

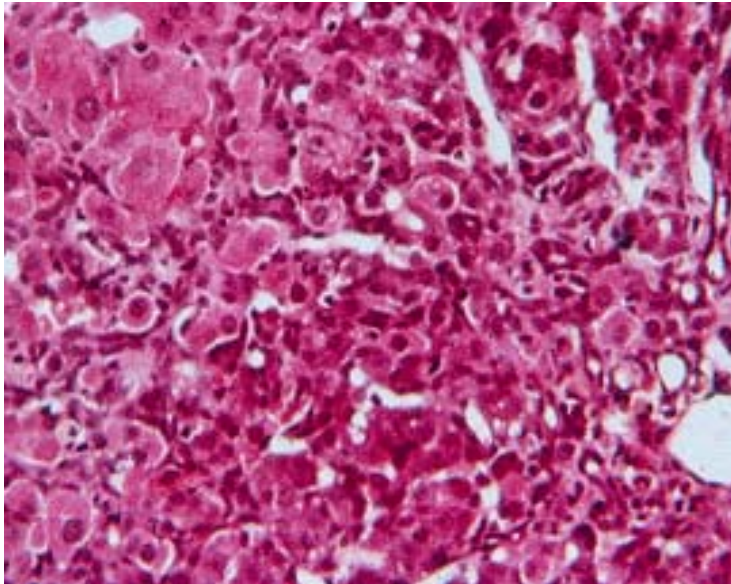
平成21年2月27日 最終講義

# 生体内における癌のでき方



# Oval Cell

# 1968-1988



[CANCER RESEARCH34, 3379-3386 December 1974]

## Demonstration of Glucose 6-Phosphatase Activity in the Oval Cells of Rat Liver and the Significance of the Oval Cells in Azo Dye Carcinogenesis'

Katsuhiro Ogawa, Takashi Minase, and Tamenori Onoe

Department of Pathology, Sapporo Medical College, Chuo-ku, Minami 1, Nishi 17, Sapporo, Hokkaido, Japan

QuickTime<sup>®</sup> Ç±ÇÄÉsÉÑÉ·ÉÉÇ¾¼â©ÇÉÇžÇ½Ç...ÇÖïKóvÇ-ÇIÄB

QuickTime<sup>®</sup> Ç²  
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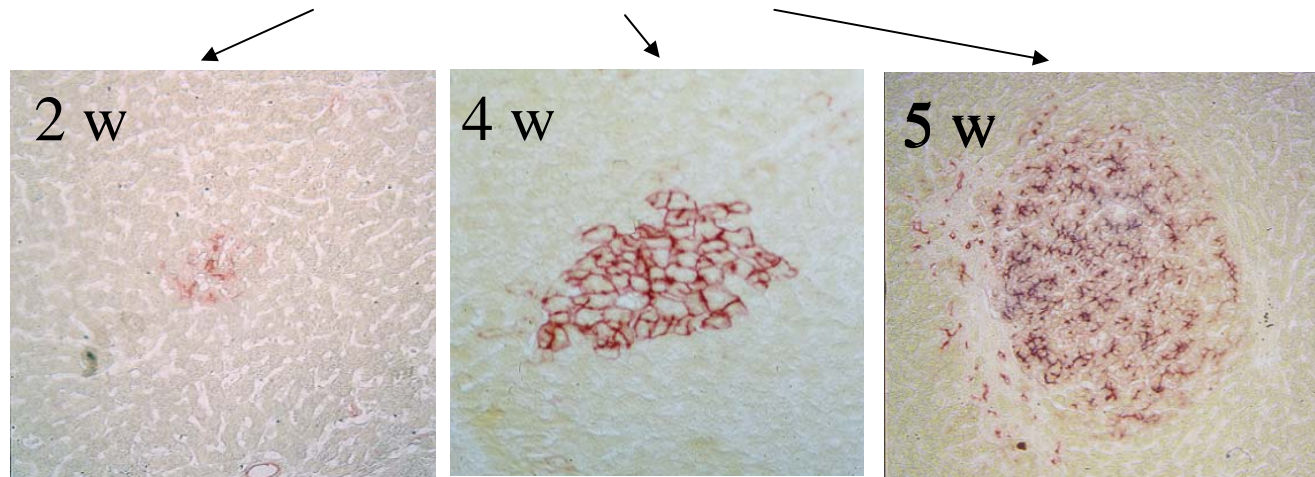
[CANCER RESEARCH 40, 725-733, March 1980]

### Phenotypic Diversity as an Early Property of Putative Preneoplastic Hepatocyte Populations in Liver Carcinogenesis<sup>1</sup>

Katsuhiko Ogawa,<sup>2</sup> Dennis B. Soft, and Emmanuel Farber<sup>3</sup>

University of Toronto, Department of Pathology, Toronto, Ontario, M5S 1A8, Canada

1976-1978



5 w

8 w

QuickTime<sup>®</sup> C<sup>2</sup>  
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GGT ( $\gamma$ -glutamyl transpeptidase)

小野江 為則 先生

- ・ 病理学—形態学
- ・ Form／Structure  
形の背景にある原理
- ・ 方法論

Emmanuel Farber 先生

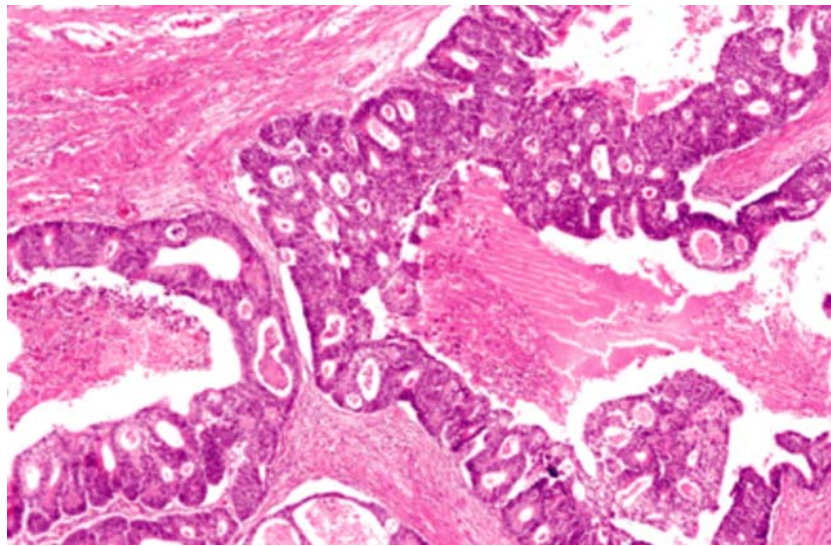
- ・ 競走馬のように  
前だけ見て進め.
- ・ 軸足を定める

# 生体内での癌のでき方

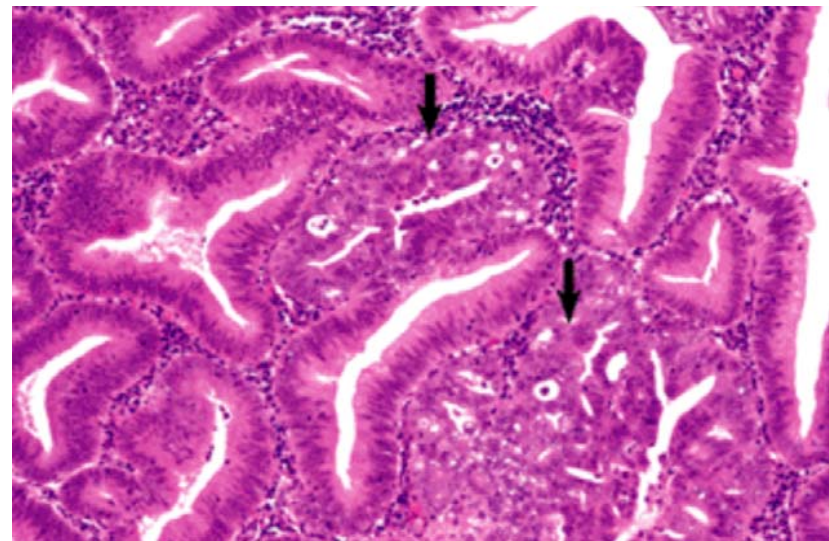
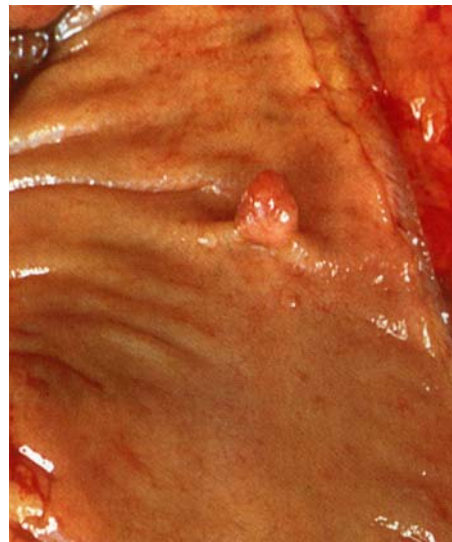
1. 癌は多段階的に発生する.
2. 癌ができるには長い年月を要する.

①多段階発癌

大腸がん

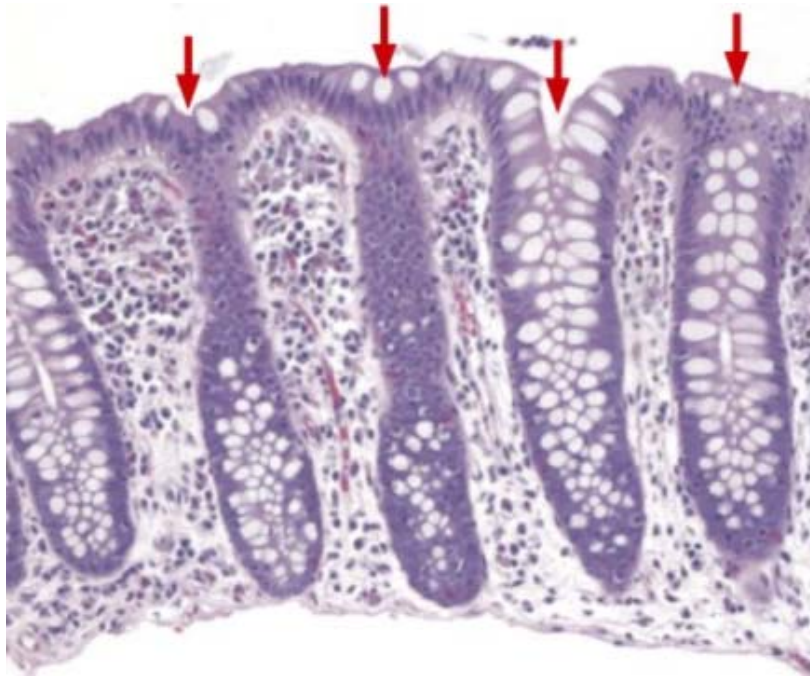


大腸ポリープ

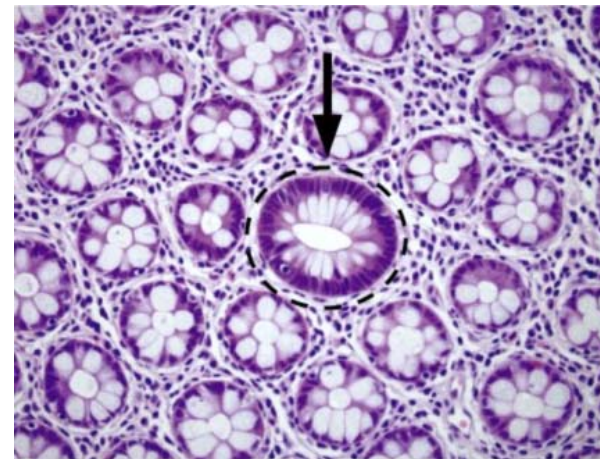


# ①多段階発癌

## 正常大腸粘膜

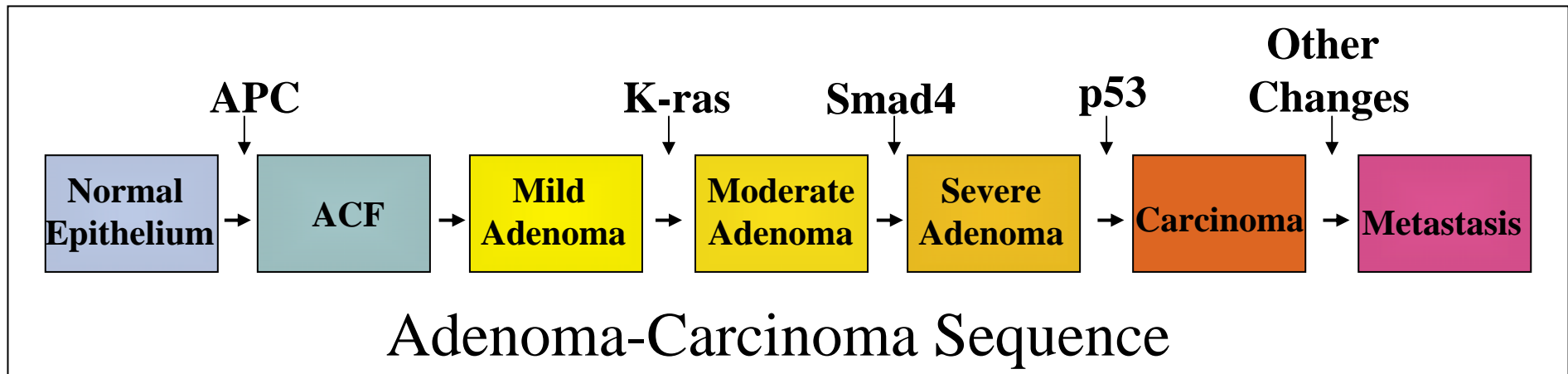
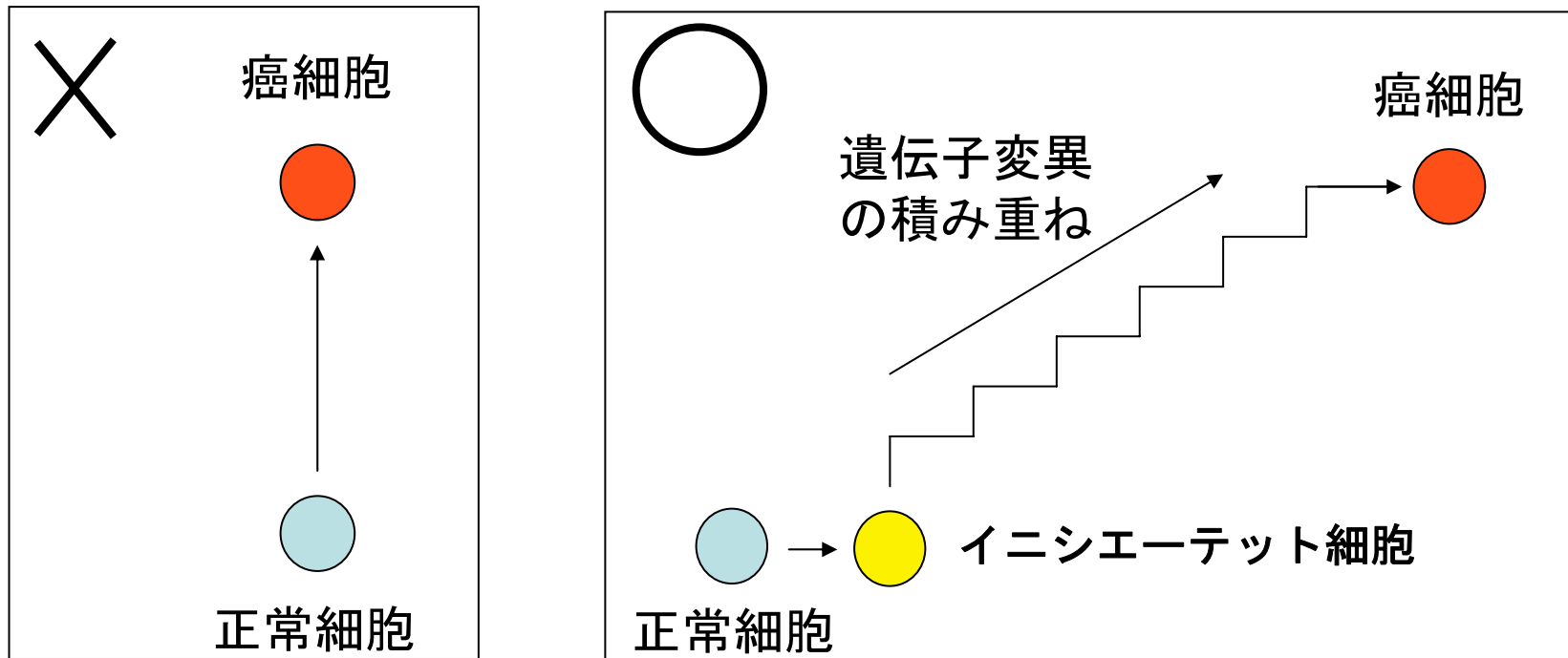


## Aberrant Cryptic Focus (ACF)



①多段階発癌

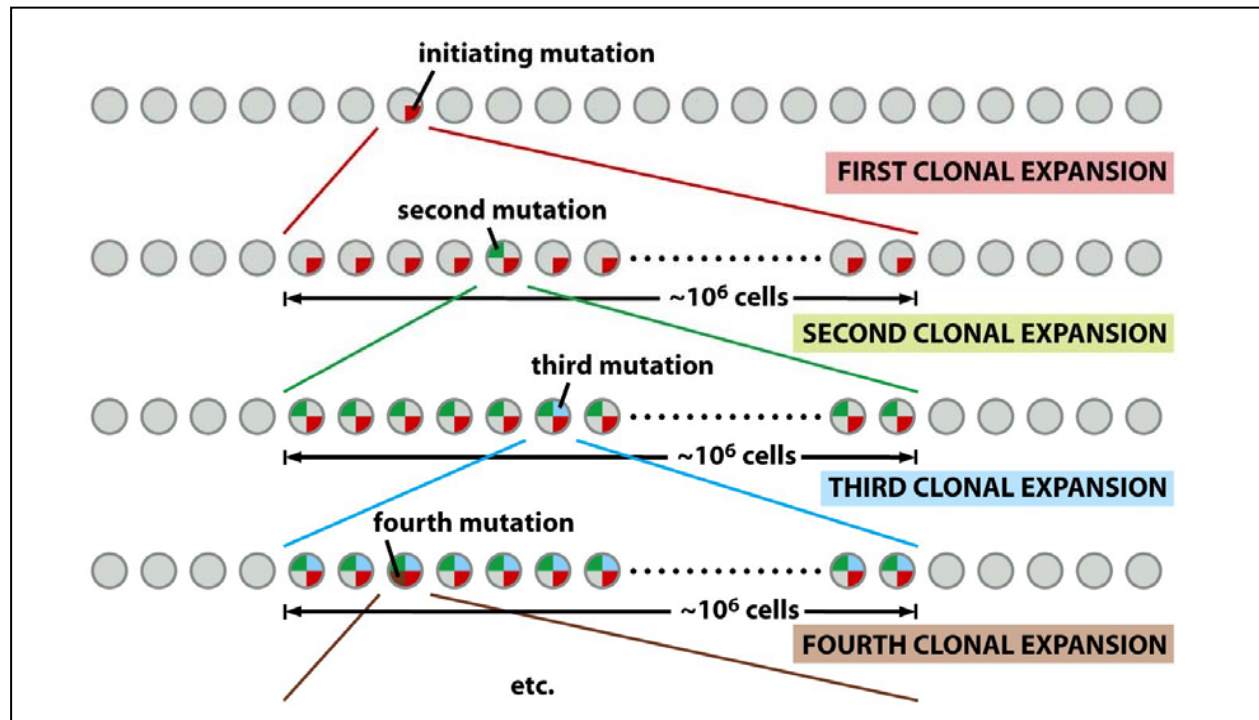
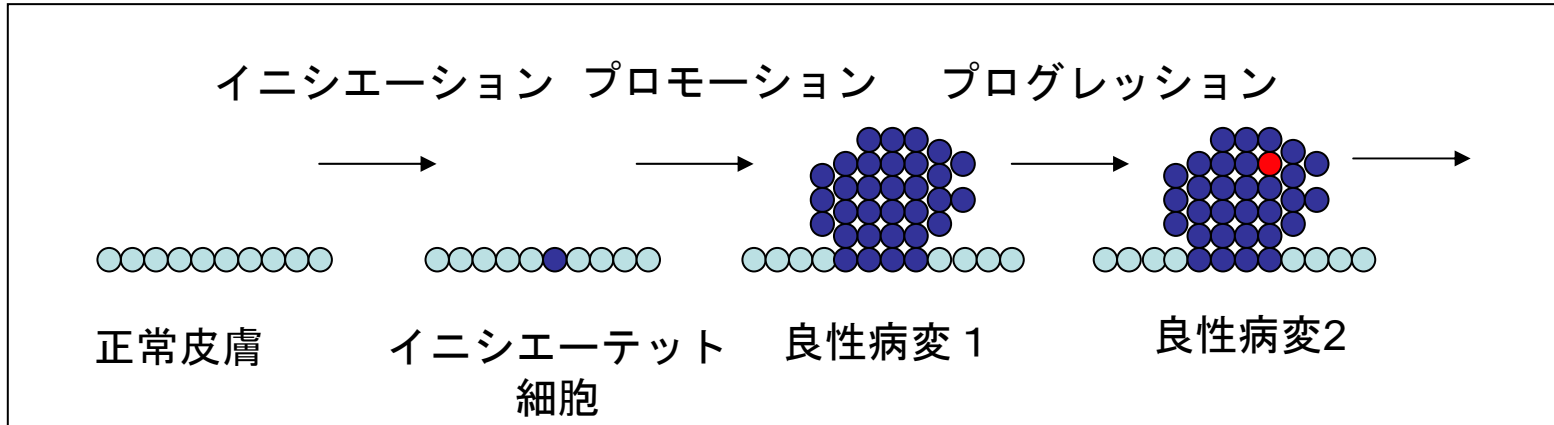
# 多段階発癌と遺伝子変異





