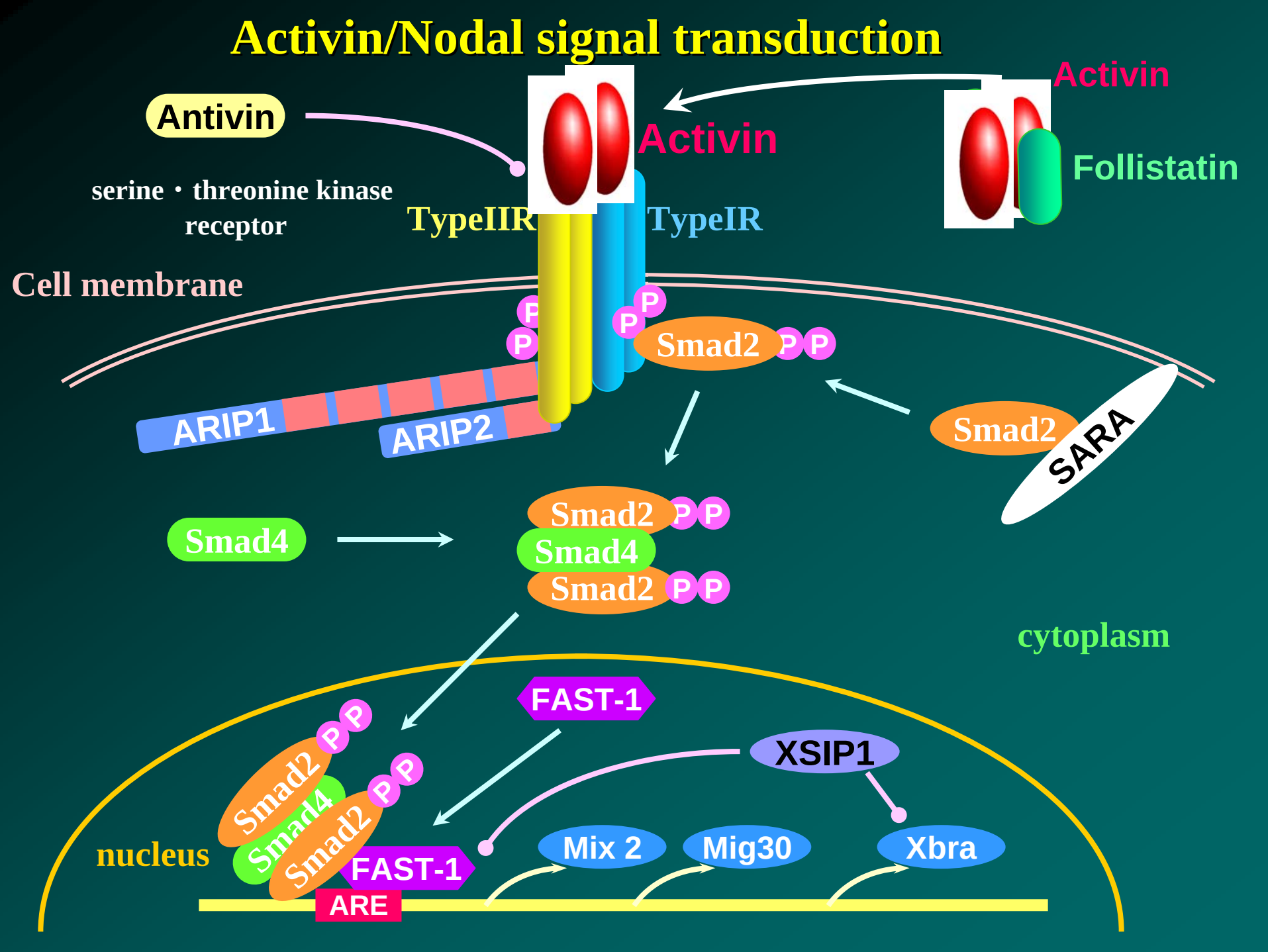
example

- **enzyme receptor** →
  - **serin・threonine kinase type receptor**
    （Activin receptor, etc.）
  - **tyrosine kinase type receptor（FGF receptor, etc.）**
- **transcription receptor** → **retinoic acid receptor**

