Infectious diseases

Mar 30, 2005

Robbins and Cotran Chapter 7

pp. 343-411

Tumor immunity

- Immune surveillance
  - Cancer immunoediting
- Tumor-specific antigens
- Tumor-associated antigens
- Anti-tumor effector mechanisms
  - CTL
  - NK cell
  - Macrophages
  - Antibodies

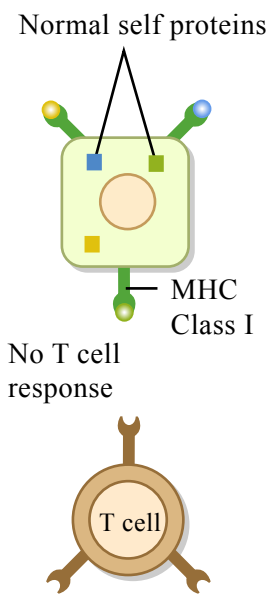
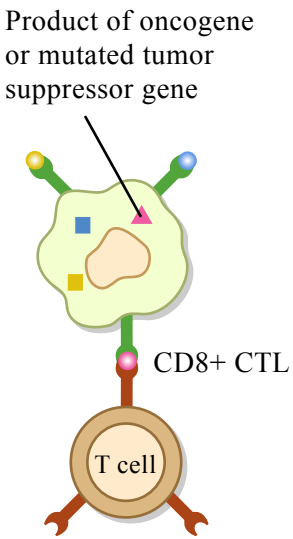
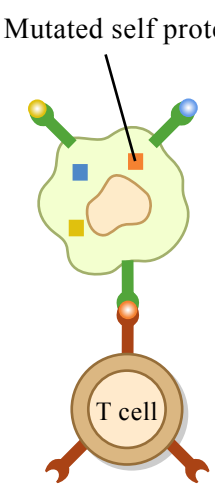
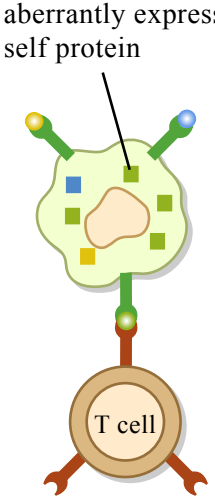
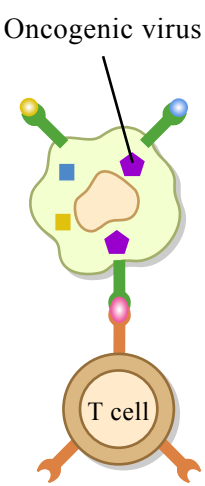
Normal host cell displaying multiple MHC-associated self antigens	Tumor cells expressing different types of tumor antigens			
				
Examples	Oncogene products: mutated RAS, Bcr/Abl fusion proteins Tumor suppressor gene products: mutated p53 protein	Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas	Overexpressed: tyrosinase, gp100, MART in melanomas Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)	Human papilloma virus E6, E7 proteins in cervical carcinoma: EBNA proteins in EBV induced lymphoma

Figure by MIT OCW.