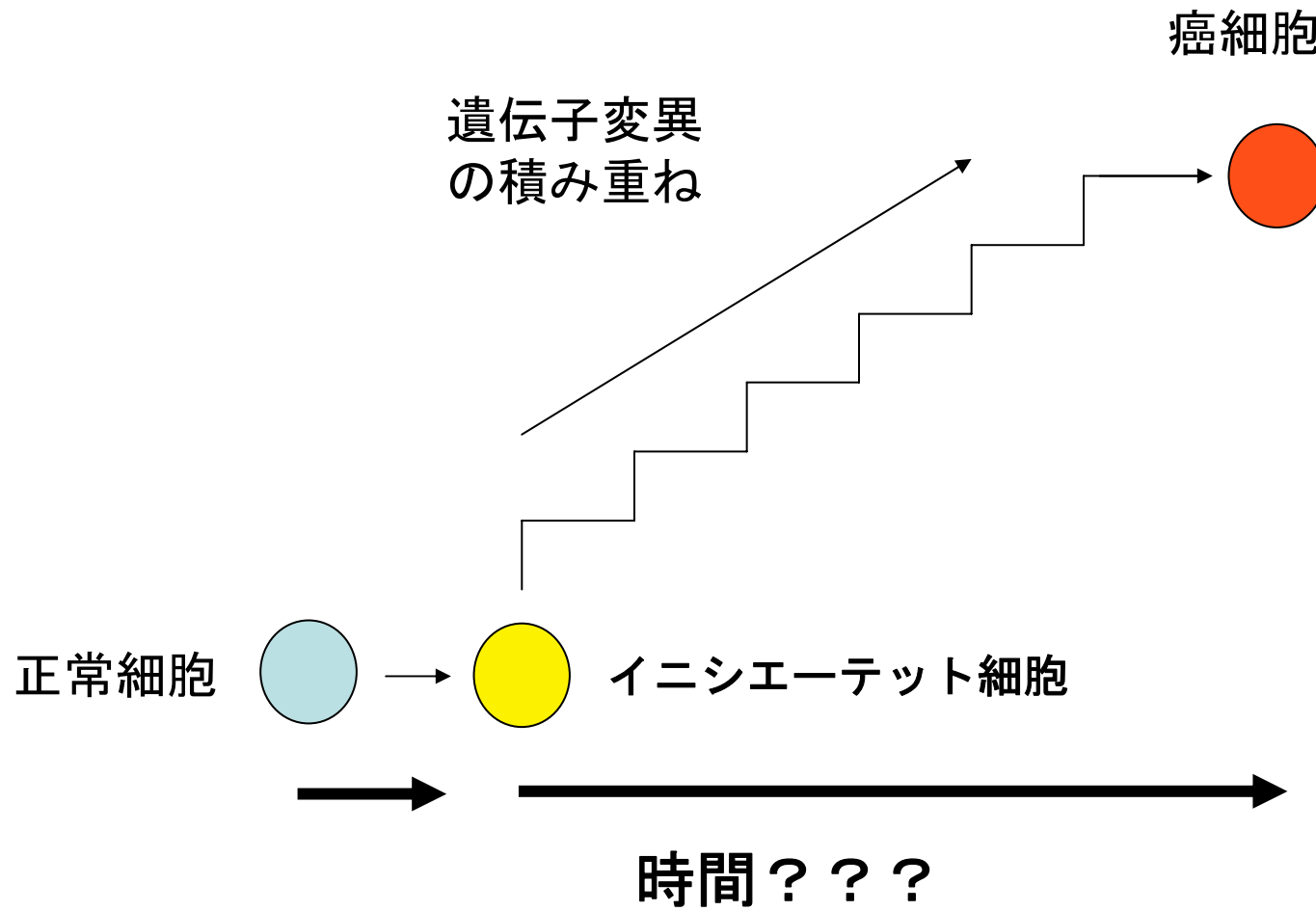
# ①多段階発癌

## 突然変異の蓄積とプロモーターの働き



①多段階発癌

# がんはどれくらいの時間をかけて出来るのか？



# ①多段階発癌

## タバコ消費量の増加と肺がん頻度の推移

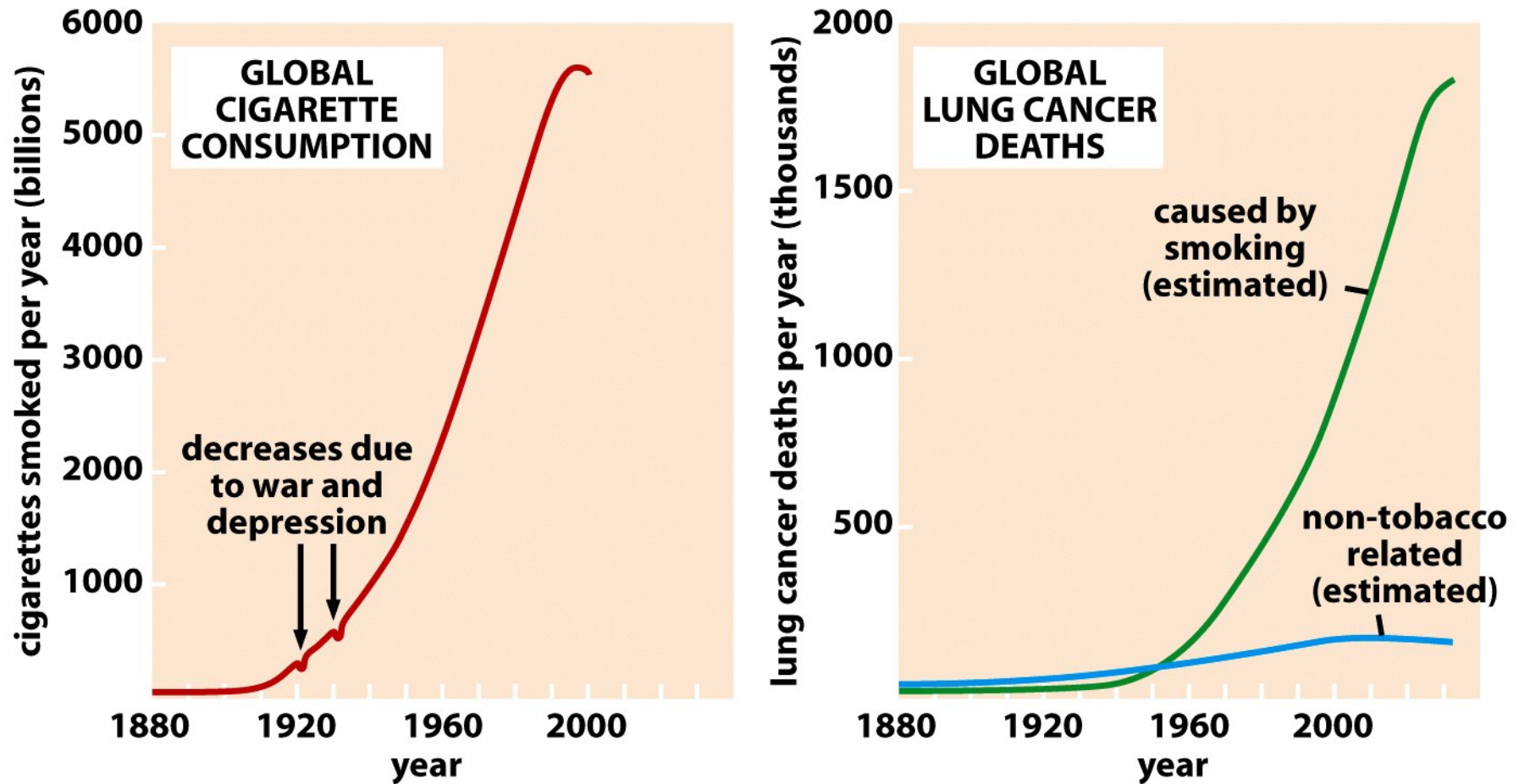


Figure 11.2 *The Biology of Cancer* (© Garland Science 2007)

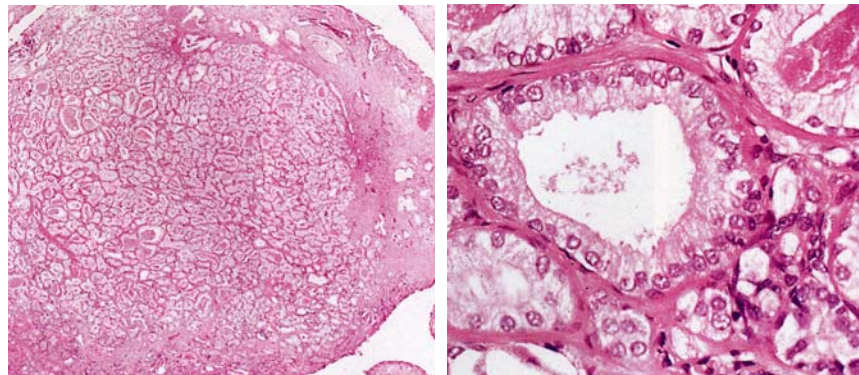
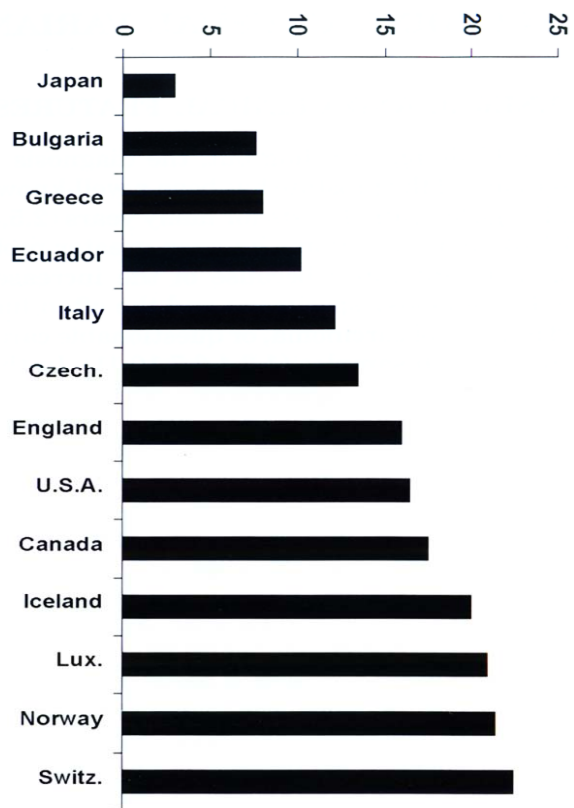
# ①多段階発癌

# 前立腺がん

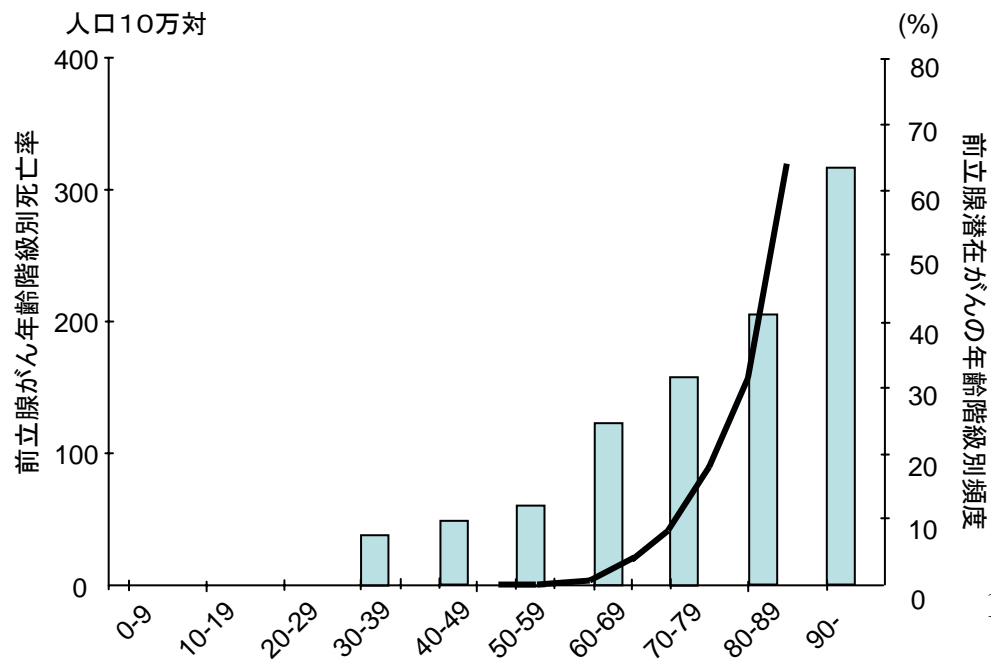
## 前立腺潜在がん

## 前立腺がんの国別頻度

Age-adjusted death rates due to prostate cancer (per 100,000 population)



## 前立腺潜在がんと前立腺がんの頻度



## ①多段階発癌

# ウイルスと発がん

◎HTLV ⇒ リンパ腫／40年

◎B型／C型肝炎ウイルス ⇒ 肝癌／20-40年

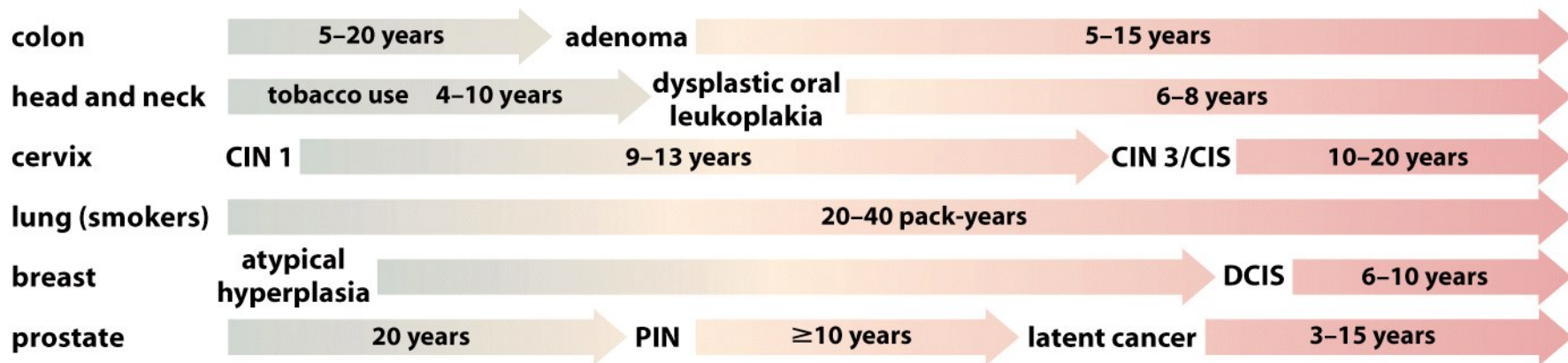
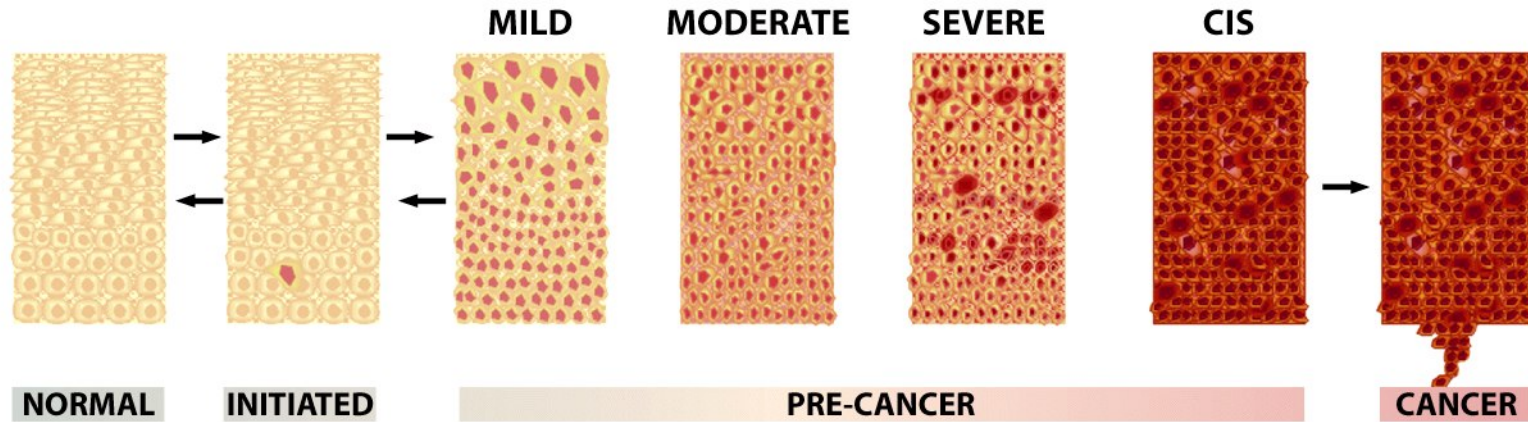
◎人パピローマウィル ⇒ 子宮頸癌／20-30年

◎EBウイルス ⇒ 鼻咽頭がん／40-50年

①多段階発癌

# ヒトの発癌に要する期間

Carcinoma in situ (CIS)



Cervical intraepithelial neoplasia (CIN)

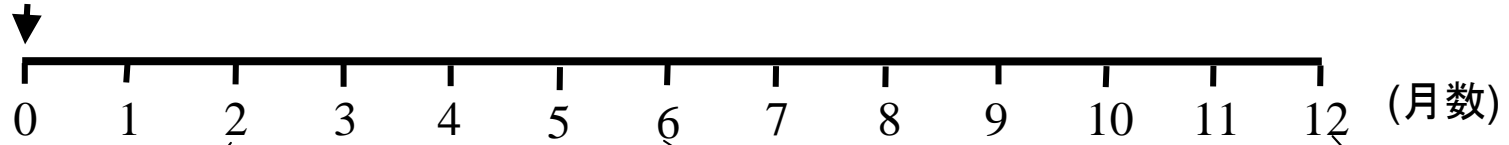
Ductal carcinoma in situ (DCIS)

Prostatic intraepithelial neoplasia (PIN)

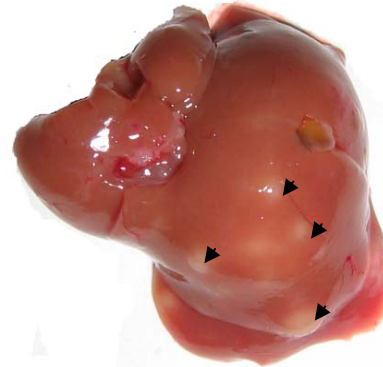
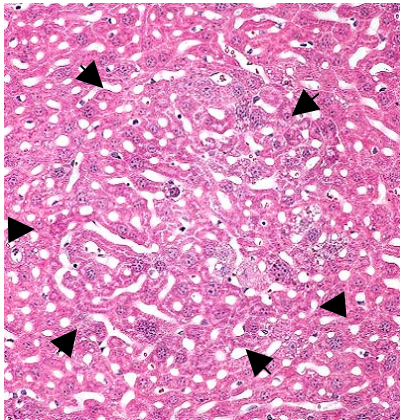
## ②肝発癌モデル

# 肝発癌モデル

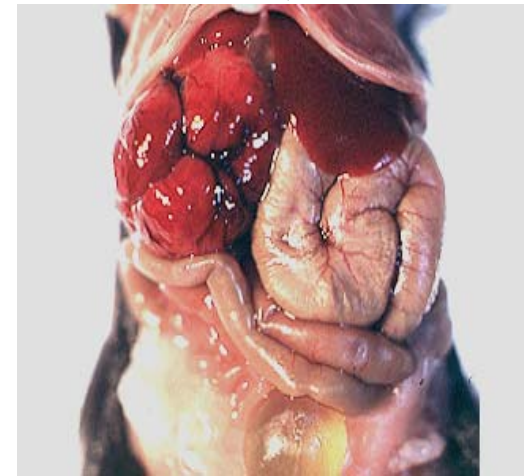
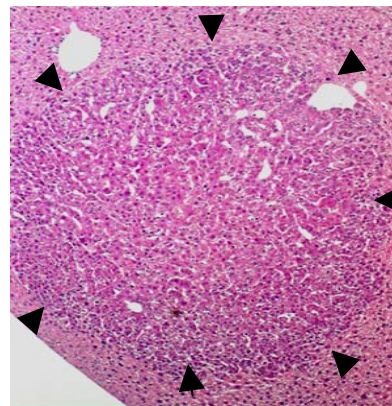
DEN B6C3F1マウス 2週令