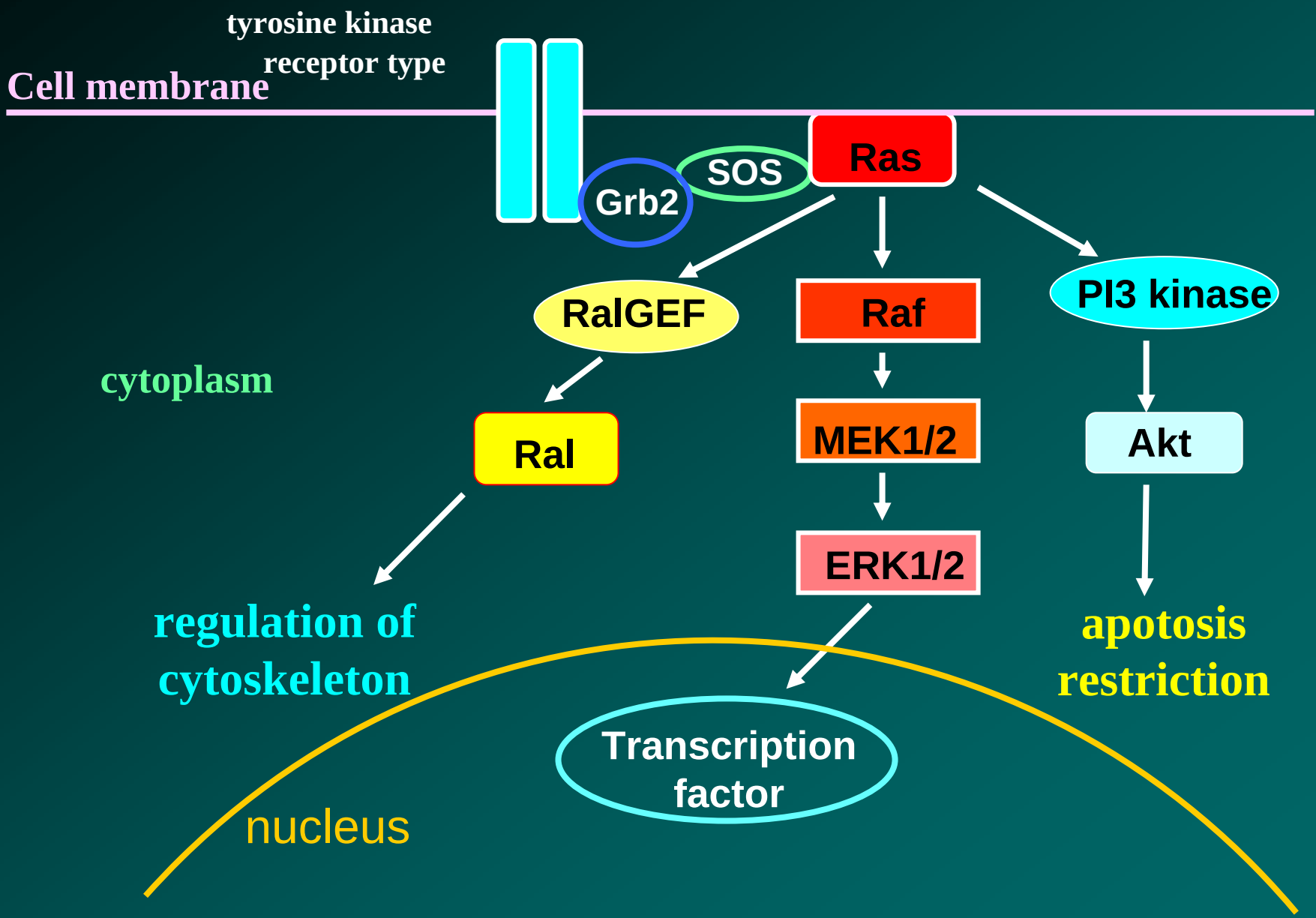
Retinoic acid signal transduction



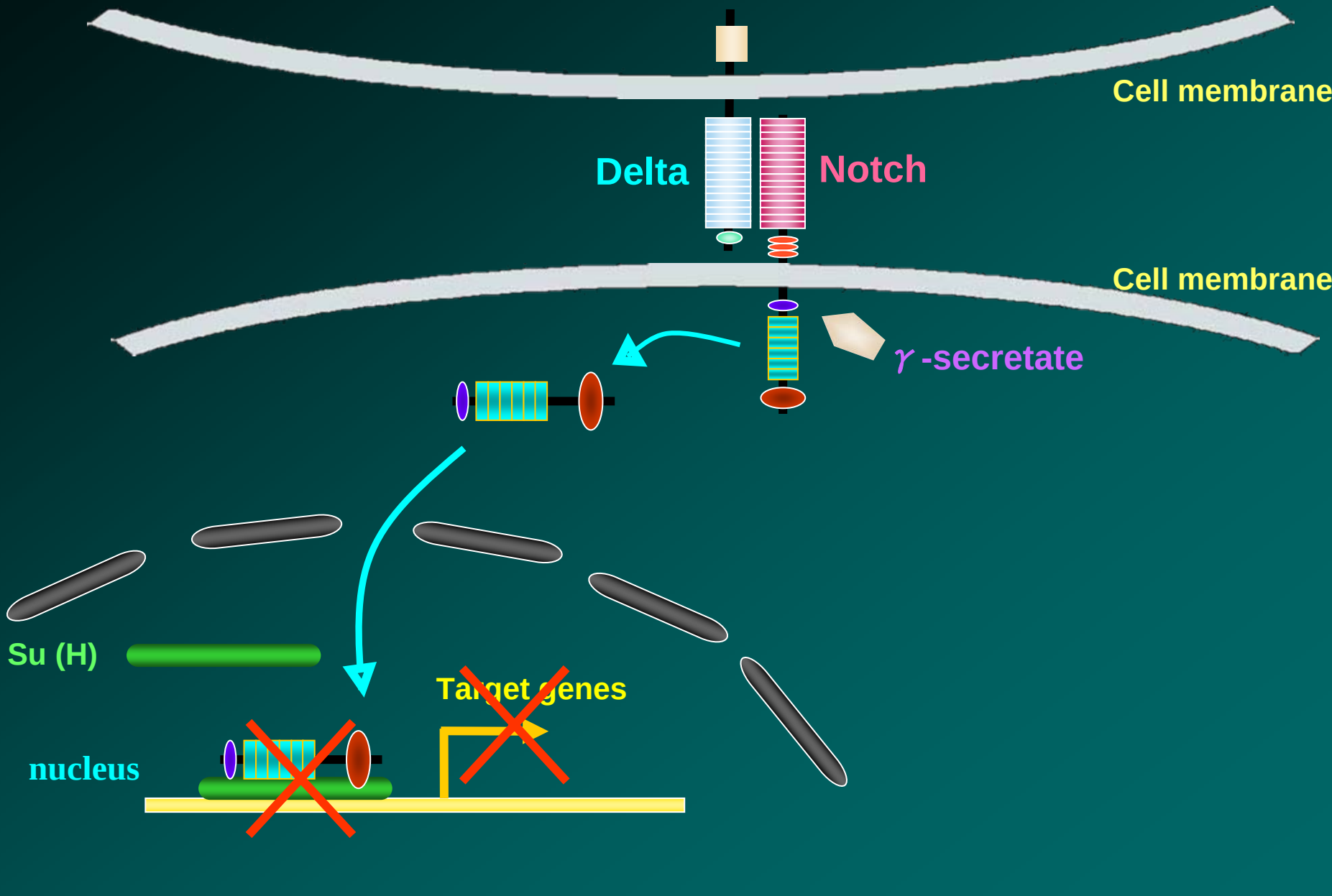
The system whose gene is regulated by changing the combinations inside the nucleus


Activin/Nodal signal transduction
Antivin
Activin
Activin
Follistatin
serine・threonine kinase receptor
TypeIIR
TypeIR
Cell membrane
P
Smad2
ARIP1
ARIP2
Smad2
SARA
Smad4
Smad2
Smad4
Smad2
cytoplasm
FAST-1
XSIP1
nucleus
Smad2
Smad4
Smad2
FAST-1
ARE
Mix 2
Mig30
Xbra