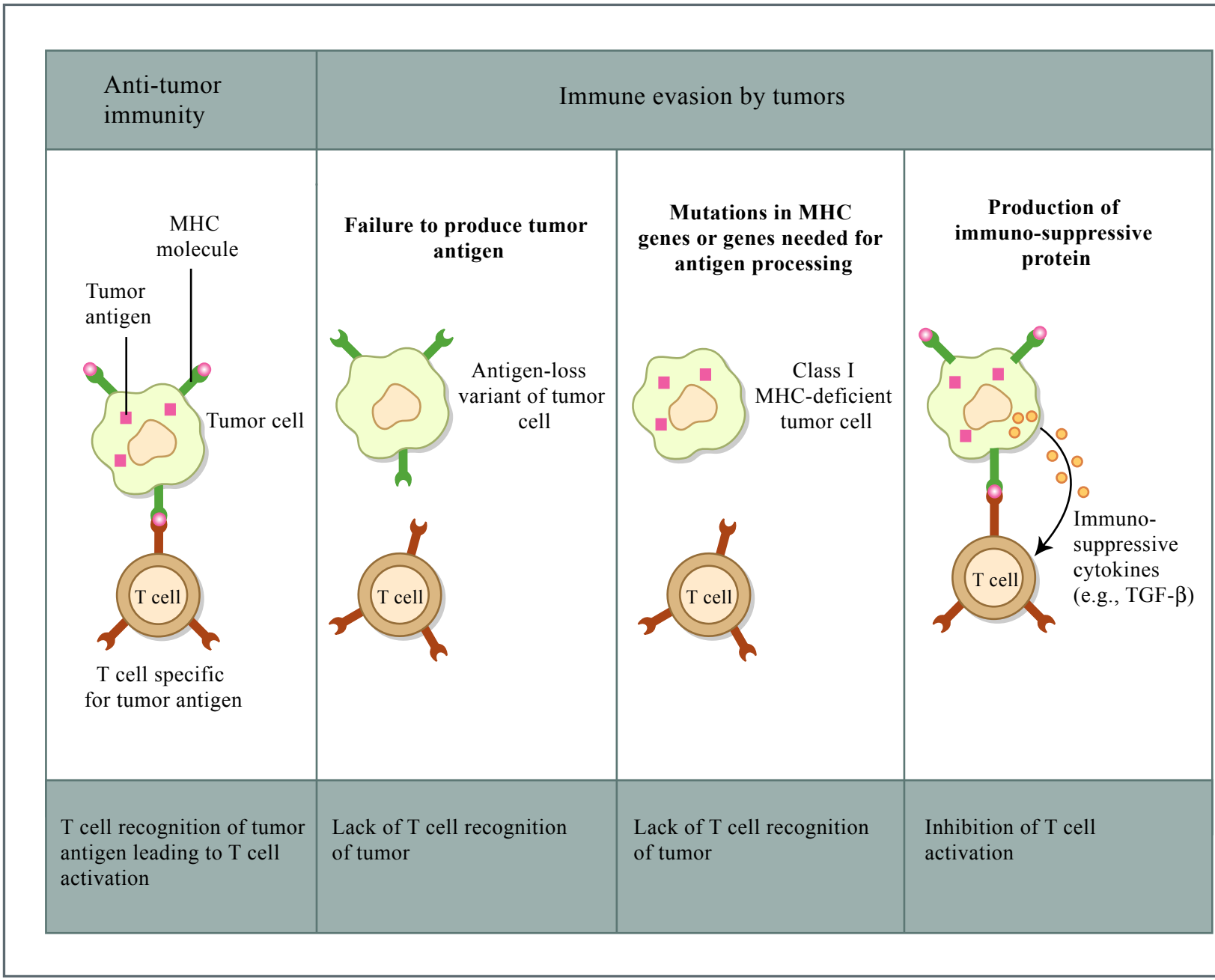


Figure by MIT OCW.

Koch's postulates

1) The organism is found in lesions of the disease
2) The organism can be isolated as single colonies on solid media
3) Inoculation of the organism causes lesions in experimental animals
4) The organism can be recovered from the experimental animal

Toxin Terminology

- **Exotoxin** = protein toxins of bacteria, in contrast to endotoxin (LPS)
  - Not all exotoxins are secreted; some accumulate inside the bacterium and are released by bacterial lysis
- **Cytotoxin** = target a wide range of cell types, in contrast to neurotoxins, leukotoxins, hepatotoxins, cardiotoxins

More Toxin Terminology

- Toxins can be named for the bacterial species that produce them, such as cholera toxin, Shiga toxin, diphtheria toxin and tetanus toxin
- Toxins can be named for their activities, such as adenylate cyclase, lecithinase
- Toxins can be simply given letter designations, such as exotoxin *A*

Toxin Classification by Mechanism

- Type I toxins bind to the host cell surface, but they are not translocated into the host cell (i.e. superantigens [Sag])
- Type II toxins disrupt eukaryotic cell membranes (i.e. phospholipases, and pore-forming toxins)
- Type III toxins are A-B toxins, which have a binding (B) component and active (A) component