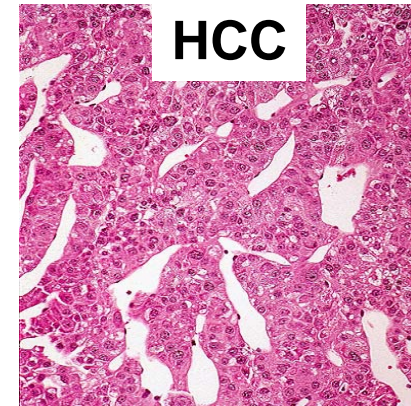
**Focus**



**Adenoma**

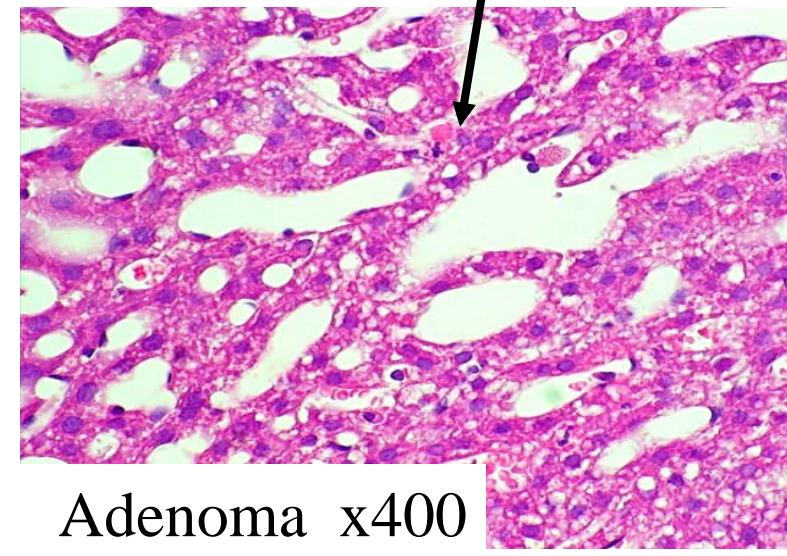
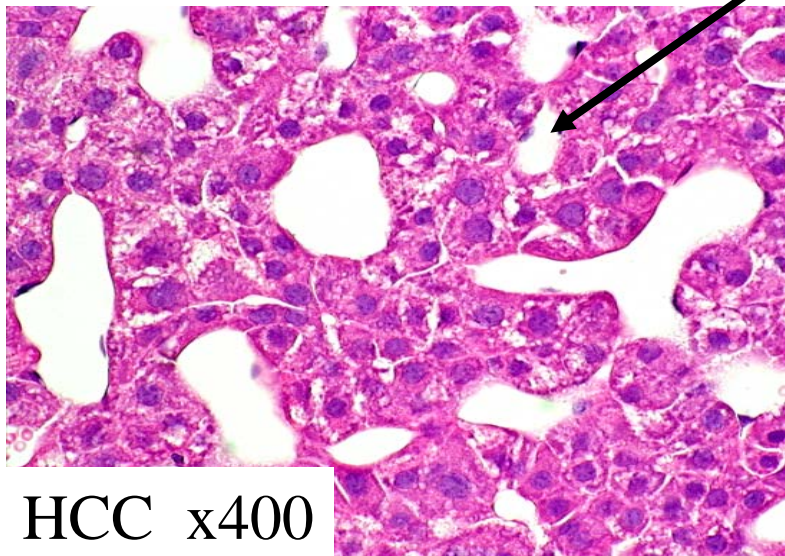
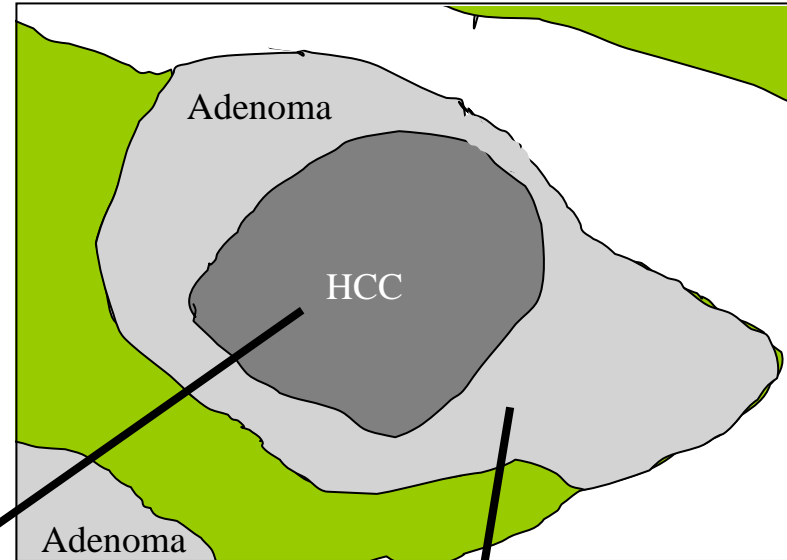
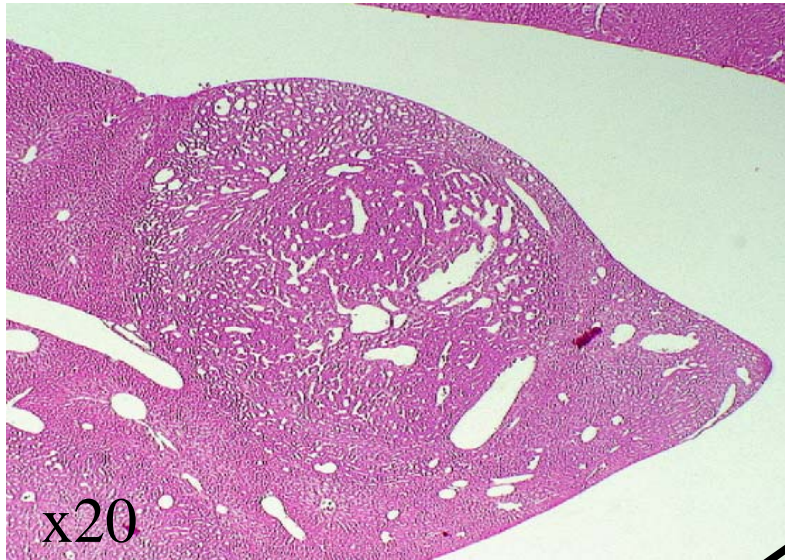


**HCC**



②肝発癌モデル

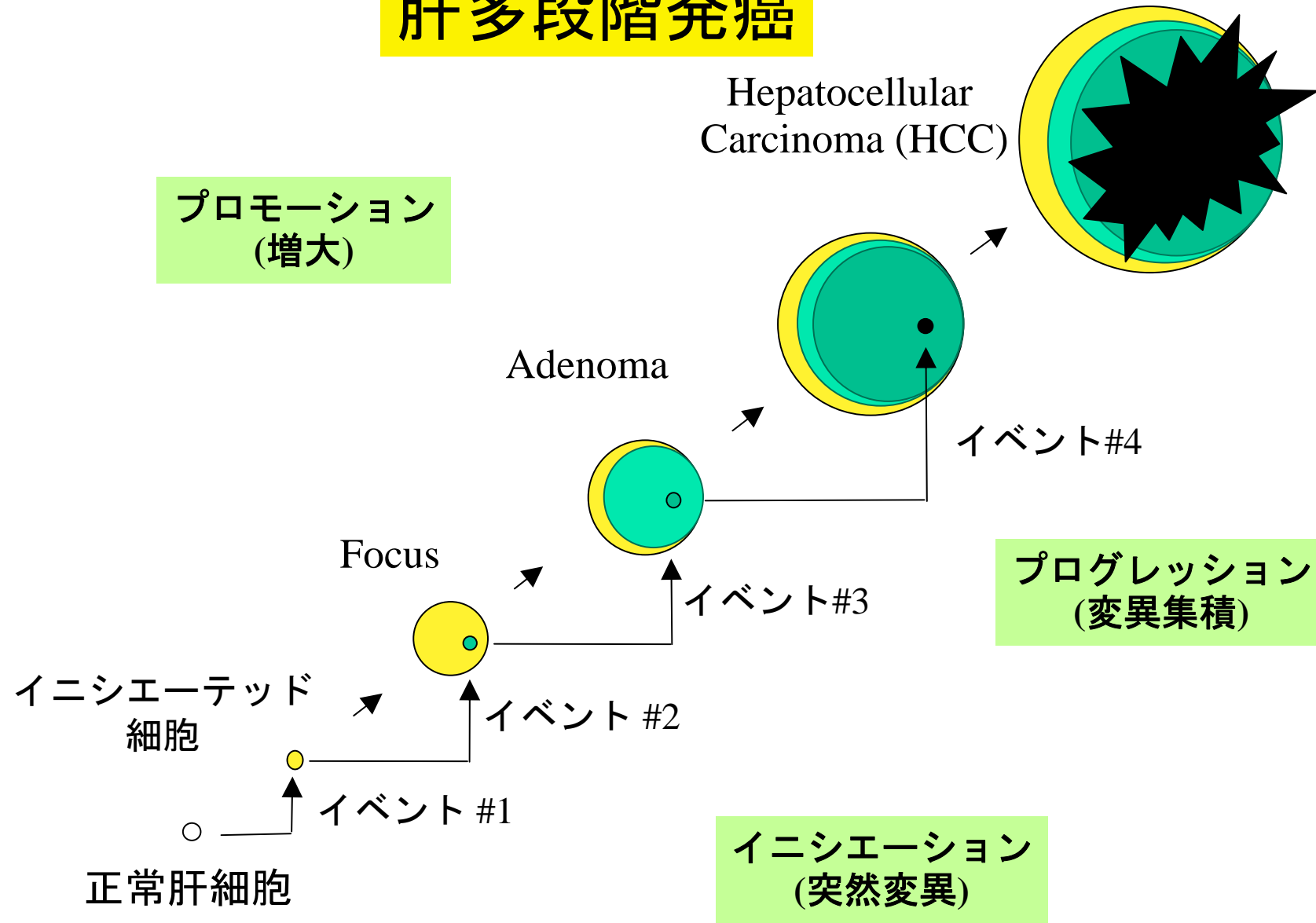
HCC in adenoma





## ②肝発癌モデル

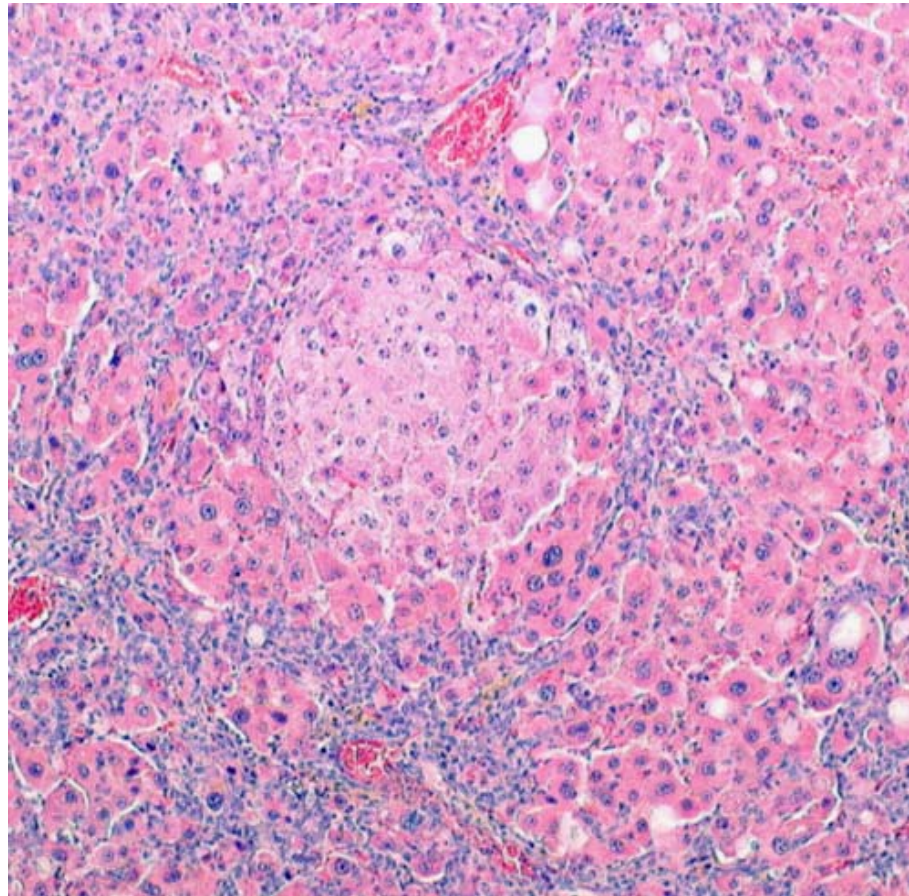
# 肝多段階発癌



## ②肝発癌モデル

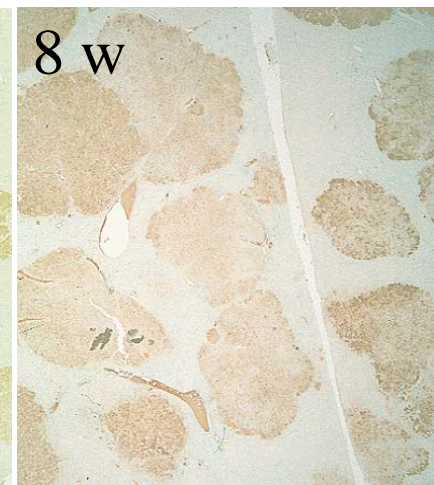
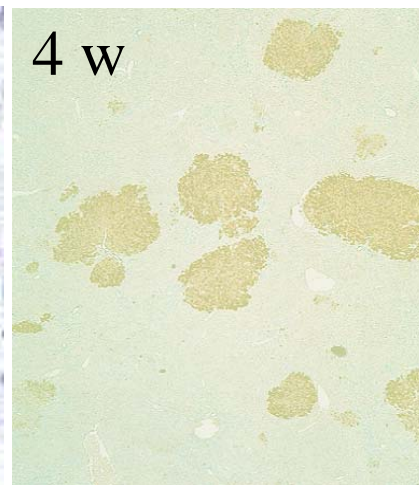
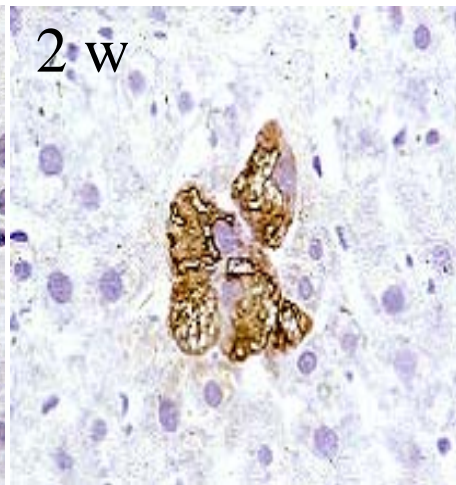
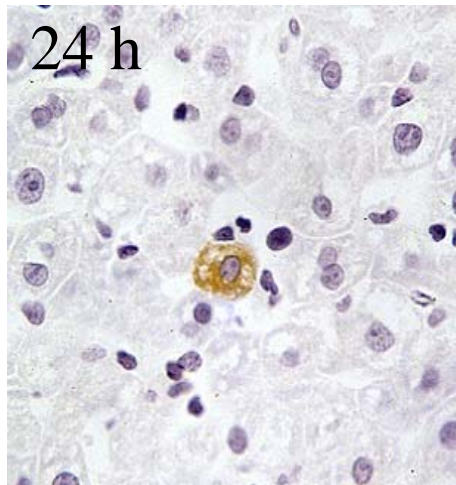
# 背景肝組織の障害

F344ラット／DEN + 2-AAF + PH



# 遺伝子発現の異常

GST-P (glutathione s-transferase, placental form)



## ②肝発癌モデル

# cDNA Array

## Under-expression

cell surface antigens	symporters & antiporters
gap junction membrane channel protein beta 1	gamma-aminobutyric acid (GABA-A) transporter 1
gap junction membrane channel protein beta 2	nucleotide metabolism
basic transcription factors, transcription activators or repressors	phenylalanine hydroxylase
nuclear DNA-binding protein	adenosine A2a receptor
stimulated by retinoic acid 14	bcl family proteins, oncogenes & tumor suppressors
hematopoietically expressed homeobox	B-cell leukemia/lymphoma 2
amino-terminal enhancer of split	other apoptosis-associated proteins
cAMP responsive element binding protein 1	T-cell death associated gene
early growth response 1	clusterin
split hand/foot deleted gene 1	growth factors, cytokines & chemokines
POU domain, class 2, associating factor 1	fibroblast growth factor 7
D site albumin promoter binding protein	fibroblast growth factor 14
cell cycle -regulating kinases, intracellular kinase networkmembers	insulin-like growth factor binding protein 4
cyclin A1	insulin-like growth factor 2
cyclin C	insulin-like growth factor 1
Cyclin-dependent kinases regulatory subunit 2 (CKS-2)	fibroblast growth factor 7
other cell cycle proteins, intracellular transducers	hormones
prothymosin alpha	relaxin
transducer of ErbB-2.1	intracellular transducers, effectors & modulators
extracellular transporters & carrier proteins	growth associated protein 43
lecithin cholesterol acyltransferase	coagulation factor II (thrombin) receptor-like 3
phospholipid transfer protein	frizzled homolog 3 (Drosophila)
transthyretin	frizzled homolog 7 (Drosophila)
neurofibromatosis 1	intracellular transducers, effectors & modulators
tumor susceptibility gene 101	Eph receptor B3
oncogenes & tumor suppressor genes	syndecan 1
SWI/SNF related, matrix associated, actin dependent regulator of chromatin	guanine nucleotide binding protein, alpha stimulating
Jun oncogene	serine proteases
insulin-like growth factor binding protein 2	plasminogen
Harvey rat sarcoma oncogene, subgroup R	serine protease inhibitor 1-2
heat shock protein, 86 kDa 1	other enzymes involved in protein turnover
heat shock 70kD protein 5 (glucose-regulated protein, 78kD)	basigin
genobiotic transporters, apoptosis-associated proteins	vitronectin
glutathione S-transferase, alpha 2 (Yc2)	intermediate filament proteins
GLUTATHIONE S-TRANSFERASE, MICROSOMAL (EC 2.5.1.18)	decorin
ligand-gated ion channels	functionally unknown
cholinergic receptor, nicotinic, delta polypeptide	WSB-2 protein
	four and a half LIM domains 1

## Over- expression

basic transcription factors, transcription activators or repressors
eyes absent 2 homolog (Drosophila)
spinal cord axial homeobox gene 1
sine oculis-related homeobox 5 homolog (Drosophila)
forkhead box D4
Kruppel-like factor 3 (basic)
engrailed 2
forkhead box F1a
cell cycle -regulating kinases, intracellular kinase networkmembers
cyclin-dependent kinase inhibitor 1B (P27)
other cell cycle proteins, intracellular transducers
cadherin 4
integrin alpha 3
extracellular transporters & carrier proteins
apolipoprotein E
oncogenes & tumor suppressor genes
v-abl Abelson murine leukemia oncogene 1
B-Raf proto-oncogene; serine/threonine-protein kinase (EC 2.7.1.-)
expressed in non-metastatic cells 2, protein (NM23B)
genobiotic transporters, apoptosis-associated proteins
glutathione S-transferase, mu 2
glutathione S-transferase, pi 2
ligand-gated ion channels
potassium channel, subfamily K, member 2
ribosomal proteins
laminin receptor 1 (67kD, ribosomal protein SA)
other apoptosis-associated proteins
clusterin
Dynein light chain 1, cytoplasmic
defender against cell death 1
baculoviral IAP repeat-containing 4
avian erythroblastosis oncogene B 2
vesicle-associated membrane protein 1
galanin
prepronociceptin
growth factors, cytokines & chemokines
bone morphogenetic protein 8a
insulin-like growth factor binding protein 6
ephrin B1
insulin-like growth factor binding protein 1
intracellular transducers, effectors & modulators
Notch gene homolog 1, (Drosophila)
suppressor of clear, C. elegans, homolog of
serine proteases
plasminogen activator, urokinase
protease inhibitors

## 遺伝子発現異常の特徴

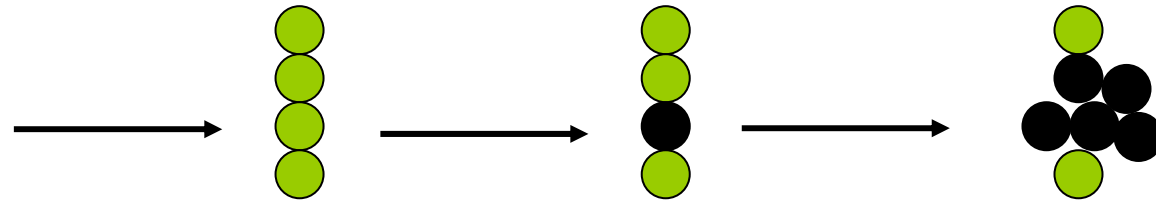
- 1) 比較的決まった遺伝子群  
増殖因子、薬物代謝酵素、エネルギー代謝、  
ストレス耐性、増殖サイクルなど
- 2) 個々の病変で比較的共通
- 3) 動物の種を超えた共通性
- 4) 初期変化から肝癌まで比較的共通