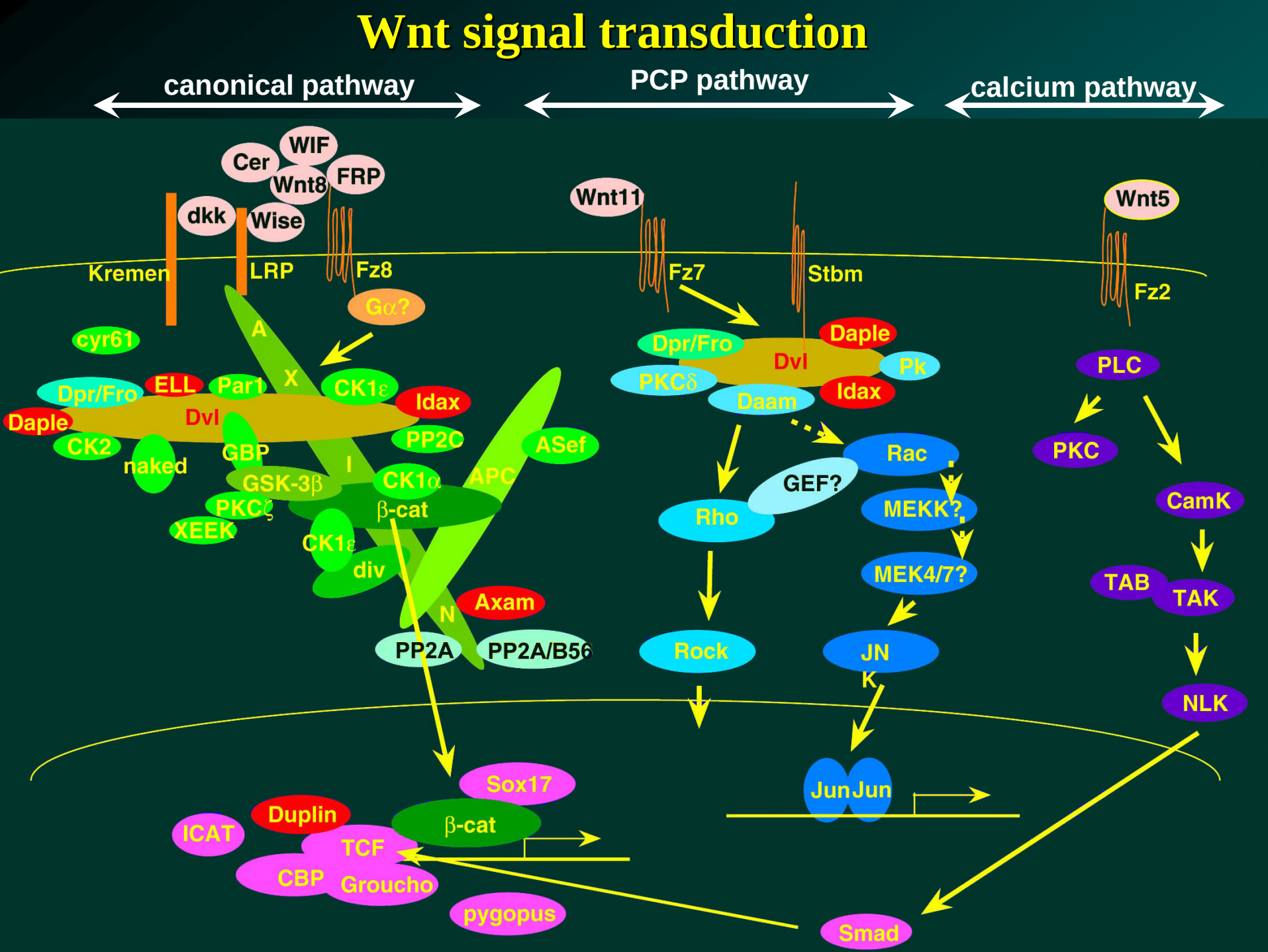
FGF signal transduction



Notch signal transduction



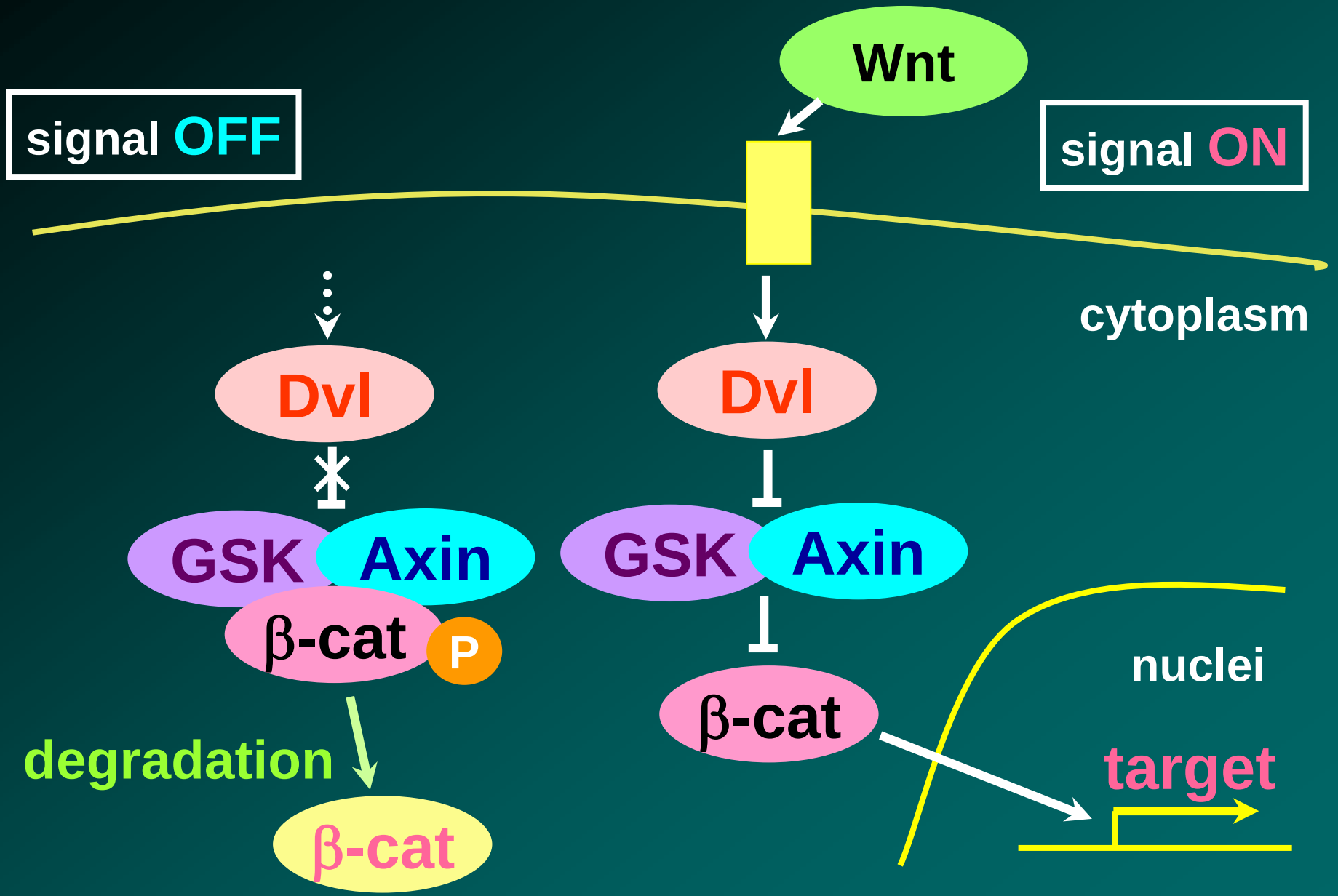
Wnt signal transduction



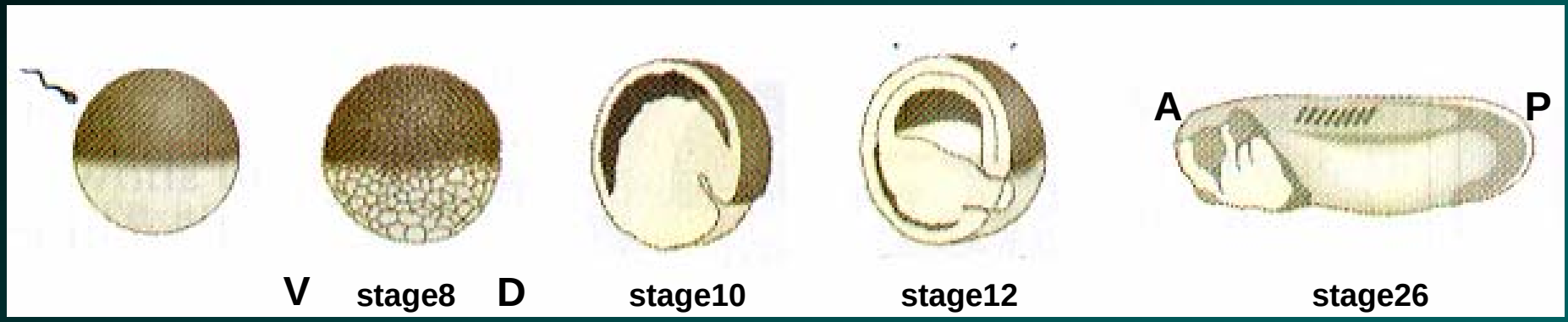
The function of a signal transduction system in development

example ①　in the case of a Wnt signal

An Outline of Wnt canonical pathway



The function of the Wnt pathway in the Xenopus

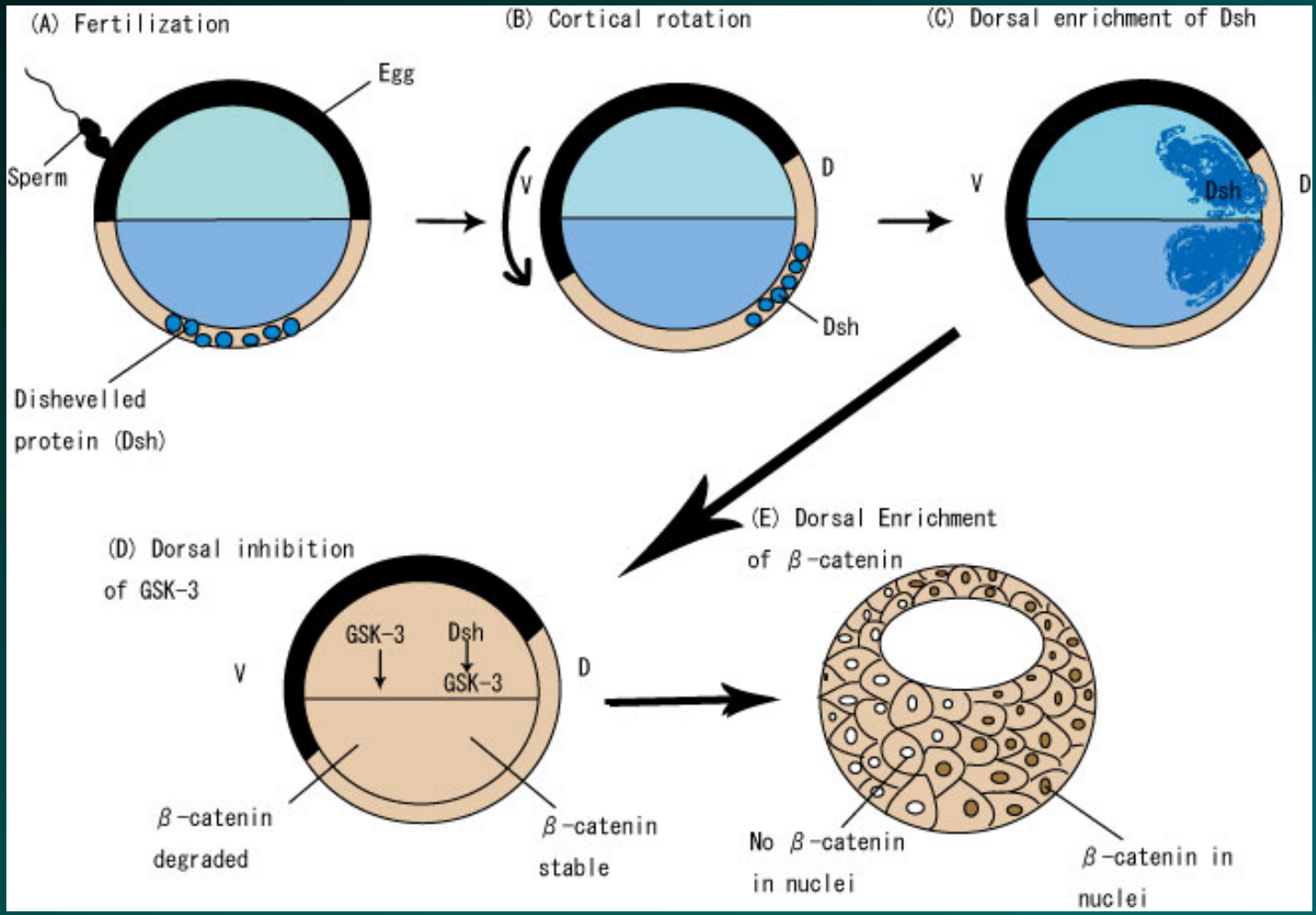


Determination of ventral-dorsal axis
(primary canonical pathway is concerned)

Determination of anterior-posterior patterning of the nerve
(later canonical pathway is involved)

gastrulation
(PCP pathway is involved)

Primary canonical pathway→ determination of the dorsal-ventral axis



Dorsal region in the future : β-catenin stabilizes at one side of the embryo, and moves into the nucleus→ an organizer gene is induced.

Later canonical pathway → determines anterior-posterior nerve pattern

Head part・the Wnt signal is regulated

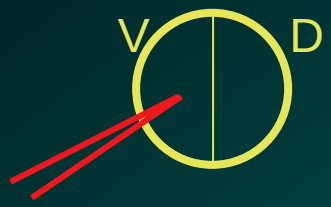
"The illustration of later canonical pathway" inserted here was omitted according to copyright issue.

	head	trunk-tail
BMP	-	-
Wnt	-	+

Secretion factors from anterior mesoderm （Cerberus, dickkopf, Frzb etc.) regulate Wnt in normal development of the head part.

