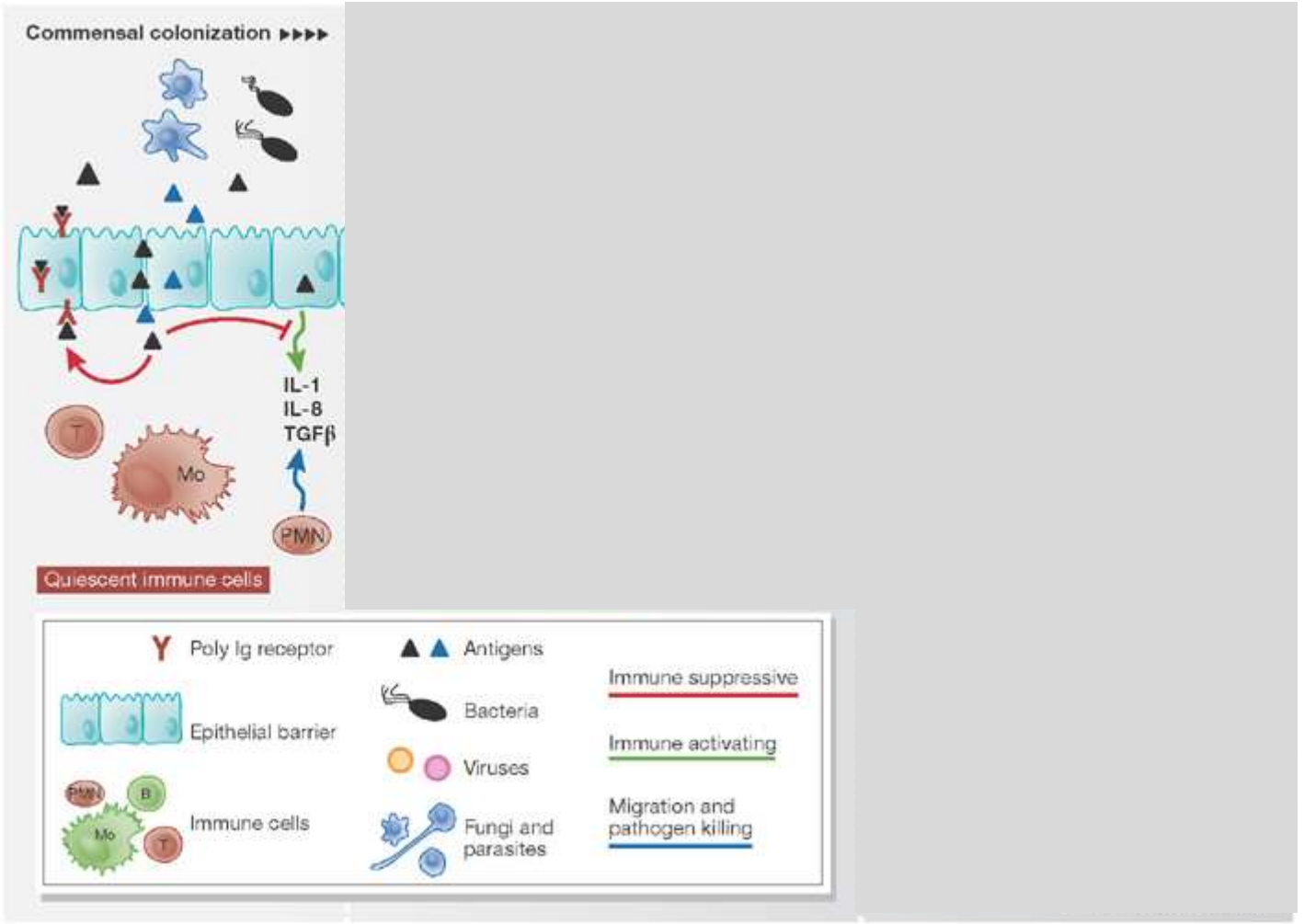
Inmunología Clínica 2009

Bioq Graciela R Svibel de Mizdraji

Inmunología en las infecciones



The diverse outcomes of host–microbe interactions. Bacteria, viruses, fungi and eukaryotic parasites occupy various niches within the host. During colonization of mucosal tissues by commensal organisms (left), immune quiescence is actively maintained by both host and microbial factors. Conversely, the host immune system is activated during invasive infections (centre), although pathogenic microbes attempt to suppress immune activation. Some non-lethal invasive infections are resolved by the elimination of the infectious agent through (often adaptive) immune responses (centre right). Alternatively, some microbes can deflect the immune response through immune suppression or activation, enabling them to establish chronic infections (right). B, B cell; CXC, CXC chemokines; DC, dendritic cell; γHSV68, γ-herpes simplex virus 68; IFNγ, interferon-γ; IL, interleukin; Mo, macrophage; PMN, polymorphonuclear cell or neutrophil; T, T cell; TGFβ, transforming growth factor-β.

EMBO reports **9**, 1, 27–32 (2008)

Relaciones entre los microorganismos y el hospedador

SIMBIOSIS		
Comensalismo	**Mutualismo**	**Parasitismo**
Un organismo se beneficia y el otro no se perjudica	Ambos organismos se benefician	Un organismo se beneficia a expensas del otro
Ej.: Bacterias de la microflora que viven a expensas de secreciones en ojos, oídos o genitales externos.	Ej.: *E. coli* en el intestino humano, sintetiza vitamina K – obtiene nutrientes y protección	Ej.: *Giardia lamblia* se adhiere a las paredes intestinales y dificulta la absorción de nutrientes.

Relaciones entre los microorganismos

Además de las anteriores, entre microorganismos ocurre

Exclusión competitiva o antagonismo microbiano

Importante entre la flora normal y los patógenos

¿Qué son las enfermedades infecciosas?

- Enfermedades producidas por agentes tales como bacterias, protozoos, hongos, virus y otros parásitos denominados **PATÓGENOS** (pero no todos los microorganismos son patógenos)
- Las fuentes más importantes de patógenos son el suelo, agua contaminada, animales infectados, incluso otras personas….

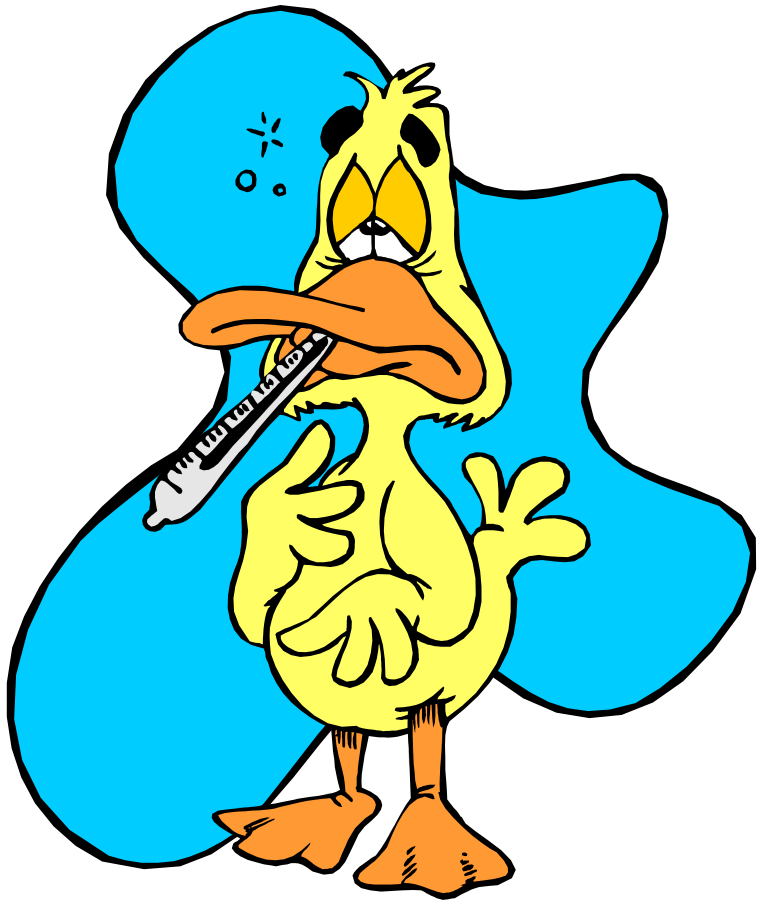


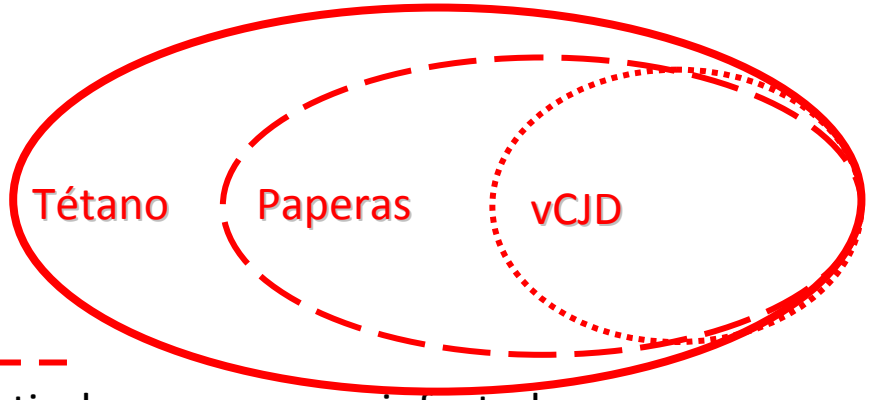
Table 14.12 Terms Used to Classify Infectious Diseases

Term	Definition
Acute disease	Disease in which symptoms develop rapidly and that runs its course quickly
Chronic disease	Disease with usually mild symptoms that develop slowly and last a long time
Subacute disease	Disease with time course and symptoms between acute and chronic
Asymptomatic disease	Disease without symptoms
Latent disease	Disease that appears a long time after infection
Communicable disease	Disease transmitted from one host to another
Contagious disease	Communicable disease that is easily spread.
Noncommunicable disease	Disease arising from outside of hosts or from opportunistic pathogen
Local infection	Infection confined to a small region of the body
Systemic infection	Widespread infection in many systems of the body; often travels in the blood or lymph
Focal infection	Infection that serves as a source of pathogens for infections at other sites in the body
Primary infection	Initial infection within a given patient
Secondary infection	Infections that follow a primary infection; often by opportunistic pathogens

Enfermedades infecciosas

Definiciones

- **Enfermedades infecciosas**
  - Causadas por un agente infeccioso
- **Enfermedades comunicables**
  - Transmisión – directa o indirecta – a partir de una persona infectada
- **Enfermedades transmisibles**
  - Transmisión– a través de rutas no convencionales – a partir de una persona infectada



Microorganismos patógenos

Infección: Invasión o colonización de una parte o la totalidad del cuerpo por microorganismos patógenos