**Neodifferentiation!**

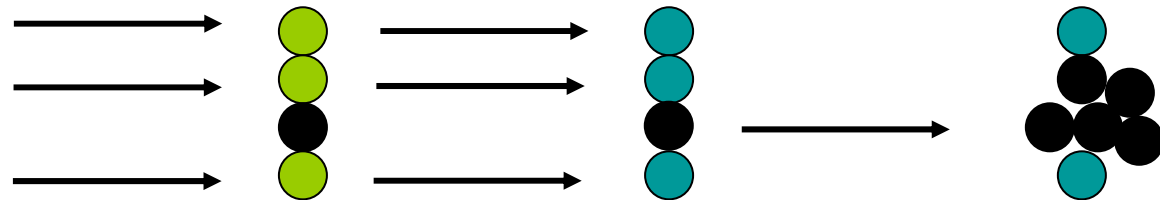
## ②肝発癌モデル

# 肝発癌の要因

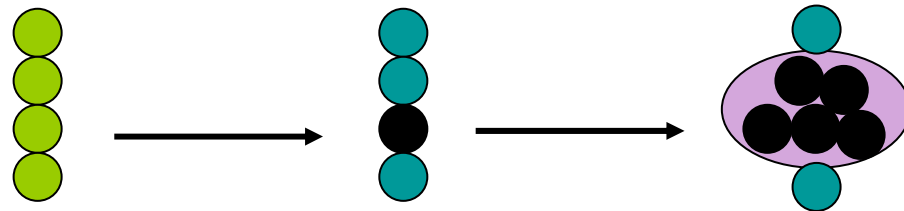
Transformation 高増殖、生存能



Selection 選択



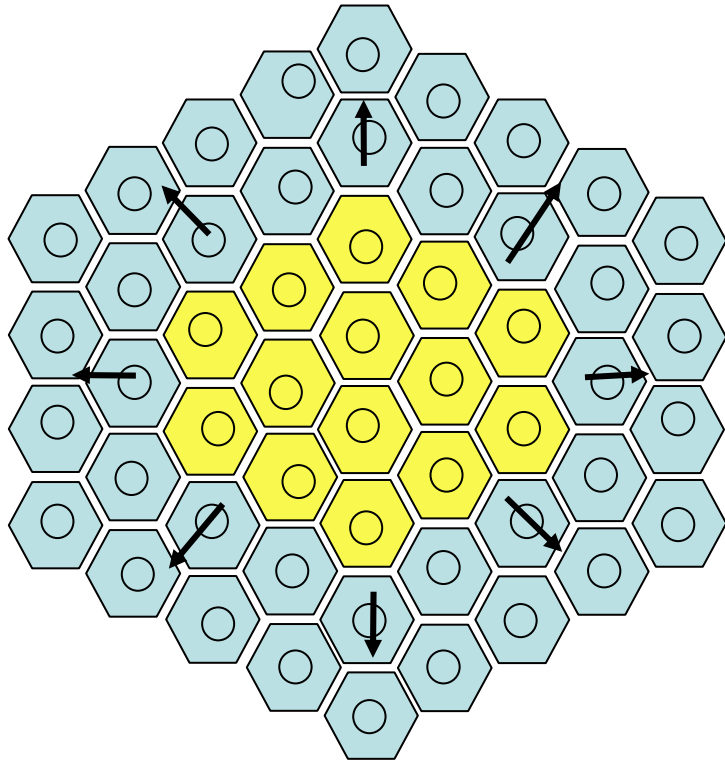
Isolation 微小環境



### ③肝発癌の要因

#### 1) Transformation

## Transformation



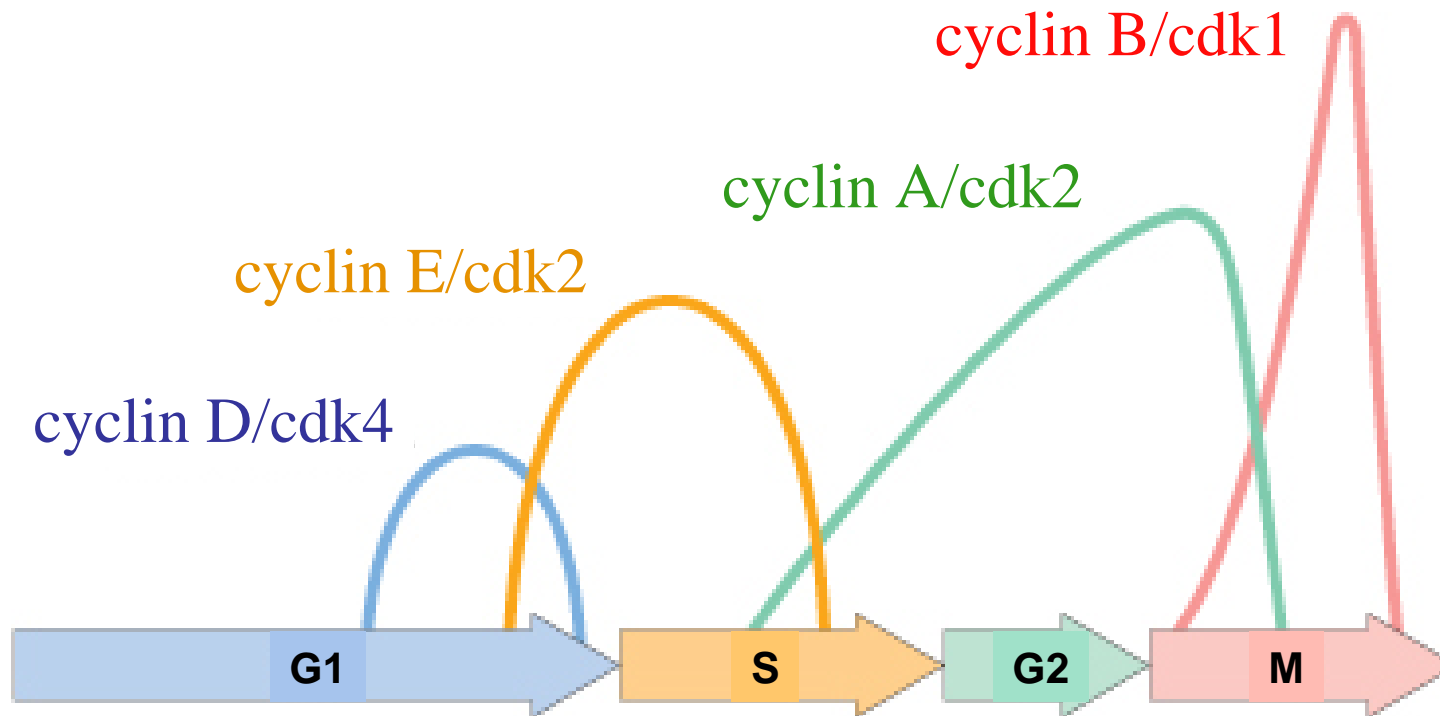
増殖、生存、抗アポトーシスなど

### 肝発癌関連遺伝子

- Oncogene activation  
(H-ras, c-Raf)
- Tumor suppressor inactivation  
(p53, Rb, p27, p21, p16)
- Wnt pathway activation  
( $\beta$ -catenin, E-cadherin)
- Cyclin activation  
(**cyclin D**, E, A)
- Growth factor activation  
(TGF- $\alpha$ , Igf-2)
- Transcription factors  
(HIF-1, FoxM, C/EBP $\alpha$ )

③肝発癌の要因  
1) Transformation

# 細胞周期とサイクリン

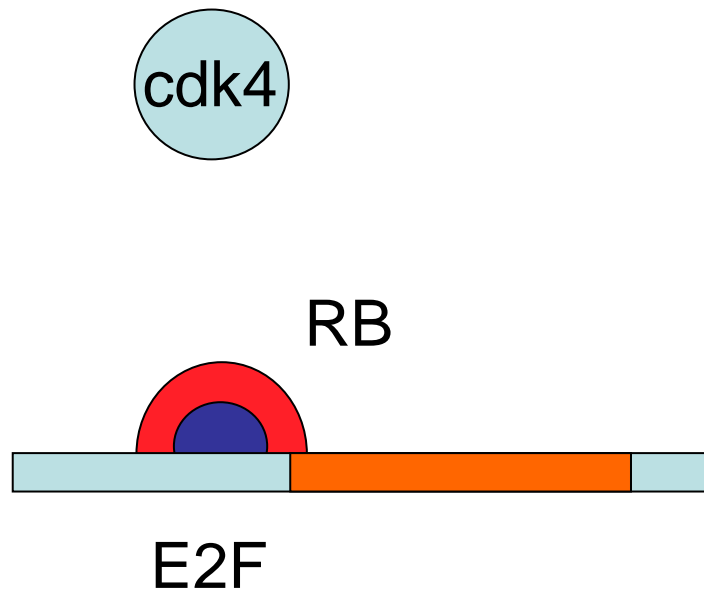




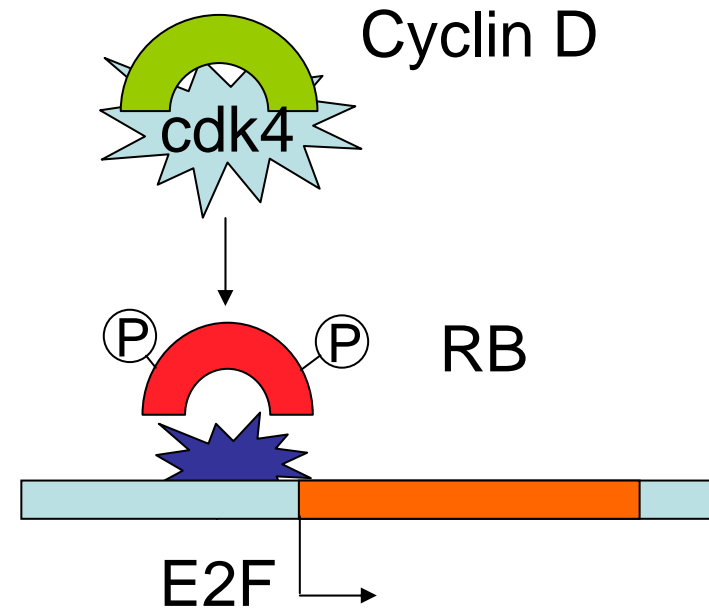
③肝発癌の要因  
1) Transformation

# Rb 経路

静止細胞



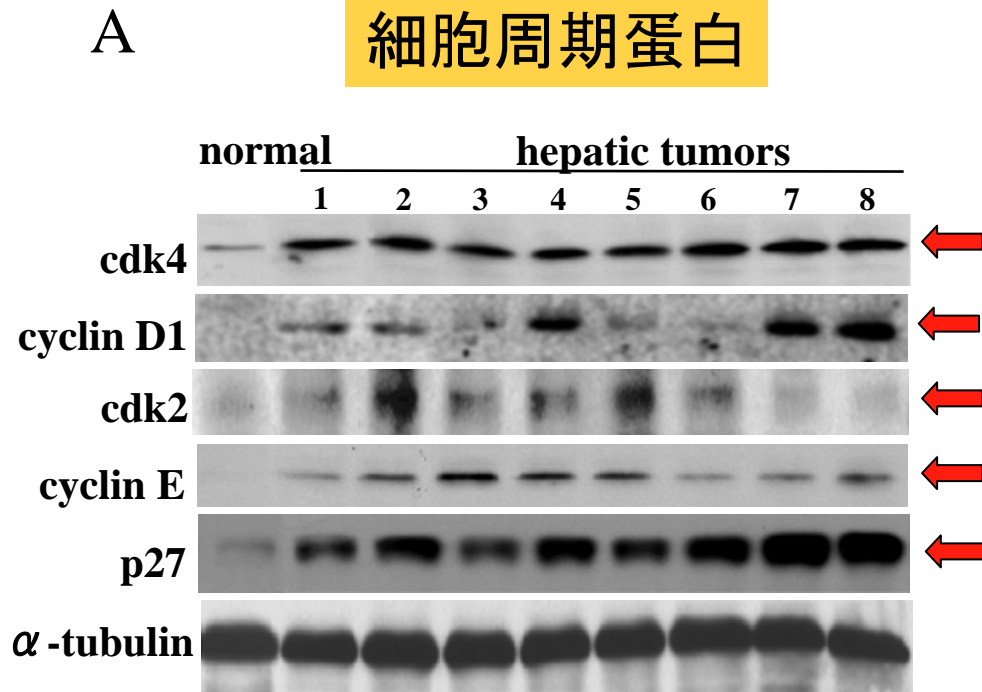
増殖細胞



cyclin E, cyclin A, DNA複製関連酵素など

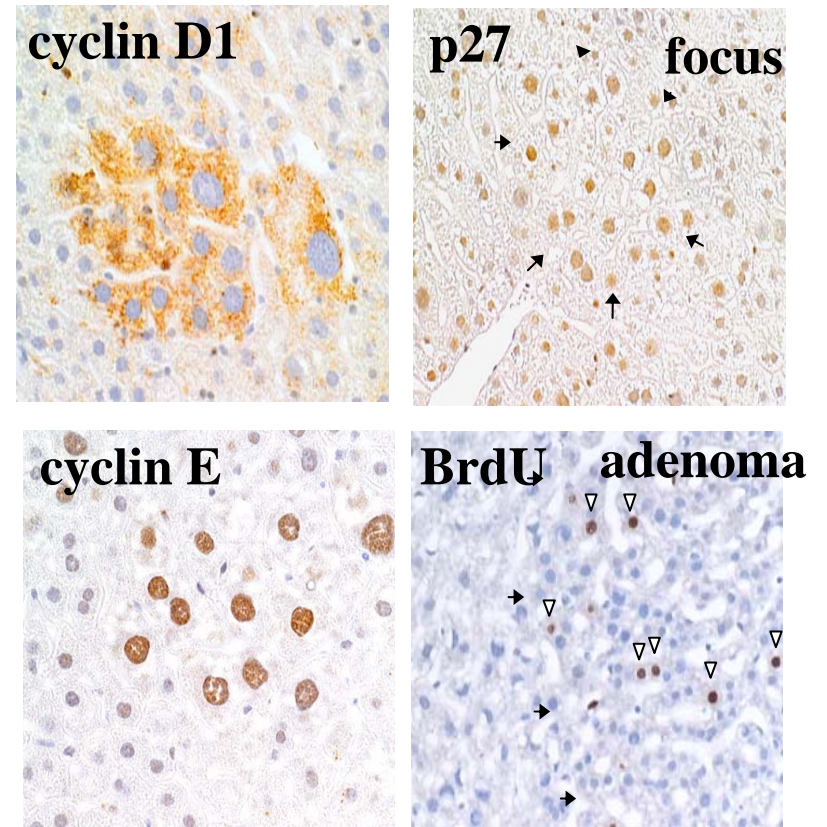
③肝発癌の要因  
1) Transformation

# Cyclin D1の発現

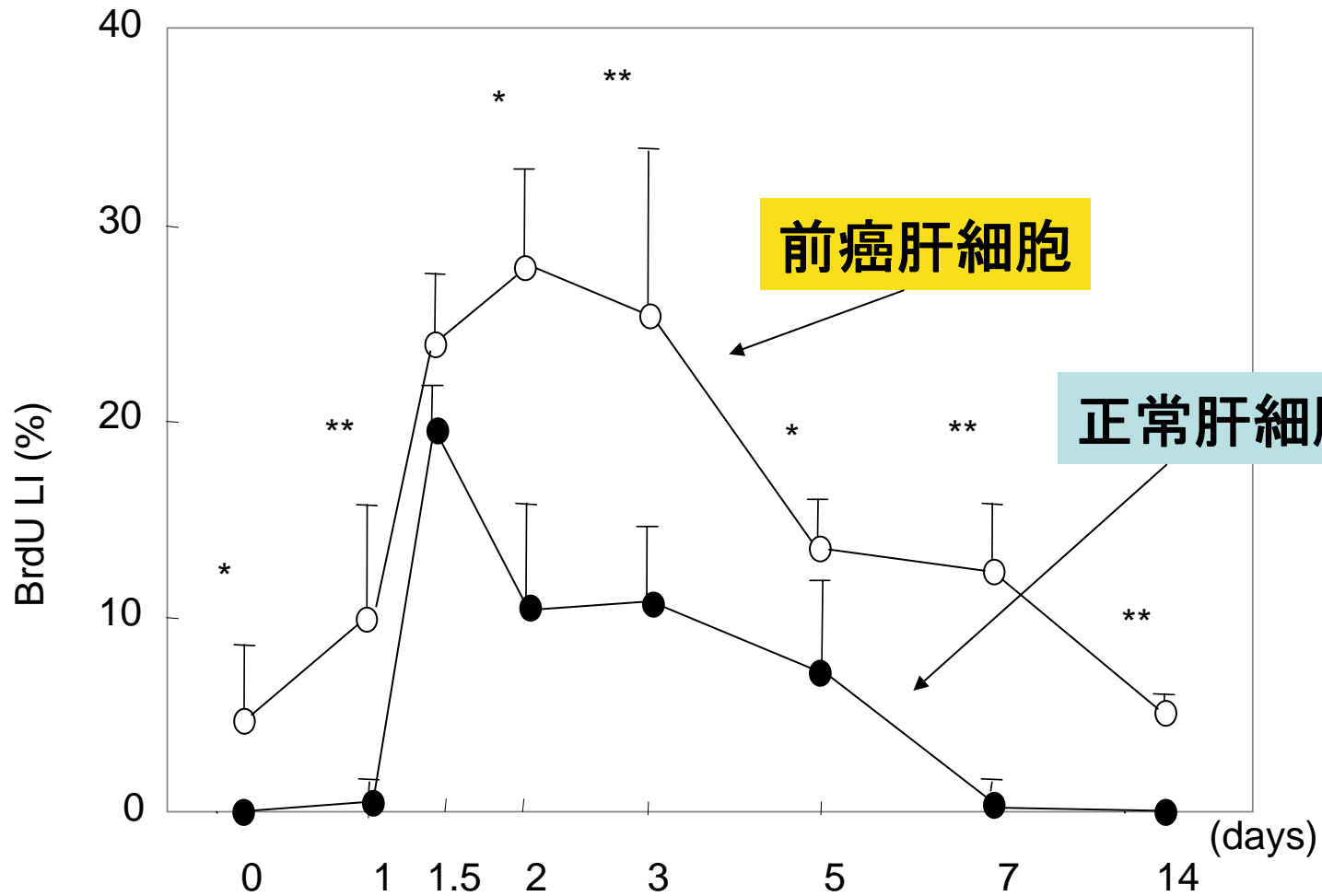


**B**

**免疫染色**



# 部分肝切除後の肝細胞の増殖

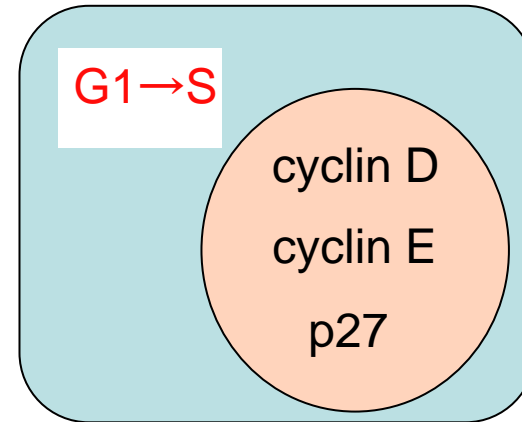
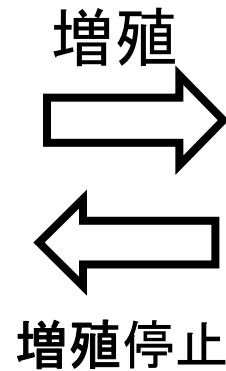
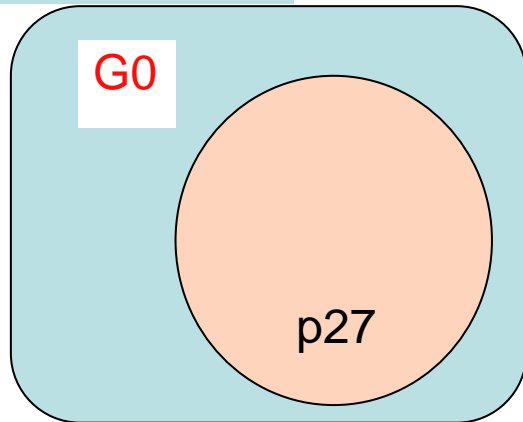


### ③多段階発癌の要因

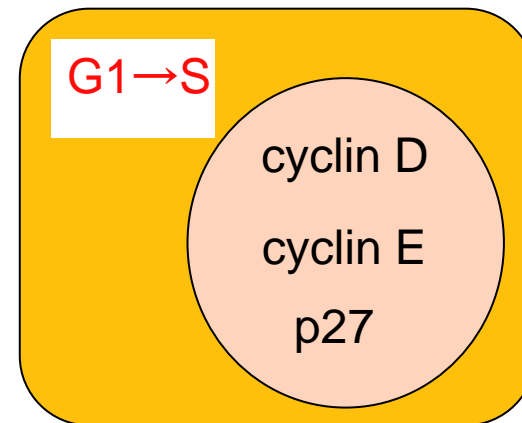
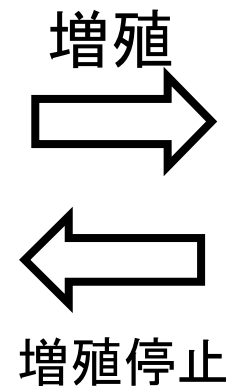
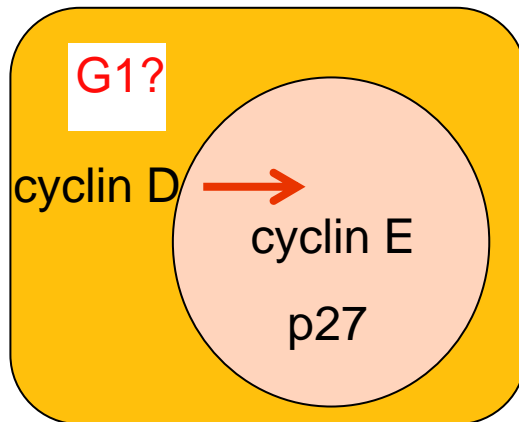
#### 1) Transformation