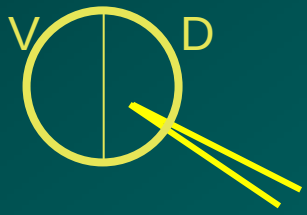
Assay of a primary canonical pathway

Injection of a slight amount of promoting factor of the Wnt pathway into the ventral region



Formation of a secondary axis

Injection of an inhibiting factor of the Wnt pathway into the dorsal region



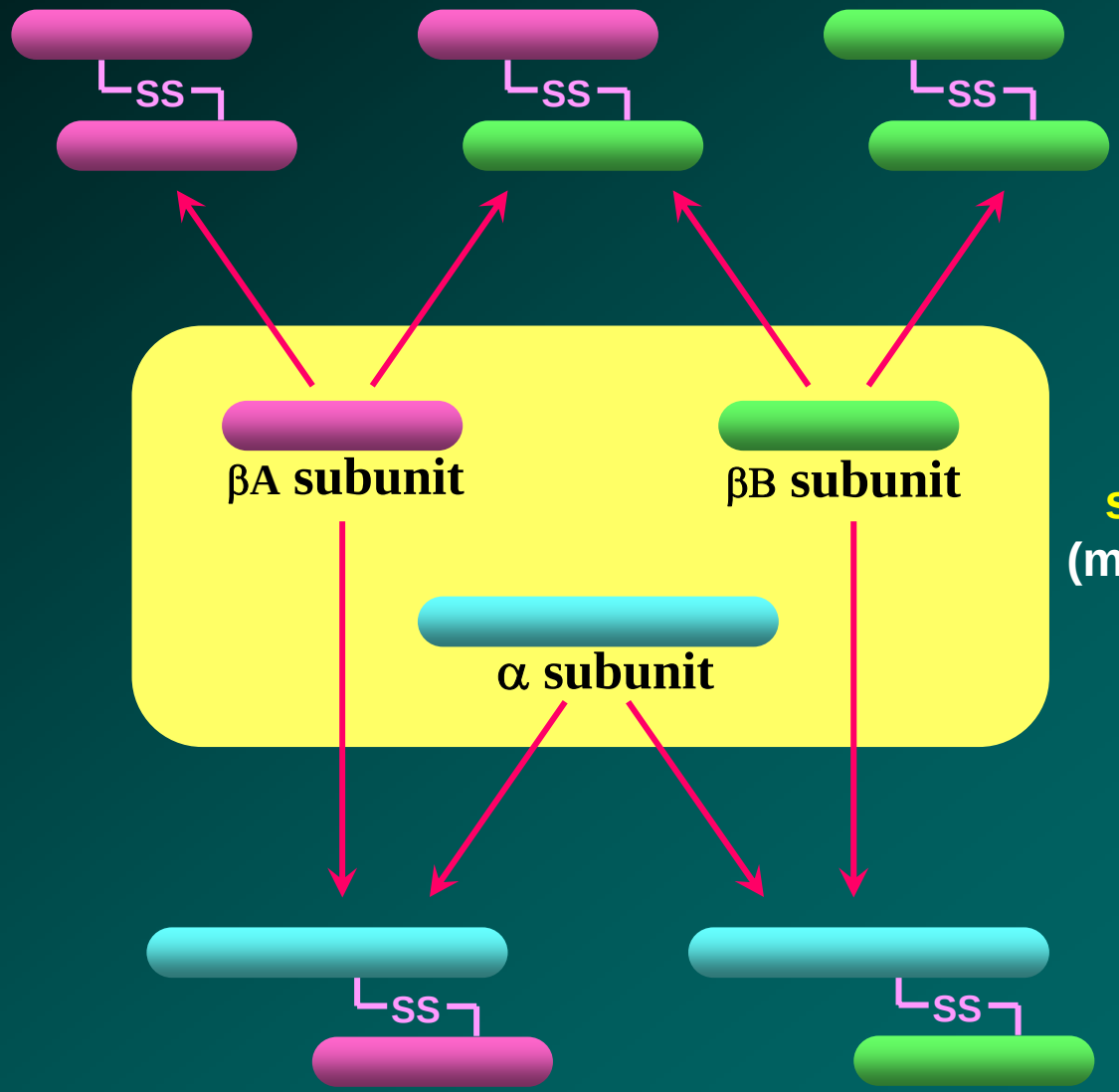
Loss of a dorsal anterior structure

The function of a signal transduction system in development

example ②　in the case of an Activin/Nodal signal

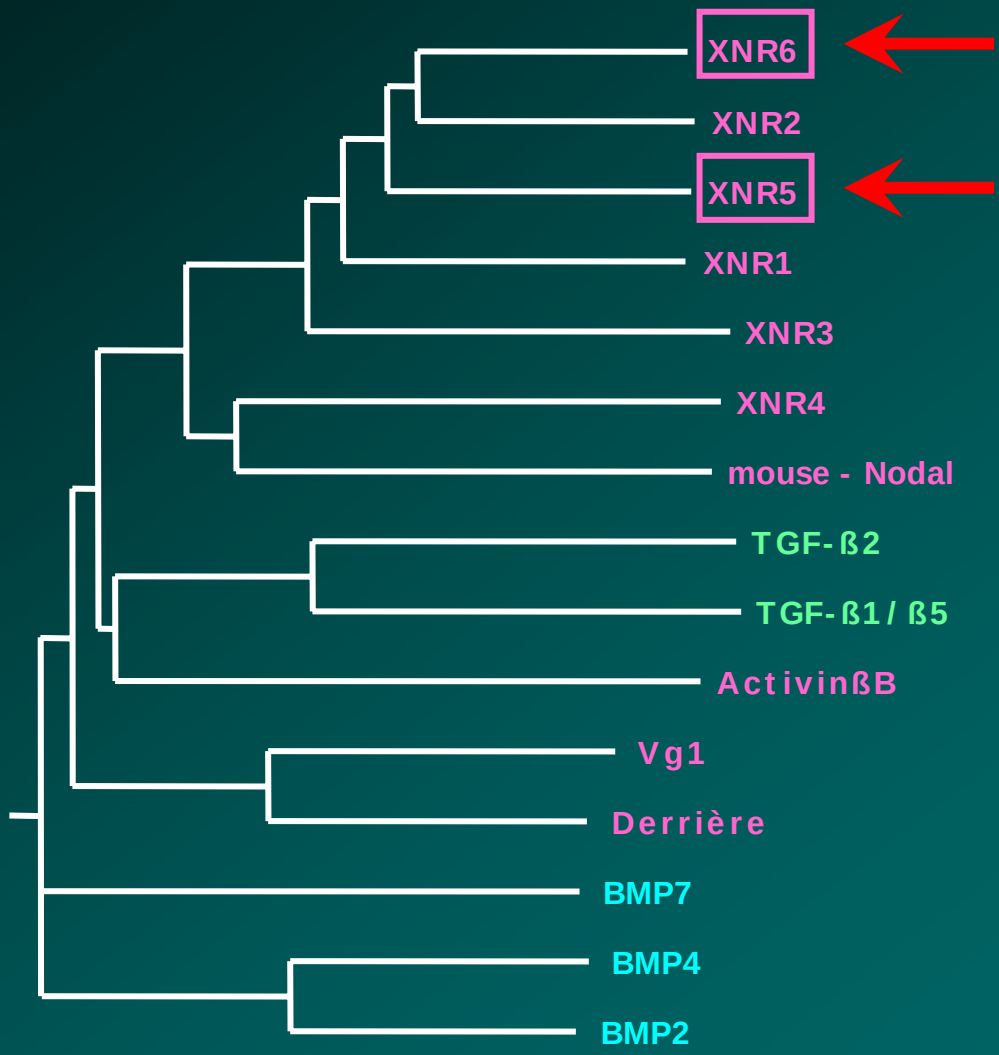
TGF-β superfamily

- TGF-βs
- BMPs
- Dpp
- Vg-1
- Univin
- activins inhibins
- 60A
- Radar
- CDMPs
- GDFs
- Dorsalin
- ADMP
- Nodal
- Screw
- Daf-7
- MIS
- Lefty
- GDNF