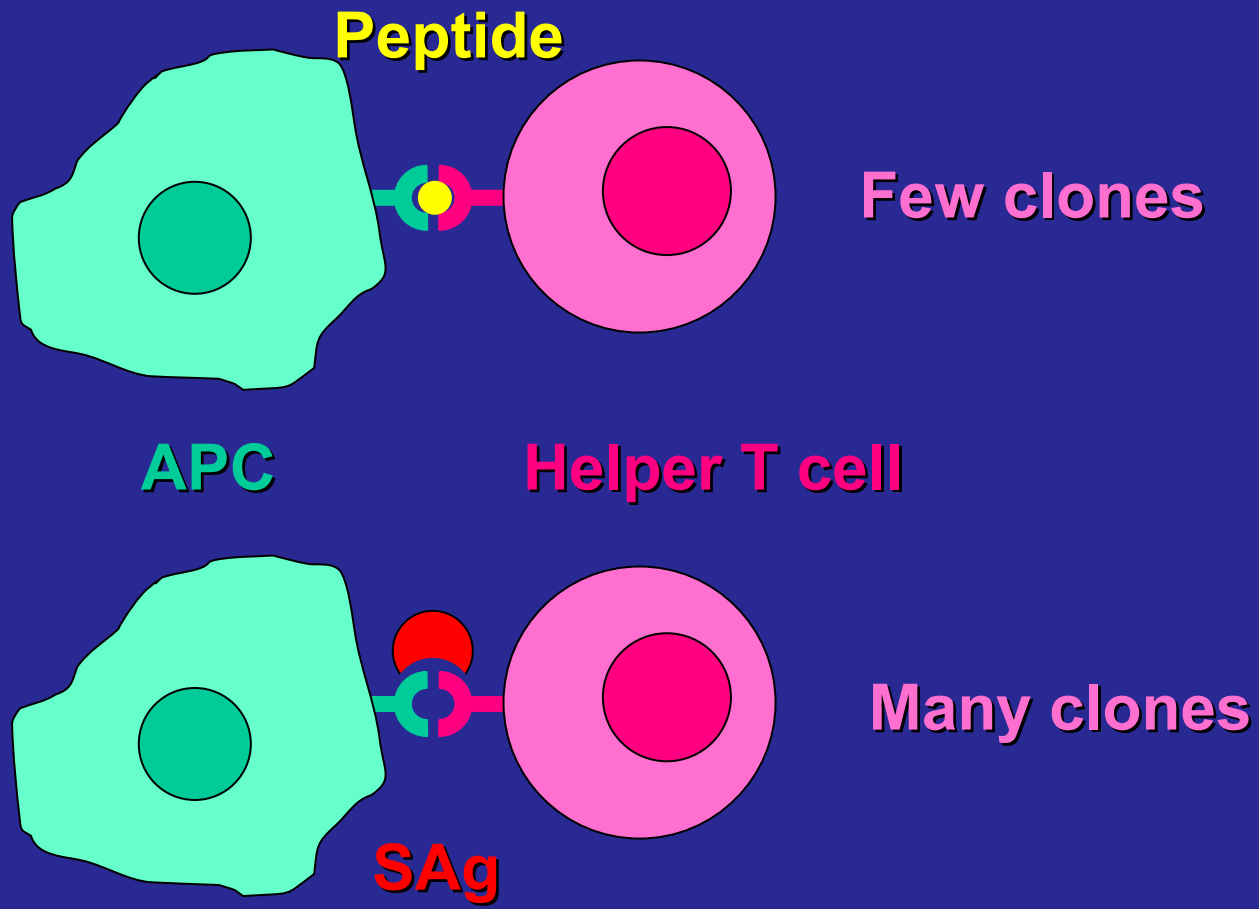
Superantigens (Type I) Toxins

- Toxic shock syndrome toxin (TSST) (toxic shock syndrome)
- Streptococcal pyrogenic exotoxin (Spe) (toxic shock-like syndrome and scarlet fever)
- Staphylococcal enterotoxin (food poisoning)