## 部分肝切除後のcyclin D1の変化

### 正常肝細胞

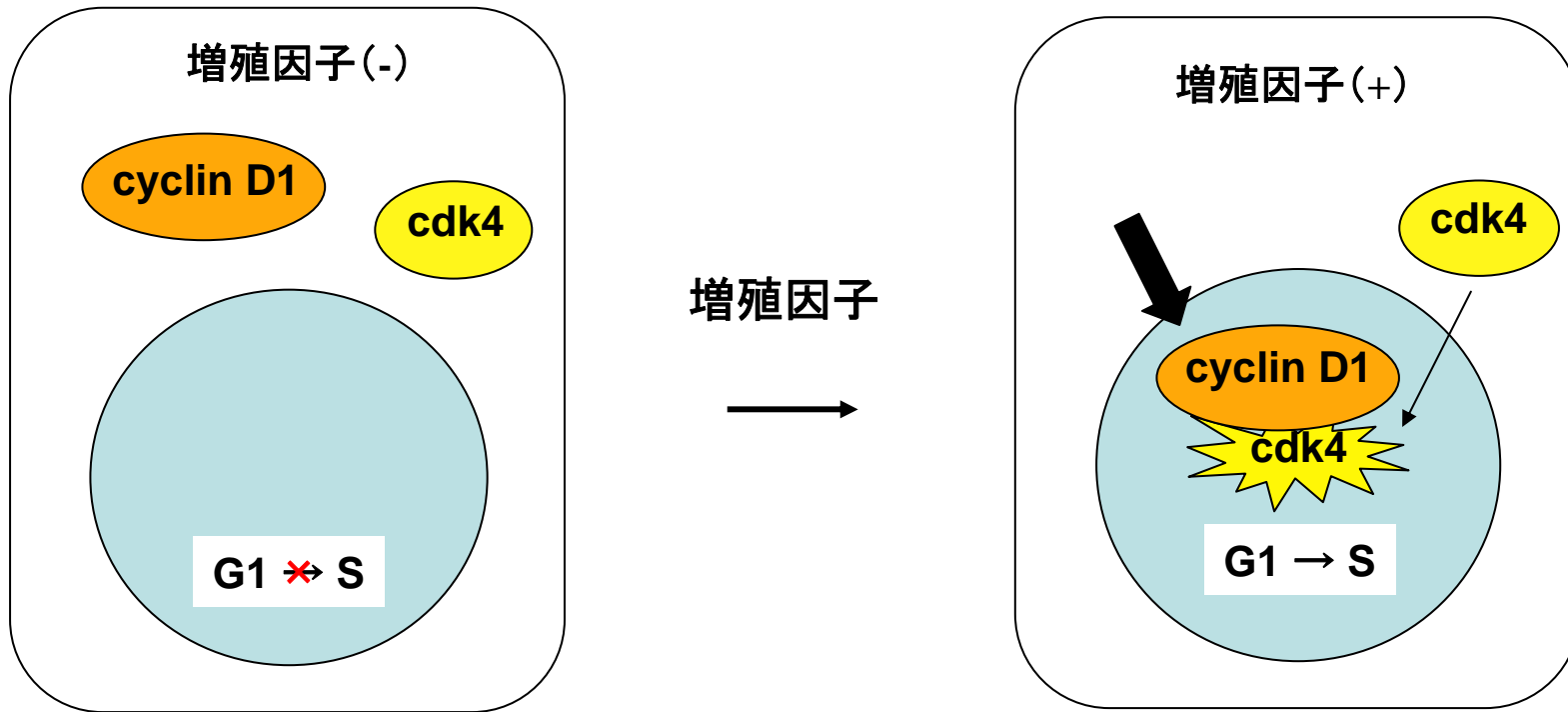


### 腫瘍細胞



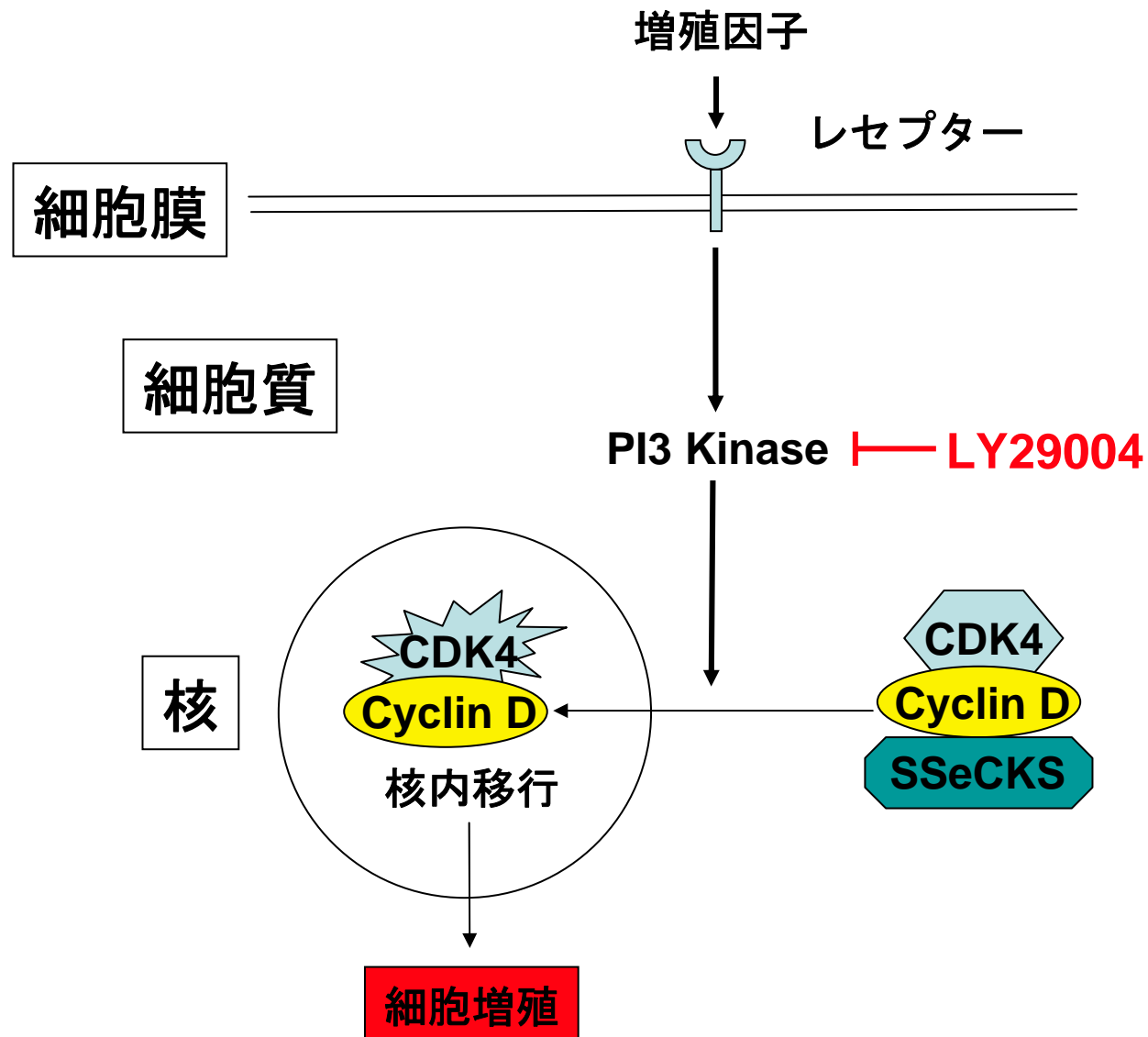
③肝発癌の要因  
1) Transformation

# 増殖因子に対する反応



③肝発癌の要因  
1) Transformation

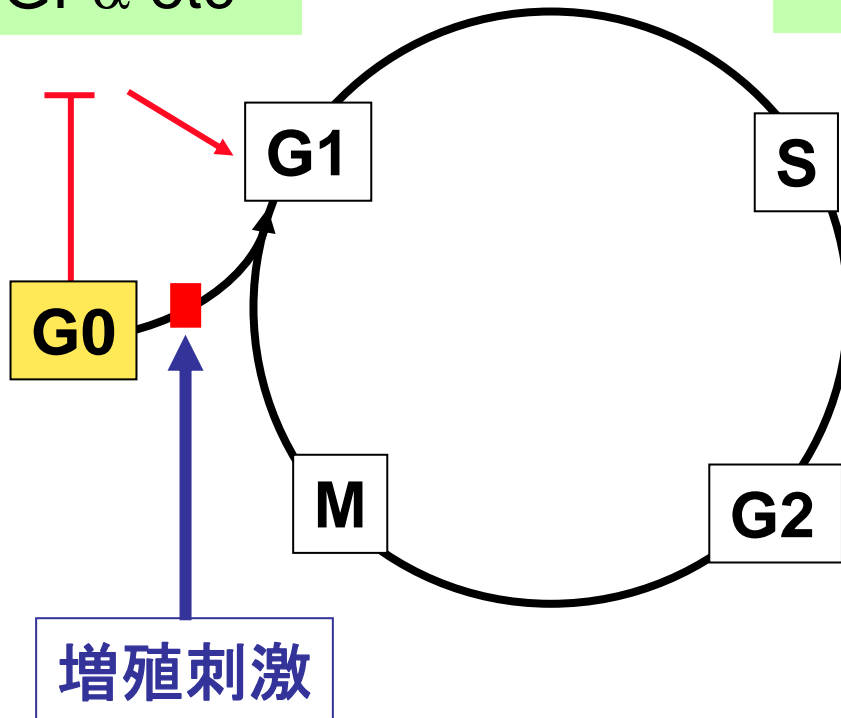
# Cyclin D とシグナル伝達経路



③肝発癌の要因  
1) Transformation

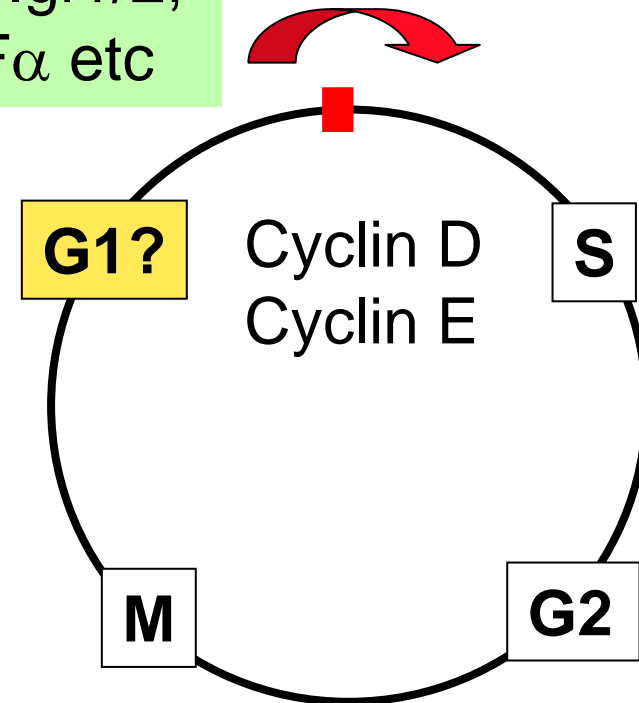
正常肝細胞

肝増殖因子  
HGF, Igf1/2,  
TGF $\alpha$  etc



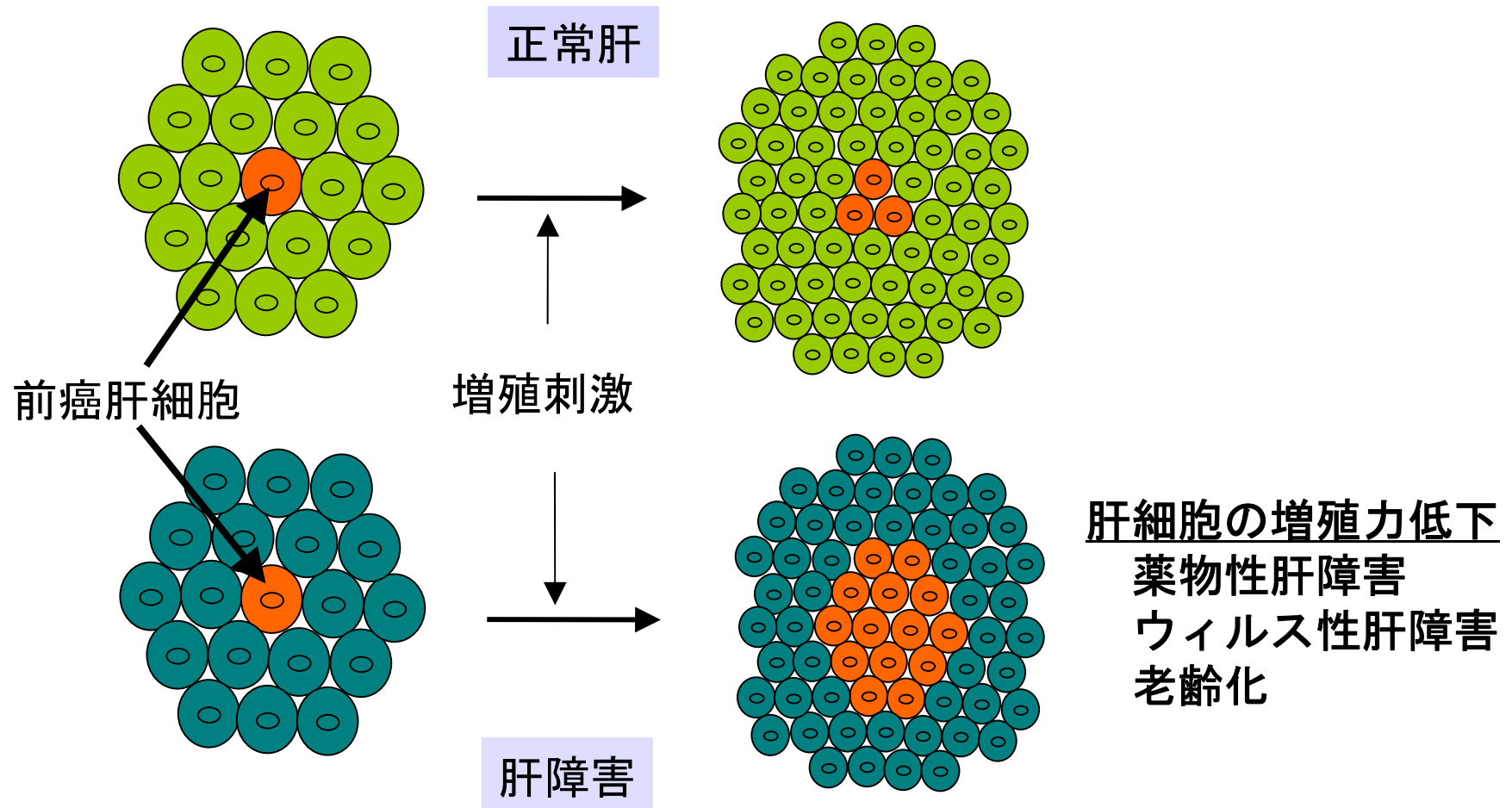
前癌肝細胞

肝増殖因子  
HGF, Igf1/2,  
TGF $\alpha$  etc



③肝発癌の要因  
2) Selection

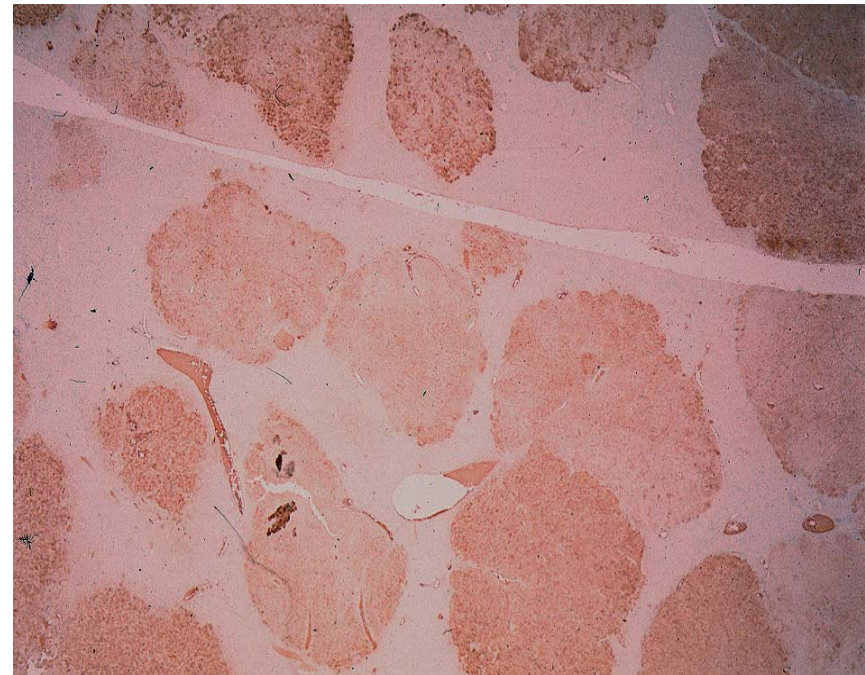
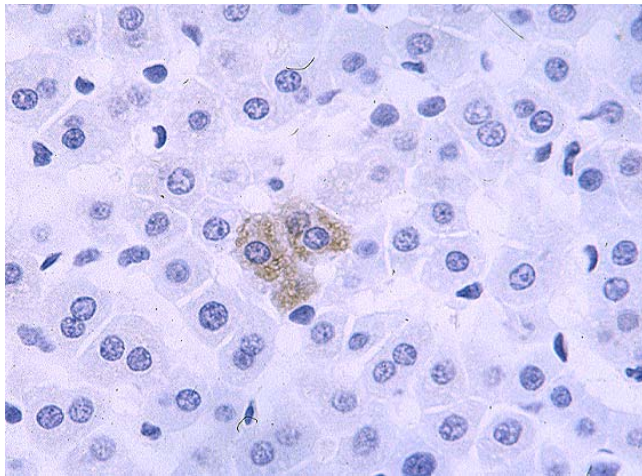
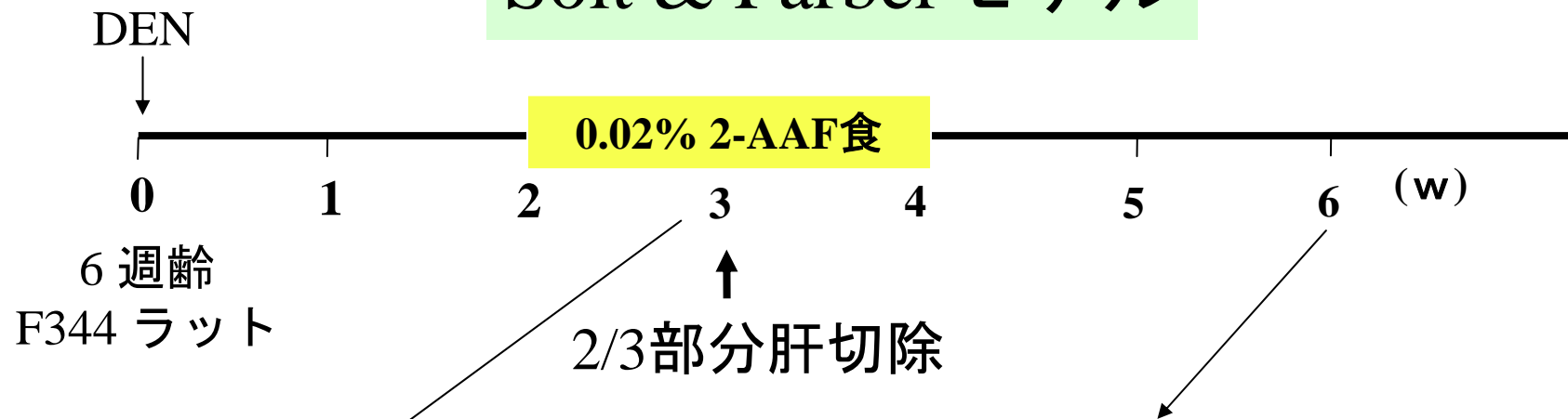
# 前癌肝細胞の選択 -Selection