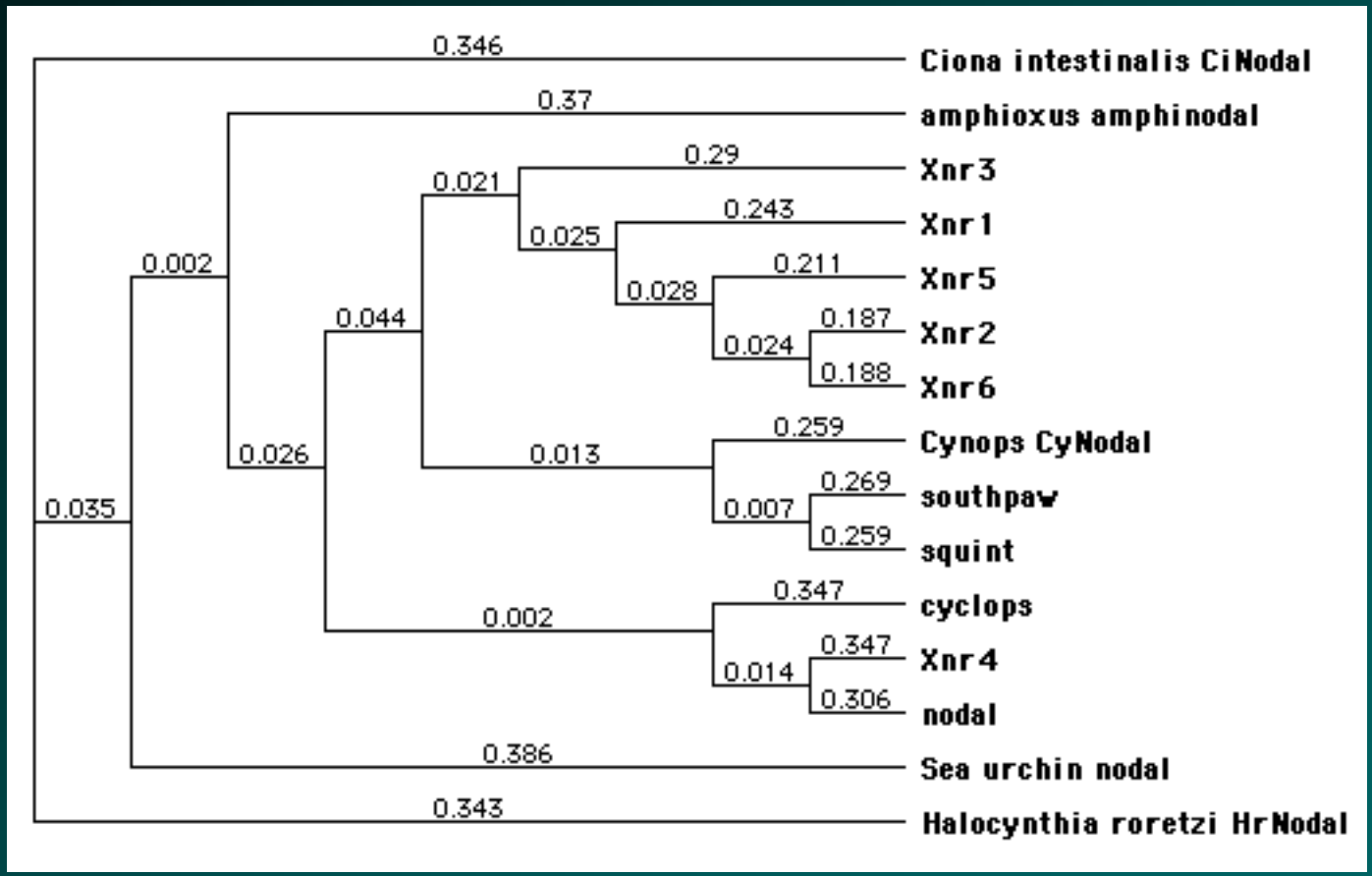


TGF-β superfamily transmits a signal into the cell through a serine・threonine kinase receptor（transcriptional receptor）

TGF-b superfamily



The nodal is preserved in many deuterostomes -compared with amino acids.



Ciona savignyi
lancelet

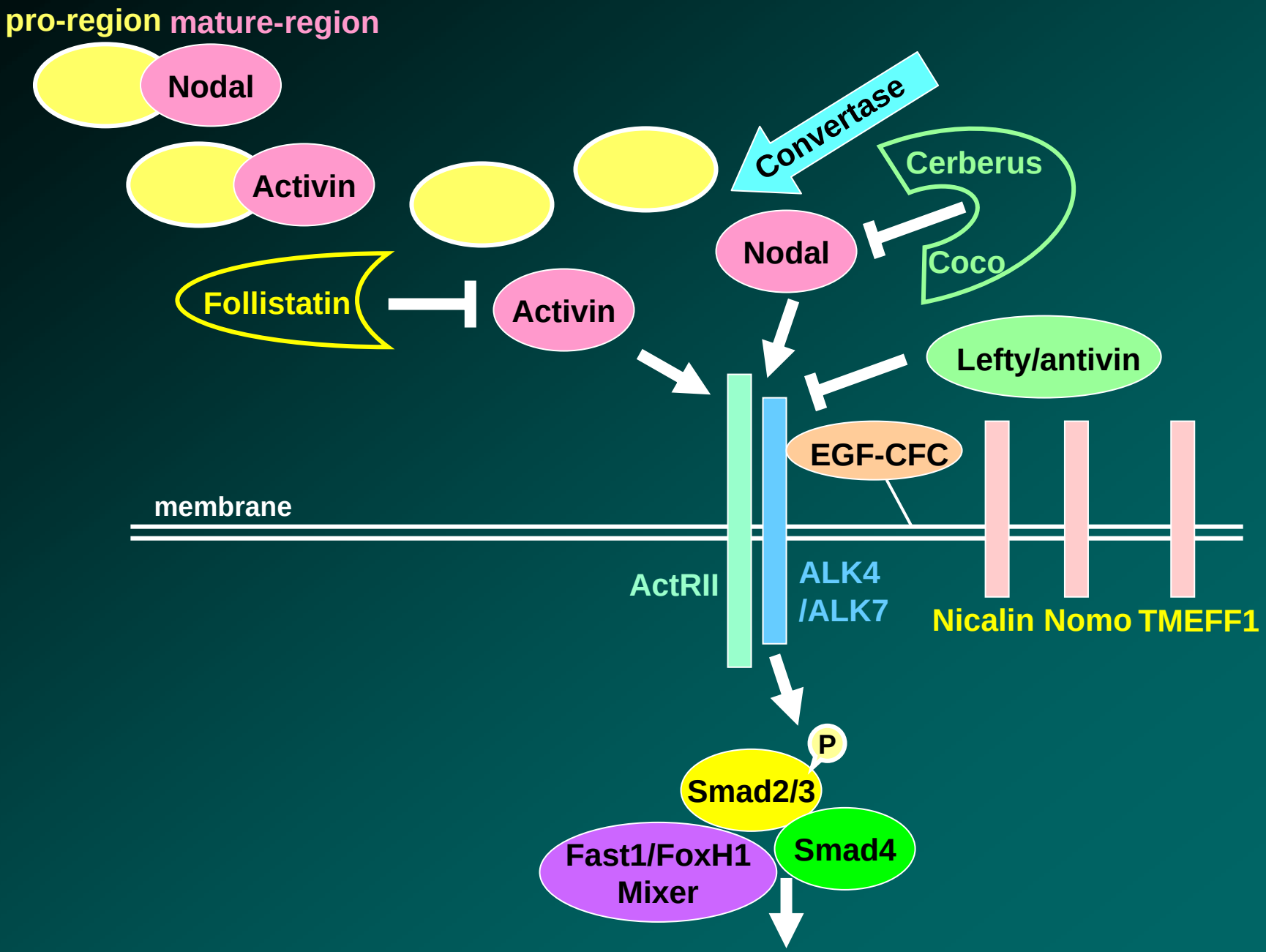
Xenopus laevis

newt

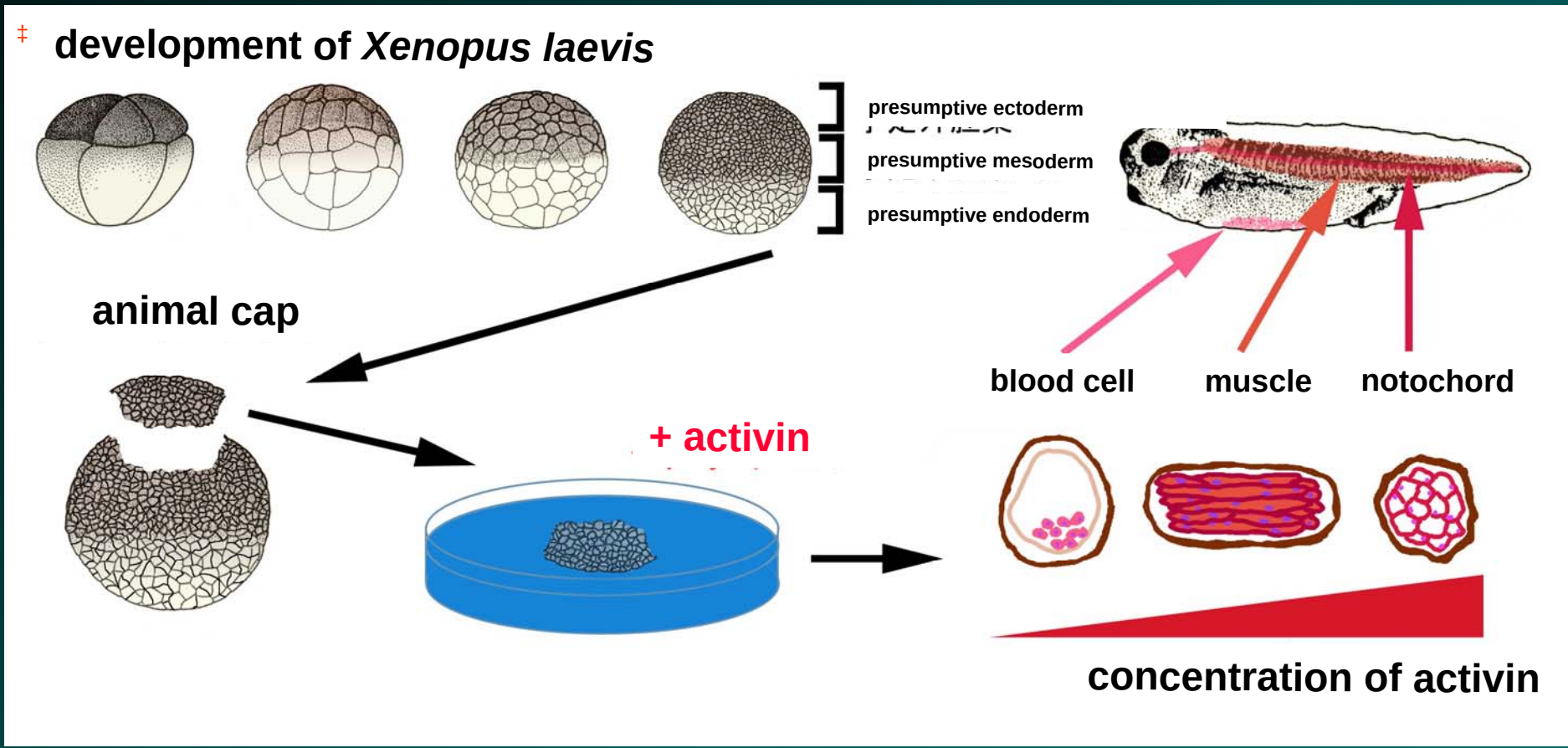
zebrafish

Xenopus laevis
mouse
sea urchin
Halocynthia roretzi.