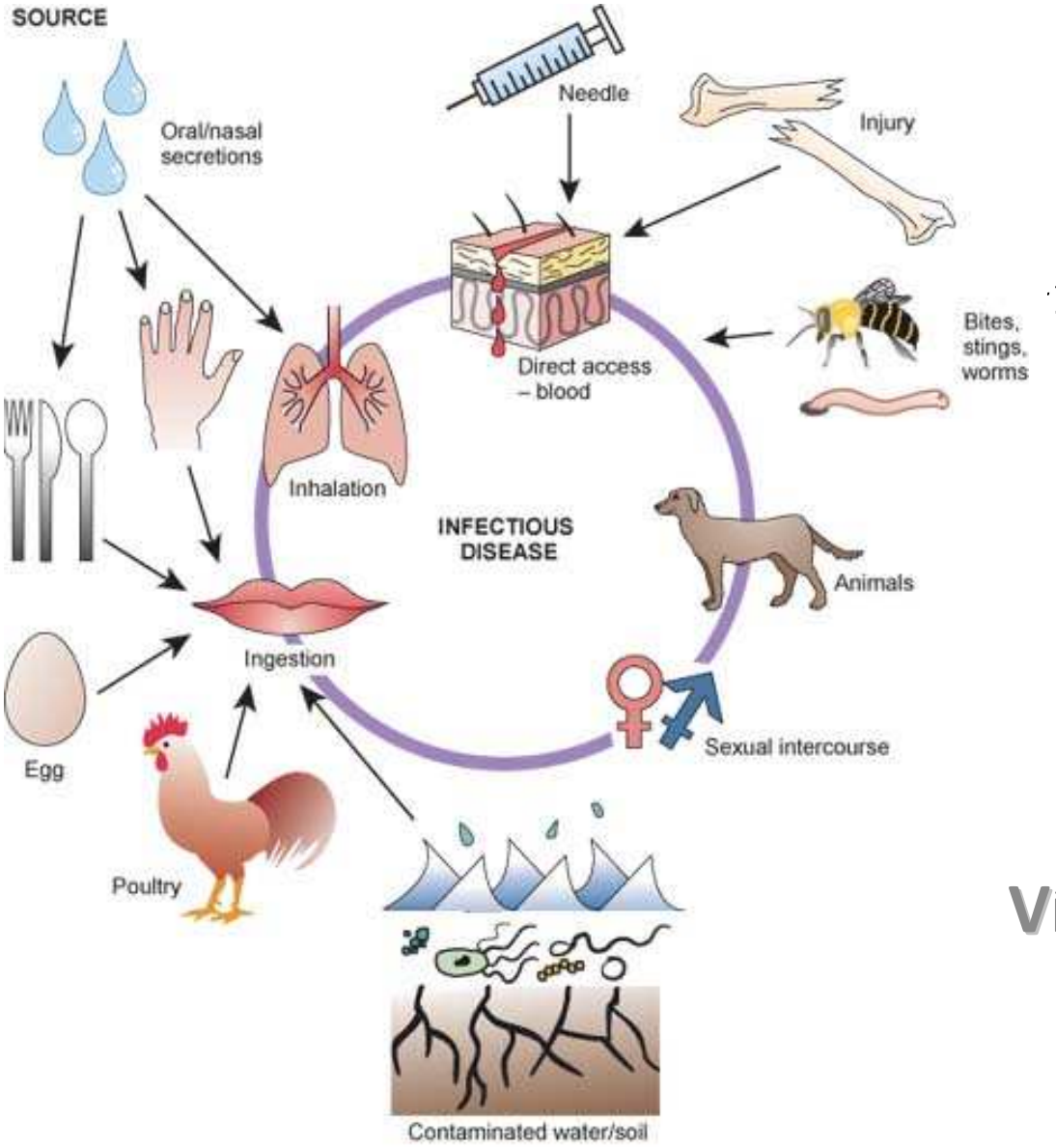
Enfermedad infecciosa: estado en el que la infección produce un daño en el cuerpo (pérdida de la salud)

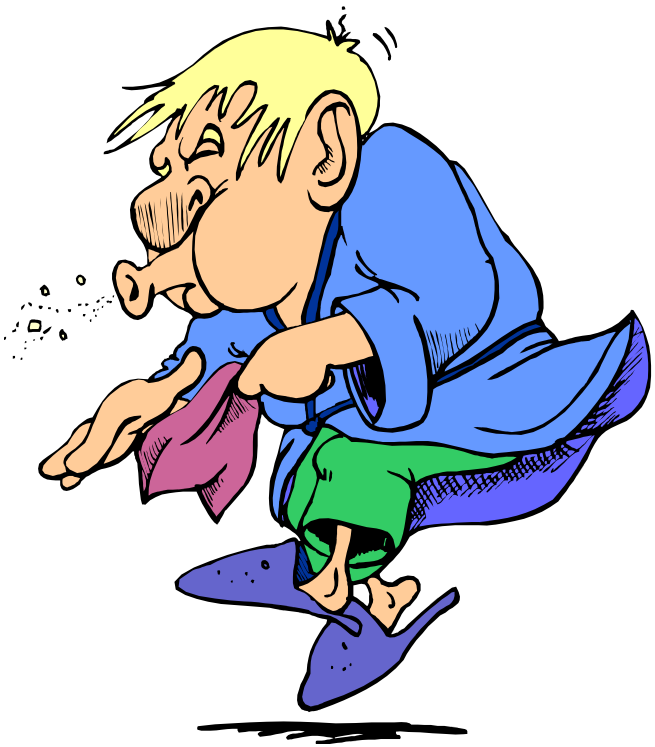
Etiología: causa de la enfermedad – Ej: "etiología infecciosa", "etiología bacteriana" "etiología viral"

RUTAS DE INFECCIÓN

Routes of infection for pathogens			
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**
Mucosal surfaces			
Airway	Inhaled droplet	Influenza virus	Influenza
	Spores	*Neisseria meningitidis*	Meningococcal meningitis
		Bacillus anthracis	Inhalation anthrax
Gastrointestinal tract	Contaminated water or food	*Salmonella typhi*	Typhoid fever
		Rotavirus	Diarrhea
Reproductive tract	Physical contact	*Treponema pallidum*	Syphilis
		HIV	AIDS
External epithelia			
External surface	Physical contact	*Trichophyton*	Athlete's foot
Wounds and abrasions	Minor skin abrasions	*Bacillus anthracis*	Cutaneous anthrax
	Puncture wounds	*Clostridium tetani*	Tetanus
	Handling infected animals	*Francisella tularensis*	Tularemia
Insect bites	Mosquito bites (*Aedes aegypti*)	Flavivirus	Yellow fever
	Deer tick bites	*Borrelia burgdorferi*	Lyme disease
	Mosquito bites (*Anopheles*)	*Plasmodium* spp.	Malaria

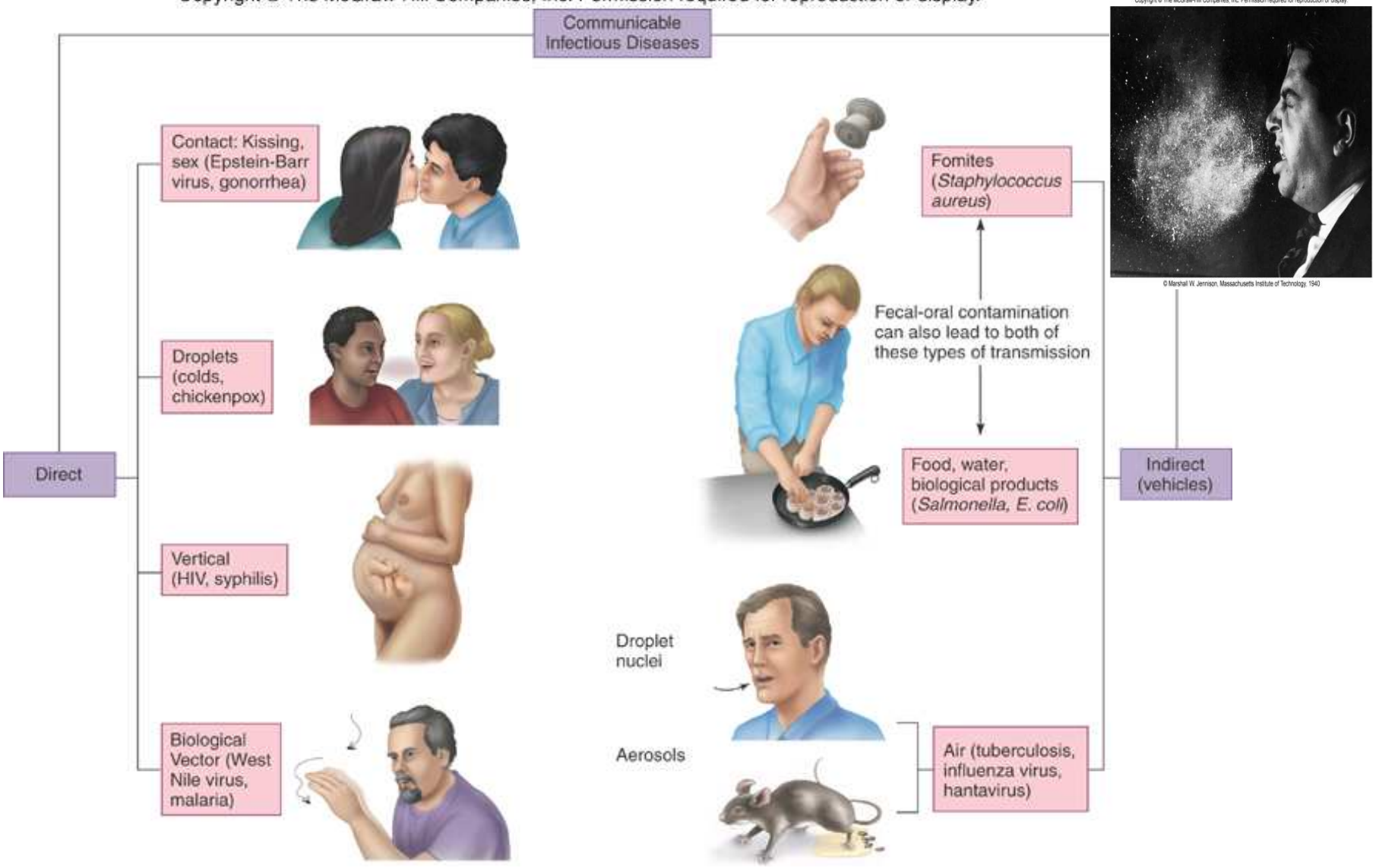
Figure 2-2 Immunobiology, 6/e. (© Garland Science 2005)





Vías de TRANSMISIÓN

MODOS DE TRANSMISIÓN de las enfermedades



Modos de transmisión , vehículos y vectores de las enfermedades…..