③肝発癌の要因  
2) Selection

Solt & Farberモデル

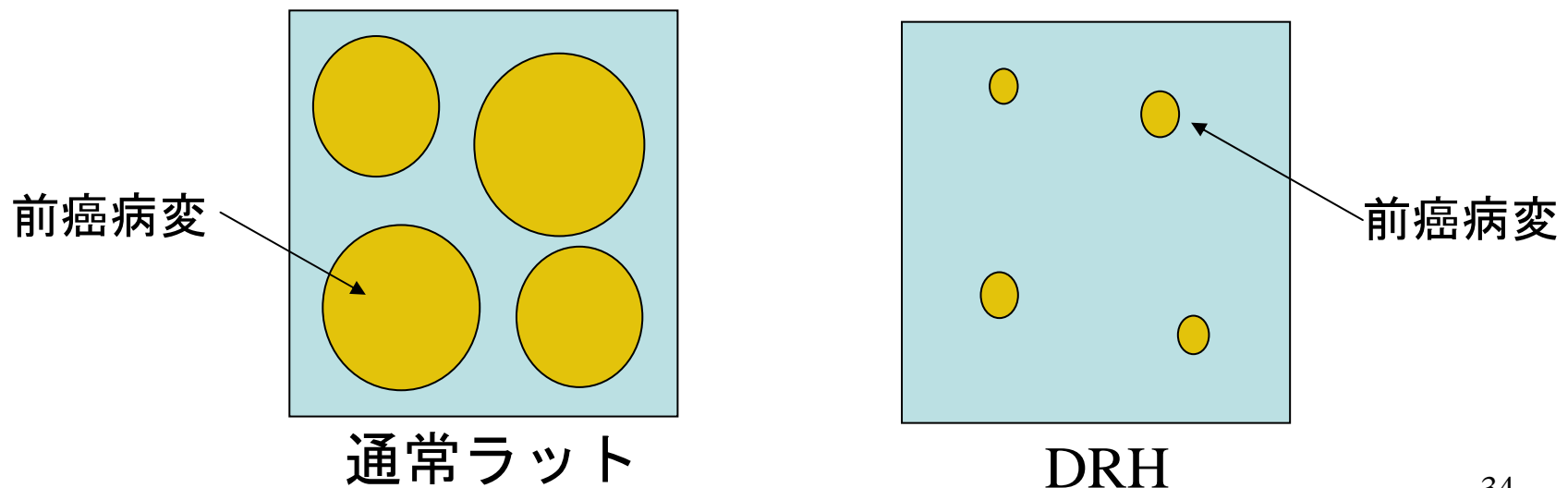


### ③肝発癌の要因

#### 2) Selection

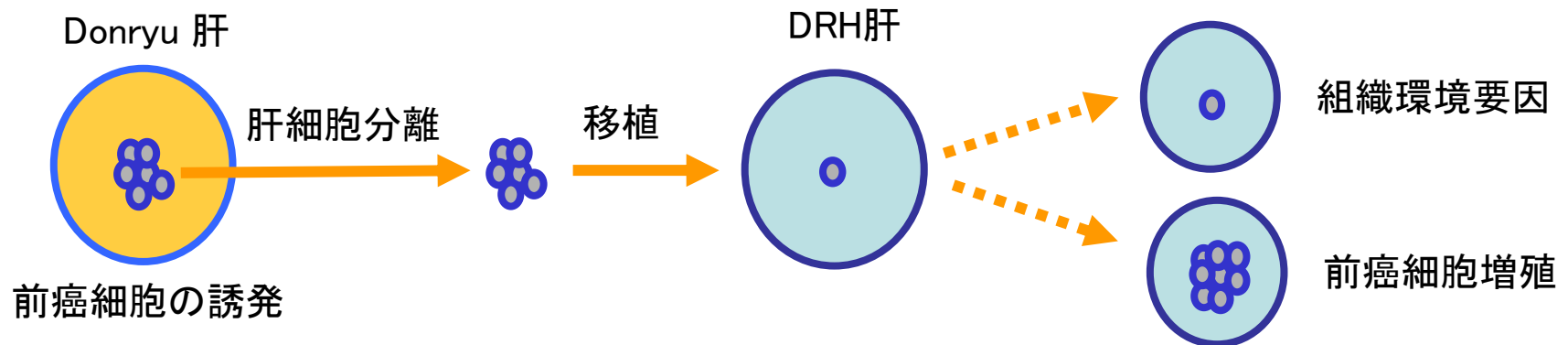
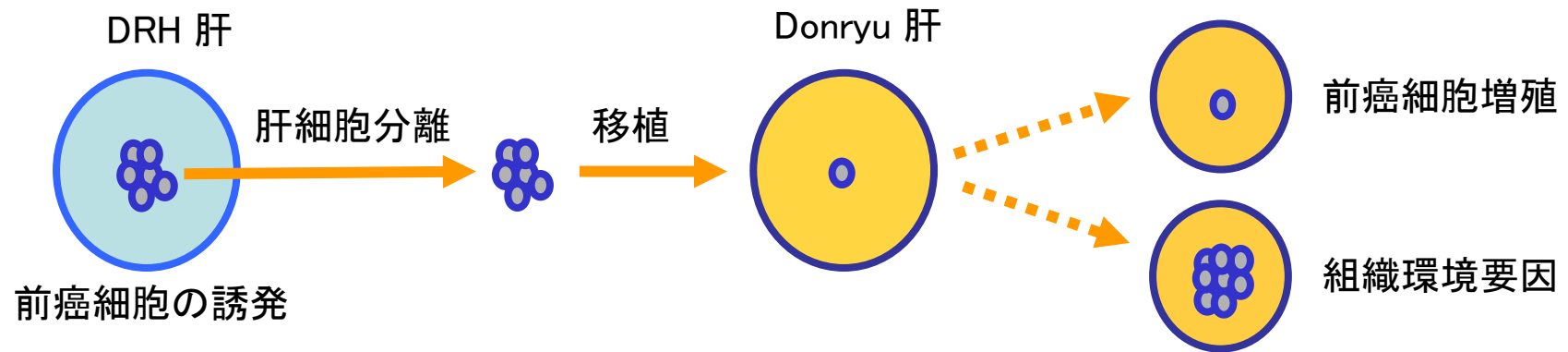
## DRHラット

- 1) Donryuラットに3'-Me-DABを投与し、その中から発癌耐性のも  
のを選択して交配して作製
- 2) 様々の肝発癌法に対して耐性
- 3) 発癌耐性は優勢形質で、ラット第1染色体、第4染色体にリンク
- 4) DRH肝では前癌病変が増大しない