Hormone Analog

- STa (heat-stable toxin) (diarrhea)

Superantigens (Type I Toxins)



Membrane-Disrupting (Type II) Toxins

- Alpha-toxin (gas gangrene)
- Alpha-toxin (necrosis)
- Listeriolysin O (LLO) (listeriosis)
- Pneumolysin (pneumonia)
- Streptolysin O (SLO) (rheumatic fever)
- Hemolysin A (Hly A) (urinary tract infections and peritonitis)

Membrane-Disrupting (Type II) Toxins

- Two types of membrane-disrupting toxins
  - Pore-forming toxins insert holes in the membrane
  - Enzymes cleave bonds in membrane phopholipids
- Erythrocytes provide a convenient method to assay activity, so these toxins are often called hemolysins

Role of Membrane Disrupting Toxins

- In some cases, the primary role appears to be killing of professional phagocytes, such as neutrophils and macrophages
- In other cases, they are used by invasive bacteria to escape from a phagosome and enter the host cell cytoplasm

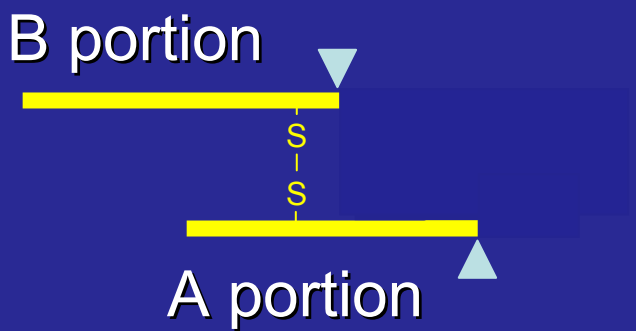
A-B (Type III) Toxins

- Diphtheria toxin (diphtheria)
- Cholera toxin (cholera)
- LT (heat-labile toxin) (infant diarrhea and traveler's diarrhea)
- Shiga toxin (dysentery and hemolytic uremic syndrome [HUS])
- Botulinum toxin (botulism)
- Tetanus toxin (tetanus)
- Pertussis toxin (whooping cough)

