第 3 6 3 次 獸 醫 組 織 病 理 會 議

一般病理學 (General Pathology)

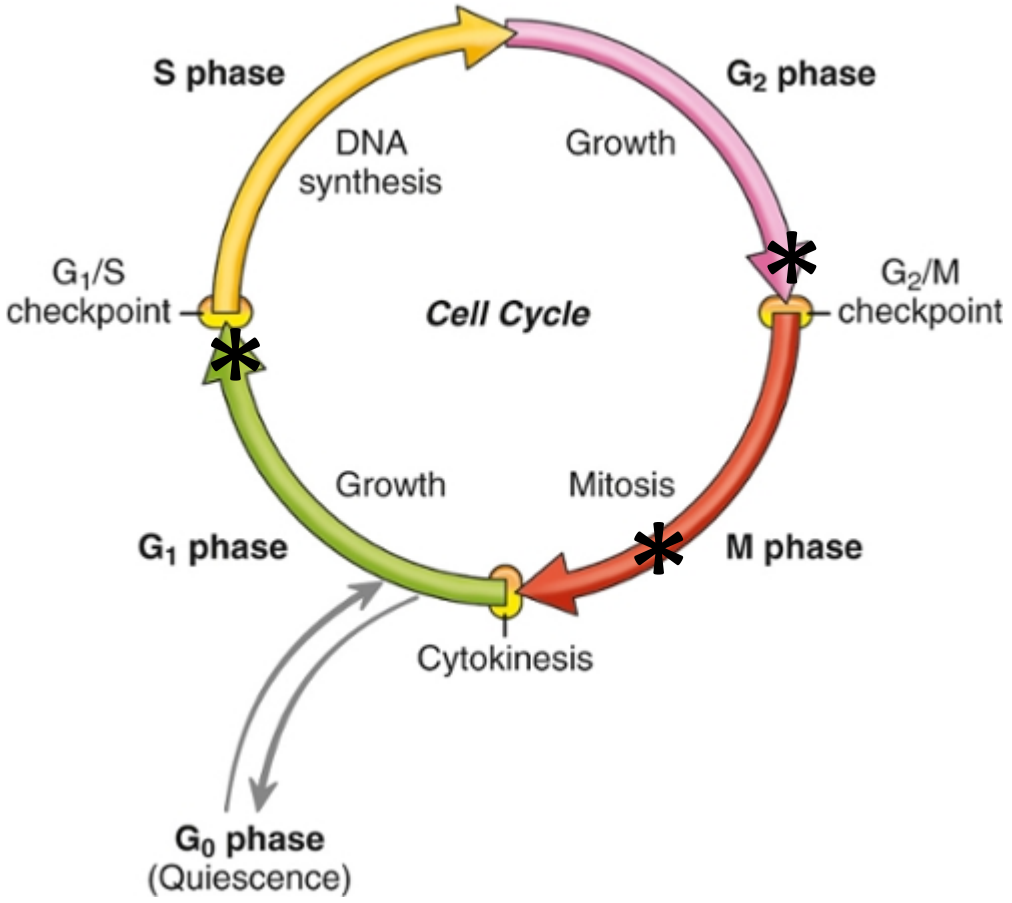
簡耀君
長青動物醫院 內科暨病理獸醫師
中華民國獸醫病理學會病理專科獸醫師
2018/6/8

General pathology

- Ch1: Mechanisms and Morphology of Cellular Injury, Adaptation, and Death
- Ch2: Vascular Disorders and Thrombosis
- Ch3: Inflammation and Healing
- Ch4: Mechanisms of Microbial Infections
- Ch5: Diseases of Immunity
- Ch6: Neoplasia and Tumor Biology

Neoplasia and Tumor Biology

Normal cell division cycle



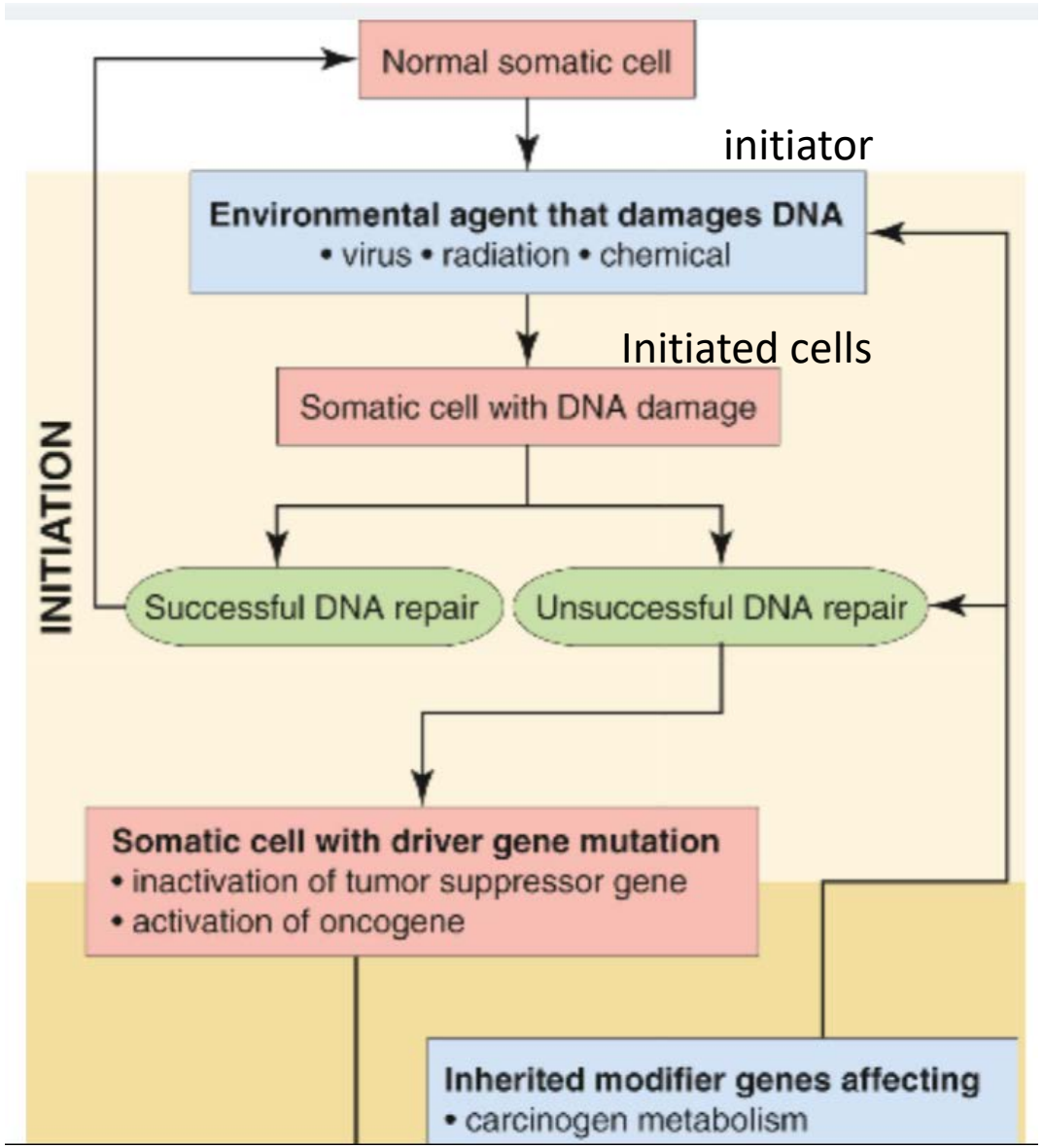
- Interphase
  - G1: presynthetic
  - S: DNA synthetic
  - G2: premitotic
- M: mitosis and cytokinesis
- G0: arrest

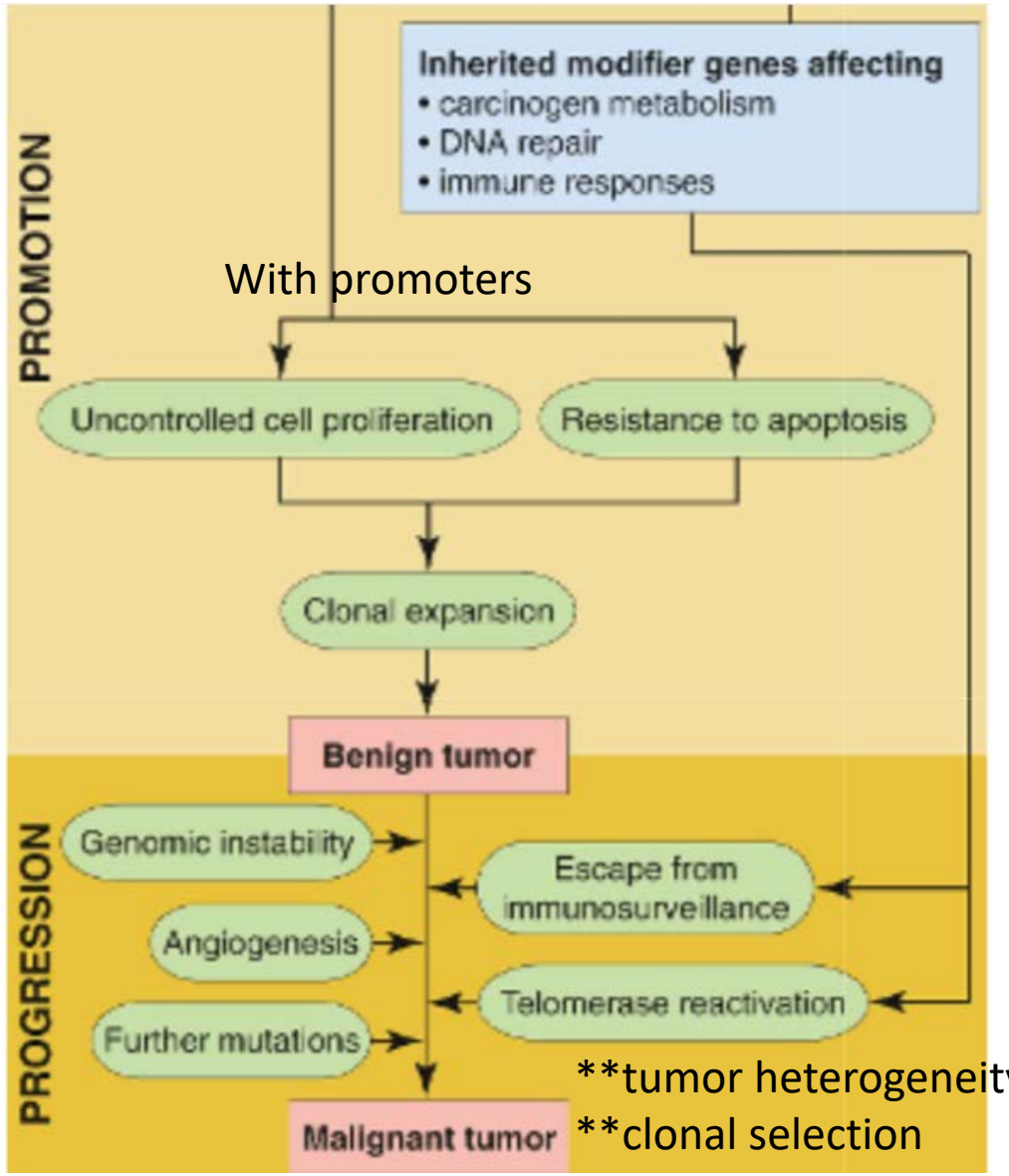
Checkpoints*

- G1/S: DNA damage, cell size, nutrient, environment
- G2/M: DNA replication
- Metaphase: spindle

Stepwise tumor development

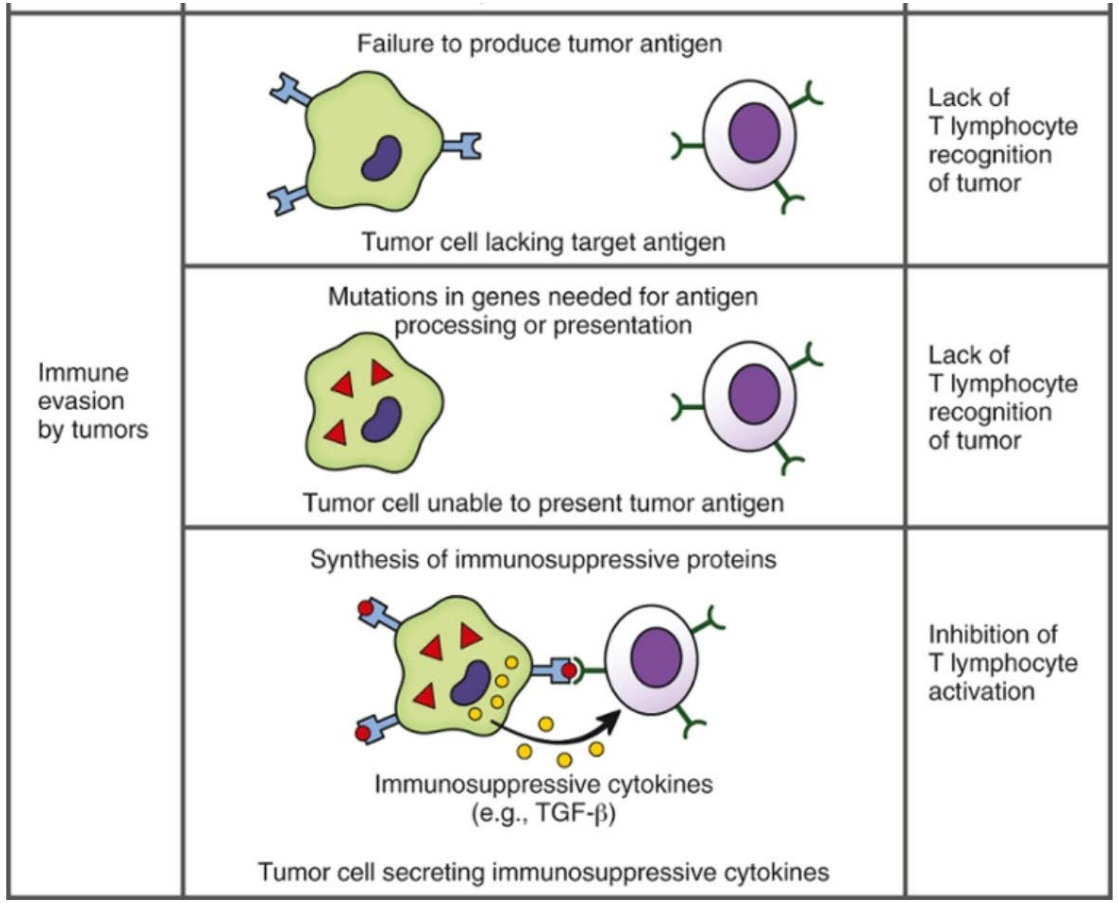
- Initiation → promotion → progression





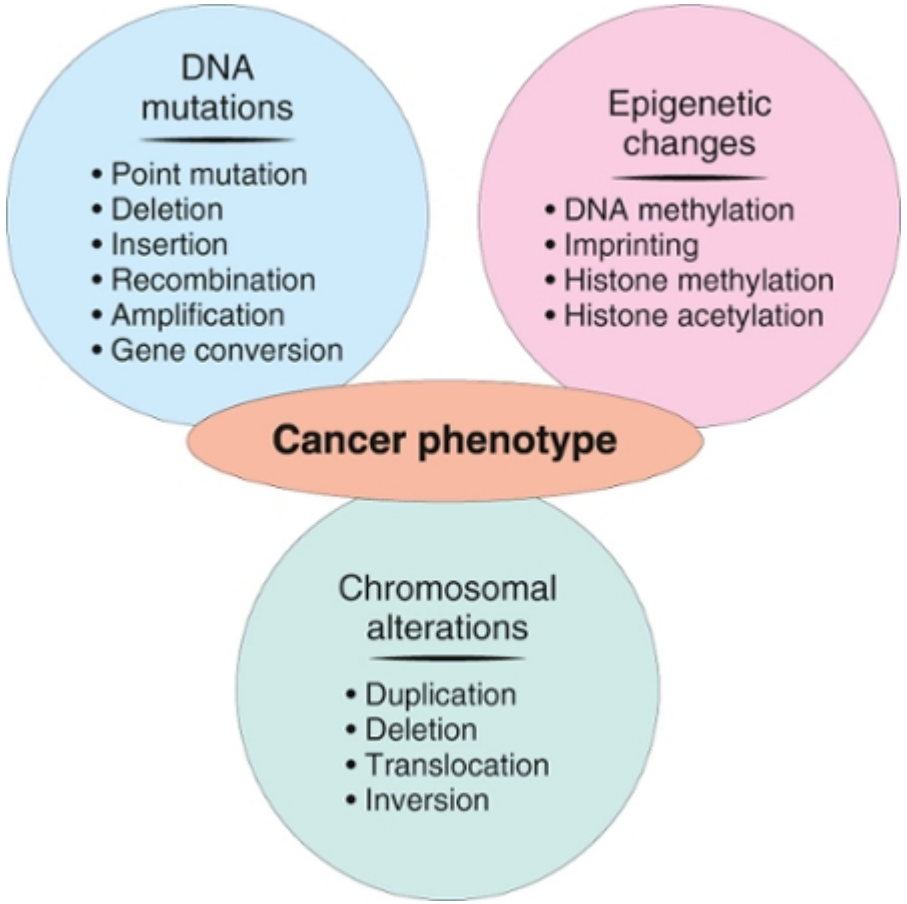
**tumor heterogeneity
**clonal selection