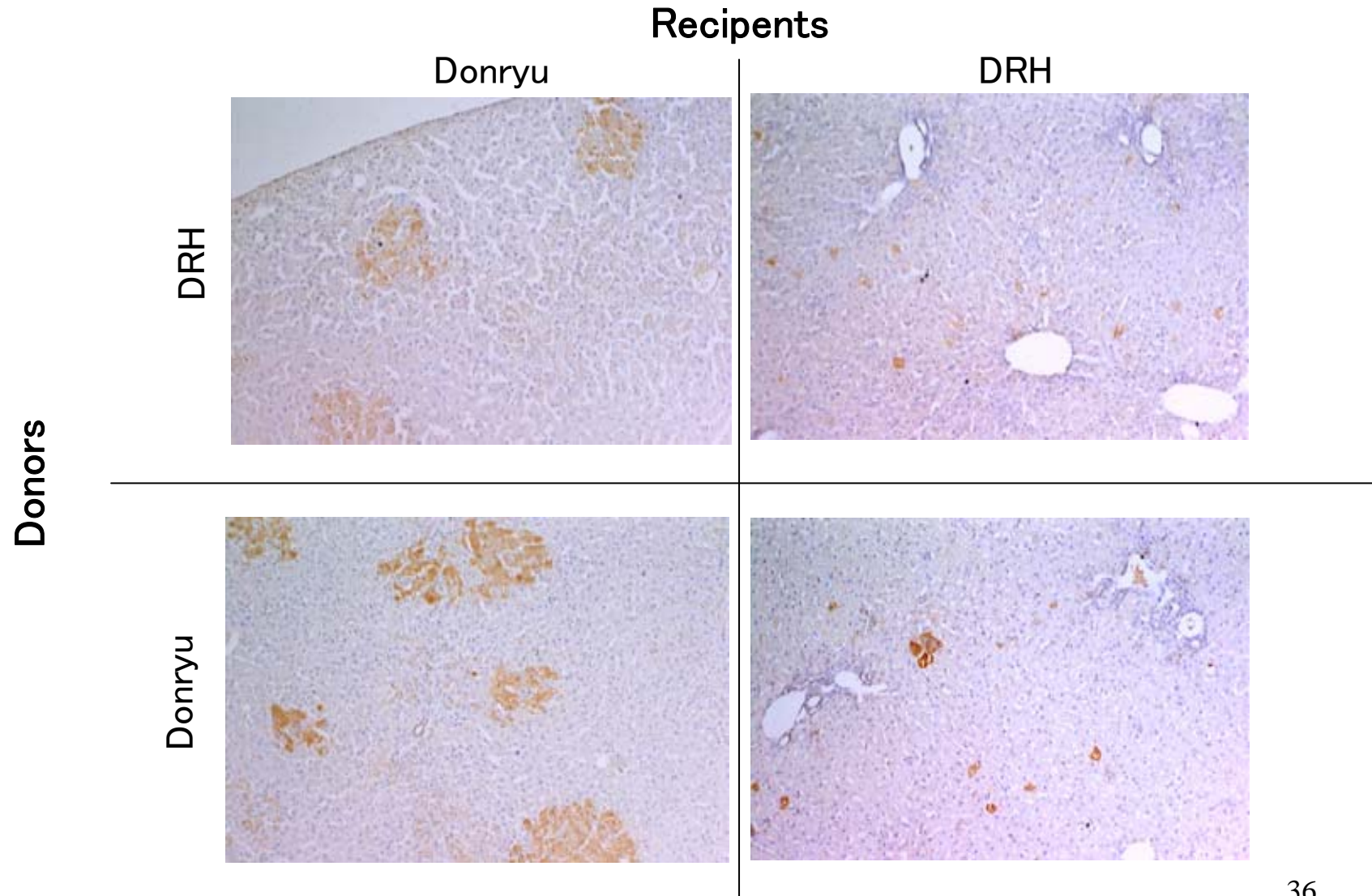
③肝発癌の要因  
2) Selection

細胞自律性 or 組織環境要因



③肝発癌の要因  
2) Selection

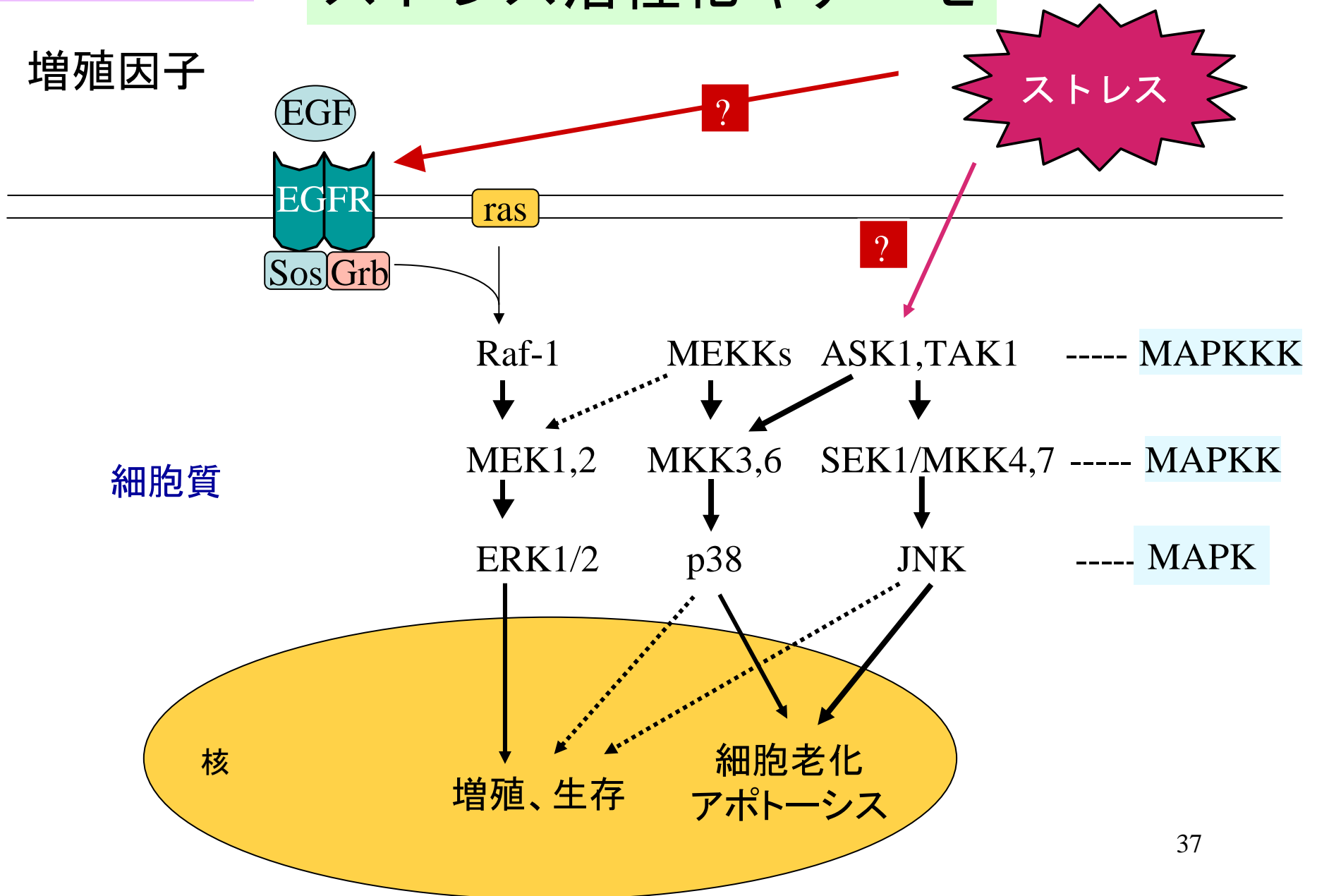
移植後の前癌肝細胞コロニー



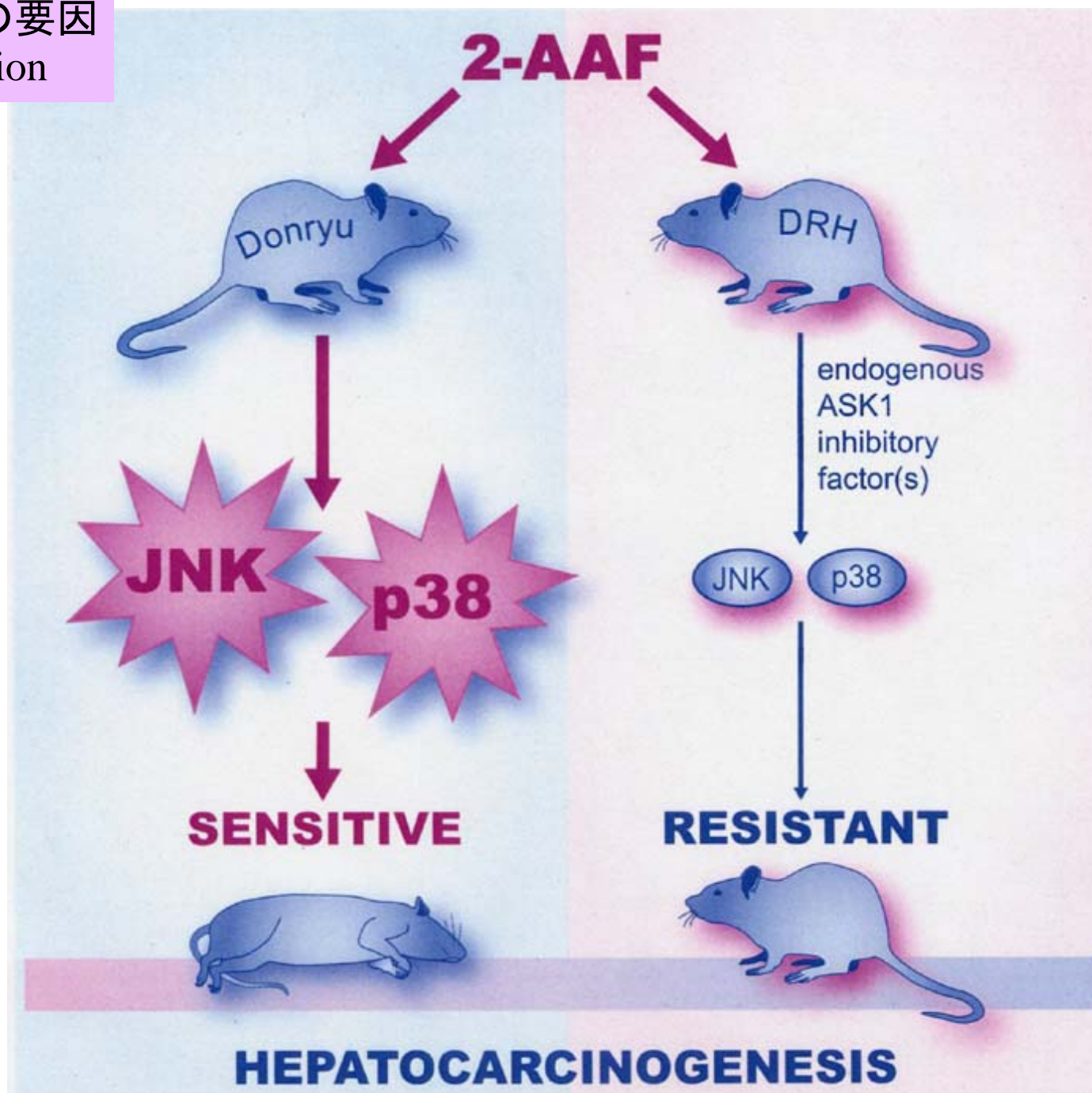
③肝発癌の要因  
2) Selection

# ストレス活性化キナーゼ

増殖因子

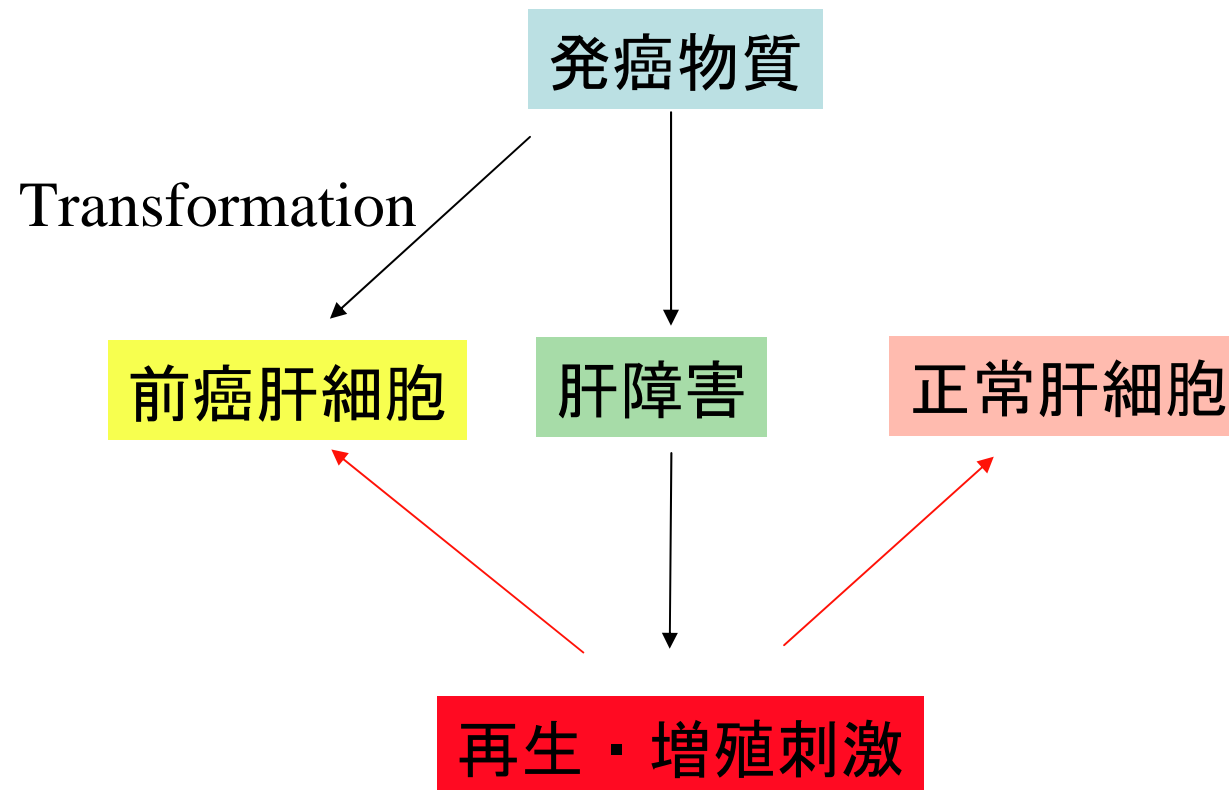


③肝発癌の要因  
2) Selection



③肝発癌の要因  
2) Selection

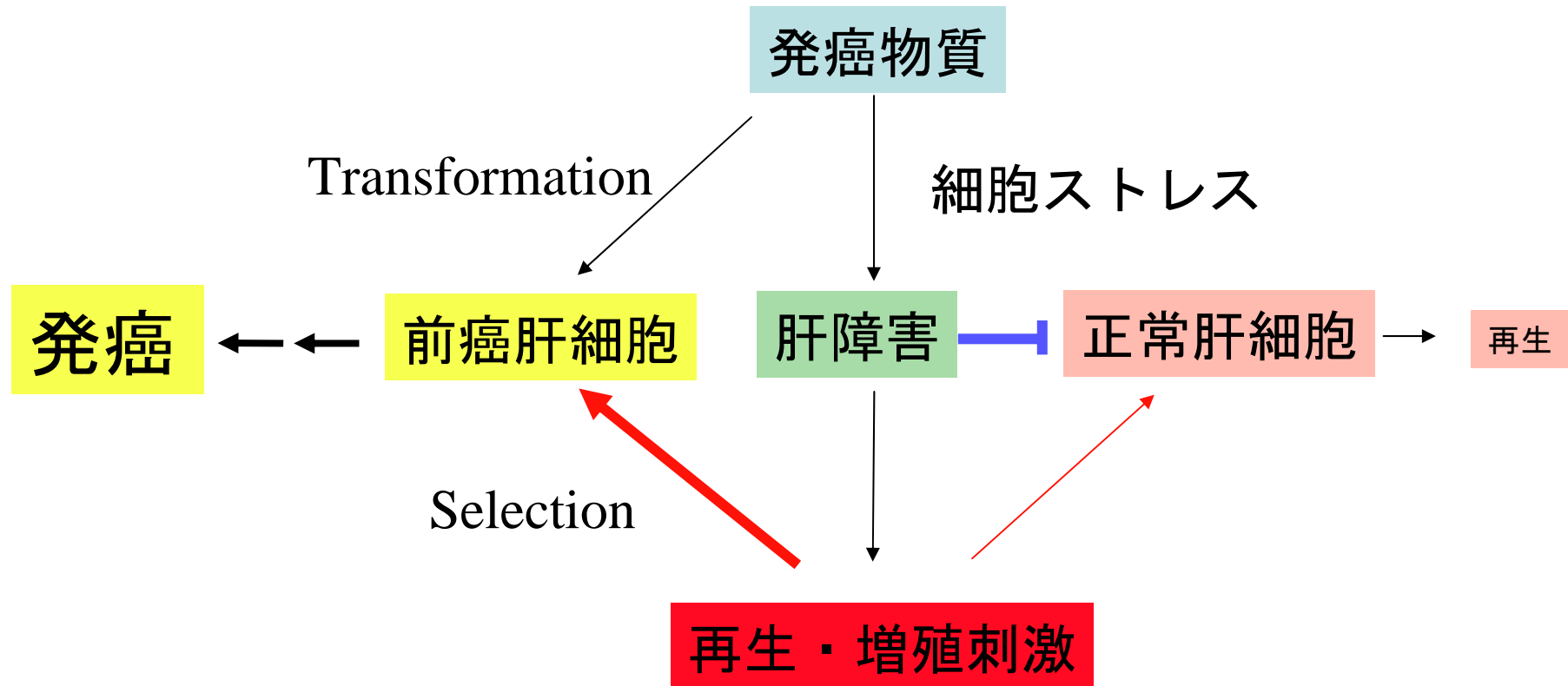
# Selection



③肝発癌の要因  
2) Selection

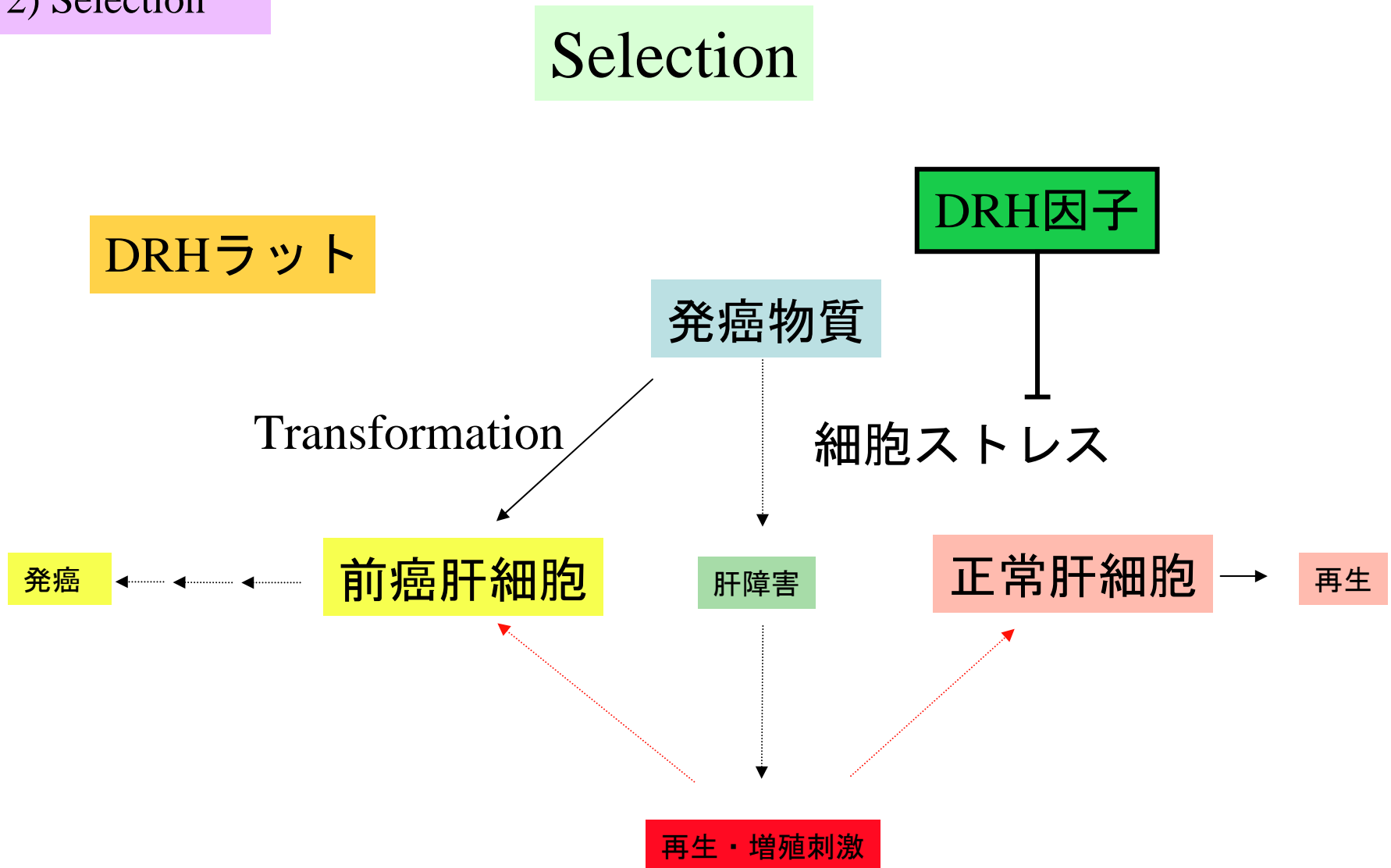
Selection

正常ラット



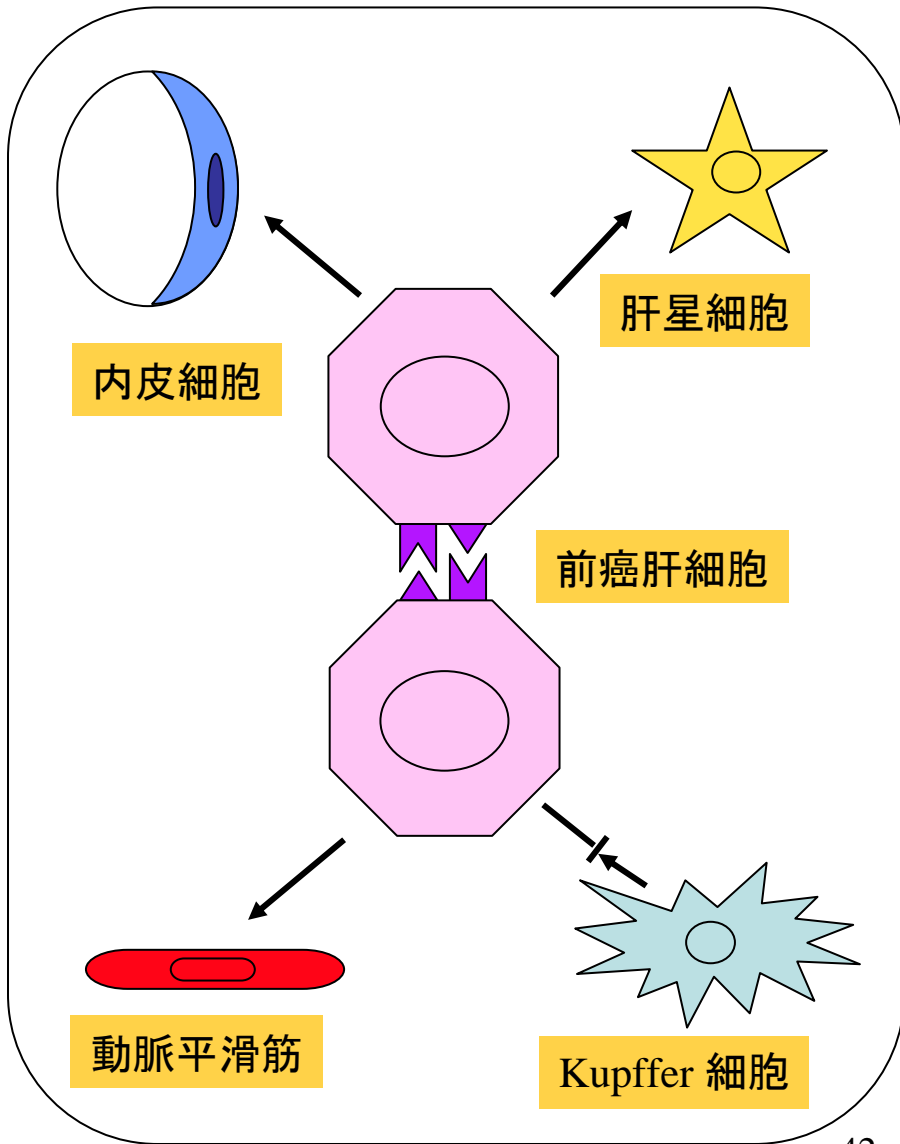
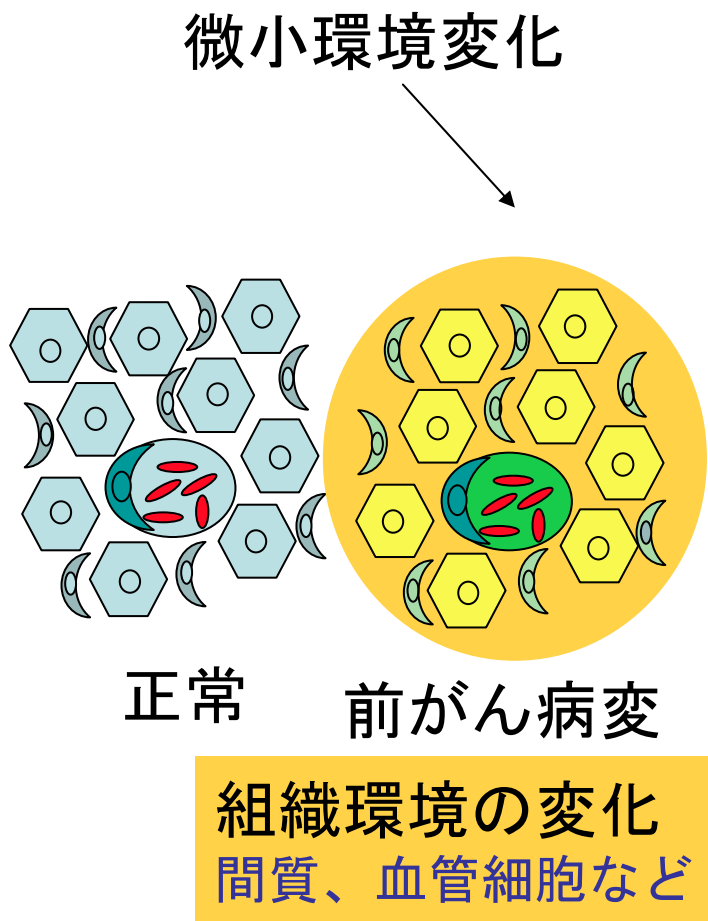


③肝発癌の要因  
2) Selection



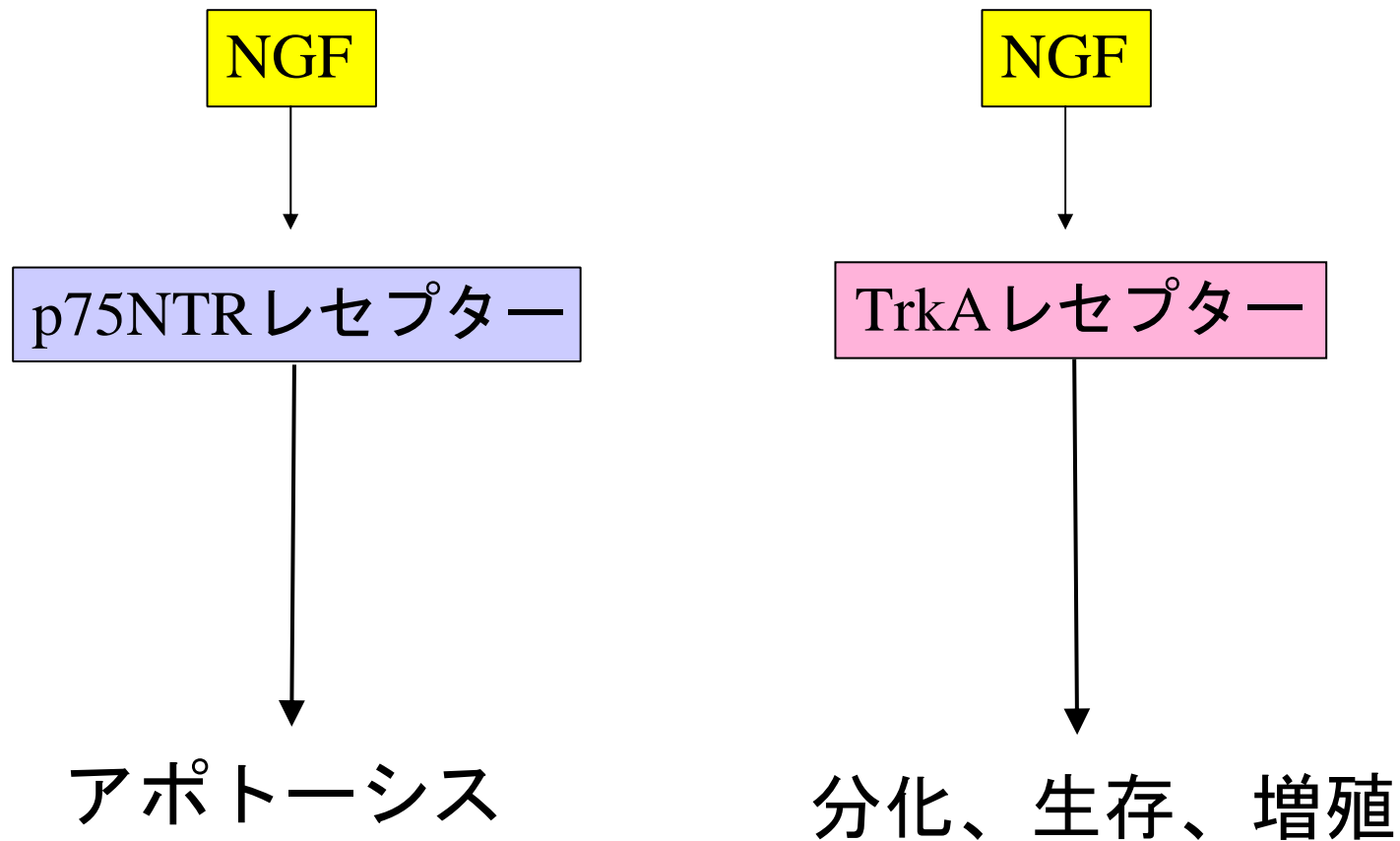
③肝発癌の要因  
3) Isolation

Isolation



③肝発癌の要因  
3) Isolation

神経成長因子  
Nerve Growth Factor (NGF)

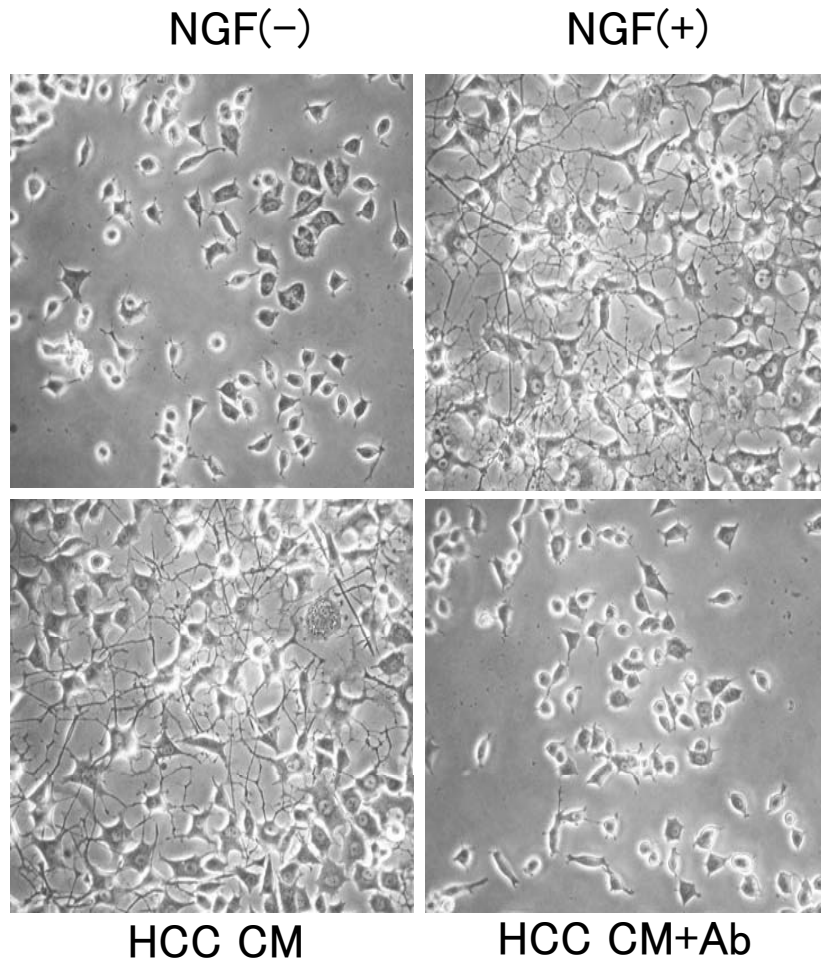


### ③肝発癌の要因

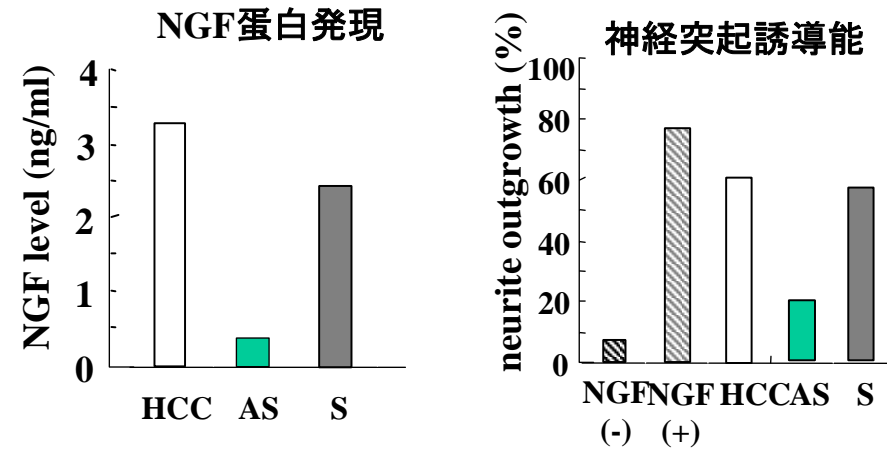
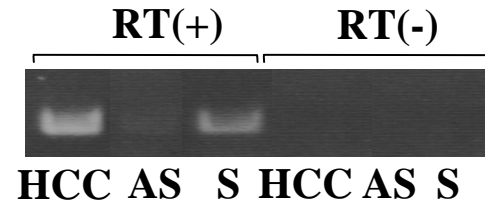
#### 3) Isolation