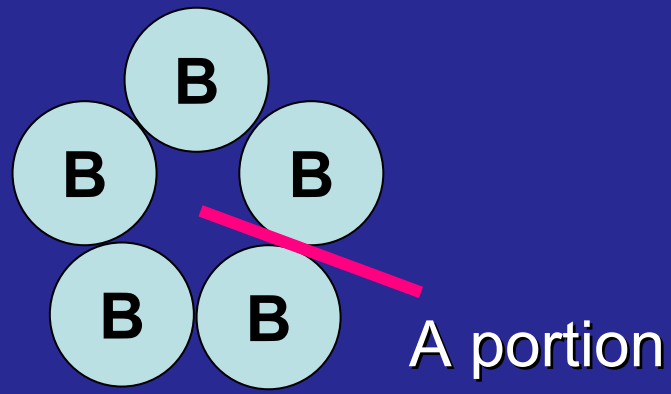
A-B (Type III) Toxins

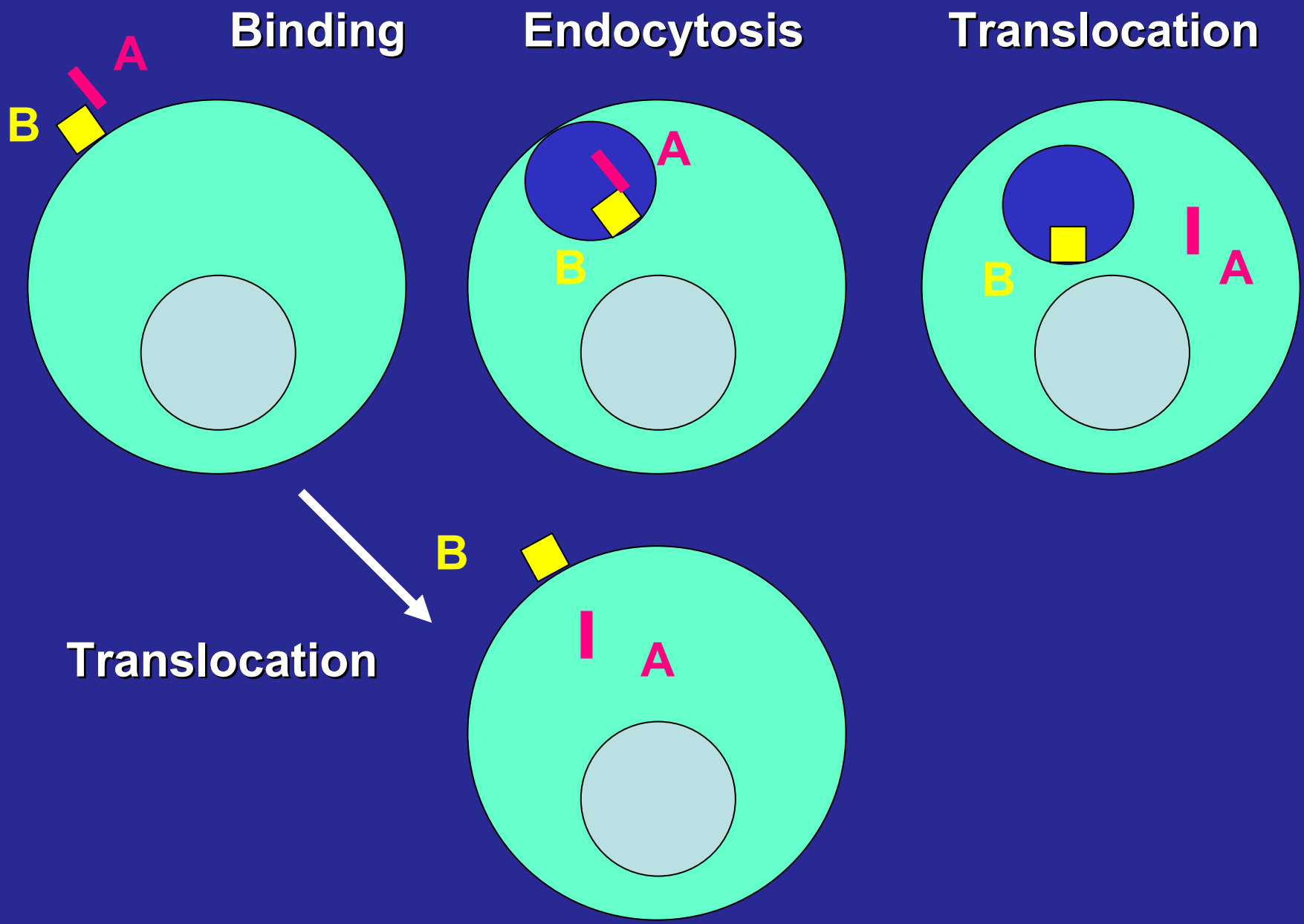
- First toxins studied
  - Historically more interest in A-B toxins than Type I or type II
- Simple A-B toxins are synthesized as a single polypeptide
  - Often A and B portions are separated during processing by proteolytic cleavage
- Compound A-B toxins are composed of multiple B monomers

Simple A-B toxin



Compound A-B toxin




Binding
Endocytosis
Translocation
A
B
A
B
B
A
Translocation
B
A

More About A-B Toxins

- Often the surface receptor for the B subunit is the carbohydrate moiety of a glycoconjugate
- Distribution of receptor determines target cell specificity
- In some cases, the A subunit needs to be enzymatically activated within the cytoplasm, by host cell proteins

Mechanisms of Action of A-B Toxins

- Although A-B toxins target many different cell types, many of them catalyze the same reaction
- ADP-ribosylation, the transfer of ADP-ribose from NAD to a target protein, changes the behavior of the target protein
  - Diphtheria toxin inactivates elongation factor-2
  - Cholera toxin constitutively activates a G_s GTP-binding protein that regulates adenylate cyclase