Evasion of immune response



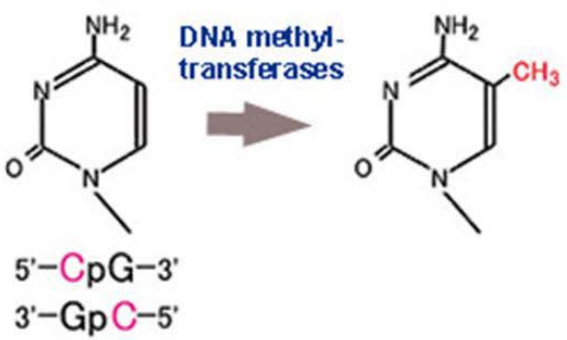
- Antigen masking
- Altered MHC expression
- Tolerance
- Immunosuppression
  - TGF-α(?) production
  - Fas ligand production -> nearby T cell apoptosis

Heritable alterations in cancer



- DNA mutations
- Chromosomal alterations
- Epigenetic changes
  - DNA methylation
  - Imprinting
  - Histone modification
  - MicroRNA

DNA methylation often inhibits transcription (gene silencing)



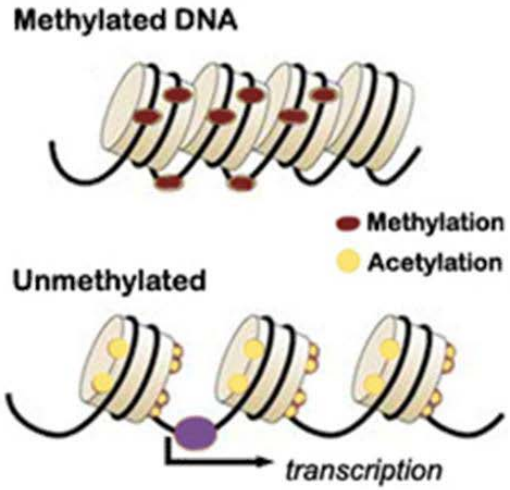
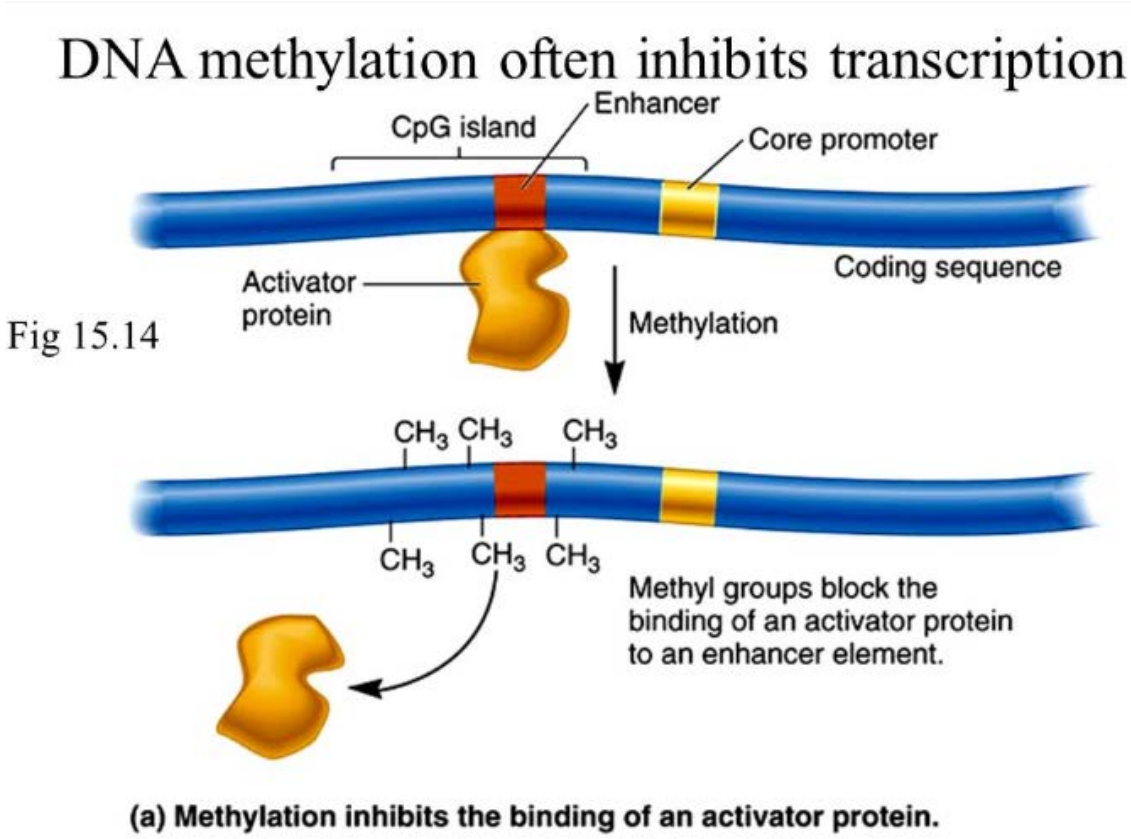


*Image courtesy of the cellscience website.

Fig 15.14

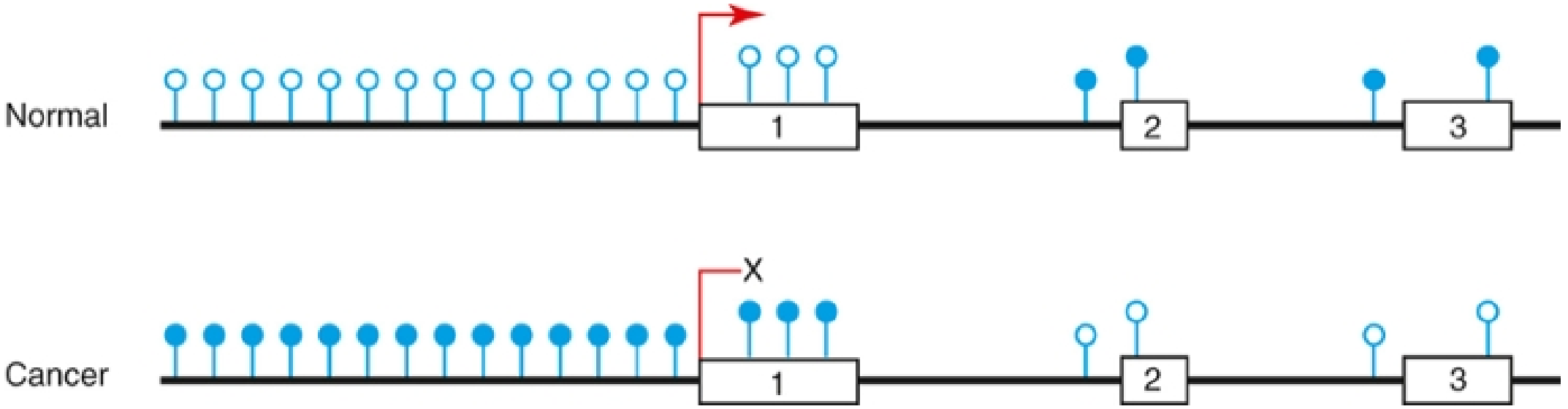


(a) Methylation inhibits the binding of an activator protein.

http://slideplayer.com/slide/8191036/

CpG island methylation

HypOmethylation - O
Hypermethylation - S



抑癌基因 promoter 區CpG islands 的過度甲基化會抑制抑癌基因的表現
使細胞發生癌變的機率提高。

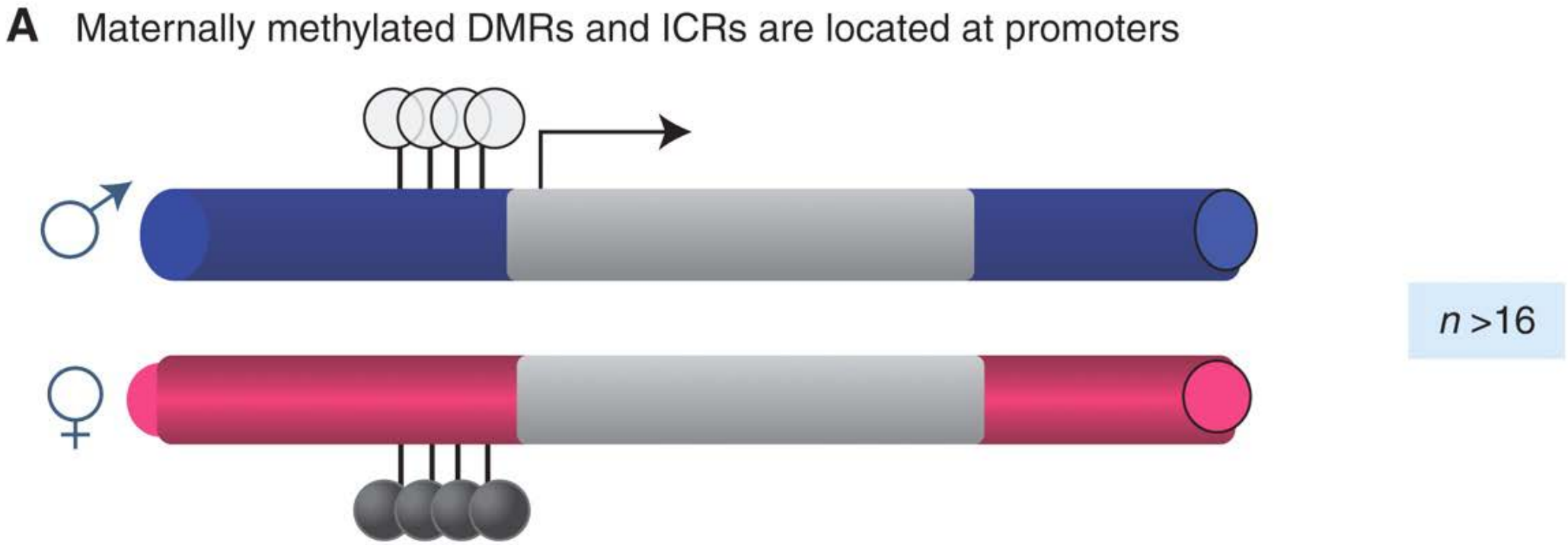
Imprinting

- 在一般二倍體生物的體細胞中擁有兩份基因組，通常這兩份基因組中的等位基因都能表現。
- 但少數（小於1%）的基因會受到銘印的影響，使其中一份基因失去作用。
- Maternal imprinting - 例如一種製造類胰島素的生長因子Insulin growth factor-2的基因，只有來自父親的等位基因能夠表現

https://zh.wikipedia.org/wiki/%E5%9F%BA%E5%9B%A0%E7%B5%84%E9%8A%98%E5%8D%B0

Imprinting

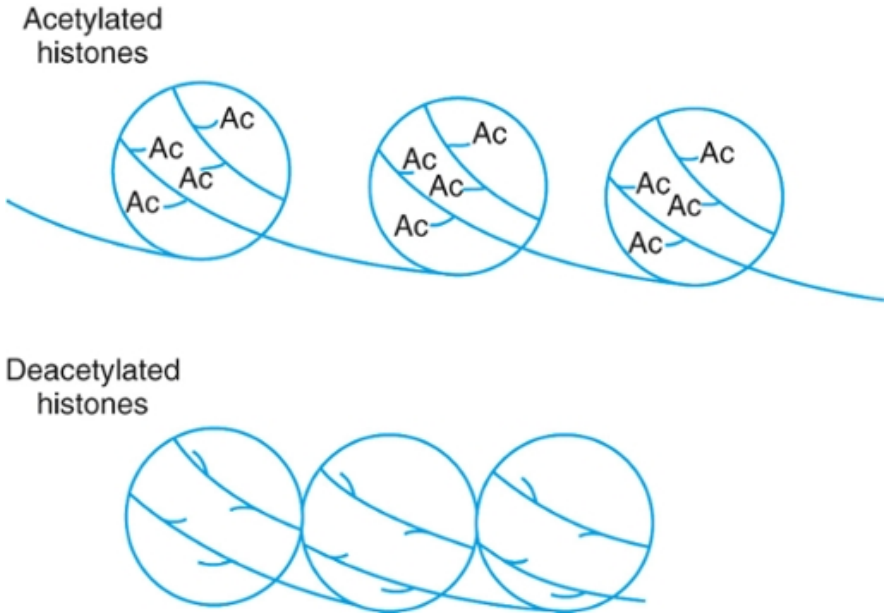
Cancer cells: lost imprinting
-> biallelic expression
-> higher than normal levels of growth-promoting gene products



http://cshperspectives.cshlp.org/content/3/7/a002592.full.pdf+html

Histone modification

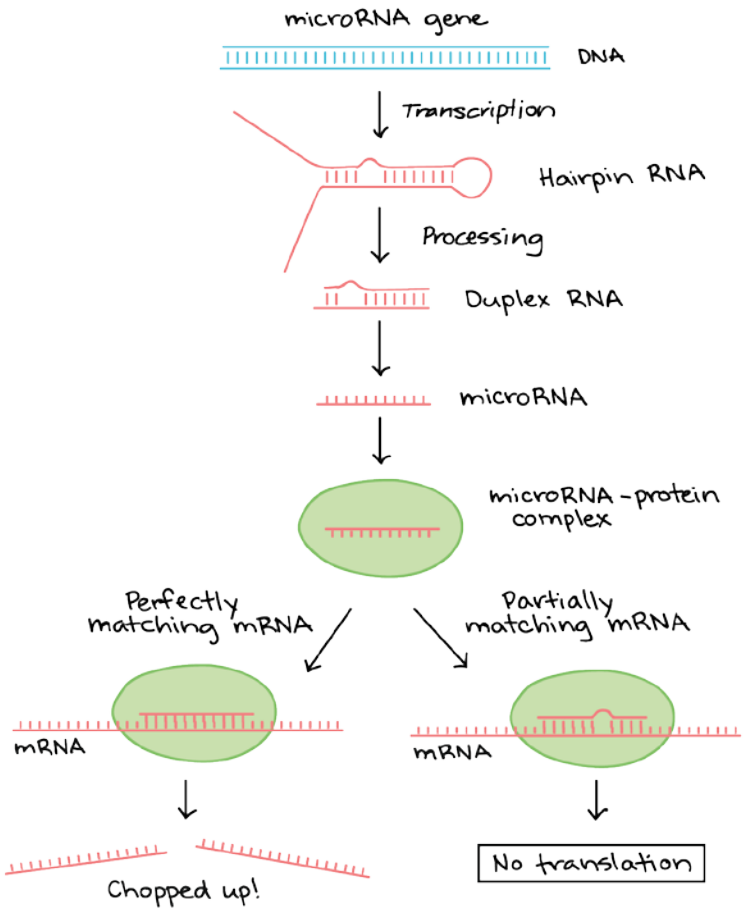
- Histone acetylation, methylation and phosphorylation alter transcription of associated DNA