Signal transduction in an Activin/Nodal pathway

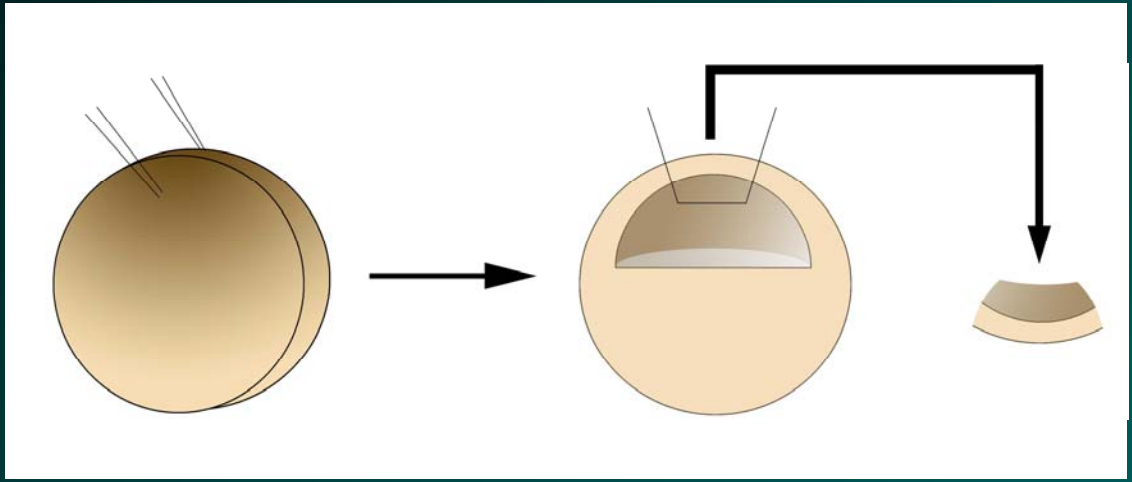


An experiment of mesoderm induction by an activin treatment



One of the nodals, Xnr5 induces mesoderms and endoderms depending on the concentration like activin.

mRNA injection



animal cap

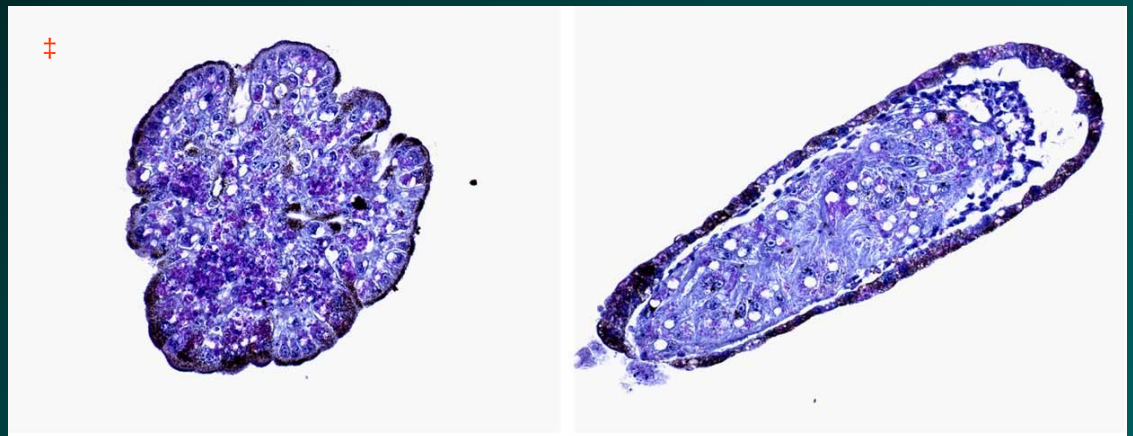
control

Xnr5 overexpression

Extends and induces mesoderms such as muscles.

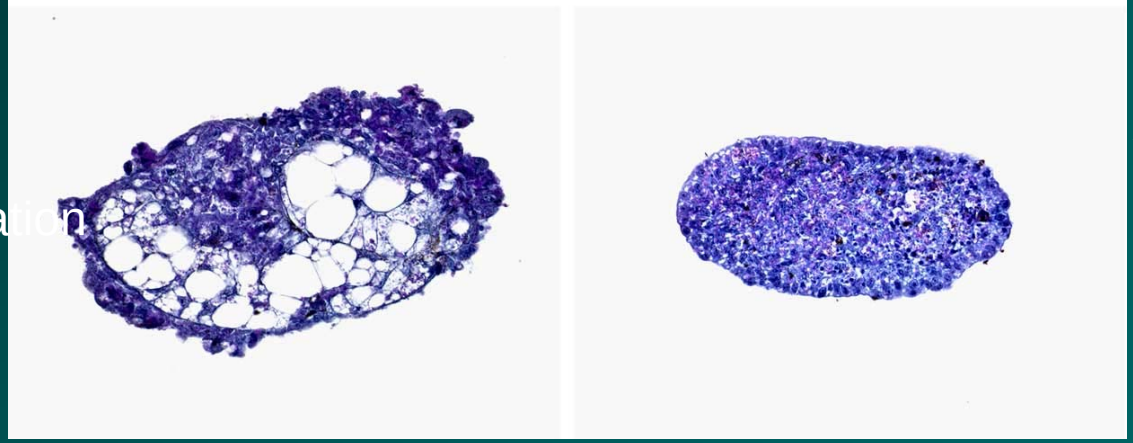
One of the nodals, Xnr5, induces mesoderm and mesoderm tissues according to its concentration, just like activin.