NIAID Category A & B Priority (Bacterial) Pathogens

Category A

- Bacillus anthracis
- Clostridium botulinum
- Yersinia pestis
- Francisella tularensis

Category B

- Burkholderia pseudomallei
- Coxiella burnetti
- Brucella species
- Burkholderia mallei
- Rickettsia prowazekii
- Ricin toxin
- Epsilon toxin of Clostridium perfringens
- Staphylococcus enterotoxin B
- Food and waterborne bacteria
  - E. coli, Vibrios, Shigella, Salmonella, Listeria, Campylobacter jejuni, & Yersinia enterocolitica

Select Agents (Partial List)

- Rickettsia prowazekii
- Rickettsia rickettsii
- Yersinia pestis
- Ricin toxin
- Shiga-like toxins
- Bacillus anthracis
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia mallei
- Burkholderia pseudomallei
- Coxiella burnetii
- Francisella tularensis
- Botulinum neurotoxin
- Clostridium perfringens epsilon toxin
- Shiga toxin
- Staphylococcal enterotoxin

Infection and cancer

- During the past 20 years, 4 new infectious causes of cancer have been discovered
  - *Helicobacter pylori*, hepatitis C virus (HCV), papillomavirus, and human herpesvirus 8 (HHV-8)
- *H. pylori* causes gastric cancer (2nd most important cause of cancer death worldwide)
- Papillomavirus causes the vast majority of cervical cancer (2nd most important cause of cancer in women)
- Liver cancer caused by hepatitis viruses (ranks 6th in worldwide cancer incidence)

Between 15 and 20% of cancers due to underlying infection

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Source:

Parsonnet, Julie. Microbes and Malignancy. 1st ed. Oxford, UK: Oxford University Press, 1999. ISBN: 0195104013.

Mammalian oncoviruses

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- Peyton Rous won a Nobel Prize in 1966 for work he published in 1911
- Dulbecco, Temin, and Baltimore 1975
- Bishop and Varmus 1989 for *v-src* (Rous sarcoma virus)

Viruses linked to human neoplasia

Virus	Acute infection	Tumor
Human T lymphotropic virus-1	Smoldering leukemia	Adult T cell leukemia
Epstein-Barr virus	Infectious mononucleosis	B cell lymphomas Burkitt's lymphoma
Hepatitis B virus Hepatitis C virus	Hepatitis B Hepatitis C	Hepatocellular carcinoma
Human papilloma virus	Squamous intra-epithelial neoplasia	Cancer of the cervix
Human herpesvirus type 8	?	Kaposi's sarcoma