Histone acetylation
-> chromatin relaxation
-> ↑accessible to transcription factors

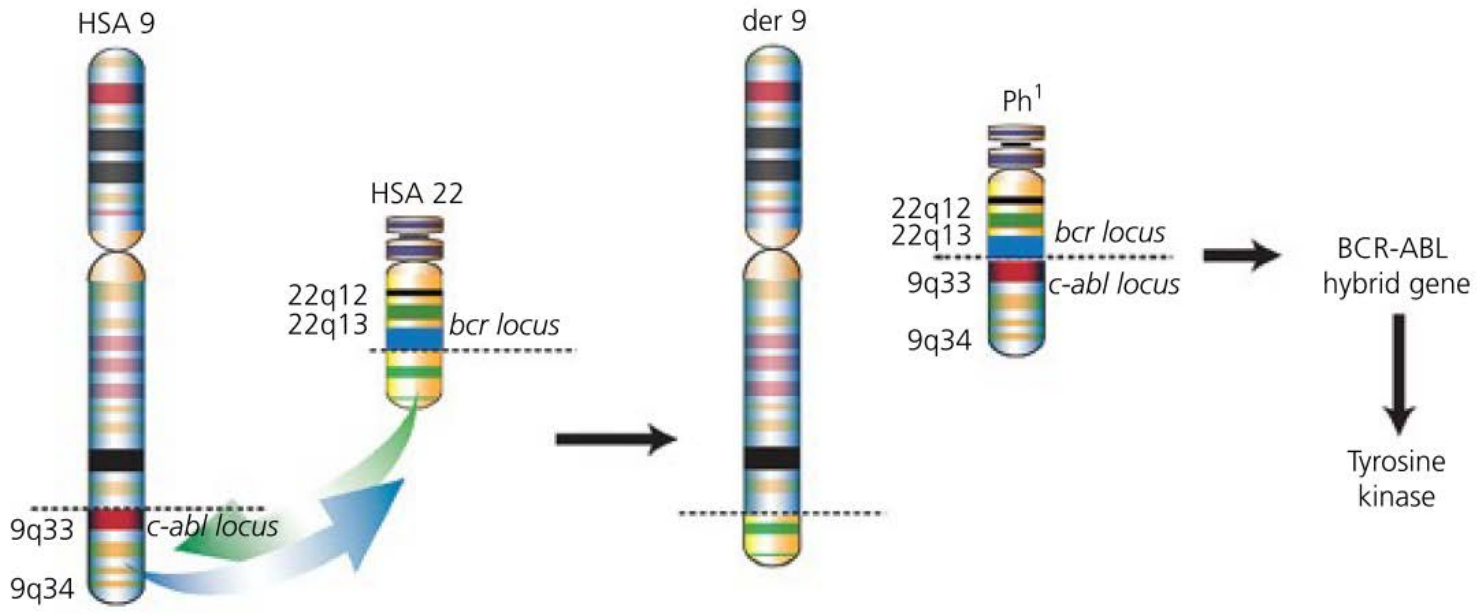
MicroRNA – noncoding RNA

- Post-translational modification
- Binding target mRNAs
  - mRNA degradation or translation repression
- ↓ Expression of target genes



https://www.khanacademy.org/science/biology/gene-regulation/gene-regulation-in-eukaryotes/a/regulation-after-transcription

Chromosome translocation: Philadelphia chromosome t(9;22)(q34;q11) in human

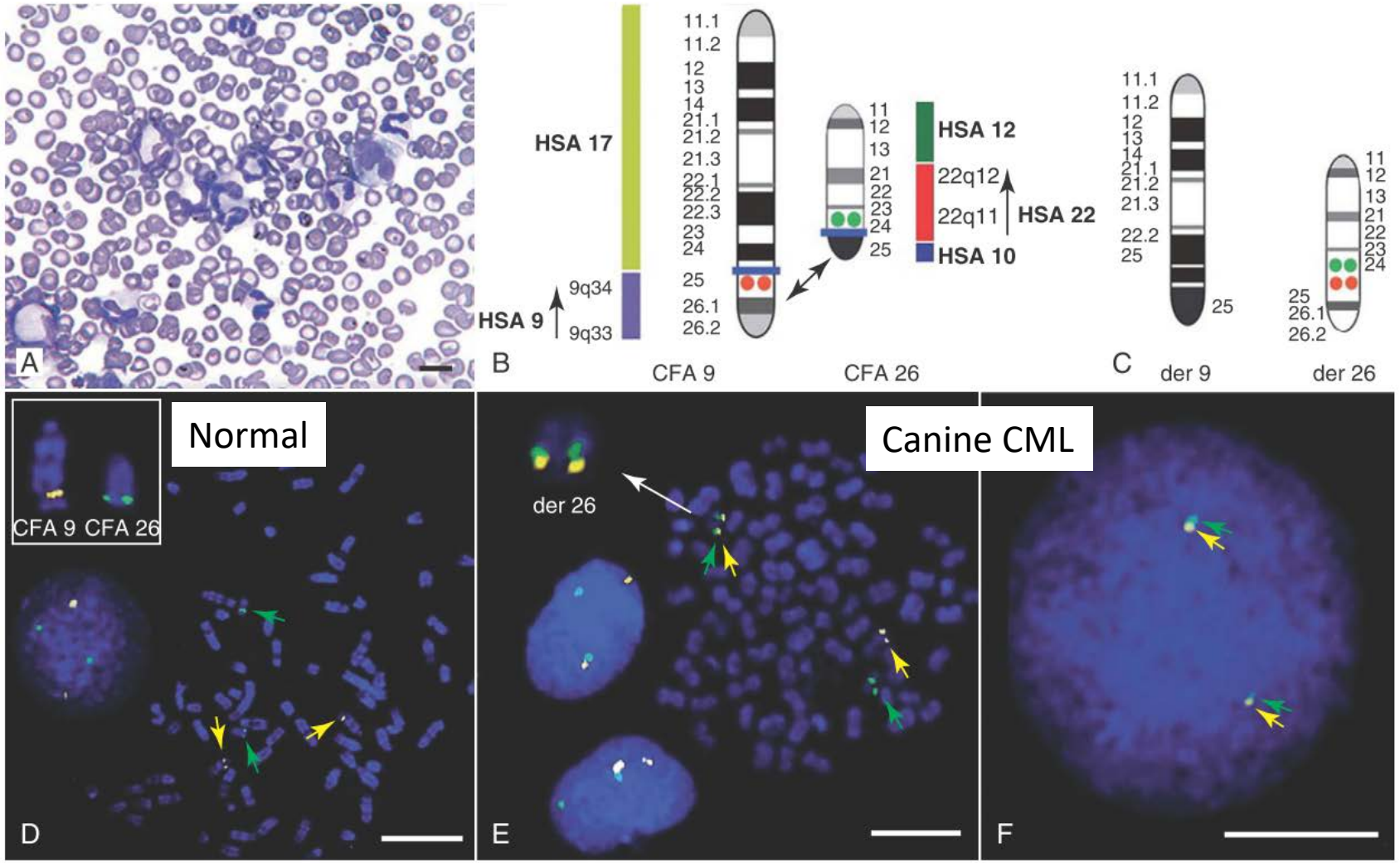


(Tumors in Domestic Animals, 5th)

BCR-ABL fusion gene

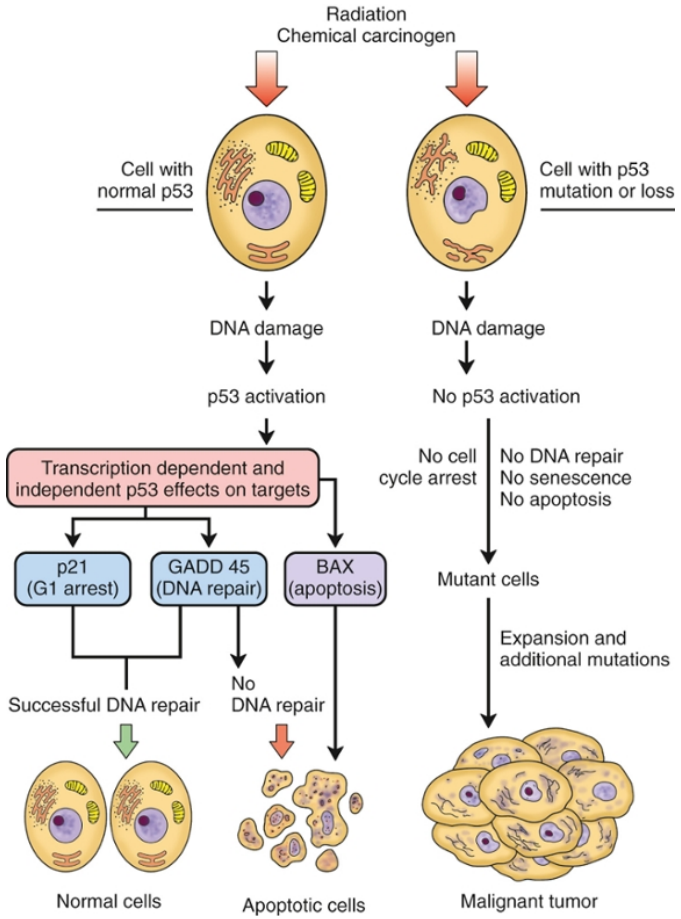
- Chronic myeloid leukemia
- Acute lymphoblastic leukemia (uncommon)

BCR-ABL translocation in canine chronic myelogenous leukemia



Withrow and MacEwen's Small Animal Clinical Oncology (Fifth Edition)

Tumor suppressor genes: p53



P53- Genomic Guardian

DNA damage
-> p53 activation
-> G1 cell cycle arrest at checkpoints
-> DNA repair

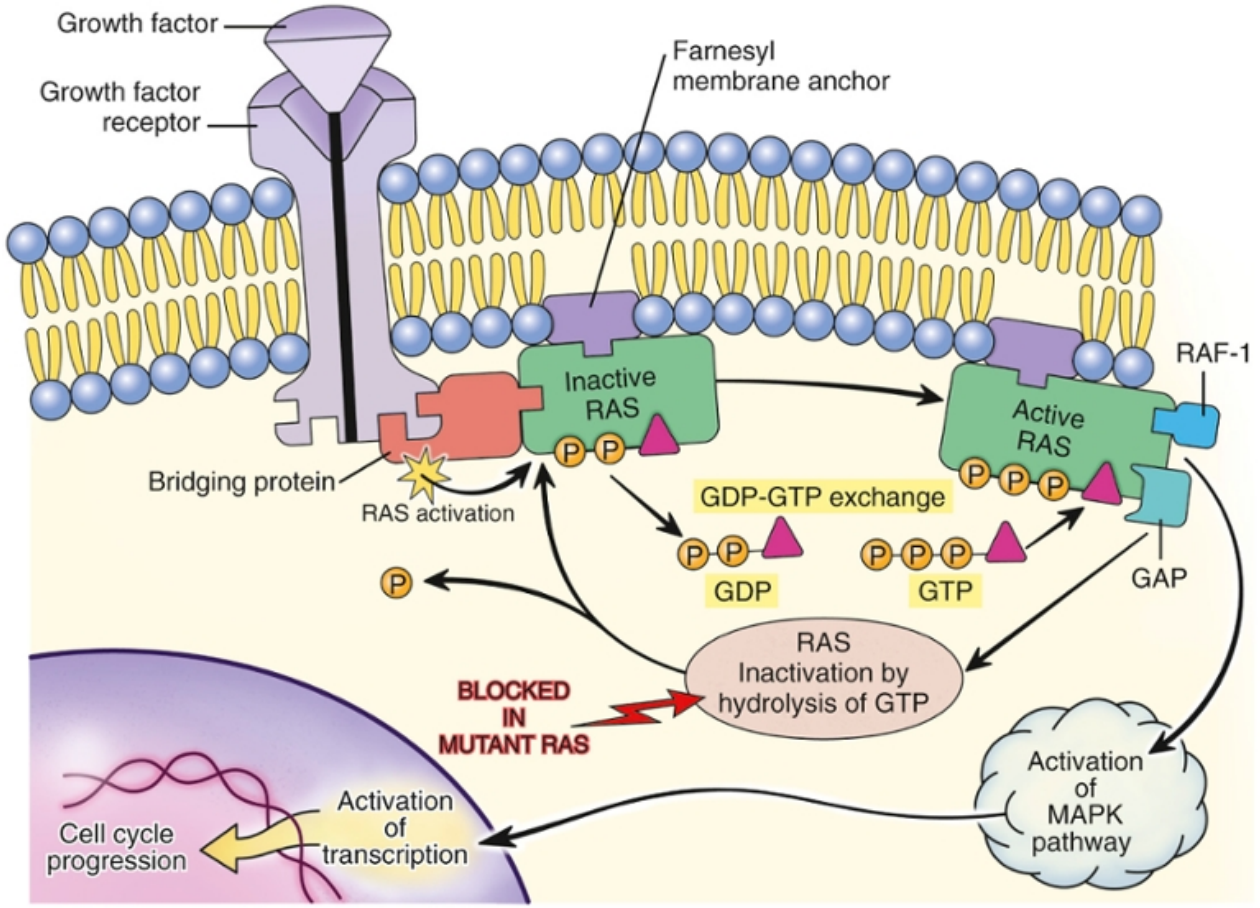
Tumor oncogenes

Oncogene	Name	Abbreviation
Growth factors	Platelet-derived growth factor	PDGF
	Epidermal growth factor	EGF
	Insulin-like growth factor-1	ILGF-1
	Vascular endothelial growth factor	VEGF
	Transforming growth factor-β	TGF-β
	Interleukin-2	IL-2
Growth factor receptors	PDGF receptor	PDGFR
	EGF receptor	EGFR, erbB-1
	ILGF-1 receptor	ILGF-1R
	VEGF receptor	VEGFR
	IL-2 receptor	IL-2R
	Hepatocyte growth factor receptor	met
	Heregulin receptor	neu/erbB-2
	Stem cell factor receptor	Kit
Protein kinases	Tyrosine kinase	bcr-abl
	Tyrosine kinase	src
	Serine-threonine kinase	raf/mil
	Serine-threonine kinase	mos
G-protein signal transducers	GTPase	H-*ras*
	GTPase	K-*ras*
	GTPase	N-*ras*
Nuclear proteins	Transcription factor	ets
	Transcription factor	fos
	Transcription factor	jun
	Transcription factor	myb
	Transcription factor	myc
	Transcription factor	rel