Without Xnr5



Xnr5
Low concentration

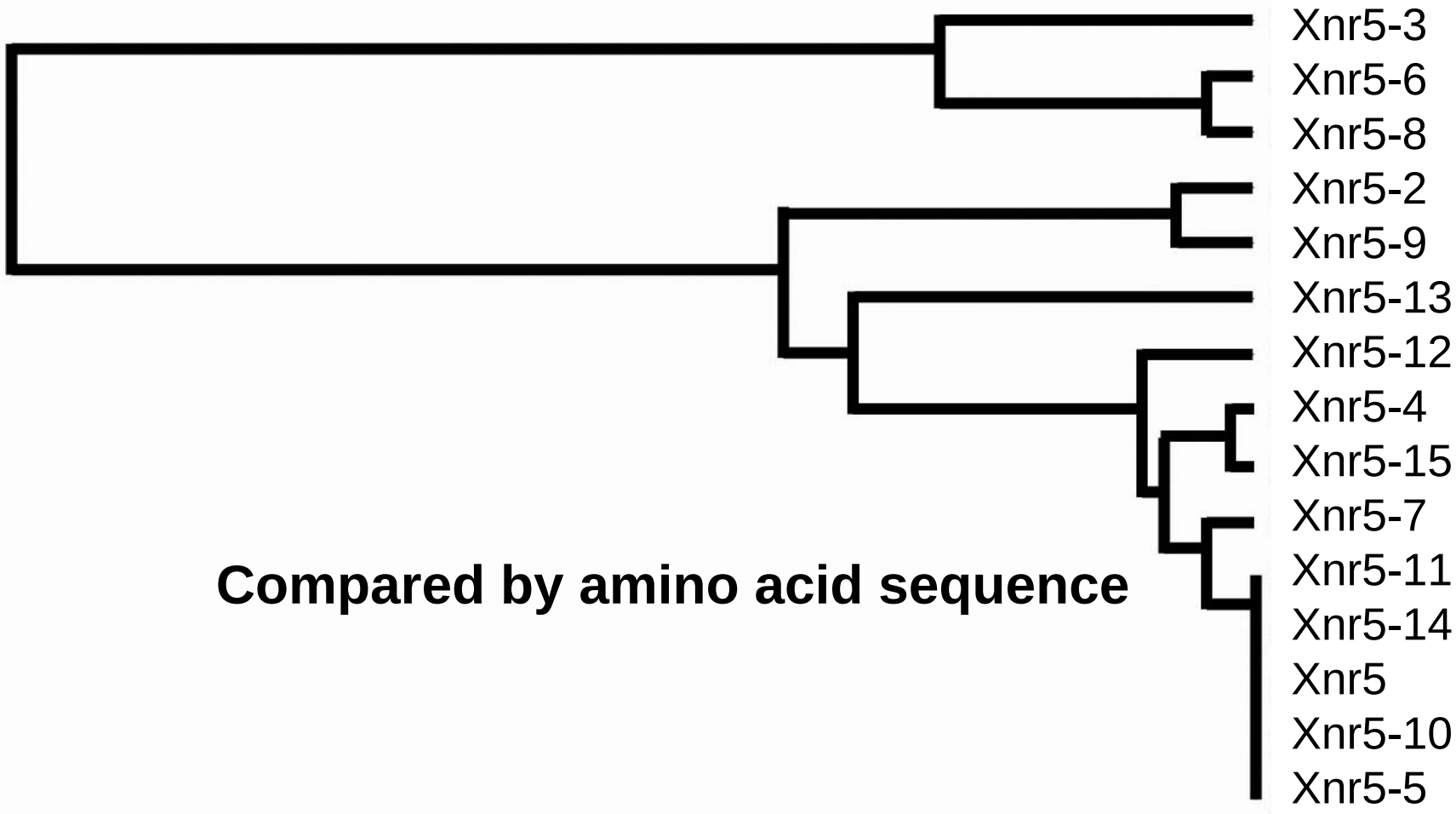
Xnr5
Middle concentration



Xnr5
High concentration

Takahashi S. et al., Development, vol 127, p5323-Fig.4(D, E, F, G), 2001

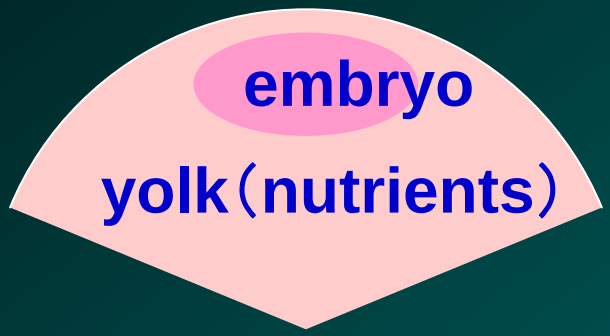
Molecular evolution of Xnr5 in *Xenopus laevis*



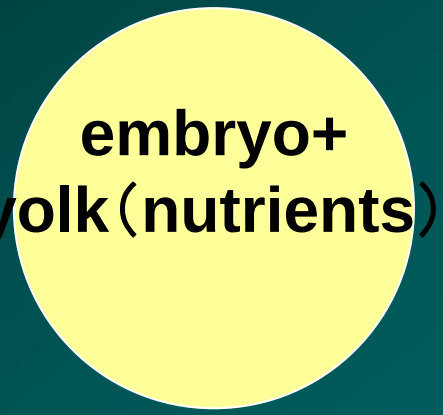
Xnr3 and*Xnr5*-increase in genomes in the *Xenopus laevis*.
There are more than 15 kinds of *Xnr5.*

Reproductive strategy to enlarge the egg

meloblastical egg
（avian、reptile）



holoblastical egg
（amphibian）



Amphibians, avians, and reptiles have chosen this strategy to enlarge their eggs. Large eggs have the advantage of fast growth or maturation since they can store many nutrients for growth. Avians and reptiles lay meloblastical eggs which can accumulate yolk without changing the size of the embryo. Amphibians' eggs are holoblastical eggs. The size of an embryo becomes larger as the amount of the yolk increases.

Number of Nodals already discovered

Size of egg and volume of yolk

1 kind
human
mouse
lancelet
sea squirt
sea urchin

about 100μm in diameter

3 kinds
zebrafish

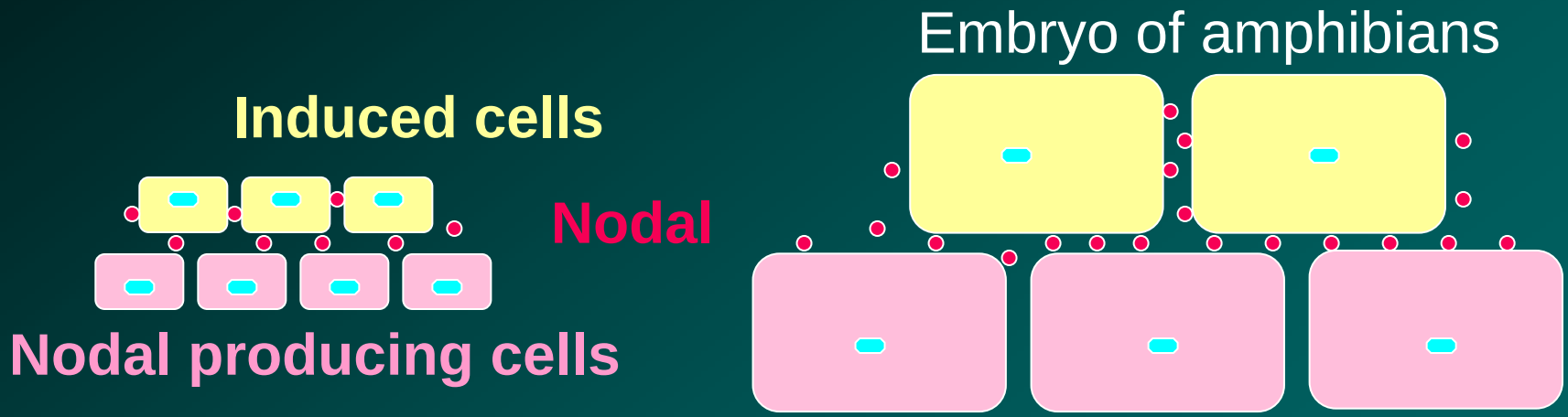
about 500μm

6 kinds
Xenopus laevis（Xenopus）
（Xnr3 and Xnr5 Increased）

about 1200μm

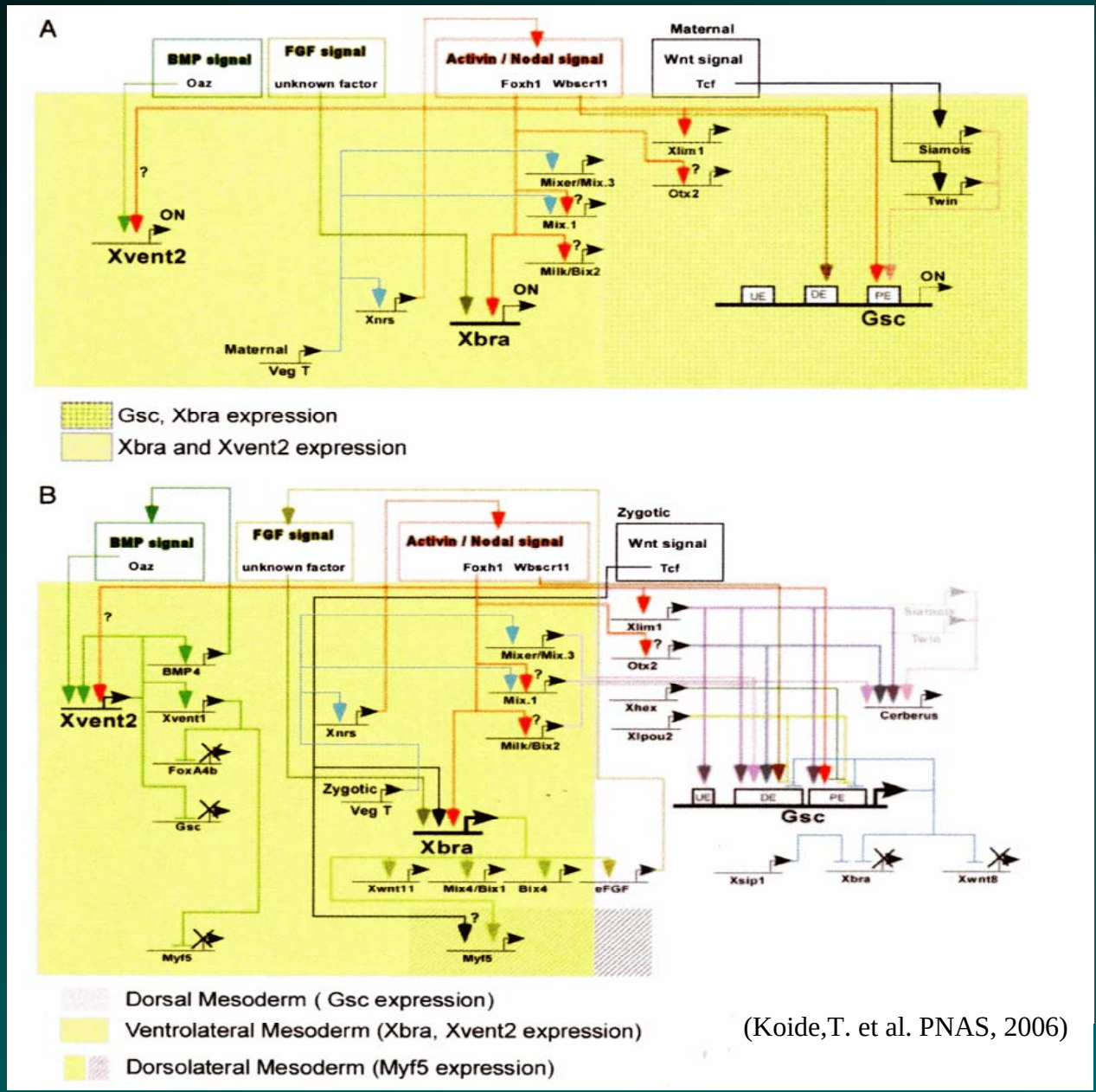
Reproductive strategy to for a larger egg, and changes in the number of Nodal genes as an inducing factor

The same concentration of inducing factor is needed for differentiation, indifferent to the size of the cell



- Cells of large amphibian embryo are induced into large cells in differentiation processes. A certain concentration of inducing factors is needed for induction; if the cells are large, the volume of space between cells becomes large, and a large number of inducing factors are needed. For this reproductive strategy, Nodal is amplified in an amphibians'genome .