Transformation by high-risk HPV

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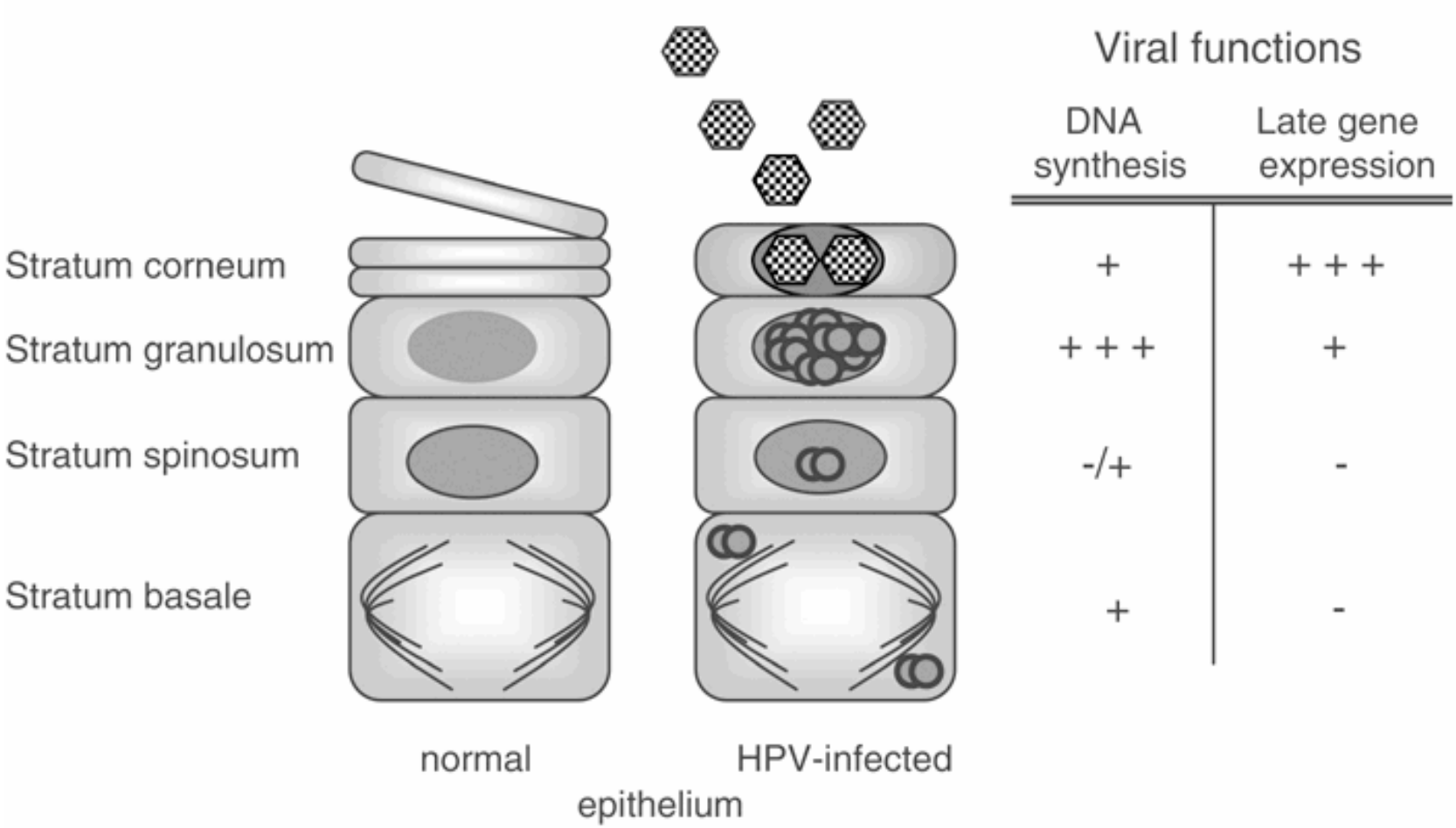
Please see:

Scheffner, M., and NJ. Whitaker. "Human papillomavirus-induced carcinogenesis and the ubiquitin-proteasome system." Seminars in Cancer Biology 13 (2003): 59 - 67.

HPV tropism for squamous epithelium



Source: Fehrmann, F. and L.A. Laimins. "Human papillomaviruses: targeting of differentiating epithelia for malignant conversion." Oncogene 22 (2003): 5201-5207.

Infectious group 1 carcinogens

Organism	Cancer	Distribution
Helicobacter pylori	Gastric cancer	Worldwide
Schistosoma haematobium	Urinary bladder cancer	Africa and the Middle East
Opisthorchis vivirreni	Bile duct cancer	Northeast Thailand

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, Liver Flukes, and *Helicobacter pylori*. Vol 61. Lyon:IARC, 1994

Geographical distribution of schistosomiasis

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Helicobacter pylori

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Suerbaum S, and P. Michetti. "*Helicobacter pylori* infection." *New England Journal of Medicine* 347 (2003):1175.