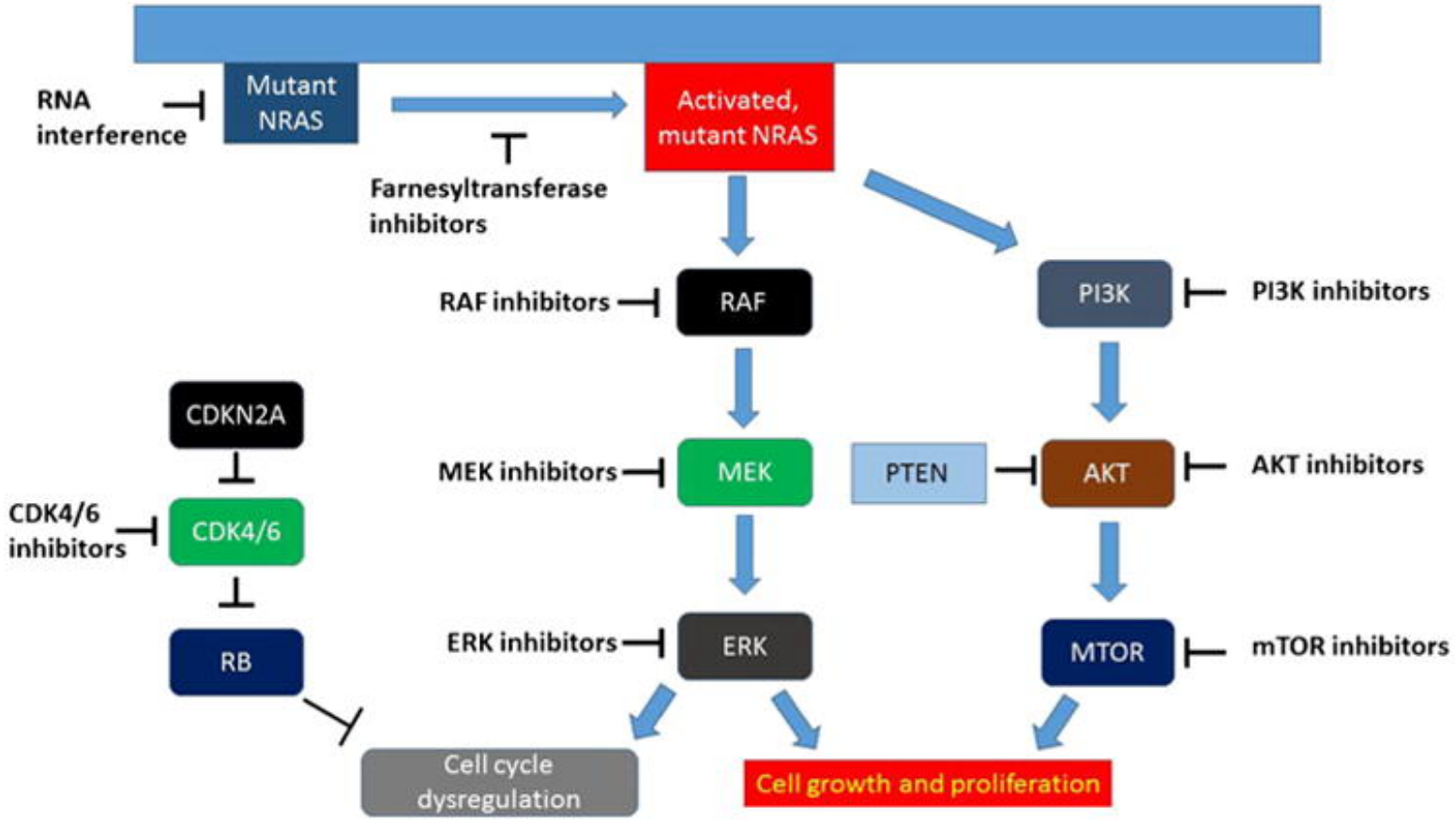
GTPase, Guanosine triphosphatase.

(Withrow and MacEwen's Small Animal Clinical Oncology, Fifth Edition)

Signal Transduction Oncogenes: RAS Family



RAS-RAF-MEK-MAPK pathway



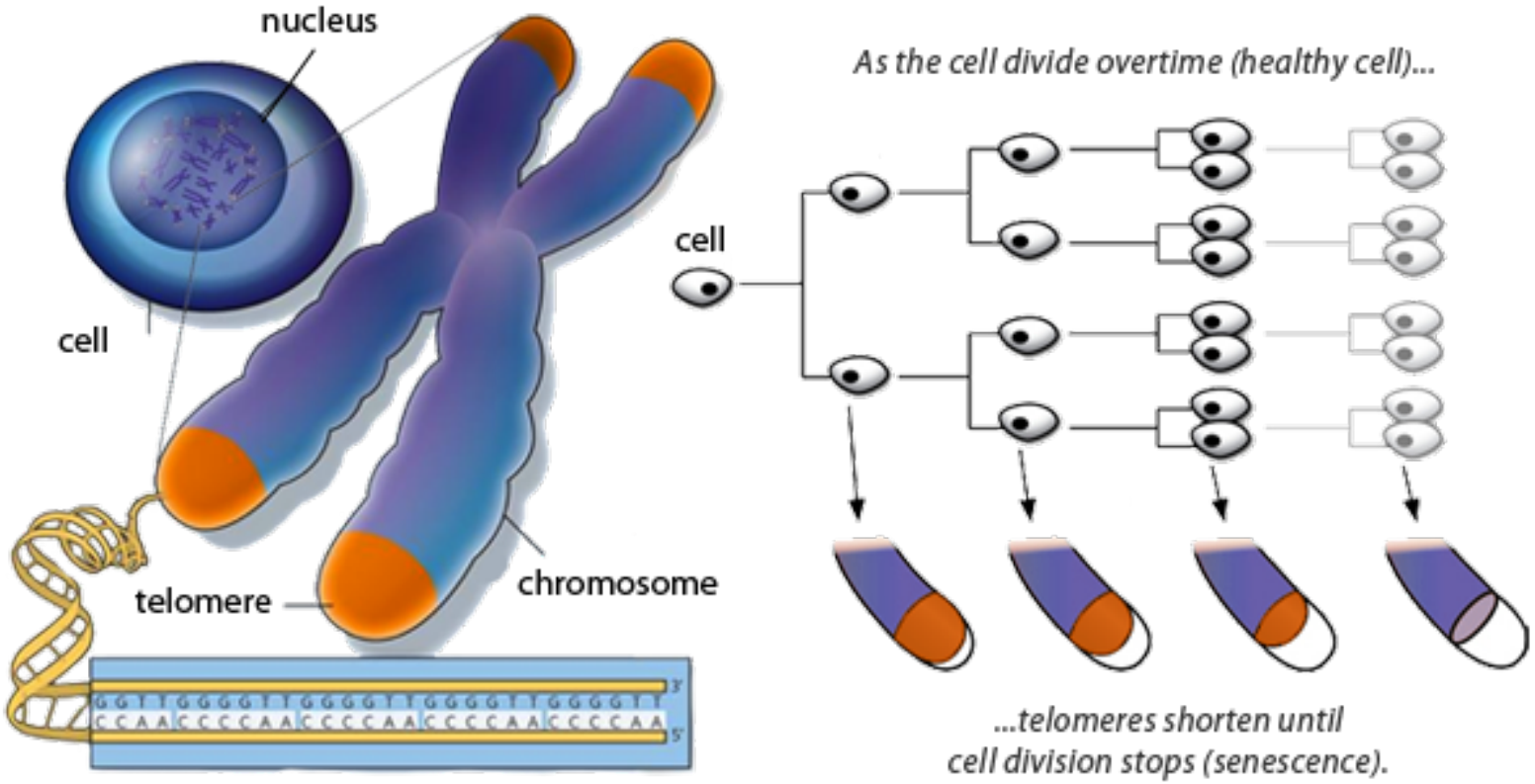
(Johnson, D. B., & Puzanov, I. (2015). Treatment of NRAS-mutant melanoma. *Current treatment options in oncology*, *16*(4), 15.)

Selected experimental and approved treatment options for advanced NRAS-mutant melanoma

Agent (reference)	NRAS specific?	Response rate	OS (median)	FDA approved?
Binimetinib [2••]	Yes	20 % (6 of 30)	*	No
Binimetinib + LEE011 [3]	Yes	33 % (7 of 21)	*	No
IL-2 [4]	No	16 %	11.4 months	Yes
Ipilimumab [5•]	No	10.9 %	10.1 months[a] (2nd line +)	Yes
Pembrolizumab [6, 7•]	No	38 % (ipi naïve) 25 % (ipi pre-tx)	*	Yes[b]
Nivolumab [8, 9]	No	31 % (ipi naïve) 25 % (ipi pre-tx)	16.8 months	No

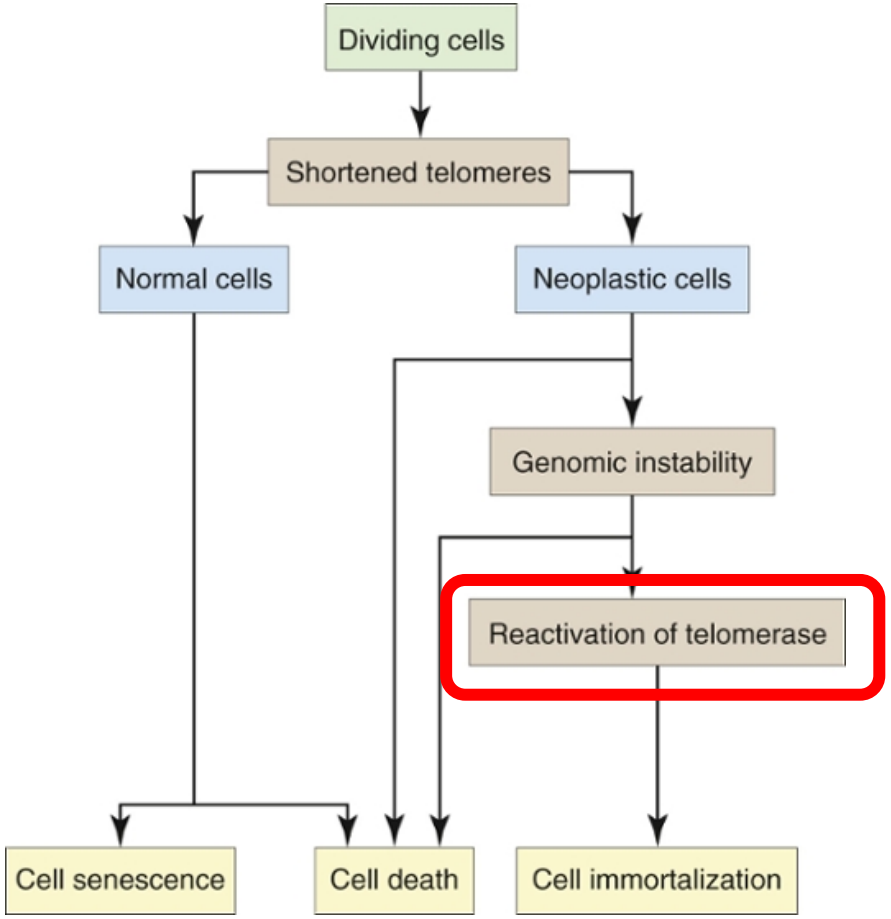
(Johnson, D. B., & Puzanov, I. (2015). Treatment of NRAS-mutant melanoma. *Current treatment options in oncology*, *16*(4), 15.)

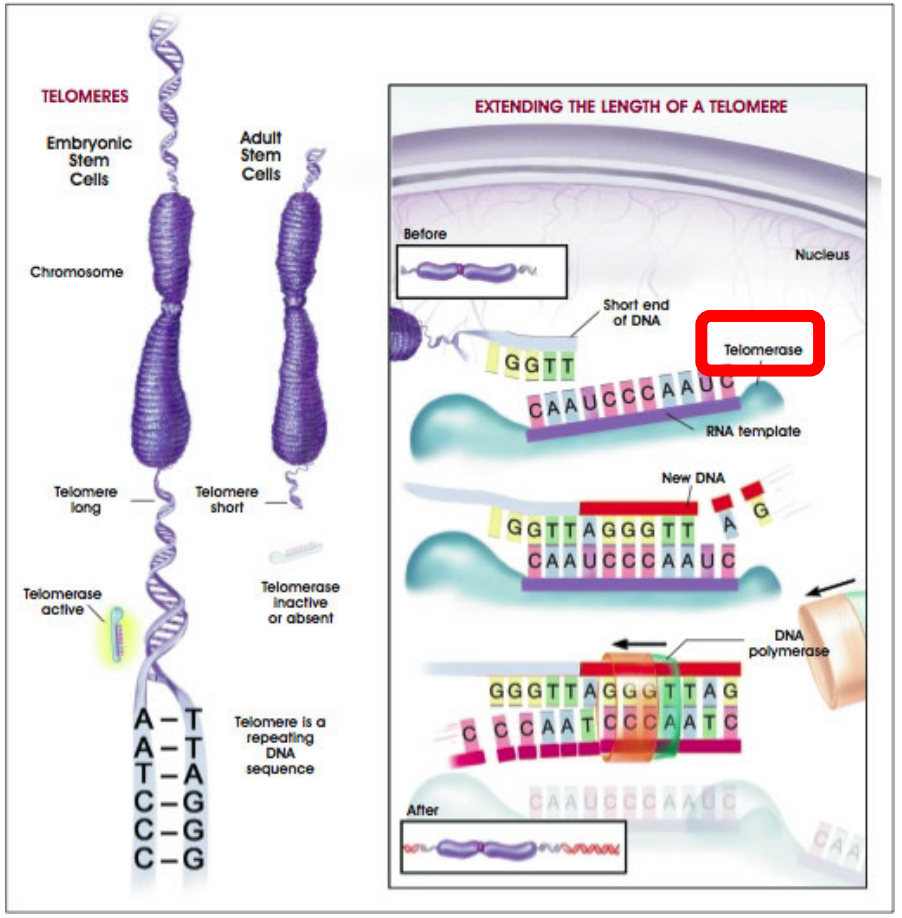
Normal cells: telomere shortening



http://pure-natur.blogspot.tw/2015/02/telomeres-tiny-segments-of-dna-that-may.html

Tumor: Reactivation of Telomerase





https://colganprograms.wordpress.com/tag/telomeres/

Mechanisms and Morphology of Cellular Injury, Adaptation, and Death

Adaptations that changes cell size, number or appearance

- Atrophy
- Hypertrophy
- Hyperplasia
- Metaplasia
  - Squamous metaplasia: chronic inflammation (mammary ducts/mastitis), hormonal imbalance (estrogen/prostate), Vit A deficiency or trauma
- Dysplasia