Table 14.10 Modes of Disease Transmission

Mode of Transmission	Diseases Spread Include:
Contact Transmission	
Direct Contact: *e.g.* handshaking, kissing, sex, bites	cutaneous anthrax, genital warts, gonorrhea, herpes, rabies, staphylococcus infections, syphilis
Indirect Contact: *e.g.* drinking glasses, toothbrushes, toys, punctures, droplets from sneezing and coughing (within one meter)	common cold, enterovirus infections, influenza, measles, Q fever, pneumonia, tetanus, whooping cough
Vehicle Transmission	
Airborne: *e.g.* dust particles	chicken pox, coccidiomycosis, histoplasmosis, influenza, measles, pulmonary anthrax, tuberculosis
Waterborne: *e.g.* streams, swimming pools	*Campylobacter* infections, cholera, *Giardia* diarrhea
Foodborne: *e.g.* poultry, seafood Mec	food poisoning (botulism, staphylococcal); hepatitis A, listeriosis, tapeworms, toxoplasmosis, typhoid fever
Vector Transmission	
Mechanical: *e.g.* (on insect bodies) flies, roaches	*E. coli* diarrhea, salmonellosis, trachoma
Biological: *e.g.* lice, mites, mosquitoes, ticks	Chagas' disease, Lyme disease, malaria, plague, Rocky Mountain spotted fever, typhus fever, yellow fever

RESERVORIOS

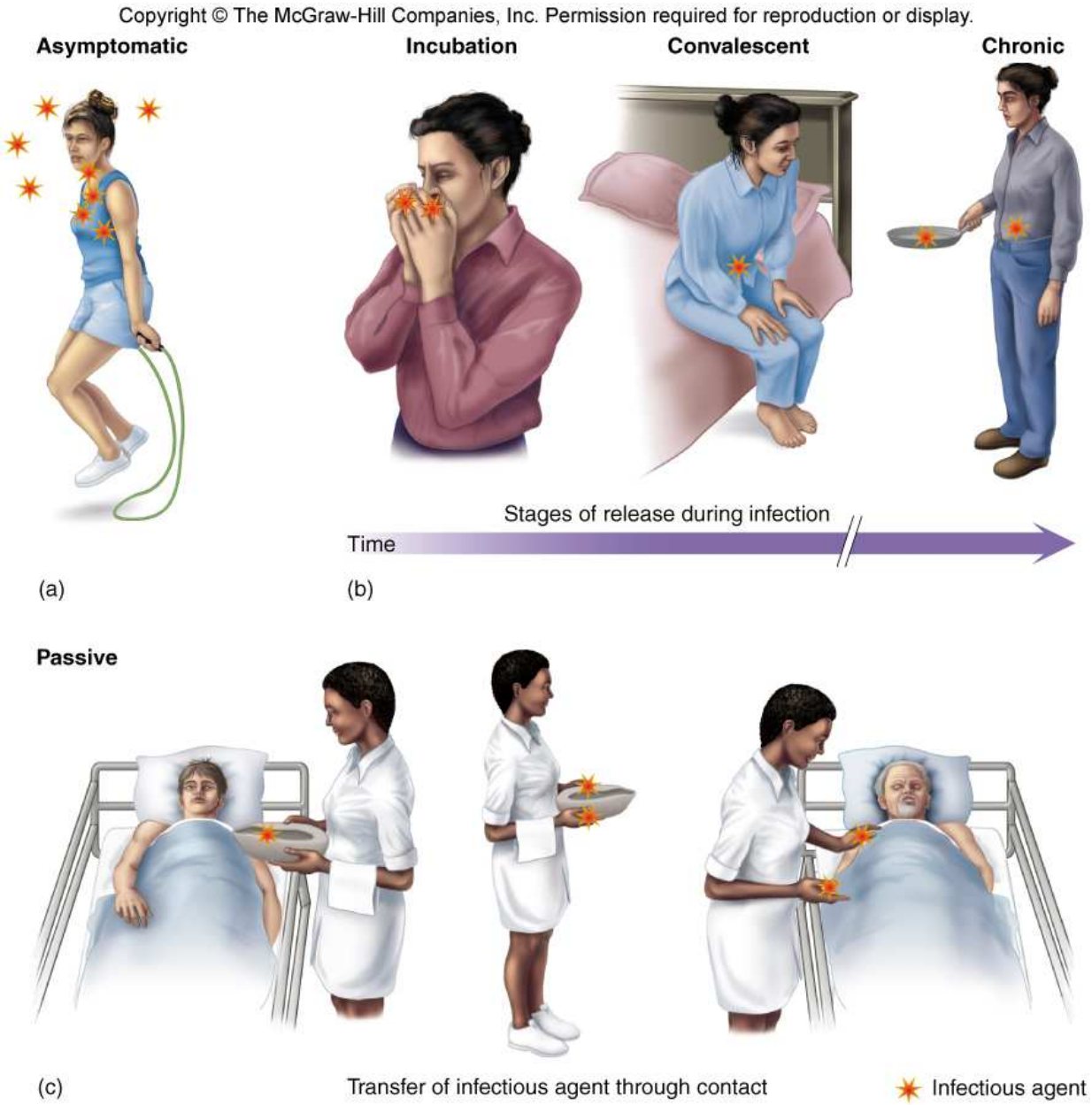


TABLE 13.10 Common Zoonotic Infections

Disease/Agent	Primary Animal Reservoirs
Viruses	
Rabies	All mammals
Yellow fever	Wild birds, mammals, mosquitoes
Viral fevers	Wild mammals
Hantavirus	Rodents
Influenza	Chickens, swine
West Nile virus	Wild birds, mosquitoes
Bacteria	
Rocky Mountain spotted fever	Dogs, ticks
Psittacosis	Birds
Leptospirosis	Domestic animals
Anthrax	Domestic animals
Brucellosis	Cattle, sheep, pigs
Plague	Rodents, fleas
Salmonellosis	Variety of mammals, birds, and rodents
Tularemia	Rodents, birds, arthropods
Miscellaneous	
Ringworm	Domestic mammals
Toxoplasmosis	Cats, rodents, birds
Trypanosomiasis	Domestic and wild mammals
Trichinosis	Swine, bears
Tapeworm	Cattle, swine, fish
Scabies	Domestic animals

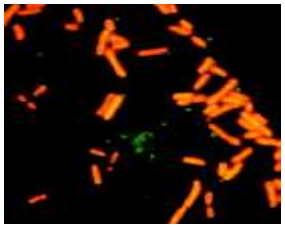
TABLE 13.9 Common Signs and Symptoms of Infectious Diseases

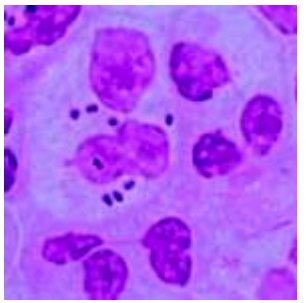
Signs	Symptoms
Fever	Chills
Septicemia	Pain, irritation
Microbes in tissue fluids	Nausea
Chest sounds	Malaise, fatigue
Skin eruptions	Chest tightness
Leukocytosis	Itching
Leukopenia	Headache
Swollen lymph nodes	Weakness
Abscesses	Abdominal cramps
Tachycardia (increased heart rate)	Anorexia (lack of appetite)
Antibodies in serum	Sore throat

Microorganismos oportunistas

Microorganismos normalmente saprófitos (benignos) que en ciertas condiciones causan enfermedad

Ej. : *Escherichia coli* es microflora normal del intestino, pero si llega a vías urinarias puede causar infección (enfermedad) urinaria.





Ej. 2: *Neisseria meningitidis* puede residir como habitante normal de vías respiratorias y causar meningitis (infección con inflamación de meninges- membranas- del encéfalo y la médula).