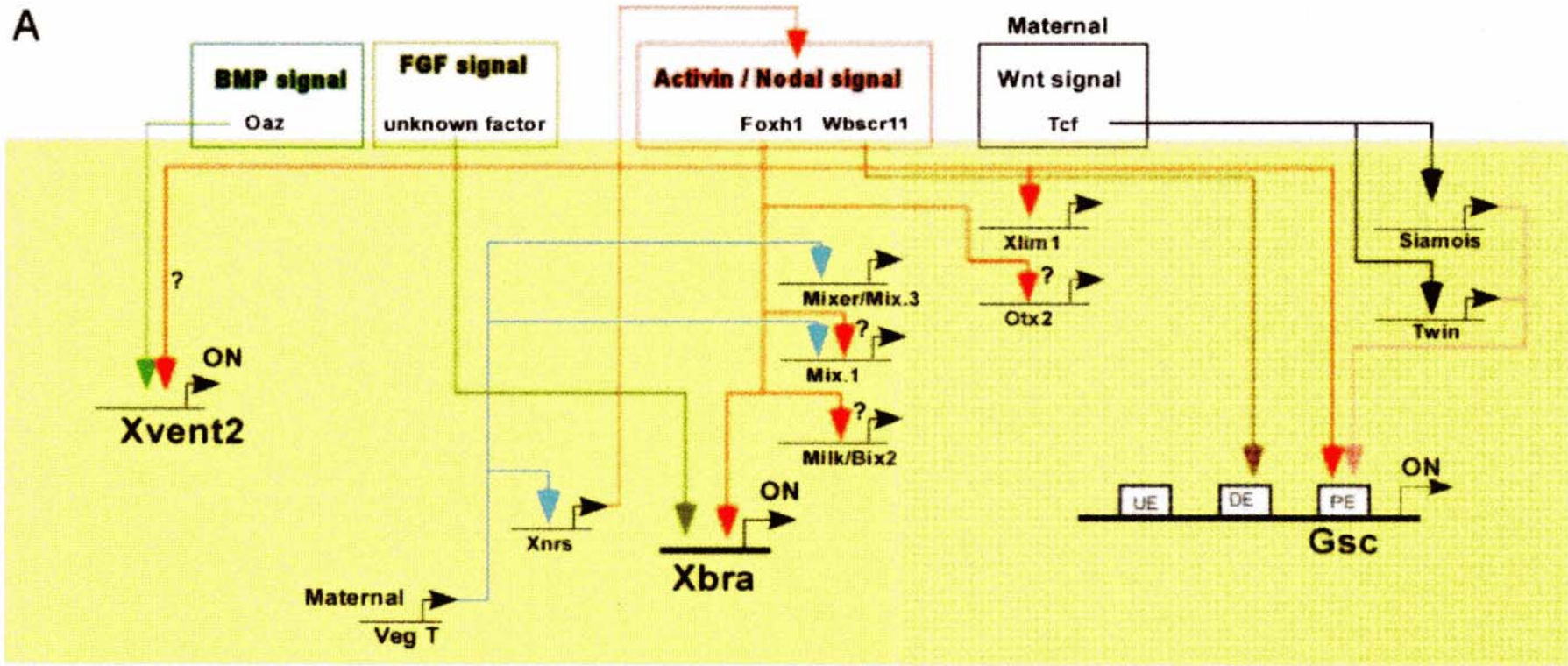
A gene cascade and the network from Activin/Nodal signals in development



(Koide,T. et al. PNAS, 2006)

A gene cascade and the network from Activin/Nodal signals in development

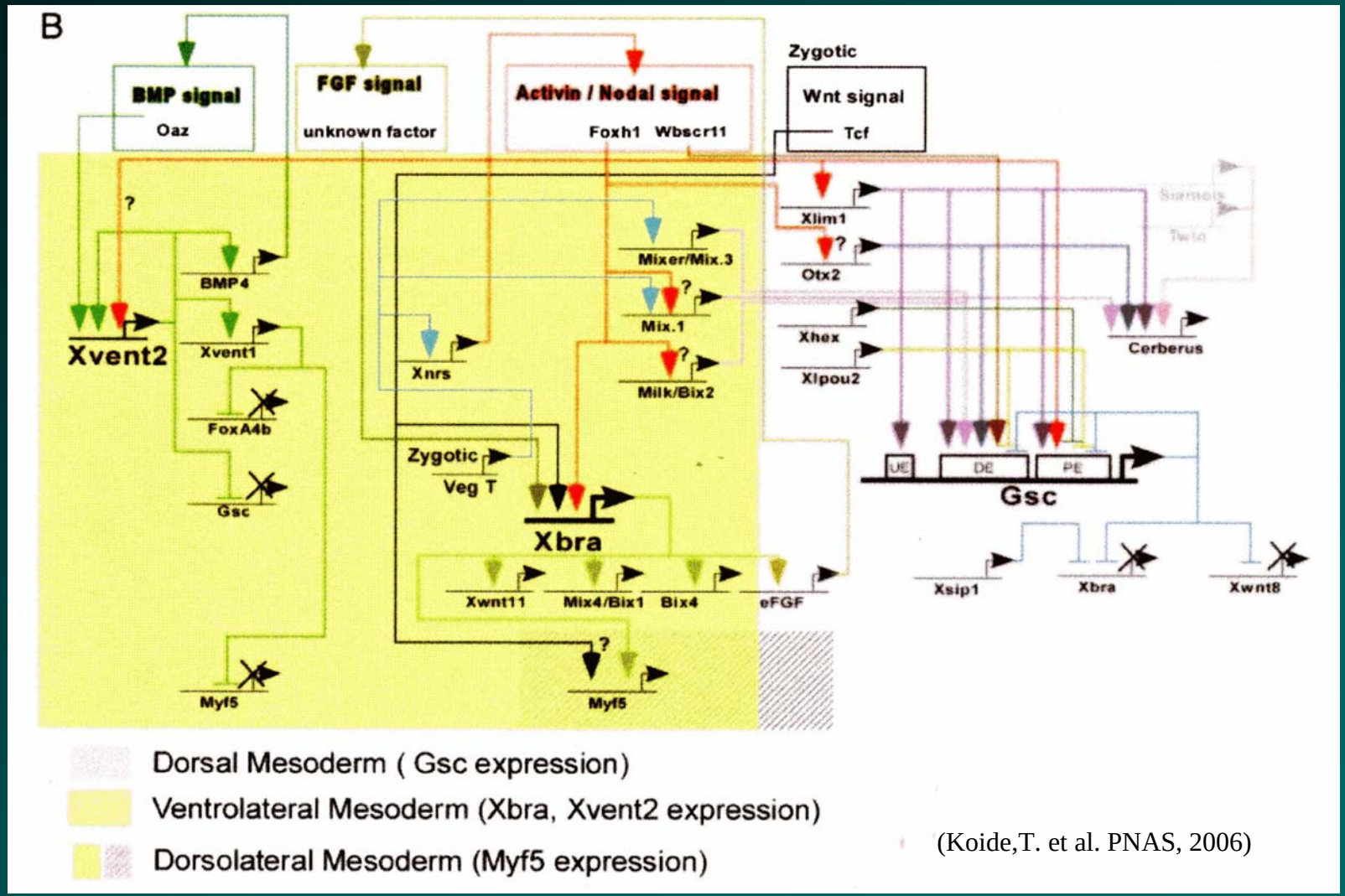
Early stage



(Koide,T. et al. PNAS, 2006)

A gene cascade and the network from Activin/Nodal signals in development

Later stage



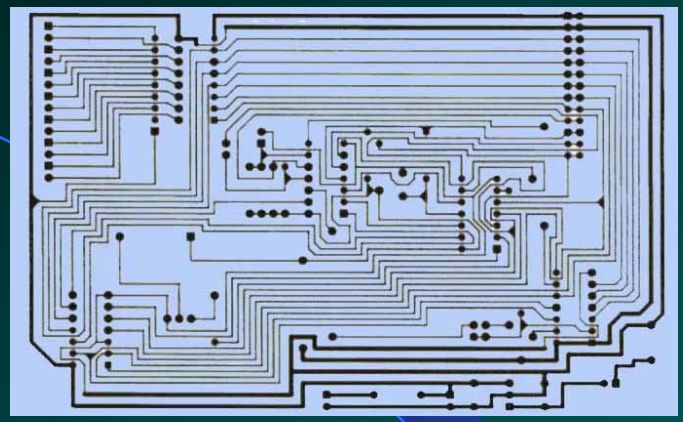
(Koide,T. et al. PNAS, 2006)

A model of organ formation

Normal cell

Various factors

Black Box



Same muscle

Animal cap、ES cell of a mouse, etc.

activin

retinoic acid