Pigments

Exogenous

- Carbon and other dusts
- Carotenoid pigments
- Tetracycline
  - Yellowish discoloration (with bright yellow fluorescence under UV light)

Nonhematogenous

- Melanin
- Lipofuscin: fat stain(+), PAS(+)
- Ceroid

Hematogenous

- Hemoglobin
- Hematin
  - Acid hematin
  - Parasitic hematin
- Hemosiderin
- Hematoidin
- Bilirubin
- Porphyria
  - Teeth, bone, urine: red-brown and fluoresce red under UV light

Vascular Disorders and Thrombosis

Endothelial cell functions and responses in homeostasis and disease

- Fluid distribution and blood flow*
- Hemostasis
- Inflammation
- Growth factors
- Fibrinolysis

Fluid distribution and blood flow

- Semipermeable membrane for fluid distribution
  - Interendothelial junctions
- Vasodilation
  - Nitric oxide
  - Prostacyclin (PGI_2)
  - Endothelial-derived hyperpolarizing factor
  - C-type natriuretic peptide
- Vasoconstriction
  - Endothelin
  - Reactive oxygen species
  - Angiotensin II
  - Products of prostaglandin H_2 (e.g., thromboxane A_2)

Shock

- Cardiogenic shock
- Hypovolemic shock
  - 35% to 45% blood loss: ↓ ↓ blood pressure and cardiac output
- Blood maldistribution
  - Anaphylactic shock
  - Neurogenic shock
  - Septic shock

Inflammation and Healing

Acute inflammatory response

- Fluidic (exudative) phase
  - Endothelial cell dynamics
  - Formation of endothelial cell gaps, in response to cytokines (IL-1 and TNF) and hypoxia
- Cellular phase

Cytokines in acute inflammation

Cytokines in Acute Inflammation		
Cytokine	**Principal Source**	**Principal role in acute inflammation**
TNF	• Macrophages • Mast cells • T lymphocytes	• Leukocyte activation • Endothelial activation • **Systemic acute phase response (next lecture)**
IL-1	• Macrophages • Endothelial cells • Some epithelial cells	• **Systemic acute phase response, greater role in fever**
IL-6	• Macrophages • ?others	• **Systemic acute phase response**

https://www.memorangapp.com/flashcards/135639/Acute+Inflammation+1%2F5/

Complement Cascade

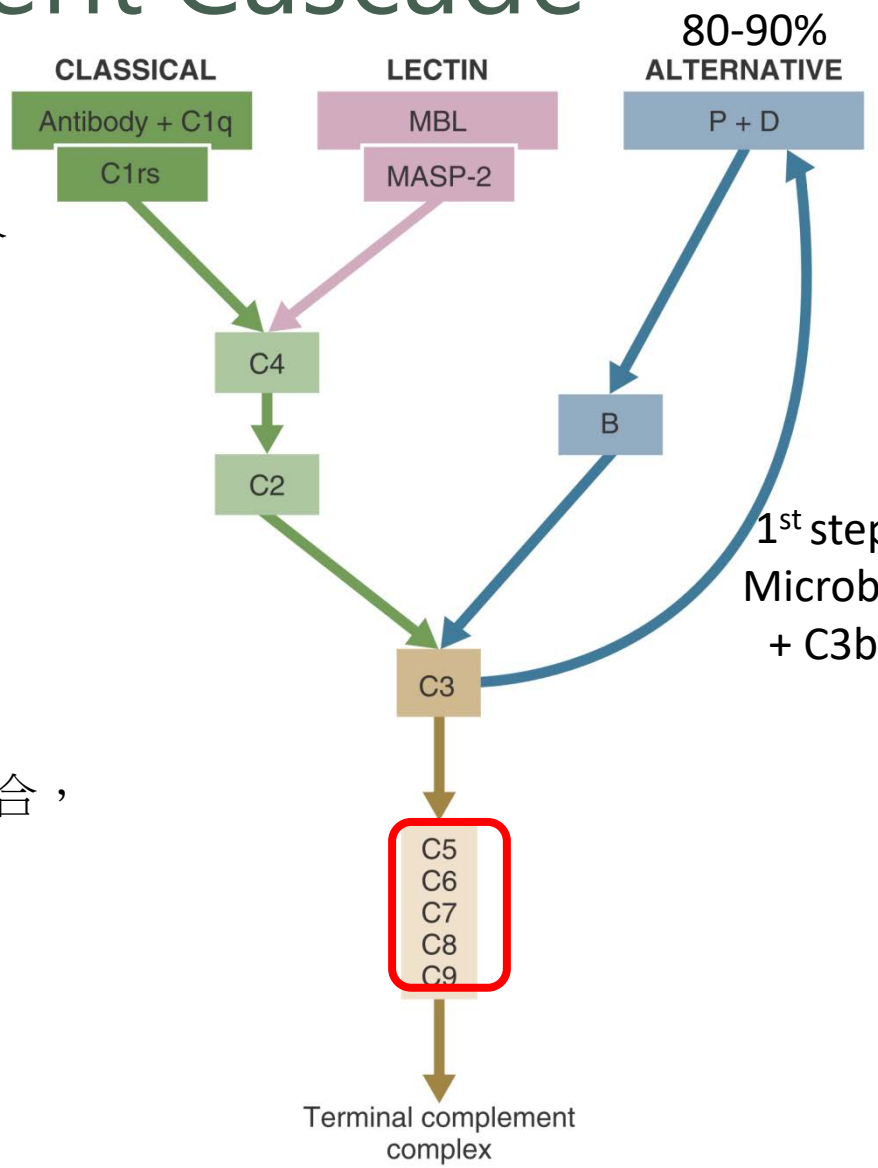
病原被辨認：
微生物表面
與補體或抗體結合

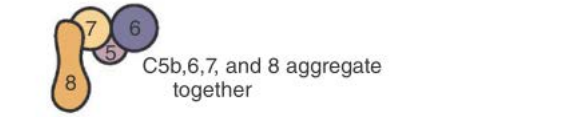
形成C3 convertase
- C4b2a
- C3bBb

切C3

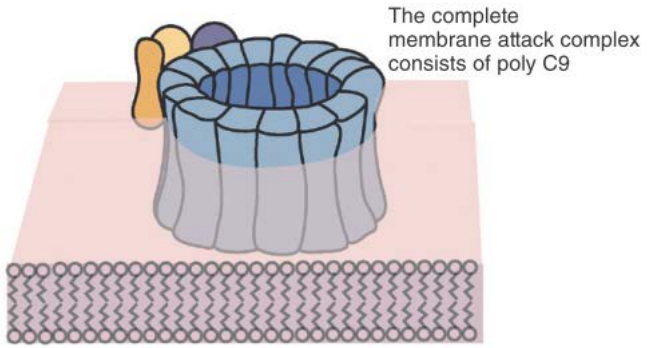
C3b與C3 convertase組合，
形成C5 convertase
- C4b2a3b
- C3bBb3b