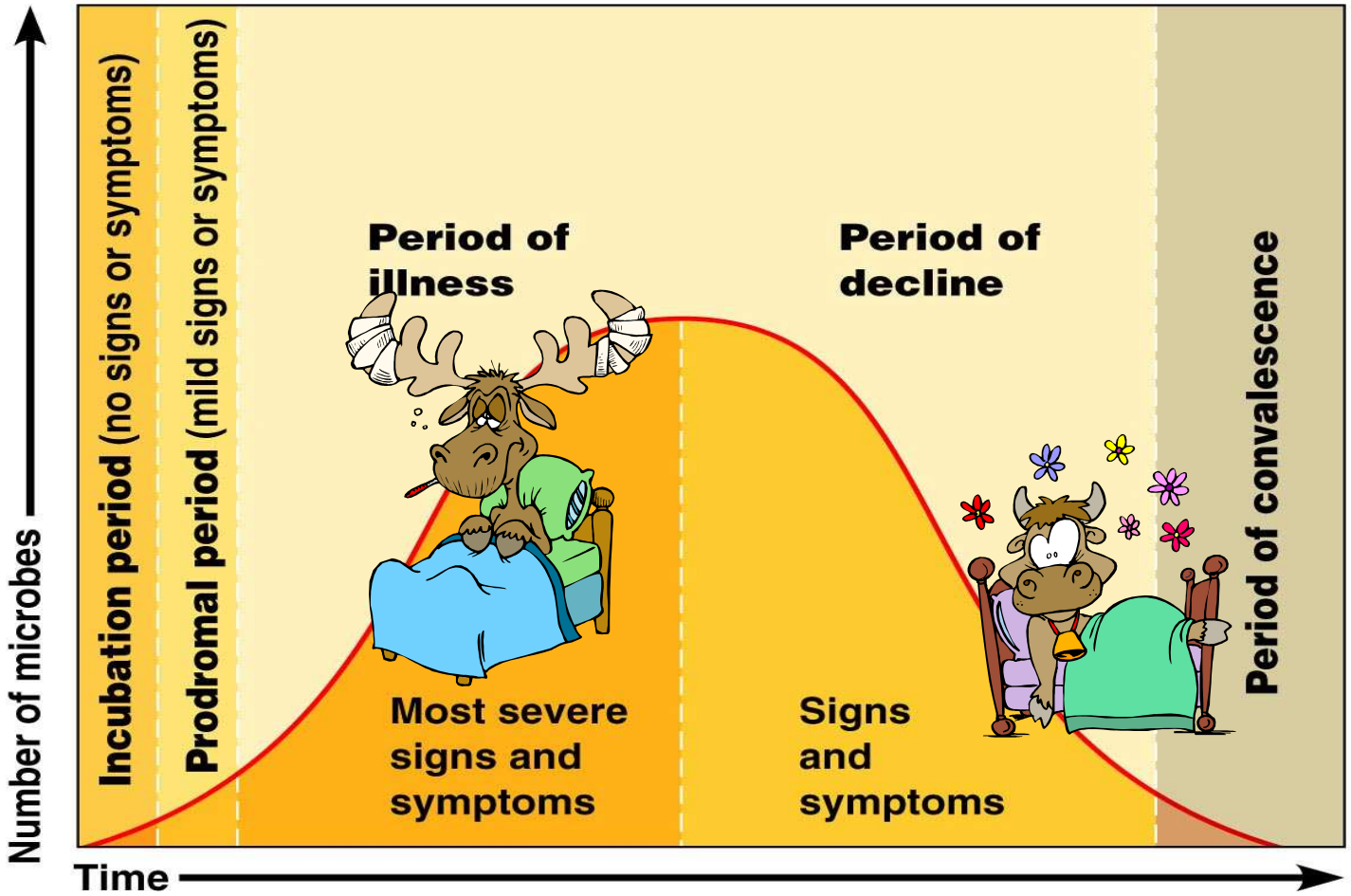
Enfermedades infecciosas

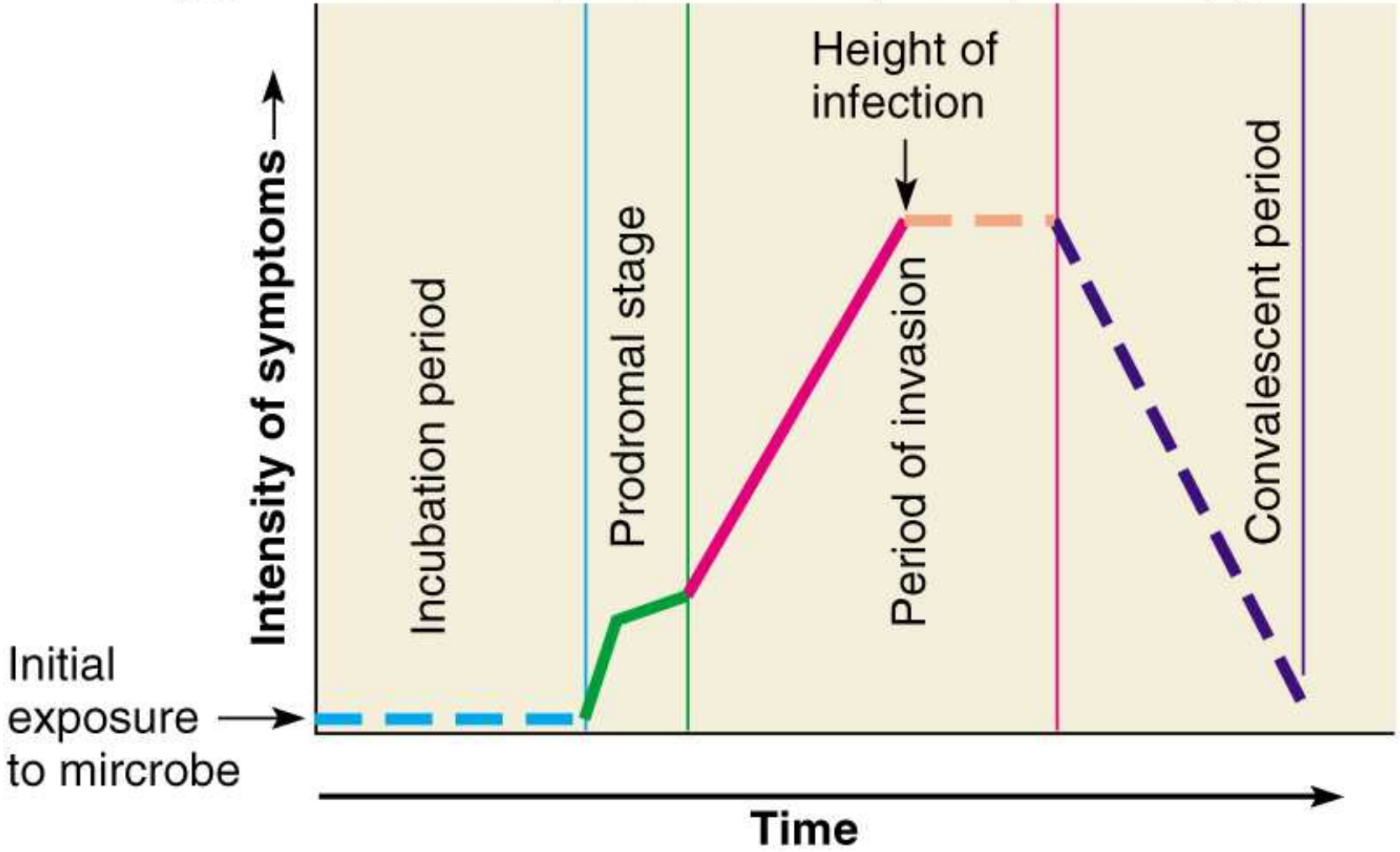
Etapas
- Período de incubación
- Período prodrómico
- Período de enfermedad
- Período de declinación
- Período de convalescencia

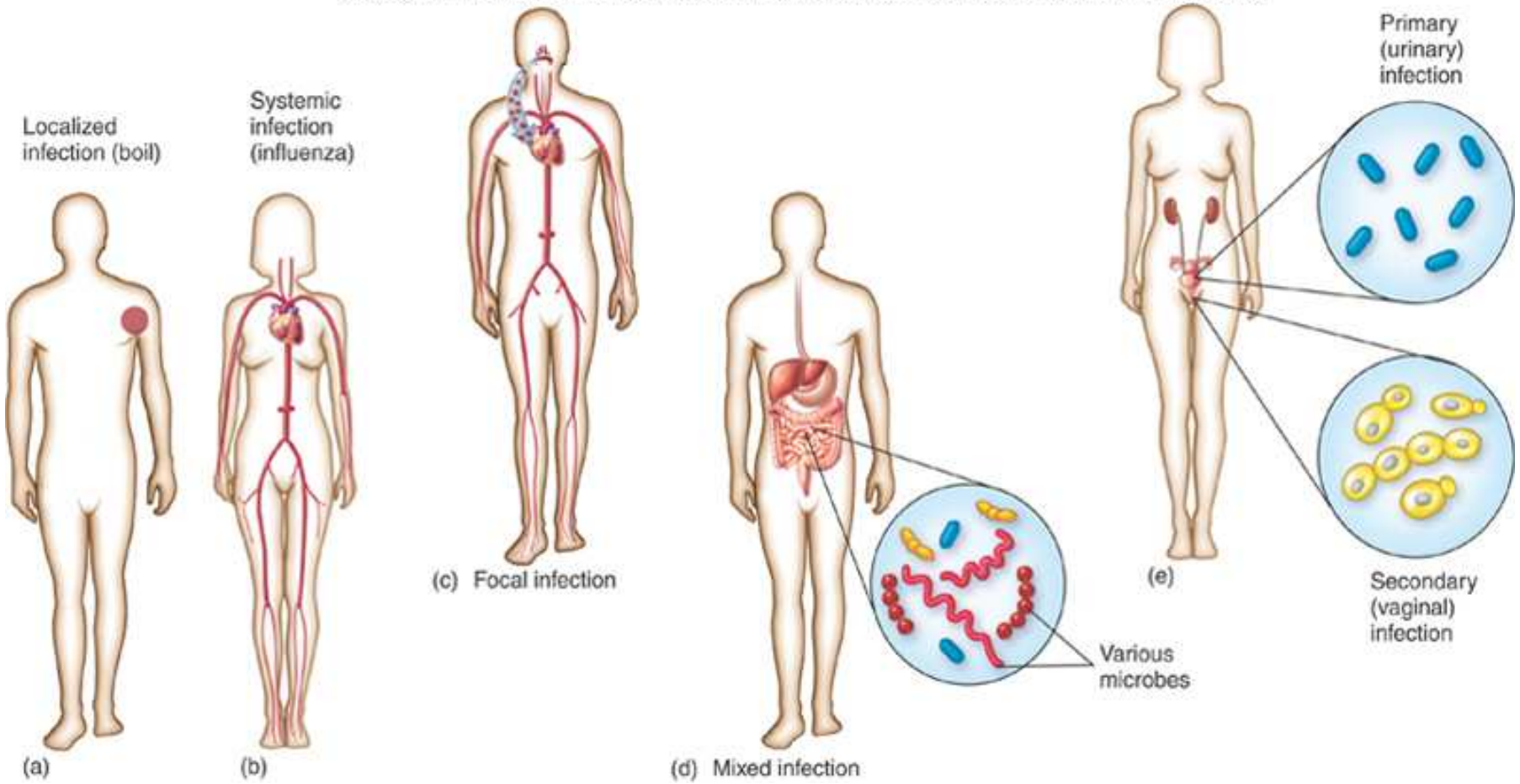
Gravedad según duración
- Enfermedad aguda
- Enfermedad subaguda
- Enfermedad crónica
- Enfermedad latente

Gravedad según compromiso del hospedador
- Infección localizada
- Infección sistémica o generalizada - Sepsis
- Infección focalizada

Fases de la enfermedad



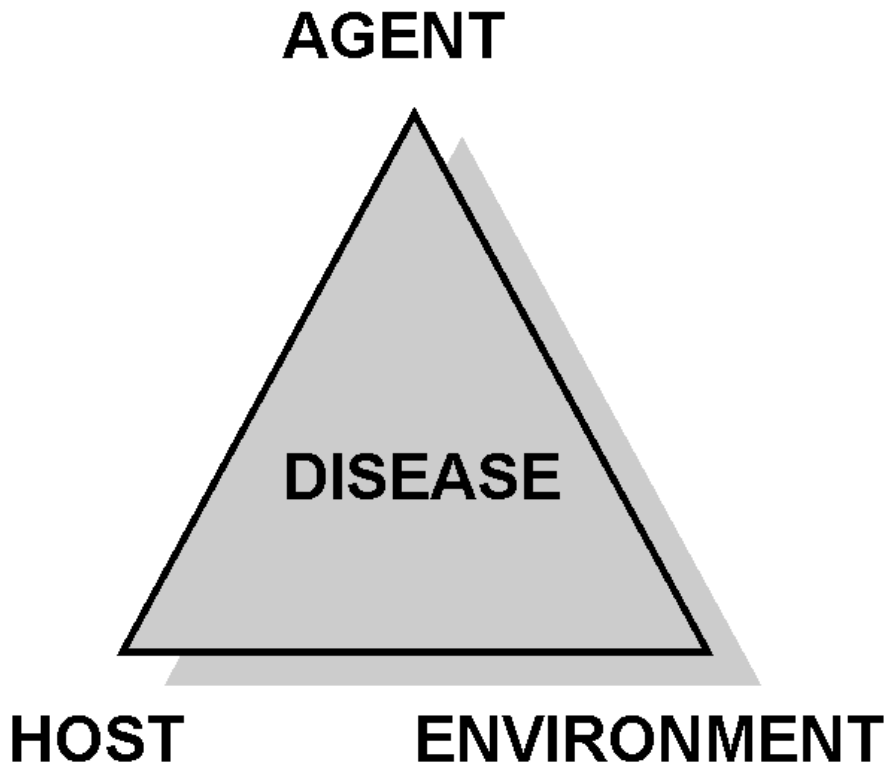




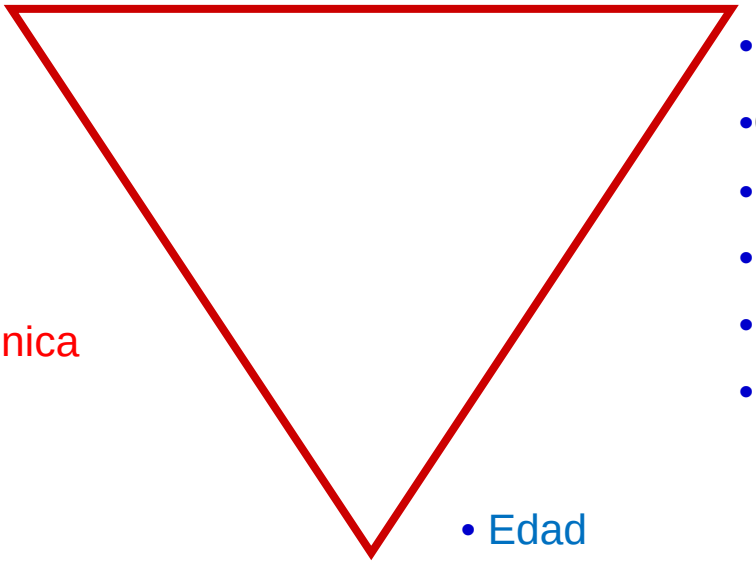
Tríada epidemiológica

La **enfermedad** es el resultado de fuerzas en un sistema dinámico, constituído por :