## PC12 細胞神経突起の誘導

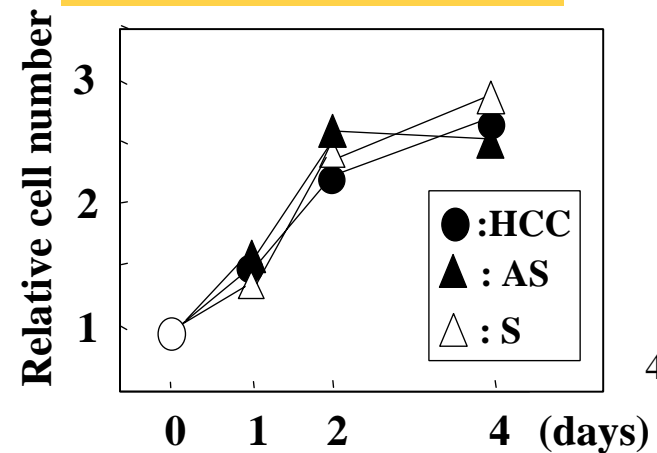
### A 神経突起誘導



### B アンチセンス導入



### C AS-HCC細胞の増殖率

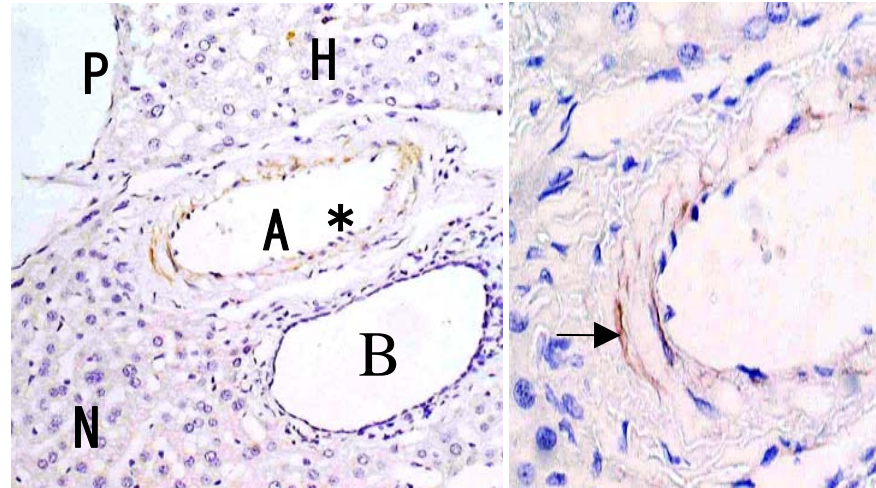


③肝発癌の要因  
3) Isolation

TrkA の発現と肝神経の変化

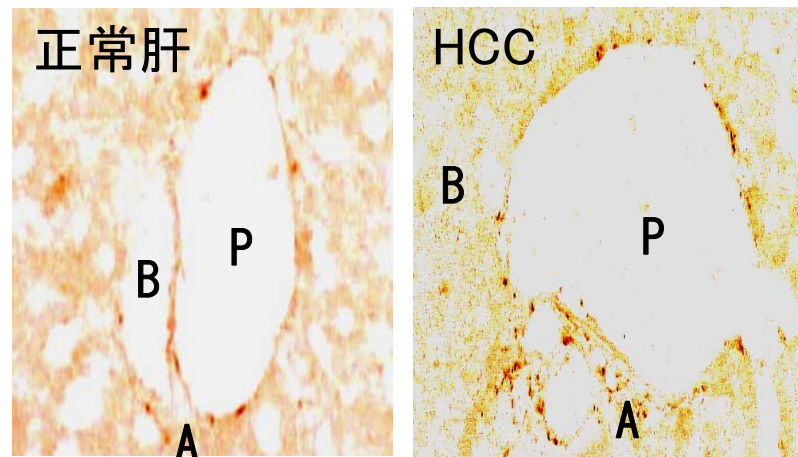
A

TrkA 免疫染色



B

神経線維 (Neuropeptide Y免疫染色)

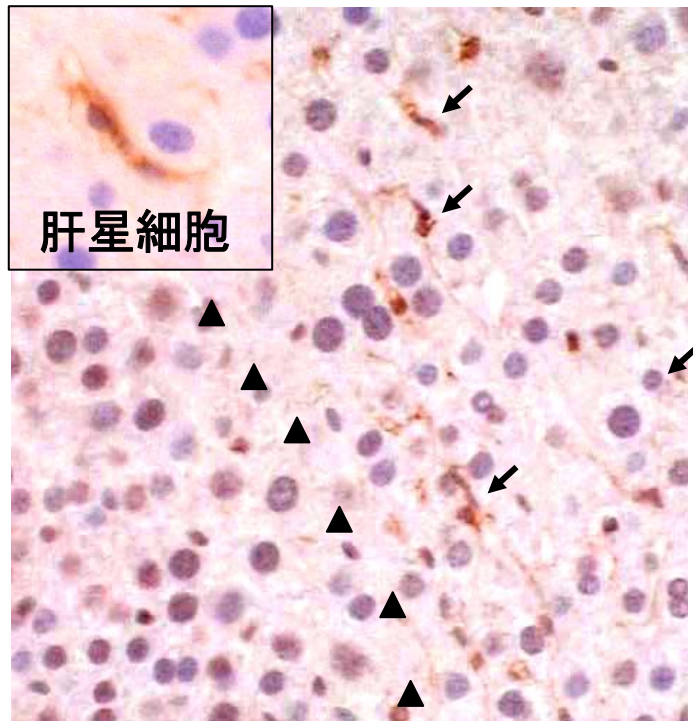


③肝発癌の要因  
3) Isolation

p75<sup>NTR</sup>発現と肝星細胞

A

p75<sup>NTR</sup>免疫染色

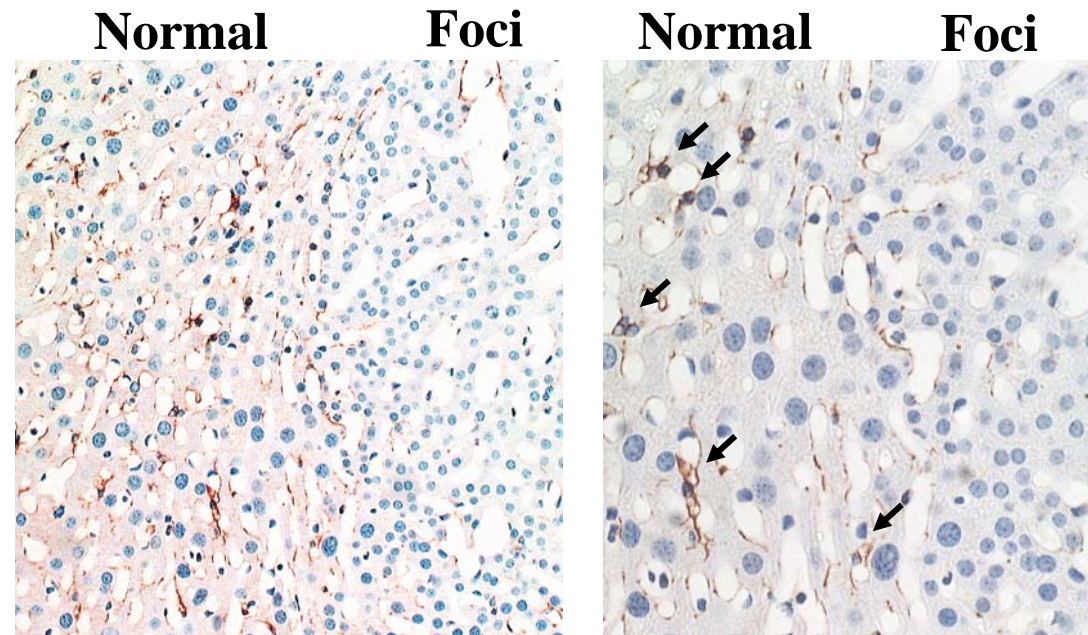


Adenoma

Normal

B

Desmin免疫染色



Normal

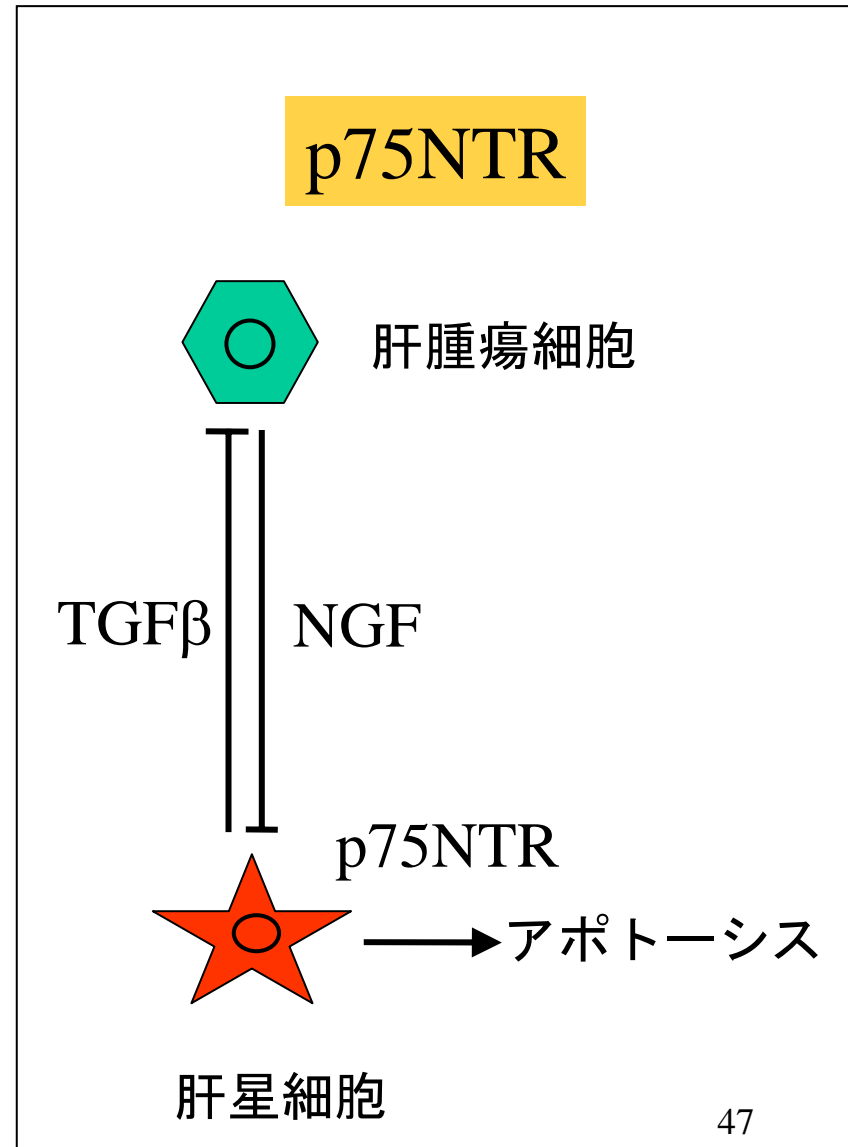
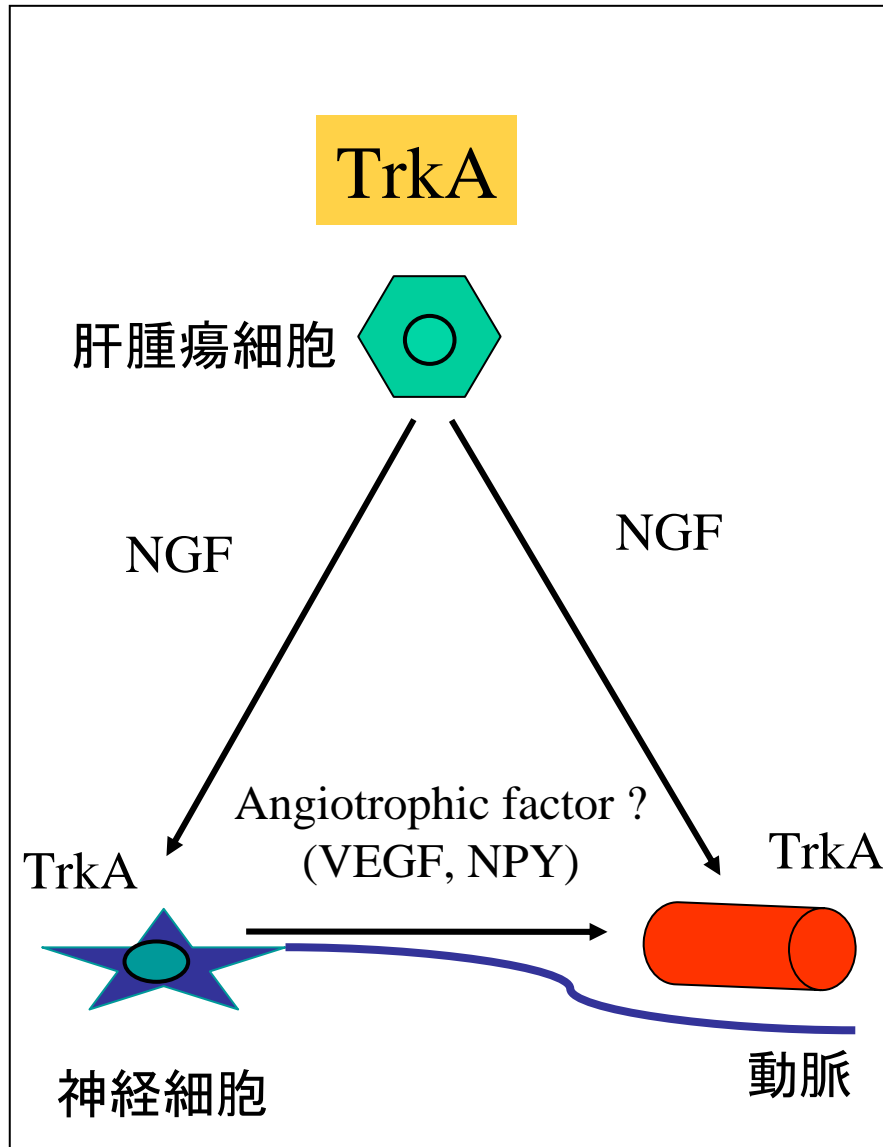
Foci

Normal

Foci

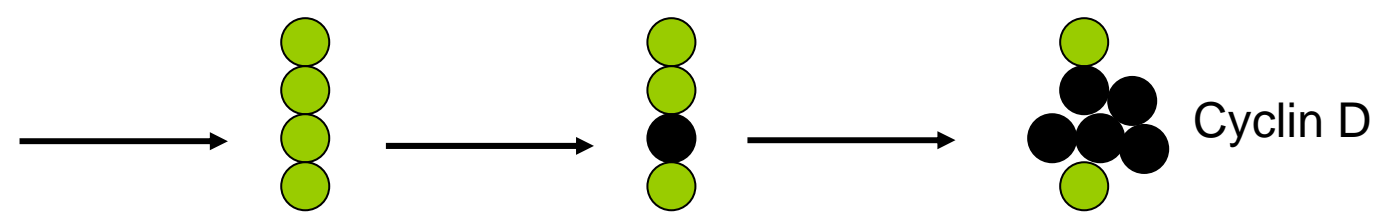
③肝発癌の要因  
3) Isolation

NGFの発現

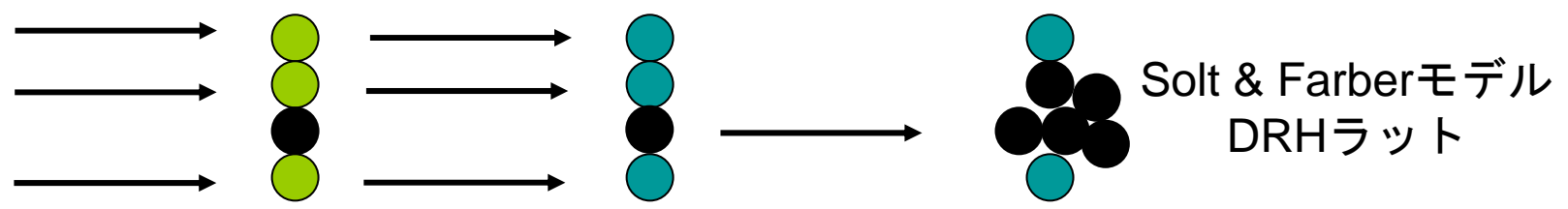


# 肝発癌の要因

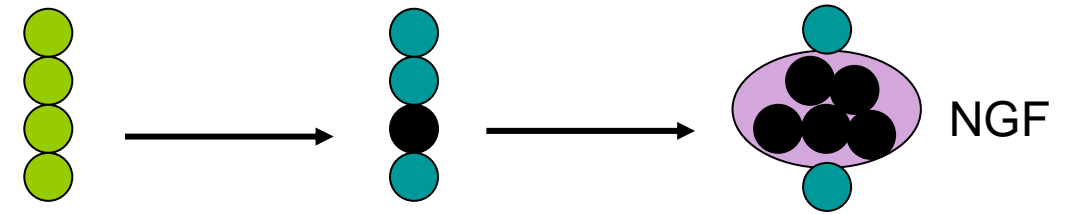
## Transformation 高増殖、生存能



## Selection 選択



## Isolation 微小環境



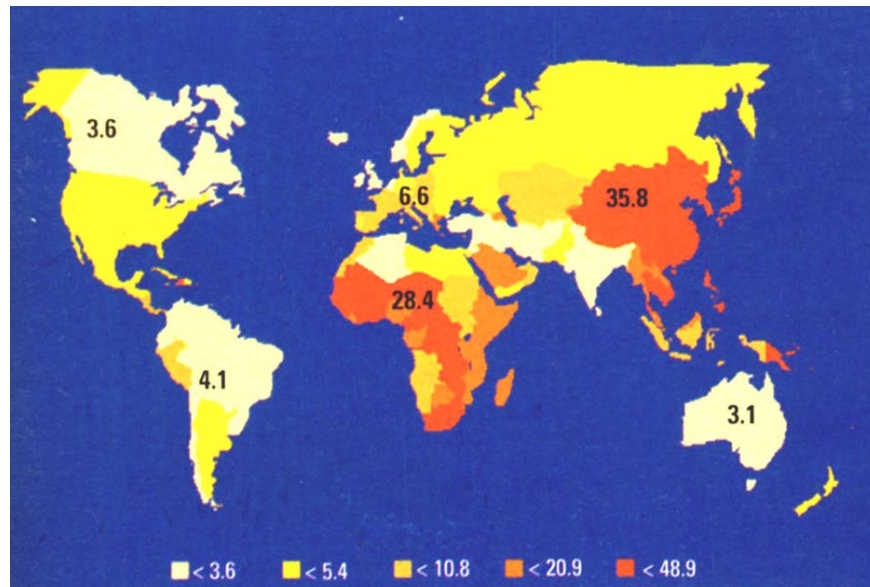


## ◎地理的分布

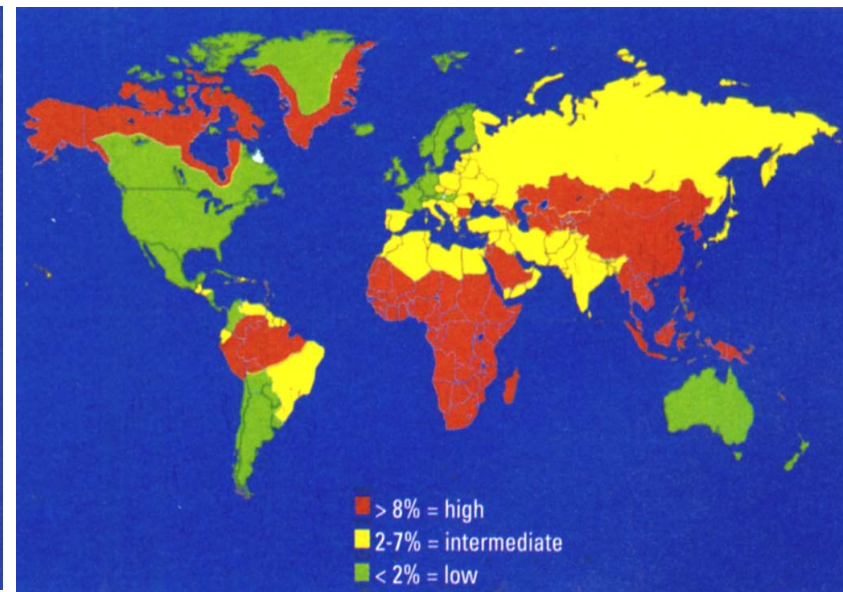
低開発国 > 先進国

高危険地域 > 20.1/10万人

サハラ以南アフリカ、東アジア、メラネシア



肝癌患者の頻度(対10万人)



HBV感染率

- HBV感染と相乗的影響

## ◎ Aflatoxin B1

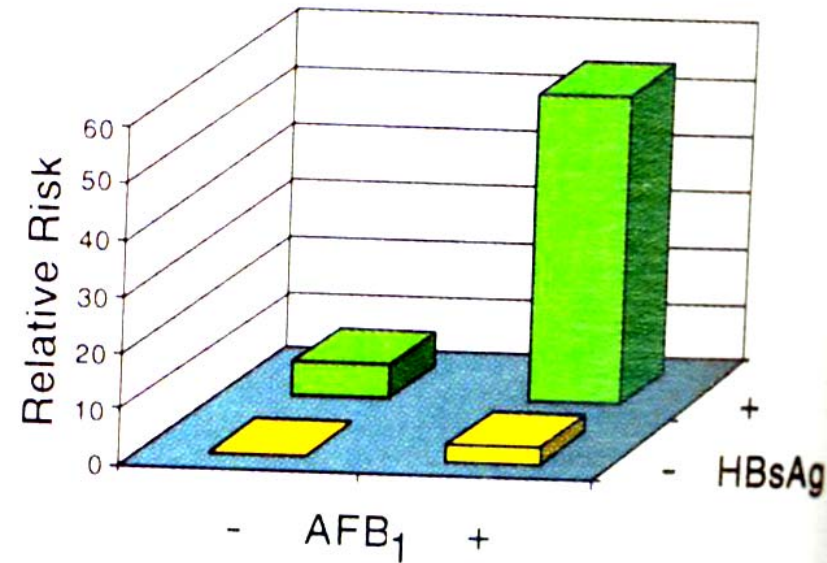
- カビの毒素

Aspergillus genus

- 実験動物にも強い肝発癌性
- 高温多湿一熱帯国

中国南部、サハラ以南アフリカ、東南アジア、メラネシア

- 穀物、ピーナツを汚染



## ◎人の肝がんの原因

- ・ アフリカ／東南アジア／中国  
B型肝炎ウイルス＋アフラトキシン
- ・ 日本／ヨーロッパ  
C型肝炎ウイルス＋アルコール

## ◎肝がんの予防

- ・ ワクチン：B型肝炎ウイルス（台湾、アフリカ）
- ・ 生活習慣：アルコール摂取、鉄摂取の制限

*It's just beginning!*