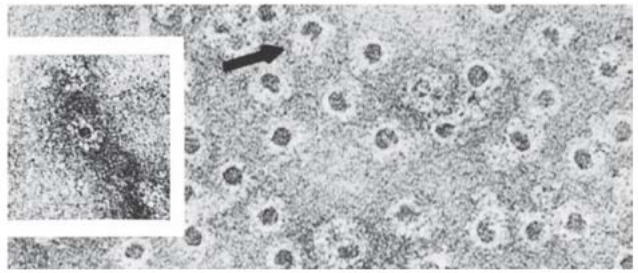
形成MAC





C5b C6 C7 C8 + C9





Veterinary Immunology - 9th Edition

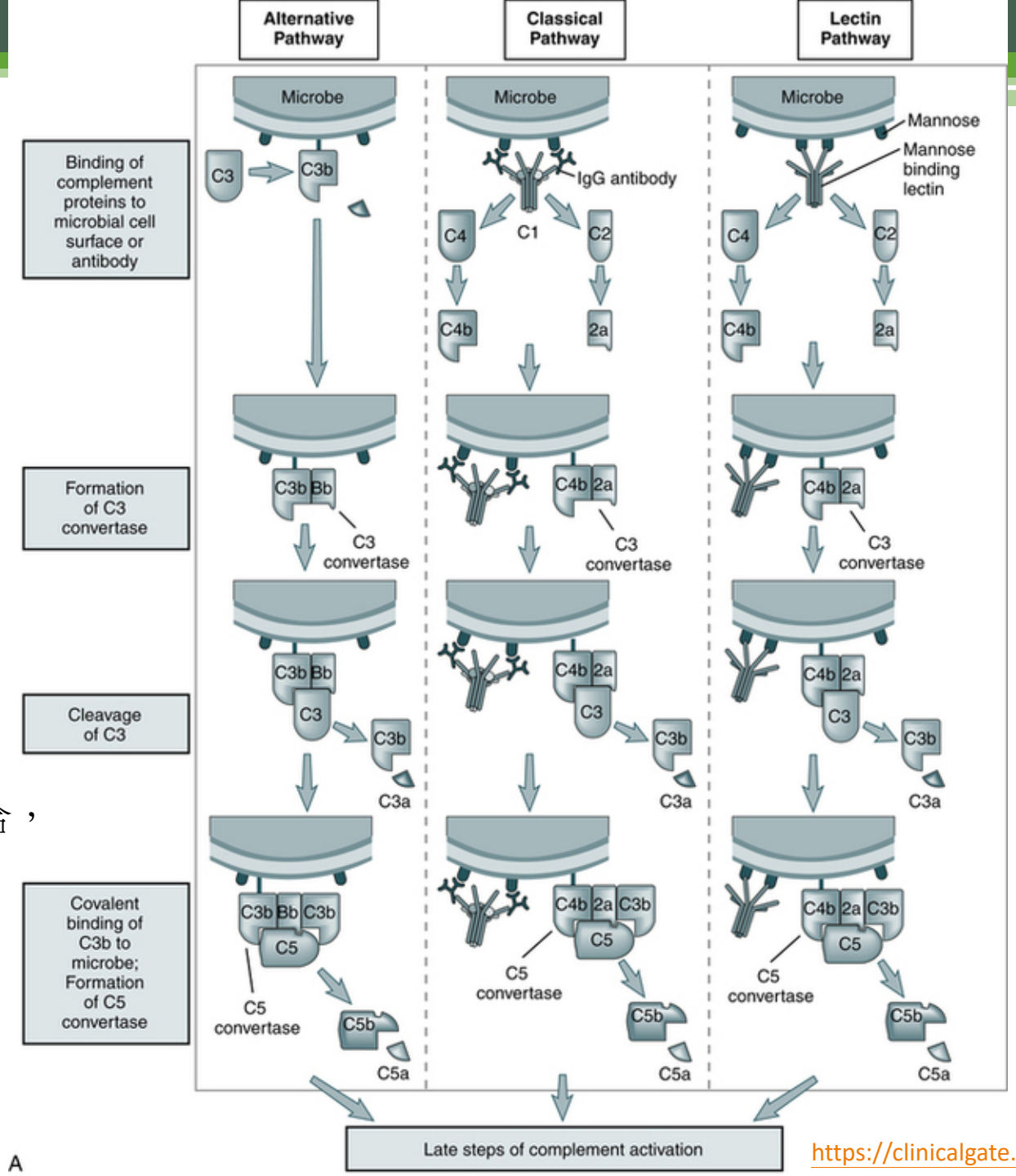
病原被辨認：
微生物表面
與補體或抗體結合

形成C3 convertase
- C4b2a
- C3bBb

切C3

C3b與C3 convertase組合，
形成C5 convertase
- C4b2a3b
- C3bBb3b

形成MAC

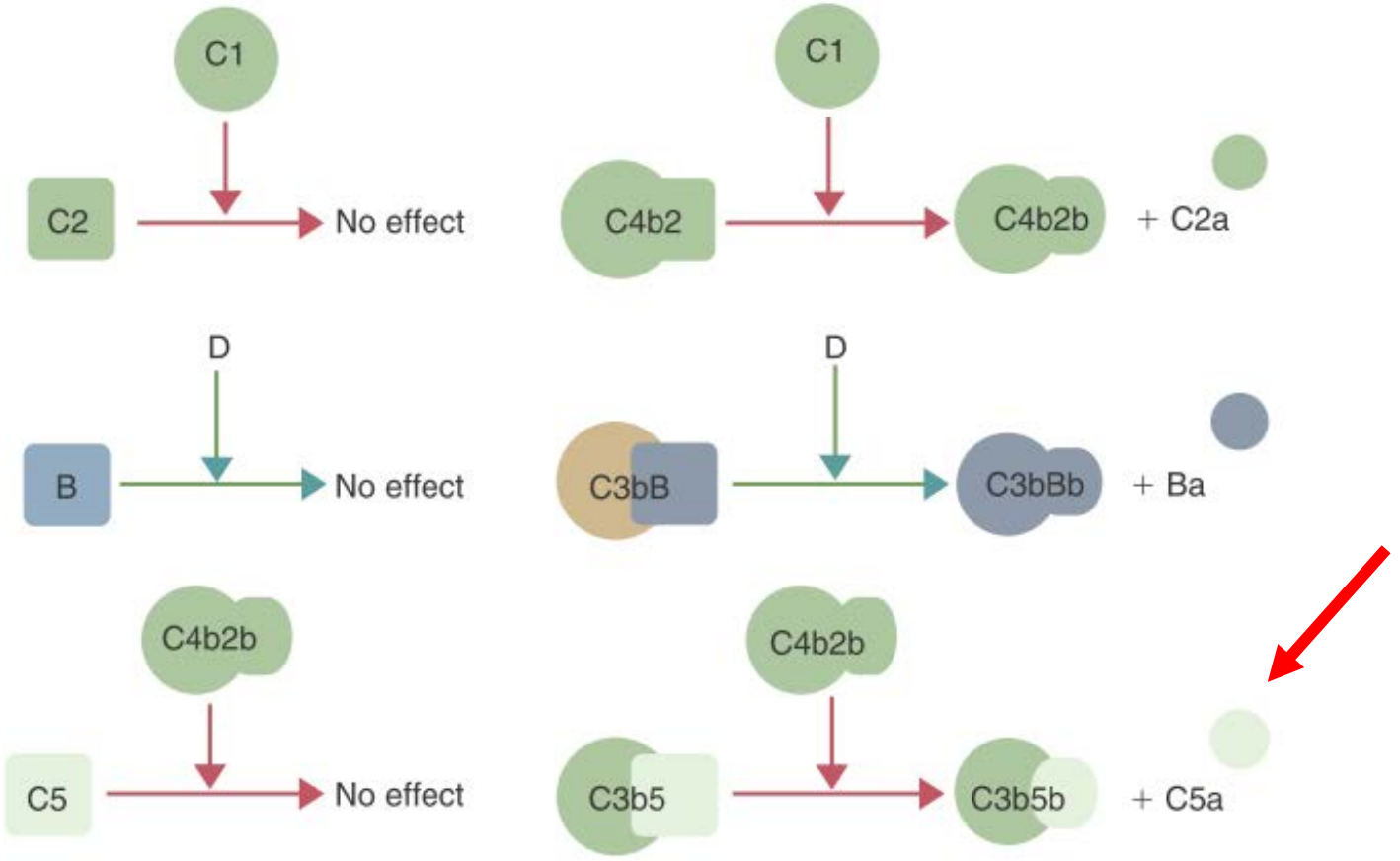


A

https://clinicalgate.com/soluble-mediators-of-the-immune-system/

Anaphylatoxin

- C3a and C5a
- Shock

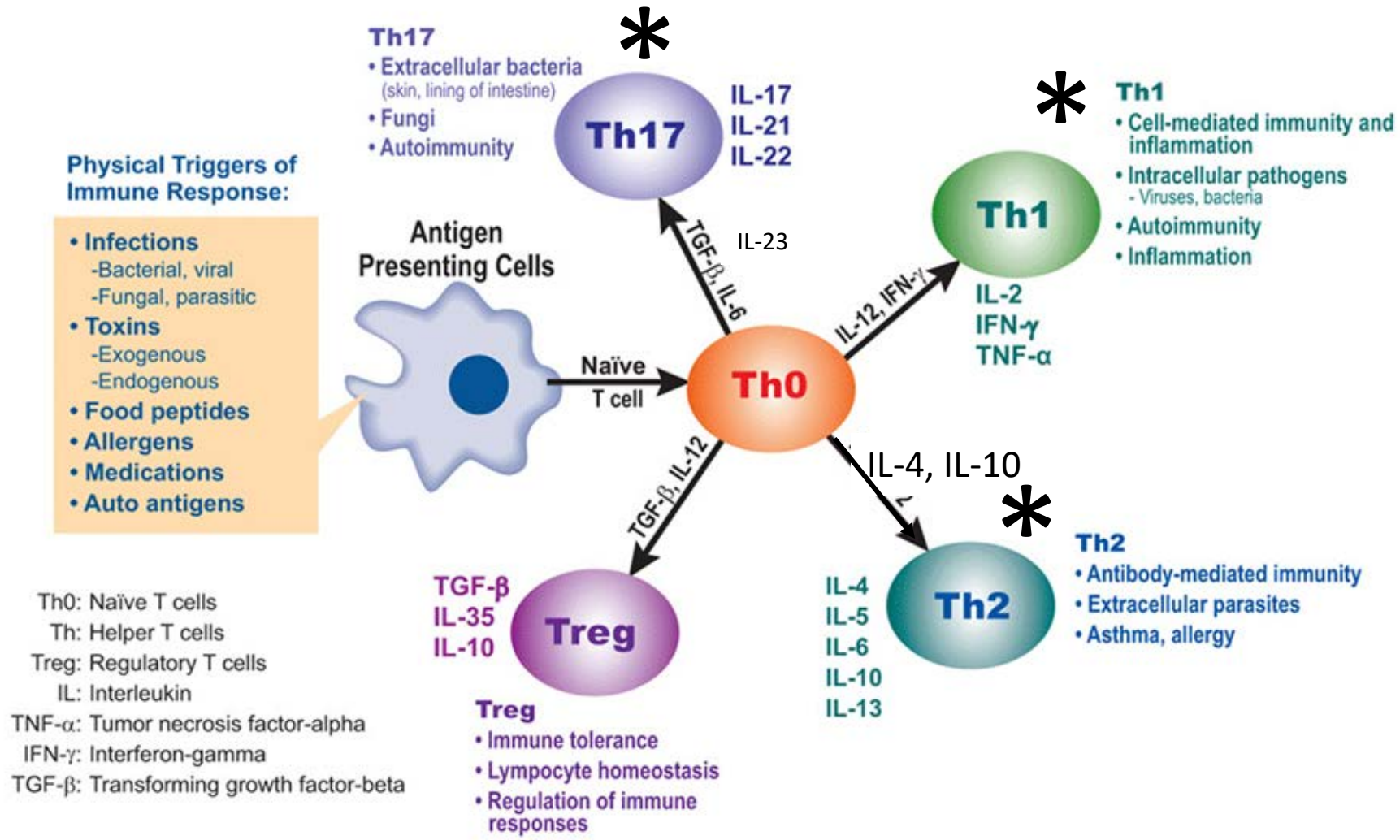


Veterinary Immunology - 9th Edition

Chronic inflammatory response

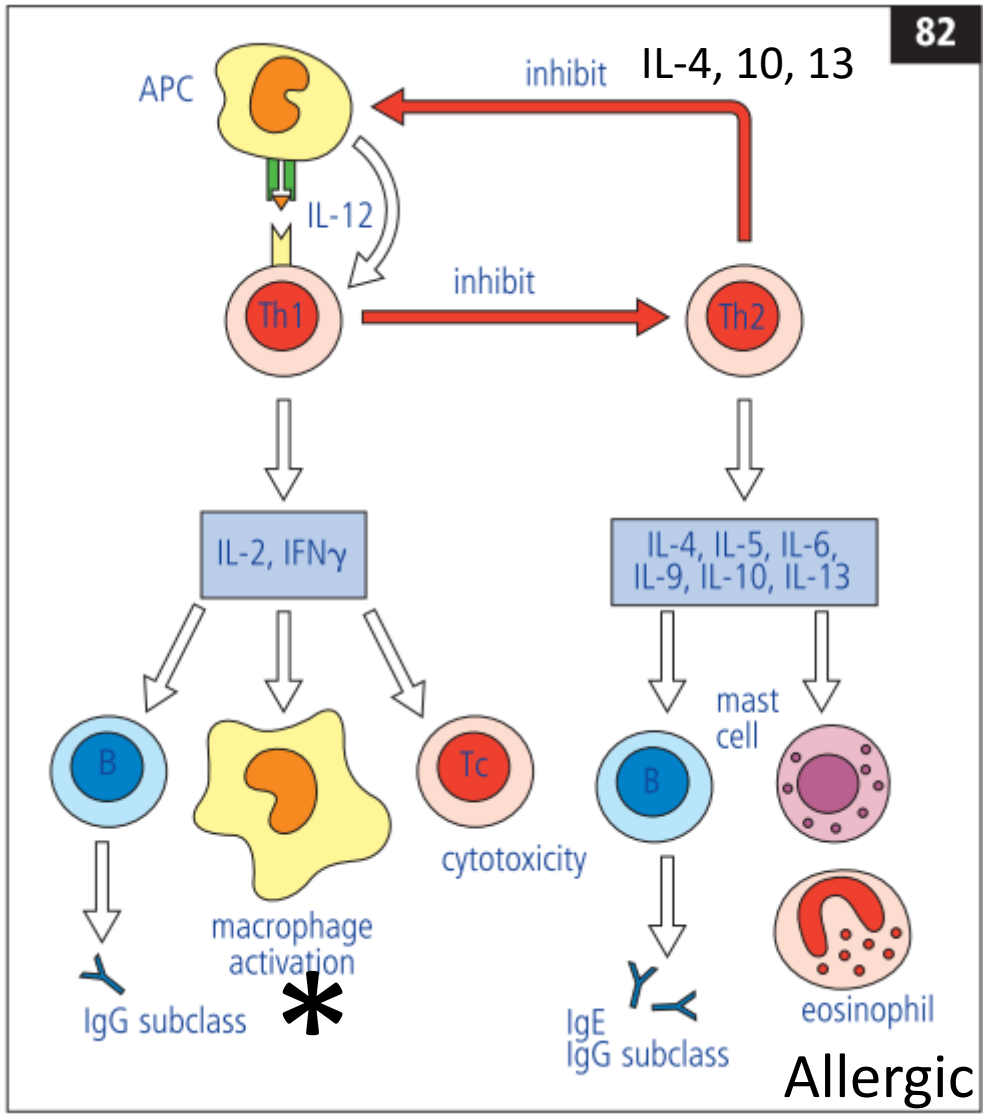
- Healing by fibrosis
- Abscess formation
- Granulomatous inflammation and granuloma formation
  - Nodular (tuberculoid) granulomas
  - Diffuse (lepromatous) granulomas
  - Sarcoids of horses
  - Eosinophilic granulomas
  - Others

Lymphocytes: immunologic responses



http://colgateimmunology.blogspot.com/2013/11/ikaros-plays-important-role-in-th17.html

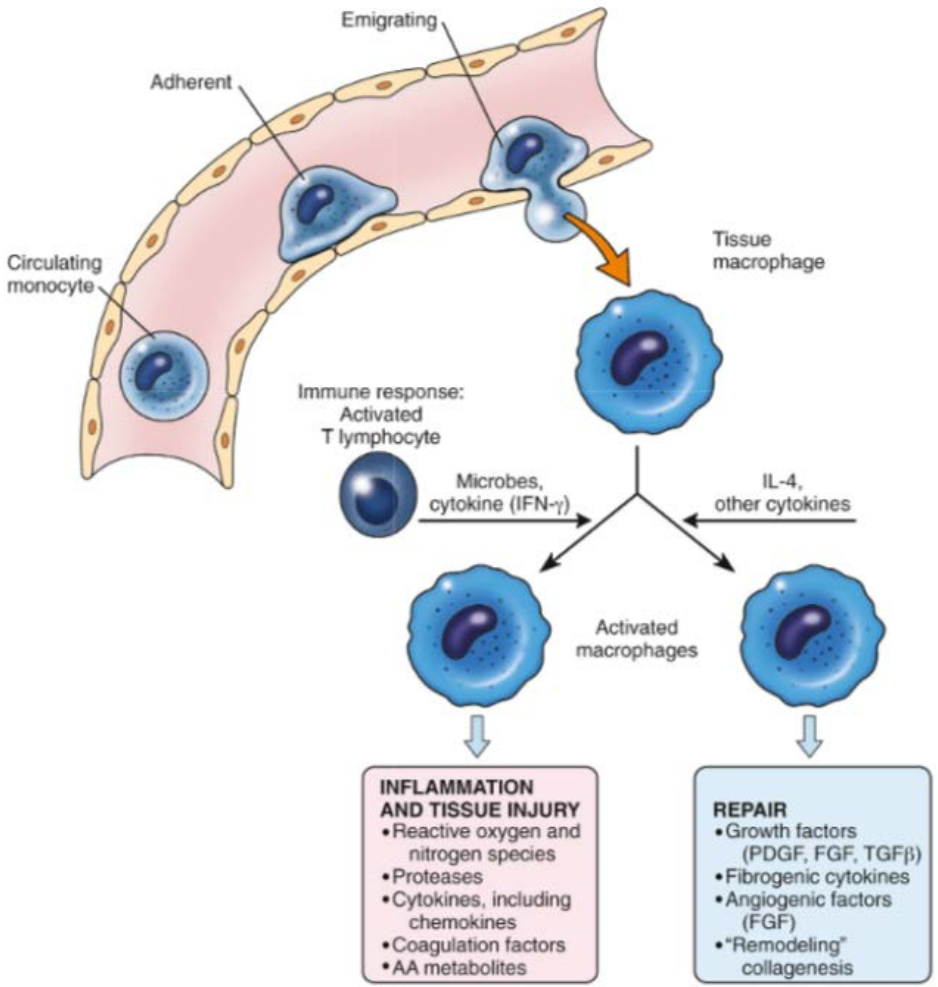
CD4+ T helper lymphocytes



Clinical Immunology of the Dog and Cat

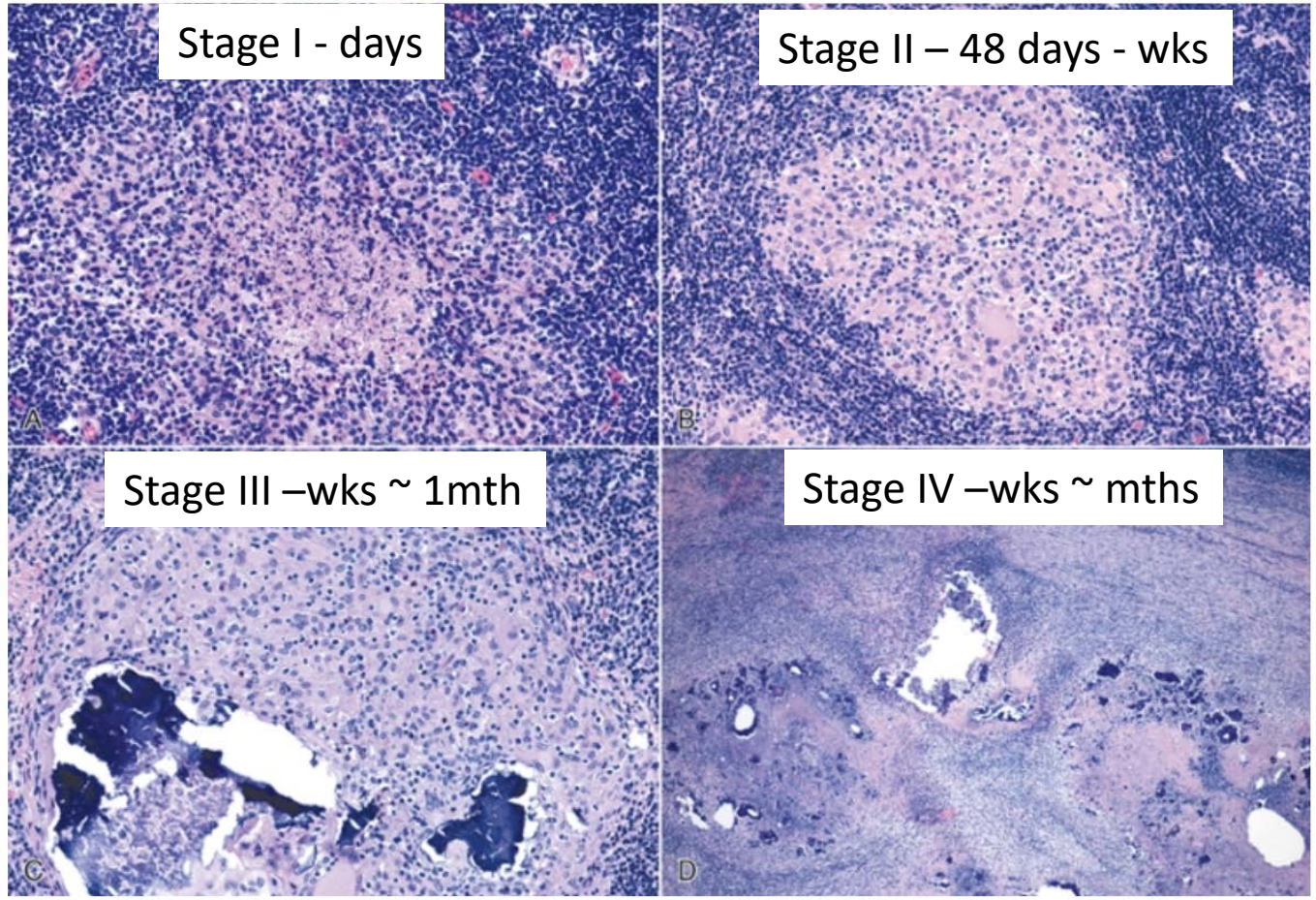
Allergic basis

Activated macrophages in chronic inflammation



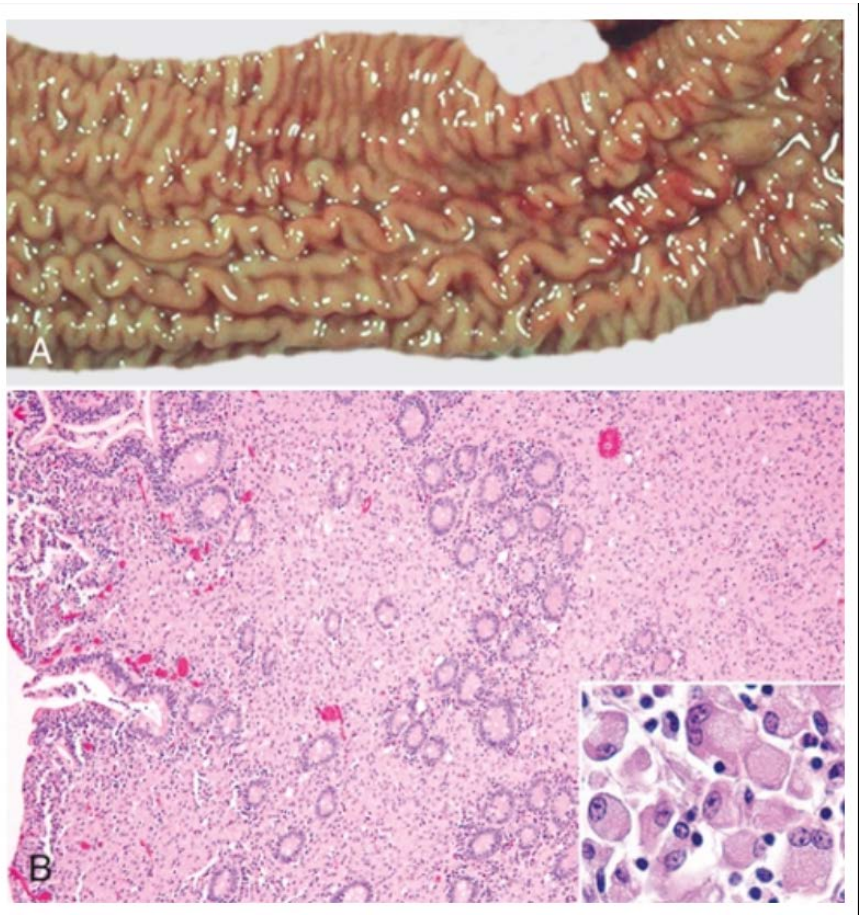
- Inflammation and tissue injury
  - Reactive oxygen and nitrogen species
  - Proteases
  - Cytokines, including chemokines
  - Coagulation factors
  - AA metabolites
- Repair
  - Growth factors (PDGF, FGF, TGF-beta)
  - Fibrogenic cytokines
  - Angiogenic factors (FGF)
  - "Remodeling" collagenesis