- Agente infeccioso
- Huésped
- Microambiente



Factores que influyen en la trasmisión de la enfermedad



Agente

- Infectividad
- Patogenicidad
- Virulencia
- Inmunogenicidad
- Estabilidad antigénica
- Sobrevida

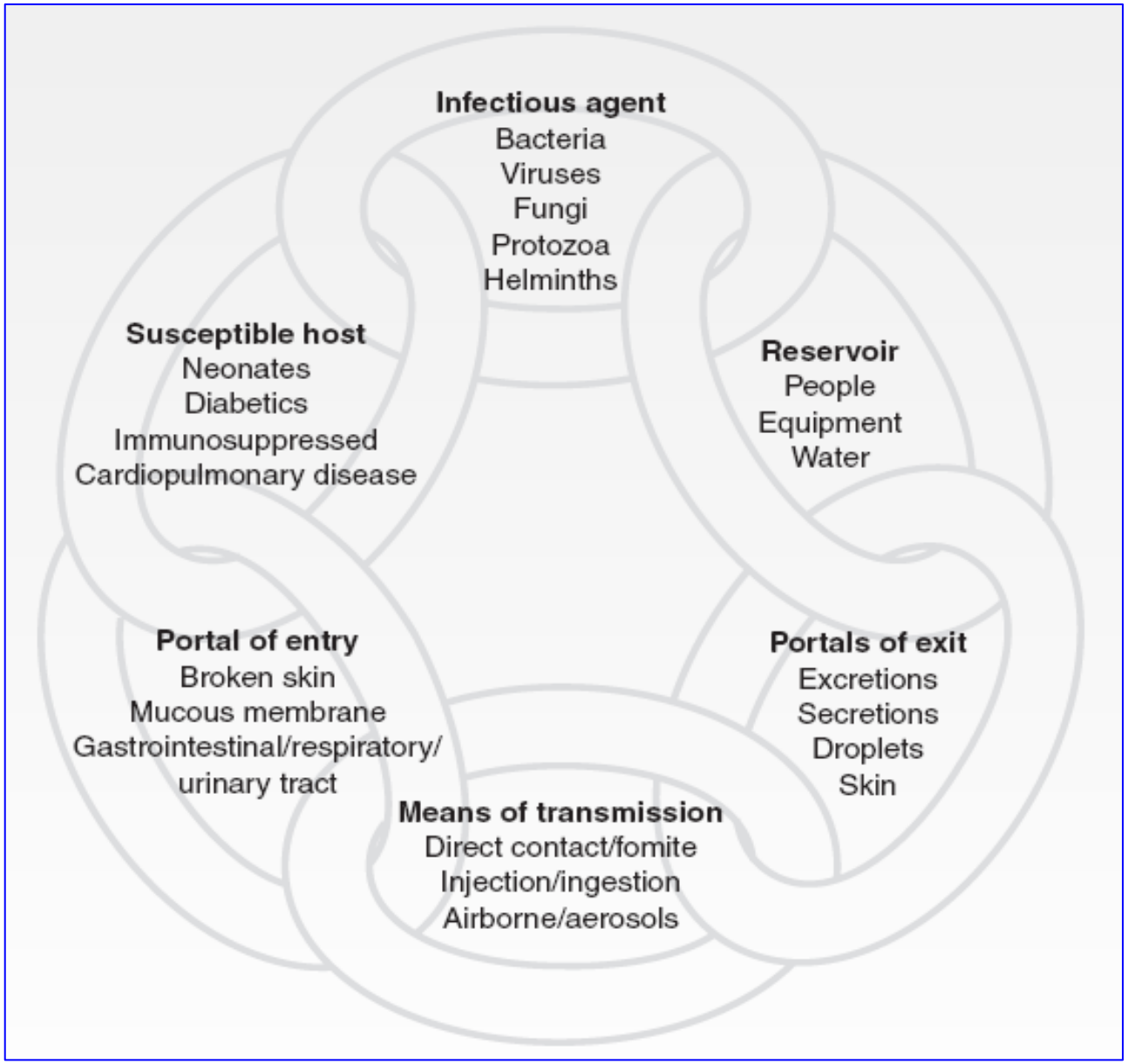
Microambiente

- Tiempo
- Geografía
- Alojamiento
- Ocupación
- Calidad del aire
- Alimentos

Huésped

- Edad
- Sexo
- Genotipo
- Comportamiento
- Estado nutricional
- Estado de salud

Cadena de infección



Horton & Parker: Informed Infection Control Practice

Enfermedades emergentes y reemergentes

Enfermedades nuevas o conocidas pero cambiantes, que están aumentando o pueden aumentar en el futuro. Se detectan por:

- **Síntomas claramente diferentes**
- **Nuevos métodos de diagnóstico**
- **Aparición en áreas nuevas o reaparición en zonas donde habían sido controladas**

Factores contribuyentes:

- ✓ **Cambios genéticos en los microorganismos – Nuevas cepas**
- ✓ **Uso indiscriminado de antibióticos – Selección de cepas resistentes y más virulentas**
- ✓ **Uso indiscriminado de pesticidas – Selección de vectores resistentes/Eliminación competidores**
- ✓ **Cambio climático y ecológico**
- ✓ **Aumento del transporte y el turismo**
- ✓ **Avance de las actividades humanas sobre zonas silvestres (deforestación, construcción)**
- ✓ **Desastres naturales y guerras**
- ✓ **Cambios de hábitos o costumbres**
- ✓ **Pobreza, desnutrición y malas condiciones higiénico –sanitarias**
- ✓ **Fallas en los sistemas de vigilancia y prevención (vacunación)**

Algunos ejemplos

En el Mundo

- SIDA
- Síndrome Urémico Hemolítico
- Enfermedad de la vaca loca
- Gripe aviar
- SARS

En Argentina

- SIDA
- Síndrome Urémico Hemolítico
- Síndrome Pulmonar por Hantavirus
- Tuberculosis (reemergente)
- Leishmaniasis (reemergente)

E. coli O157-H7 sobre células del epitelio intestinal deformadas

Síndrome Urémico Hemolítico (SUH)

- *E. coli* O157-H7, cepa productora de toxina Shiga
- Adquirida por carne poco cocida, lácteos, jugos y verduras crudas
- Muerte
- Daño renal crónico
- 1º causa de transplante renal en niños en Argentina
- Secuelas con diálisis y/o tratamientos prolongados

Río Negro tiene el mayor % de incidencia del país (sobre todo la zona atlántica, pero también la andina).

Mecanismos de patogenicidad y factores de virulencia

Virulencia: capacidad relativa de un m.o. para causar enfermedad

Dosis infectiva y dosis letal

DI_{50} :dosis del m.o. capaz de infectar al 50 % de la población de prueba

DL_{50} : dosis del m.o. capaz de matar al 50 % de la población de prueba

La virulencia depende del m.o., pero también de la vía de entrada. Ejemplo:

Bacillus anthracis

- vía cutánea – DI_{50} = 10 - 50 esporas
- vía respiratoria - DI_{50} = 10.000 – 20.000 esporas
- vía oral - DI_{50} = 250.000 – 1.000.000 esporas

Factores de virulencia

1- Adherencia a células

•Adhesinas superficiales

•Fimbrias /pilis

2- Invasión de los tejidos

Enzimas

•Hialuronidasa

•Colagenasa

•Coagulasa

•IgA proteasa

•Fibrinolisina

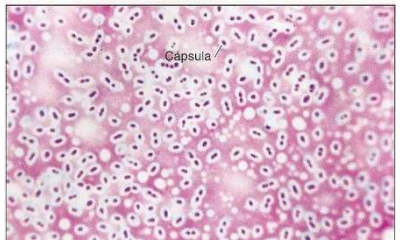
3- Evasión de las defensas del huésped

•Cápsulas

•Proteínas de pared

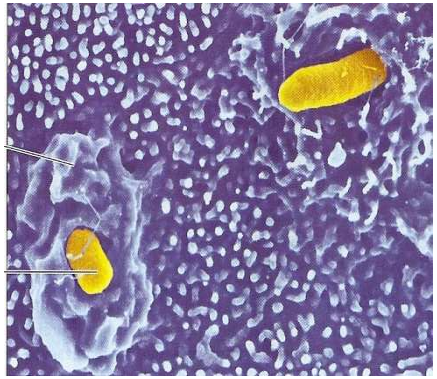
•Acido micólico (TB)

•Variación antigénica



4- Invasión a la célula

•Invasinas y cambios por modificación de la actina del citoesqueleto



5- Daño celular y tisular

•Uso de nutrientes del hospedador

•Daño directo (invasión – lisis)

•Daño a distancia (toxinas)