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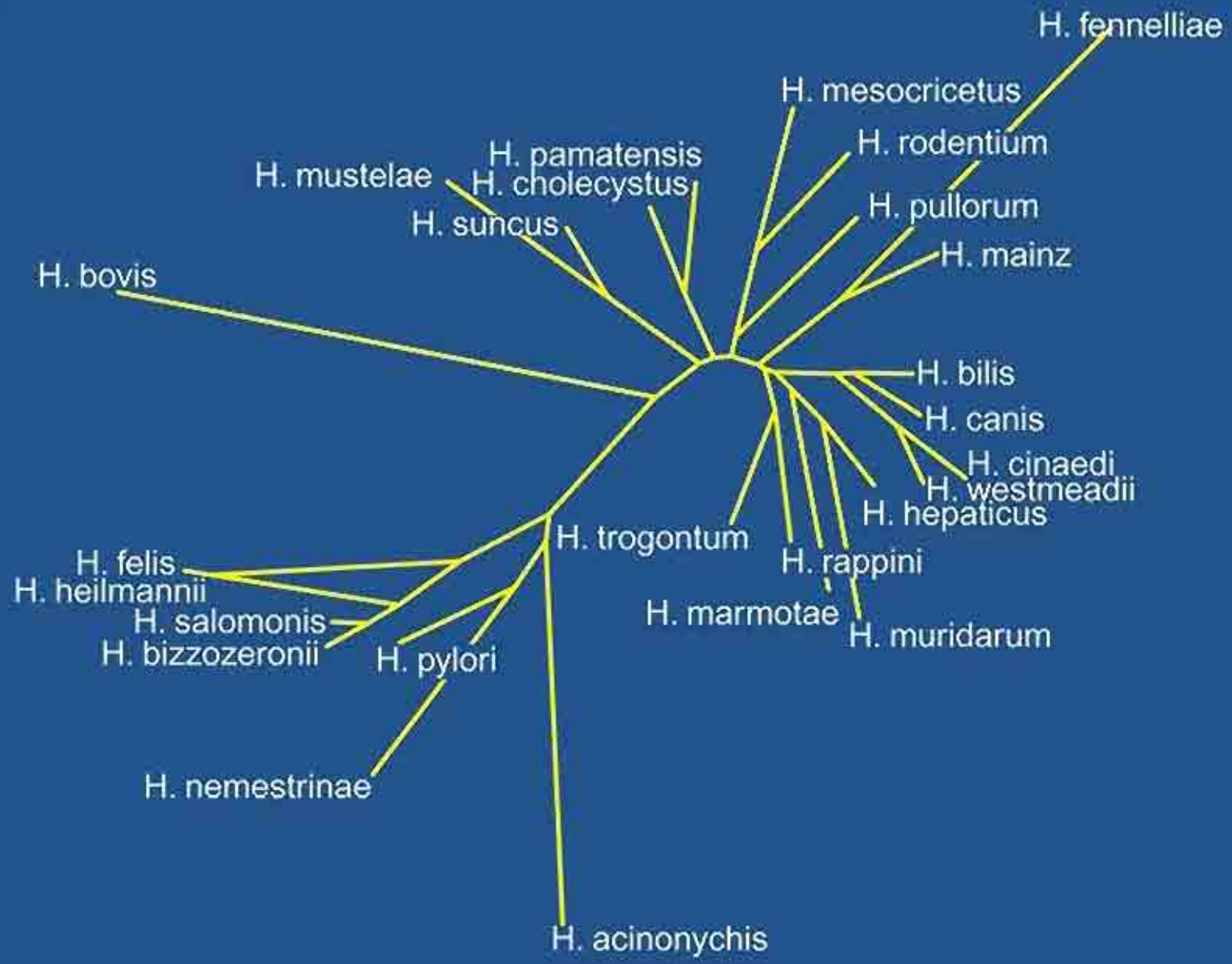
Please see:

Haruma, K., and M. Ito. "Review article: clinical significance of mucosal-protective agents: acid, inflammation, carcinogenesis and rebamipide." Aliment Pharmacology Therapy 18, Supplement 1 (2003): 153.


H. fennelliae
H. mesocricetus
H. rodentium
H. pullorum
H. mainz
H. pamatensis
H. cholecystus
H. mustelae
H. suncus
H. bovis
H. bilis
H. canis
H. cinaedi
H. westmeadii
H. hepaticus
H. trogontum
H. rappini
H. marmotae
H. muridarum
H. felis
H. heilmannii
H. salomonis
H. bizzozeronii
H. pylori
H. nemestrinae
H. acinonychis