Nodular (tuberculoid) granulomas: T_H-1 biased

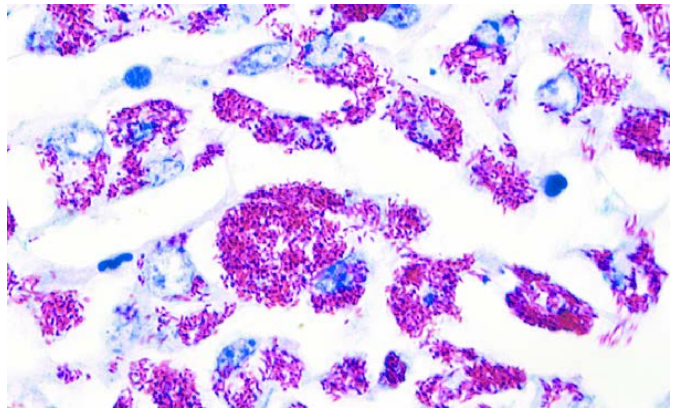


- Pathogens
  - *Mycobacterium bovis*
  - *Mycobacterium tuberculosis*
  - deep fungal infections, (i.g., coccidioidomycosis)
- Caseating granulomas
- Noncaseating granulomas

Diffuse (lepromatous) granulomas: T_H-2 biased



- Human: leprosy (*Mycobacterium leprae*)
- Cat: leprosy (*M lepraemurium)*
- Dog: leproid granuloma
- Cattle, sheep, goats: Johne's Diseae (*Mycobacterium avium* subsp. *Paratuberculosis)*



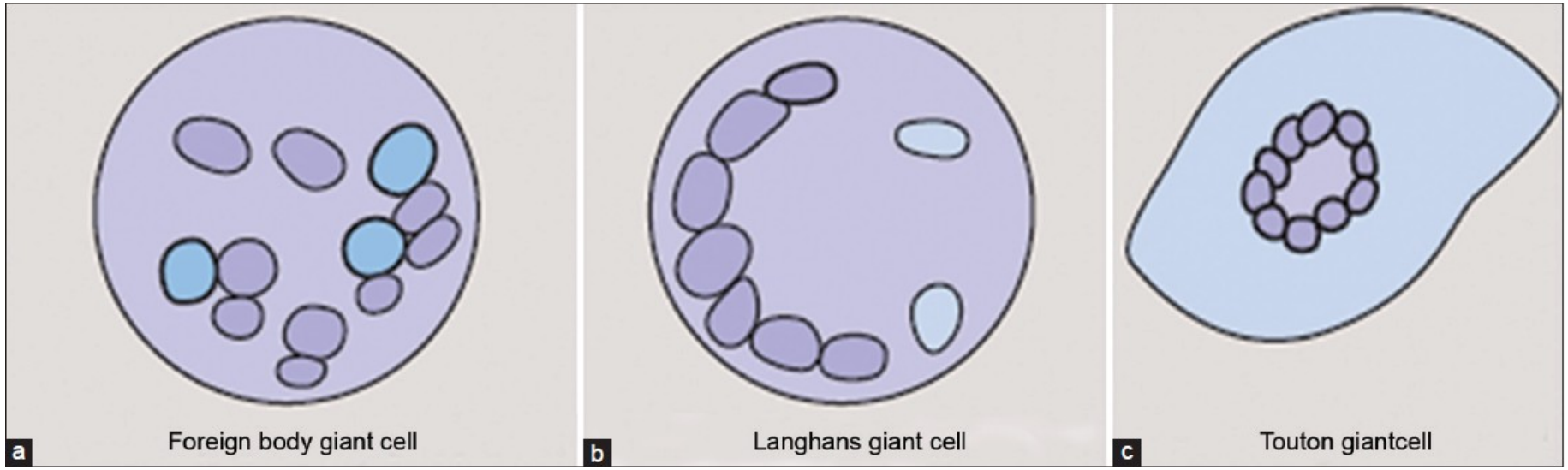
https://johnes.org/handouts/files/VA%20deer%20Sleeman.pdf

Epithelioid macrophages

- In response to foreign bodies or persistent intracellular pathogens
- ↓ Phagocytic capacity
- ↑ Presumed secretory capacity (↑ rER, Golgi complex, vesicles and vacuoles)

Multinucleated giant cells

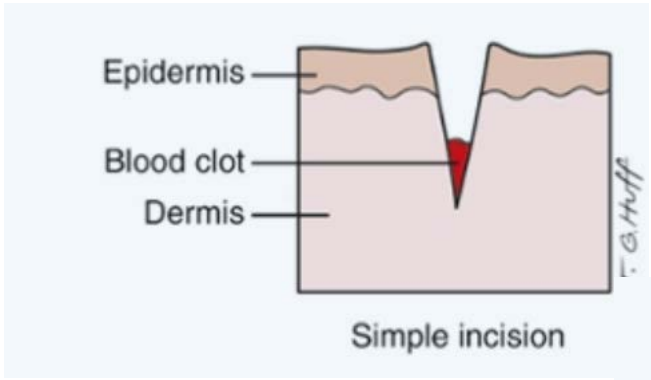
- In response to foreign bodies or persistent intracellular pathogens
- Formed by fusion of two or more activated macrophages

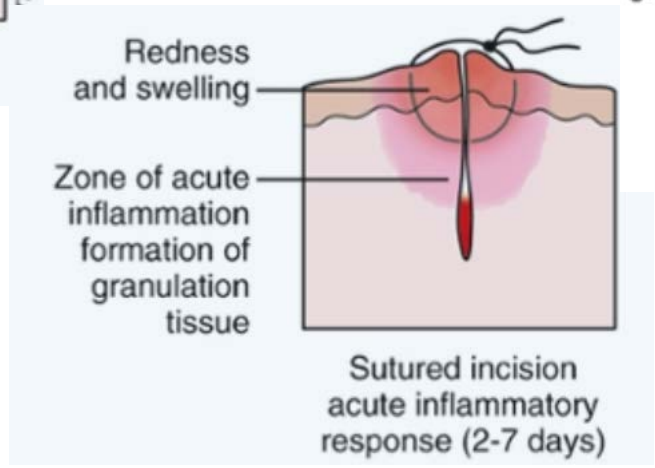


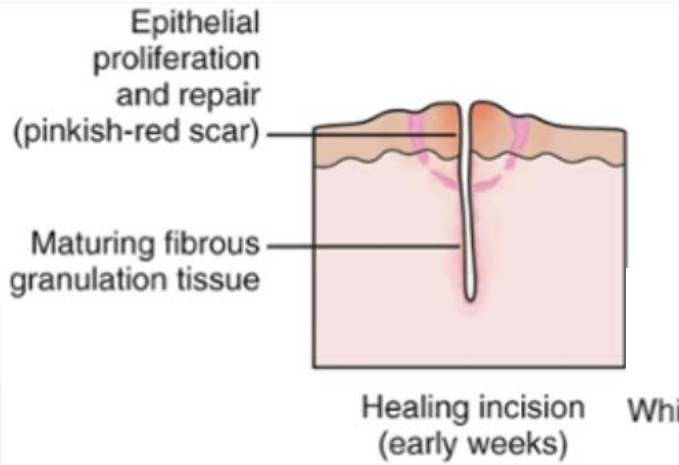
http://www.e-ijd.org/article.asp?issn=0019-5154;year=2014;volume=59;issue=5;spage=481;epage=484;aulast=Gupta

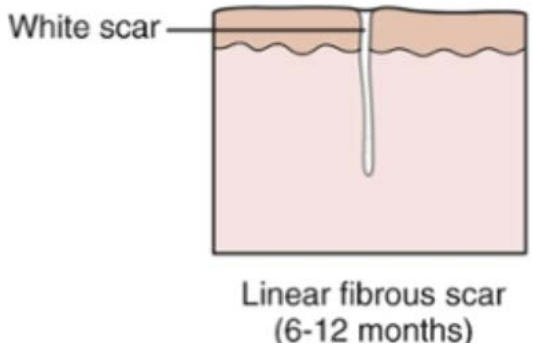
Wound healing and angiogenesis

- Wound healing by primary intention



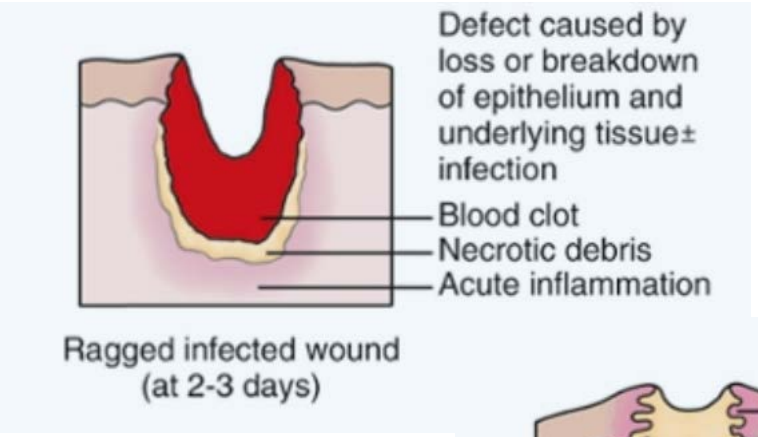




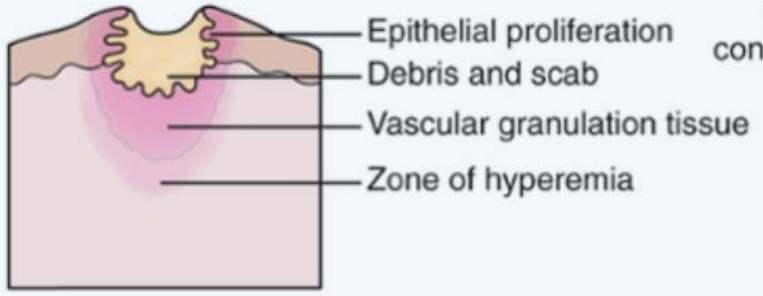


Wound healing and angiogenesis

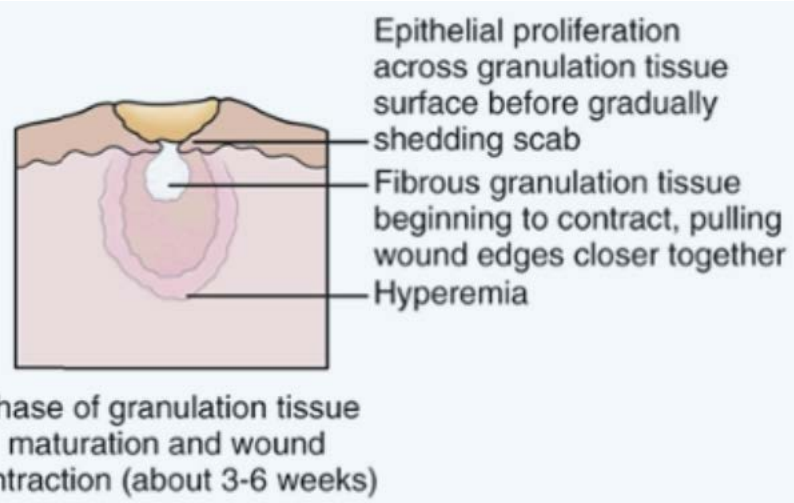
- Wound healing by secondary intention



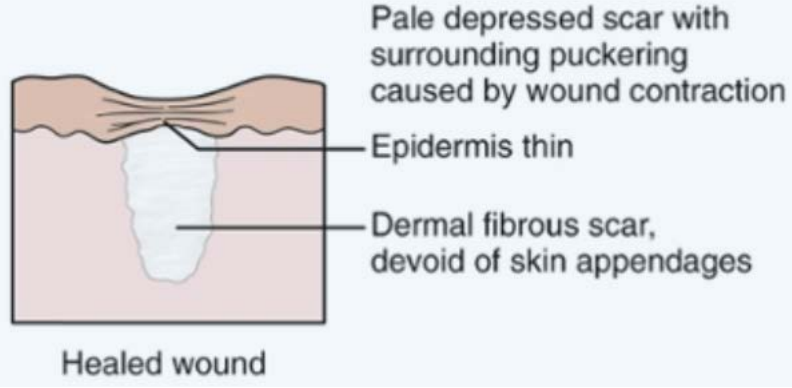
Ragged infected wound (at 2-3 days)



Phase of rapid proliferation of vascular granulation tissue (about 1-2 weeks)