•Reacciones de hipersensibilidad

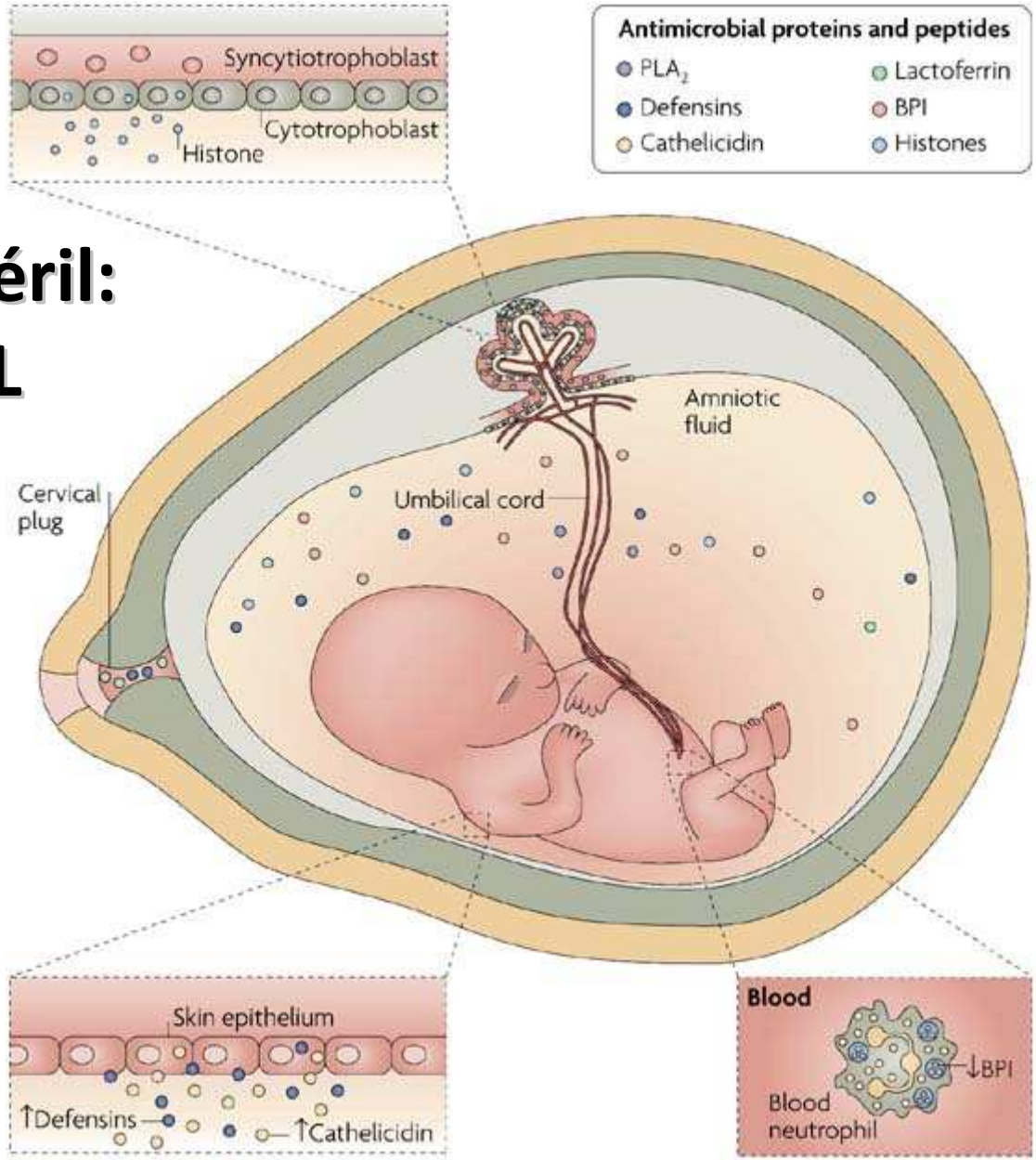
Factores de virulencia: exotoxinas y endotoxinas

PROPIEDAD	EXOTOXINA	ENDOTOXINA
Fuente bacteriana	Gram + (principalmente)	Gram -
Relación con el m.o.	Producto metabólico	Parte de los LPS de ME de pared Liberada por lisis celular
Composición química	Proteínas	Lípido A de los LPS
Efecto	**Específica** sobre distintos tipos celulares (nervios, tracto GI)	**General:** dolores, debilidad, fiebre, shock
Estabilidad al calor	Termosensibles (60 – 80 ºC) salvo la enterotoxina de *S. aureus*	Termoestables (121 ºC-1 h)
Toxicidad	Alta	Baja
Fiebre	No	Si
Relación con Ac	Se pueden convertir en toxoides para inmunización – Se neutraliza con la antitoxina	No se convierte fácilmente en toxoide – No se neutraliza con Ac
Dosis letal	Pequeña	Mayor
Enfermedades	Botulismo – *Clostridium botulinum* – Toxina botulínica en alimentos Tétanos – *C. tetani* – Heridas profundas, sucias Gangrena Gaseosa – *C. perfringens* – Heridas quirírgicas/necrosis Gastroenteritis – *S. aureus* – Enterotoxina en alimentos Difteria – *Corynebacterium difteriae* – Membrana en vías aereas altas Cólera- *Vibrio cholerae* –Toxina colérica (Verotoxina) Enteritis aguda Escarlatina – *S. pyogenes* – Toxina eritrogénica	*Salmonella typhi* – Fiebre tifopidea *S. enteritidis* – Enteritis *E. coli* entero patógena *Proteus sp.* Infecciones urinarias *Klebsiella neumoniae* – neumonía – inf. Urin. *Neisseria meningitidis* – meningitis

El cuerpo humano existe en un estado de equilibrio dinámico……

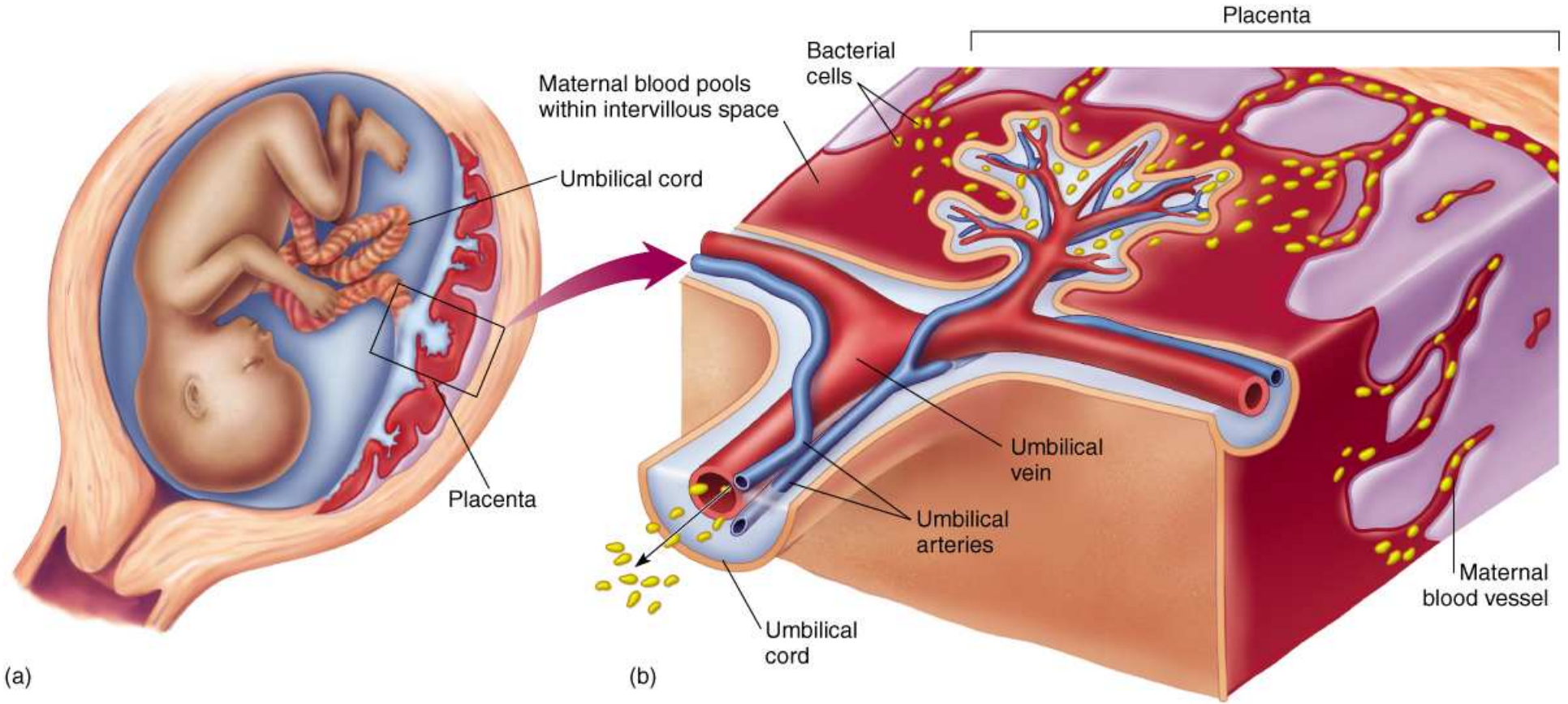
LA COLONIZACIÓN DEL CUERPO HUMANO INVOLUCRA UN CONSTANTE "DAR Y TOMAR"….

Ambiente estéril: VIDA FETAL



Nature Reviews Immunology 7, 379-390 (May 2007)

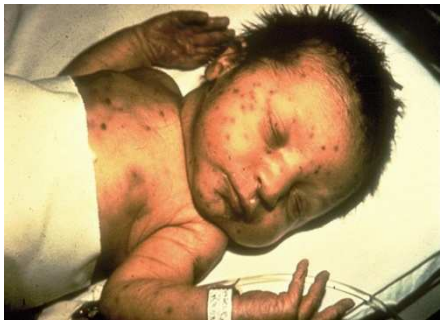
TRANSMISIÓN DE PATÓGENOS…..