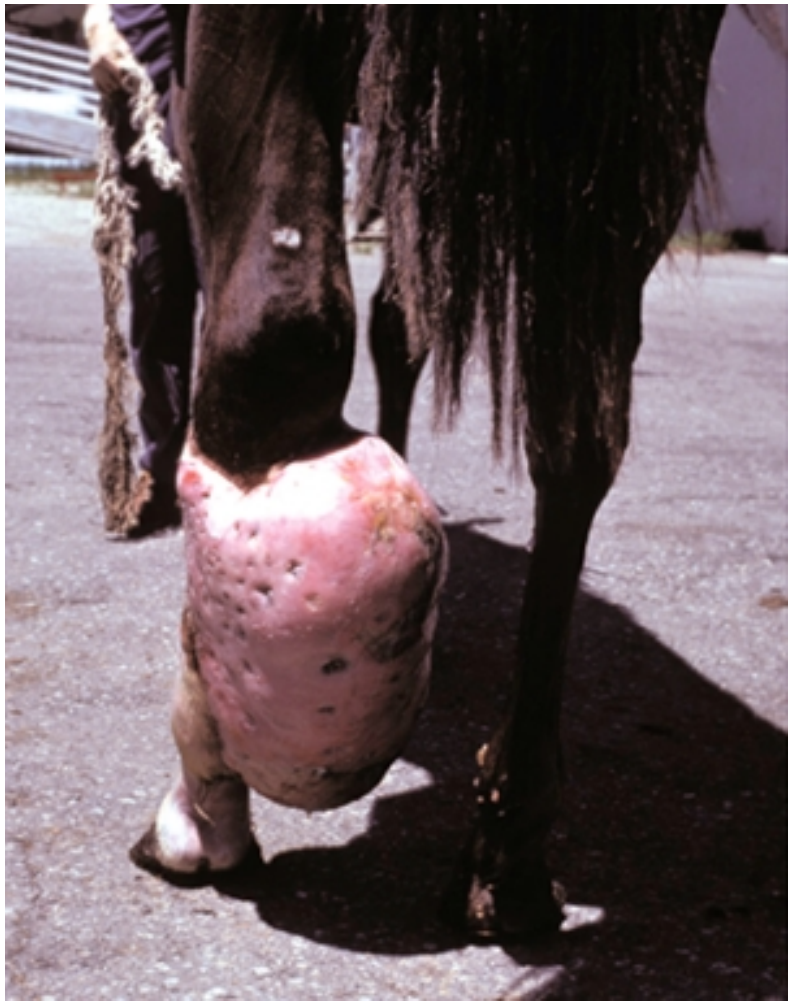
Phase of granulation tissue maturation and wound contraction (about 3-6 weeks)



Healed wound

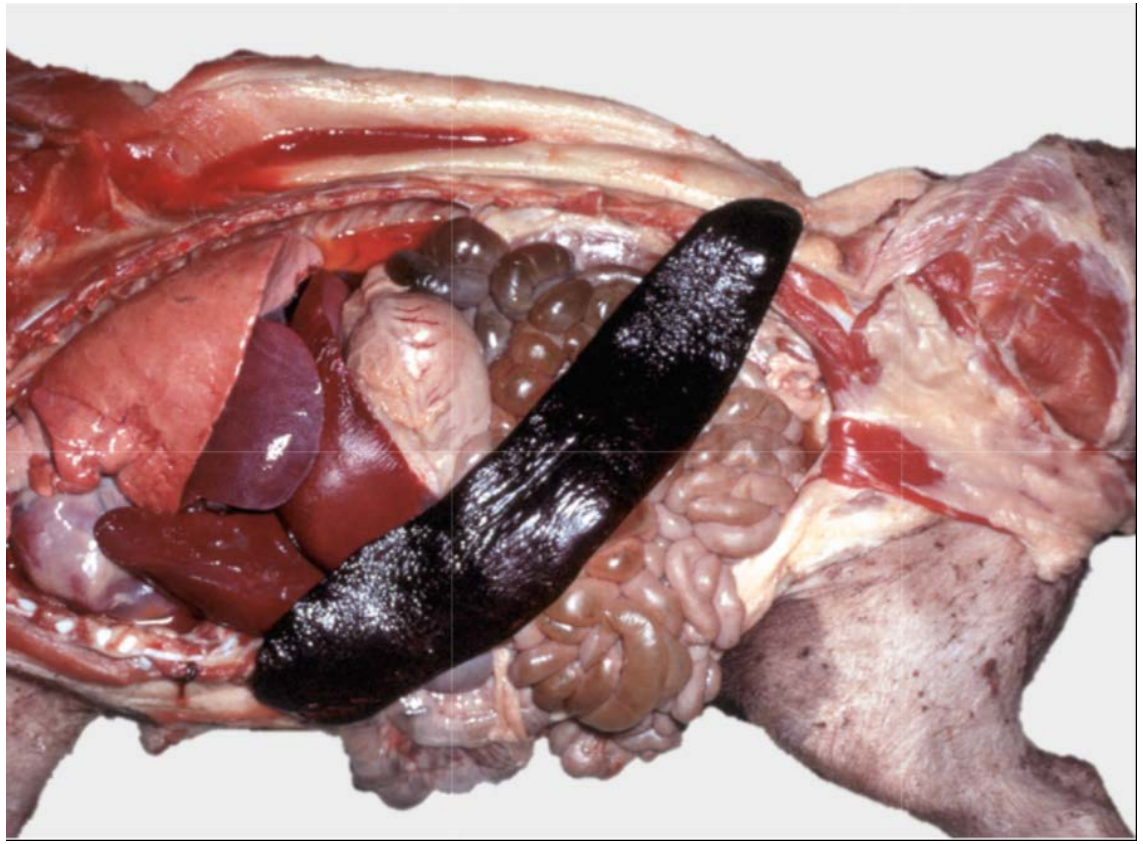
Granulation tissue

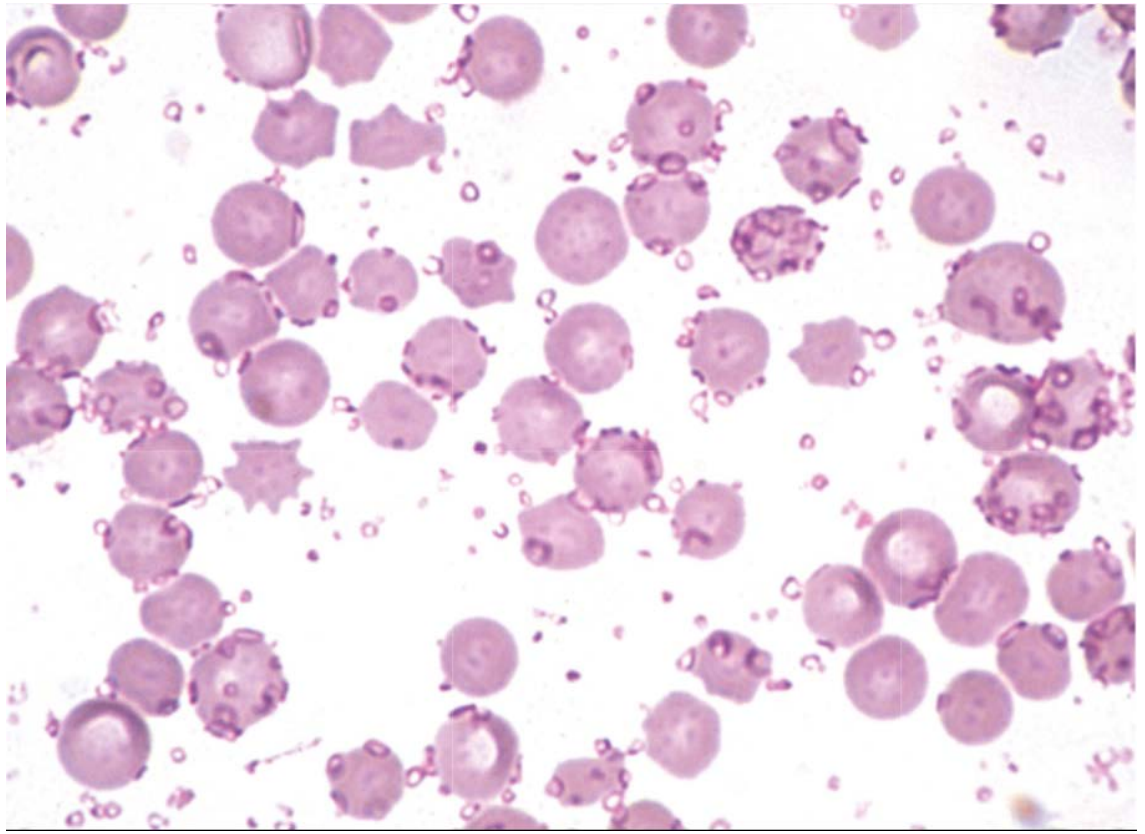
- Specific arrangement
  - Fibroblast parallel to wound surface
  - Fibroblast perpendicular to vessels
- Proud flesh in horses
  - Exuberant granulation tissue
  - Distal limbs



Mechanisms of Microbial Infections

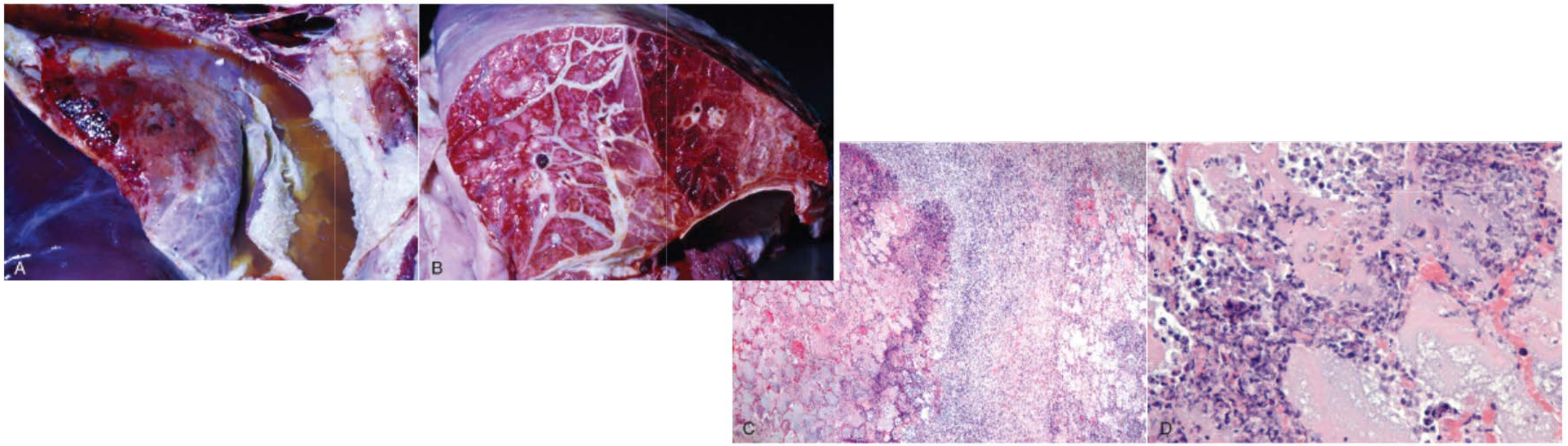
Mycoplasma suis (formerly *Eperythrozoon suis*)





Contagious bovine pleuropneumonia

- *Mycoplasma mycoides* var. *mycoides* small colony
- Vasculitis -> lung thrombosis, ischemia, infarction

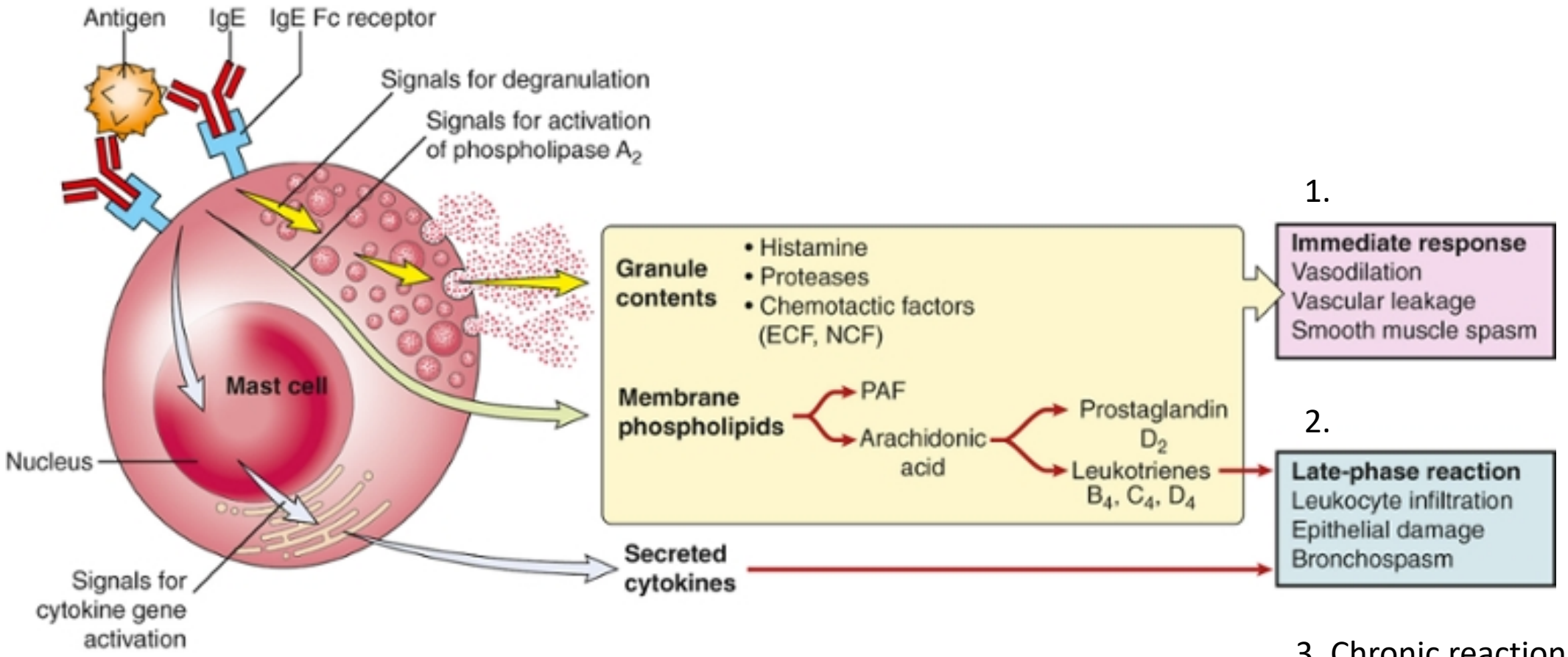


Diseases of Immunity

Type I (immediate) hypersensitivity

Items	Components
Immune component	IgE
Antigen	Allergens
Prototype	Anaphylaxis, allergies (atopic forms)
Mechanism	IgE -> vasodilation -> inflammatory cells
Lesions	Vasodilation, edema, smooth m contraction, inflammation

Degranulation and activation of mast cells



3. Chronic reaction

Type II (Ab-mediated) hypersensitivity

Items	Components
Immune component	IgG and IgM
Antigen	Cell- or matrix-associated antigens, cell surface receptor
Prototype	IMHA, isoerythrolysis, transfusion reaction, drug reaction, pemphigus
Mechanism	Binding and destroy target cells by activated complement or Fc receptors
Lesions	Cell lysis; inflammation

Type III (Immune-complex) hypersensitivity

Items	Components
Immune component	IgG and IgM
Antigen	Soluble Ag (e.g., bac/viral Ag)
Prototype	SLE, glomerulonephritis*, serum sickness, Arthus reaction
Mechanism	Deposition of IC -> inflammation
Lesions	Necrotizing vasculitis (fibrinoid necrosis); inflammation

Type IV (cell-mediated) hypersensitivity

Items	Components
Immune component	T lymphocytes
Antigen	Soluble Ag, contact Ag, Cell-associated Ag
Prototype	Contact dermatitis, transplant rejection, tuberculosis, chronic allergic diseases
Mechanism	Cytokine/macrophage activation; T-cell cytotoxicity
Lesions	Perivascular infiltrates, edema, cell destruction, granuloma