Algunos patógenos atraviesan la placenta

Table 14.3 Some Pathogens that Cross the Placenta

	Pathogen	Condition in the Adult	Effect on Embryo or Fetus
Protozoan	*Toxoplasma gondii*	Toxoplasmosis	Abortion, epilepsy, encephalitis, microcephaly, mental retardation, blindness, anemia, jaundice, rash, pneumonia, diarrhea, hypothermia, deafness
Bacteria	*Treponema pallidum*	Syphilis	Abortion, multiorgan birth defects, syphilis
	Listeria monocytogenes	Listeriosis	Granulomatosis infantiseptica (nodular inflammatory lesions and infant blood poisoning), death
DNA viruses	*Cytomegalovirus*	Usually asymptomatic	Deafness, microcephaly, mental retardation
	Parvovirus B19	Erythema infectiosum	Abortion
RNA viruses	*Lentivirus* (HIV)	AIDS	Immunosuppression (AIDS)
	Rubivirus rubella	German measles	Severe birth defects or death



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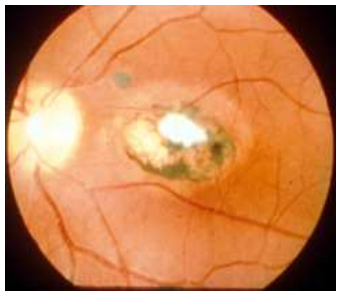
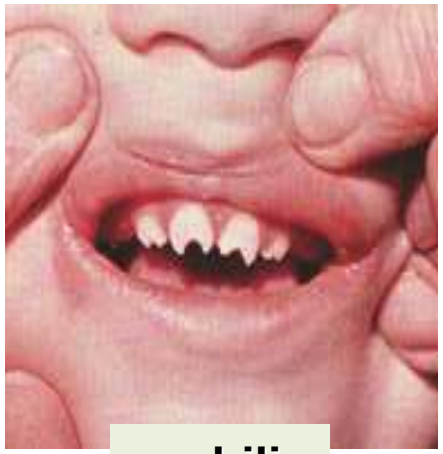
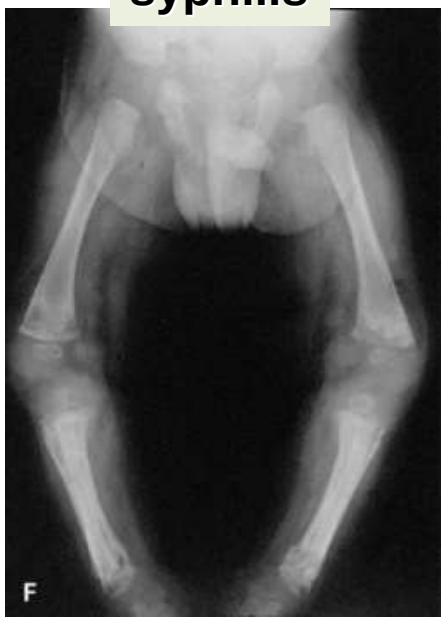


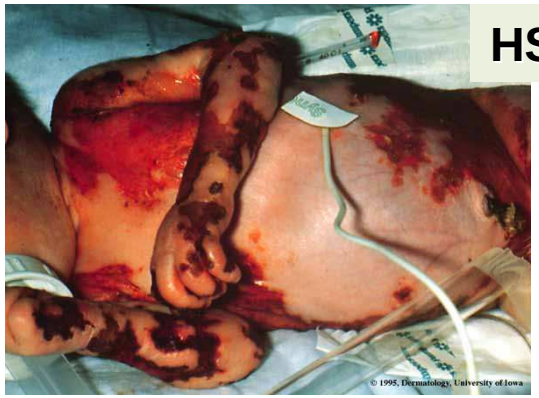


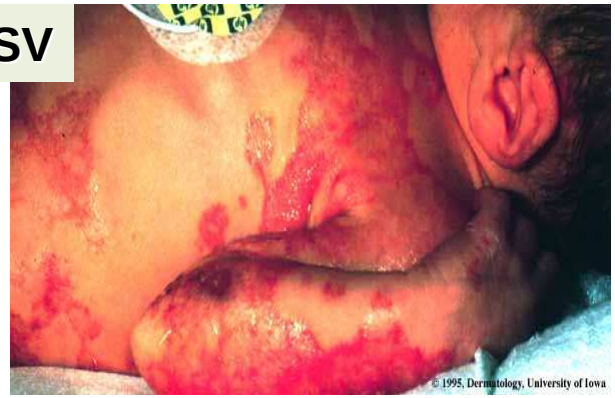
- T=toxoplasmosis
- O=other (syphilis)
- R=rubella
- C=cytomegalovirus (CMV)
- H=herpes simplex (HSV)

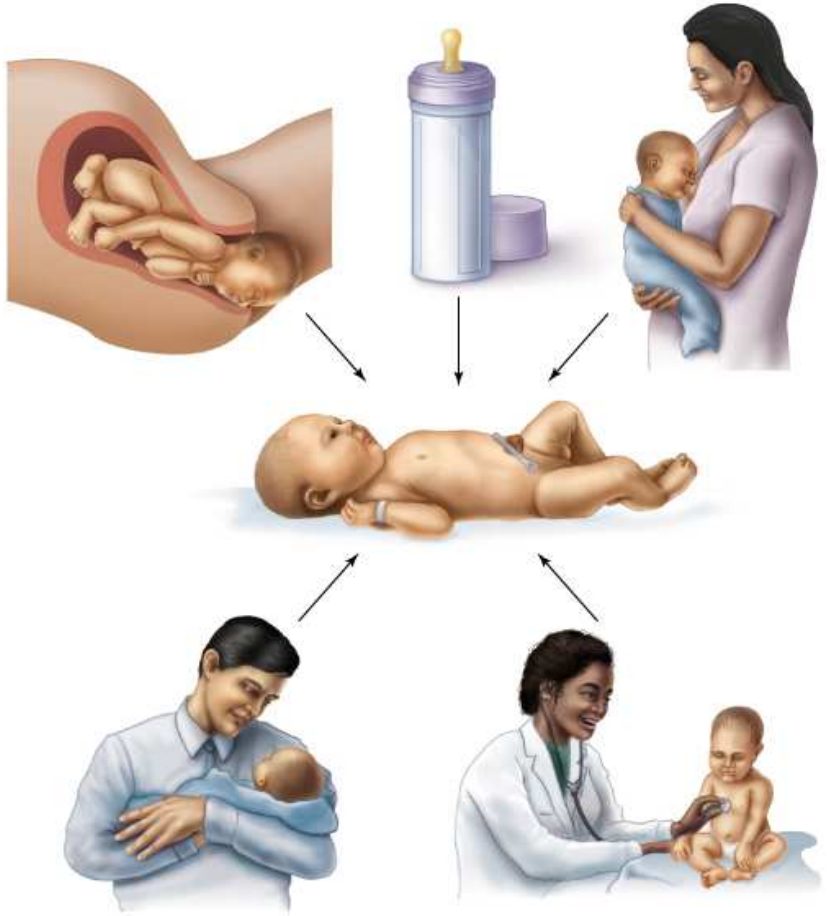
syphilis



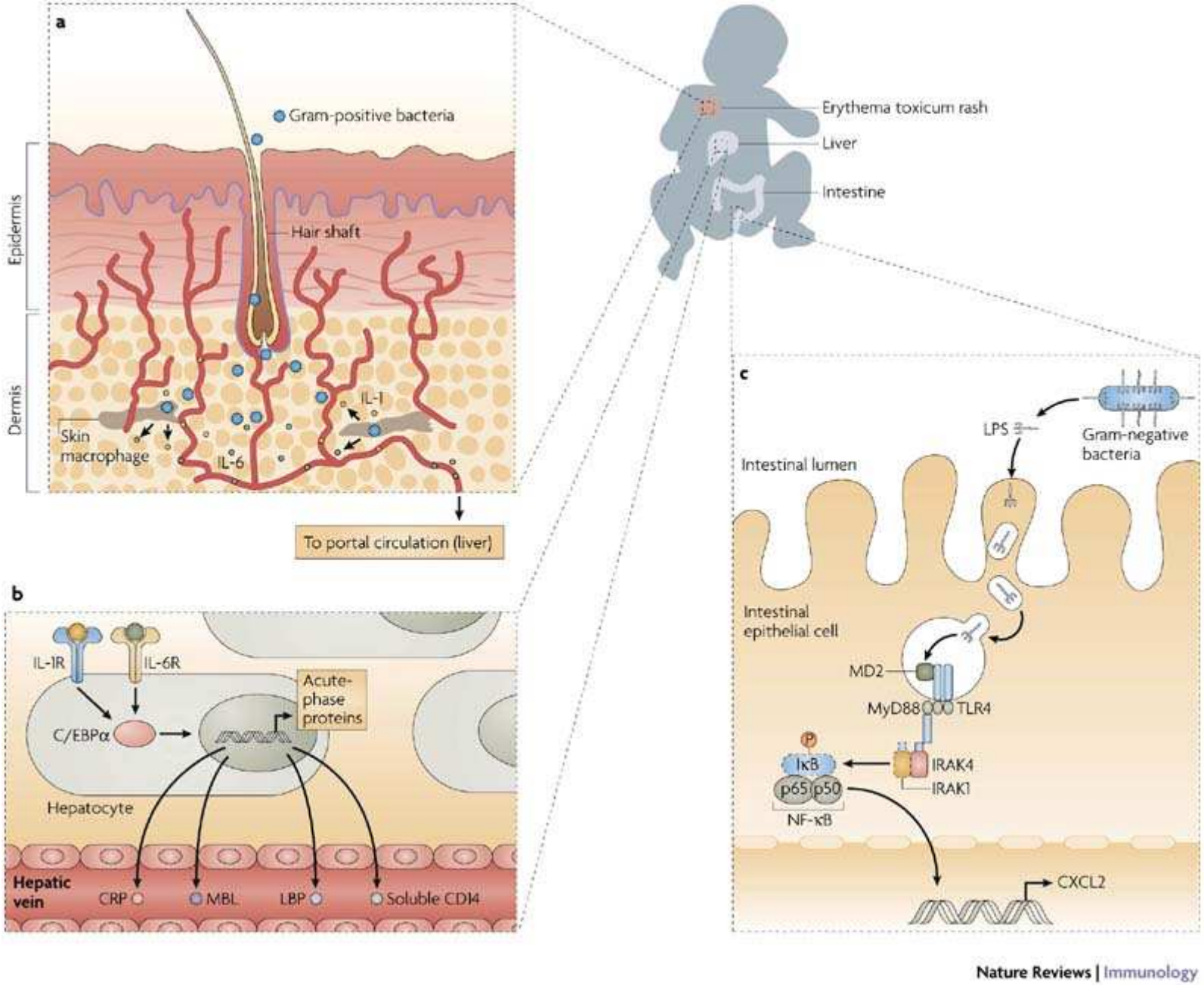
HSV



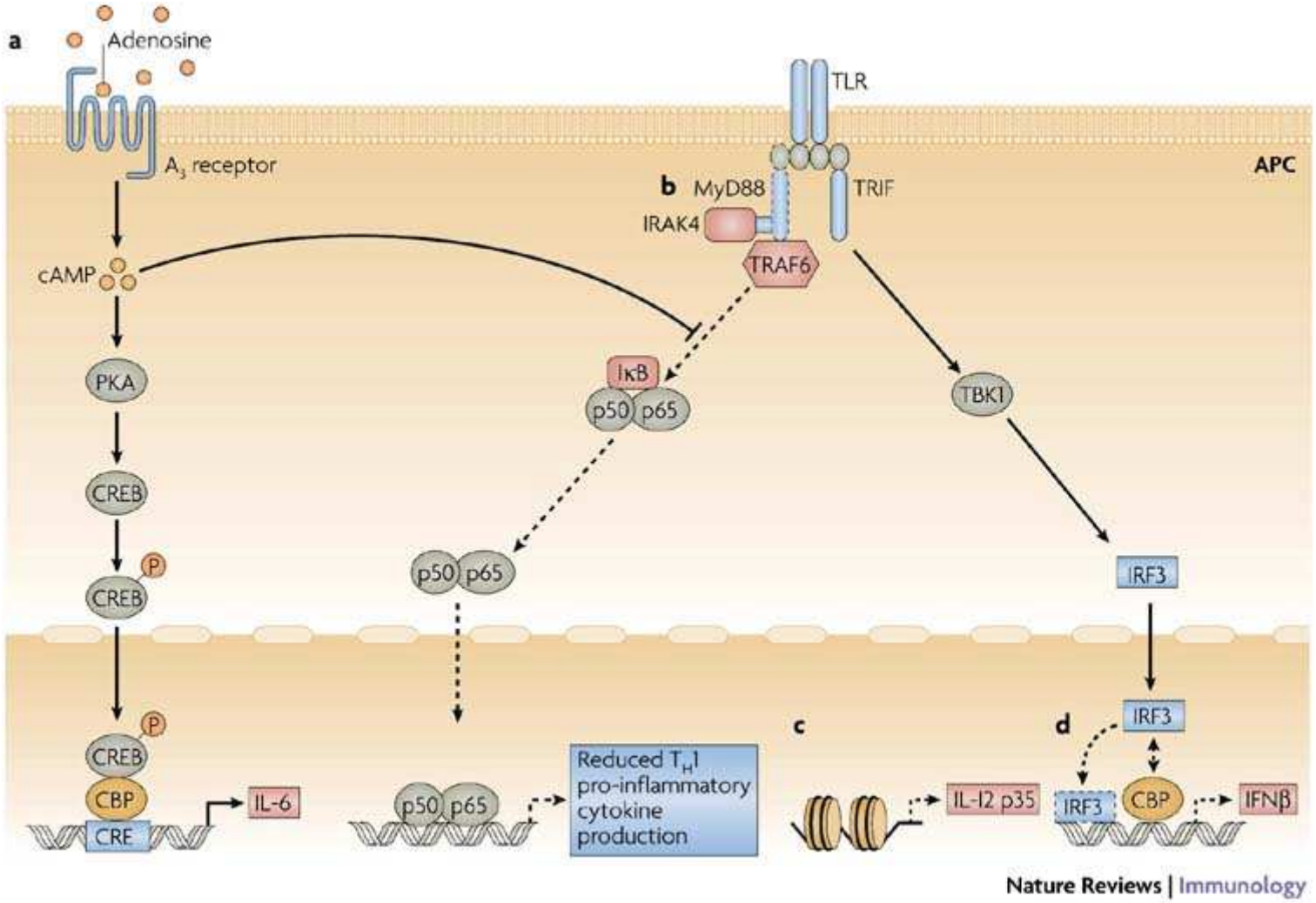




COMIENZA LA COLONIZACIÓN



Nature Reviews Immunology 7, 379-390 (May 2007)



High concentrations of adenosine, an endogenous immunomodulatory purine metabolite, in neonatal blood plasma act through adenosine A_3 receptors on neonatal mononuclear cells to induce high (20-fold greater than adult levels) intracellular concentrations of cyclic AMP (cAMP). cAMP is a secondary messenger that, through both protein kinase A (PKA)-dependent and PKA–independent pathways, can inhibit Toll-like receptor 2 (TLR2)-mediated tumour-necrosis factor (TNF) production while preserving production of interleukin-6 (IL-6).

Nature Reviews Immunology 7, 379-390 (May 2007)

- Shortly after birth the newborn is colonized by microbial flora. a | Neonatal skin is colonized by Gram-positive bacteria (for example, coagulase-negative staphylococci) that often gain access to the skin through hair follicles and induce a benign rash known as erythema toxicum. At sites of eythema toxicum rash, neonatal macrophages produce interleukin-1 (IL-1) and IL-6.
- b | IL-1 and IL-6, through activation of the transcription factor CCAAT/enhancer-binding protein-α(C/EBPα), can contribute to the acute-phase response, triggering hepatocyte production of plasma proteins, such as C-reactive protein (CRP), lipopolysaccharide (LPS)-binding protein (LBP), soluble CD14 and mannose-binding lectin (MBL), which have roles in the clearance and detoxification of microbes and microbial toxins.
- c | At (or soon after) birth the intestinal tract of the newborn is first exposed to LPS that is derived from Gram-negative flora. Fetal (and pre-term neonatal) intestinal epithelial cells have markedly enhanced inflammatory responses to LPS. **Mouse studies indicate that in full-term newborns, potentially harmful inflammatory responses to LPS are usually dampened by internalization of LPS by intestinal epithelial cells that induces downregulation of IL-1-receptor-associated kinase 1 (IRAK 1), thereby contributing to intestinal endotoxin tolerance.** Such adaptations are central to the development of commensal relationships. CXCL2, CXC-chemokine ligand 2; IκB, inhibitor of nuclear factorκ-B; MyD88, myeloid differentiation primary-response gene 88.

TABLE 13.1 Sites That Harbor a Normal Flora

- Skin and its contiguous mucous membranes
- Upper respiratory tract
- Gastrointestinal tract (various parts)
- Outer opening of urethra
- External genitalia
- Vagina
- External ear and canal
- External eye (lids, lash follicles)

TABLE 13.2 Sterile (Microbe-Free) Anatomical Sites and Fluids

All Internal Tissues and Organs

Heart and circulatory system

Liver

Kidneys and bladder

Lungs

Brain and spinal cord

Muscles

Bones

Ovaries/testes

Glands (pancreas, salivary, thyroid)

Sinuses

Middle and inner ear

Internal eye

Fluids within an Organ or Tissue

Blood

Urine in kidneys, ureters, bladder

Cerebrospinal fluid

Saliva prior to entering the oral cavity

Semen prior to entering the urethra

Amniotic fluid surrounding the embryo and fetus

Flora indígena en regiones específicas

TABLE 13.3 Life on Humans: Sites Containing Well-Established Flora and Representative Examples

Anatomic Sites	Common Genera	Remarks
Skin	**Bacteria:** *Staphylococcus, Micrococcus, Corynebacterium, Propionibacterium, Streptococcus*	Microbes live only in upper dead layers of epidermis, glands, and follicles; dermis and layers below are sterile.
	Fungi: *Candida, Malassezia*	Dependent on skin lipids for growth
	Arthropods: *Demodix* mite	Present in sebaceous glands and hair follicles
Gastrointestinal Tract		
Oral cavity	**Bacteria:** *Streptococcus, Neisseria, Veillonella, Fusobacterium, Lactobacillus, Bacteroides, Actinomyces, Eikenella, Treponema, Haemophilus*	Colonize the epidermal layer of cheeks, gingiva, pharynx; surface of teeth; found in saliva in huge numbers
	Fungi: *Candida* sp.	Can cause thrush
	Protozoa: *Entamoeba gingivalis*	Inhabit the gingiva of persons with poor oral hygiene
Large intestine and rectum	**Bacteria:** *Bacteroides, Fusobacterium, Bifidobacterium, Clostridium,* fecal streptococci and staphylococci, *Lactobacillus,* coliforms (*Escherichia, Enterobacter*), *Proteus* sp.	Areas of lower gastrointestinal tract other than large intestine and rectum have sparse or nonexistent flora. Flora consists predominantly of strict anaerobes; other microbes are aerotolerant or facultative.
	Fungi: *Candida*	Yeast can survive this habitat.
	Protozoa: *Entamoeba coli, Trichomonas hominis*	Feed on waste materials in the large intestine
Upper Respiratory Tract	Microbial population exists in the nasal passages, throat, and pharynx; owing to proximity, flora is similar to that of oral cavity.	Trachea may harbor a sparse population; bronchi, bronchioles, and alveoli have no normal flora and are essentially sterile due to local host defenses.
Genital Tract	**Bacteria:** *Lactobacillus, Streptococcus, diphtheroids* (*Corynebacterium* and relatives) *Escherichia, Gardnerella*	In females, flora occupies the external genitalia and vaginal and cervical surfaces; internal reproductive structures normally remain sterile. Flora responds to hormonal changes during life.
	Fungi: *Candida*	Cause of yeast infections
Urinary Tract	**Bacteria:** *Staphylococcus, Streptococcus, Corynebacterium, Lactobacillus*	In females, flora exists only in the first portion of the urethral mucosa; the remainder of the tract is sterile. In males, the entire reproductive and urinary tract is sterile except for a short portion of the anterior urethra.
Eye	**Bacteria:** coagulase-negative staphylococci, *Streptococcus, Neisseria*	The lids and follicles harbor similar microbes as skin; the conjunctiva has a transient population; deep tissues are sterile.
Ear	**Bacteria:** staphylococci, diphtheroids	The external ear is similar to the skin in content; areas internal to the tympanum are generally sterile.
	Fungi: *Aspergillus, Penicillium, Candida,* yeasts	

DESARROLLO DE LA INFECCIÓN

FASES DE LA RESPUESTA INMUNE

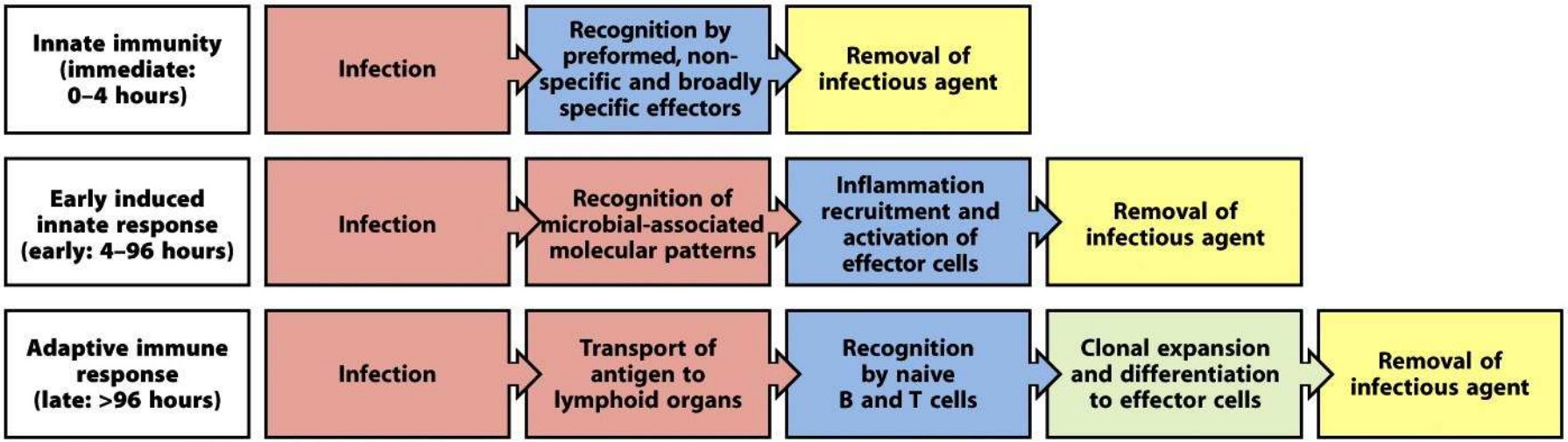


Figure 2-1 Immunobiology, 7ed. (© Garland Science 2008)

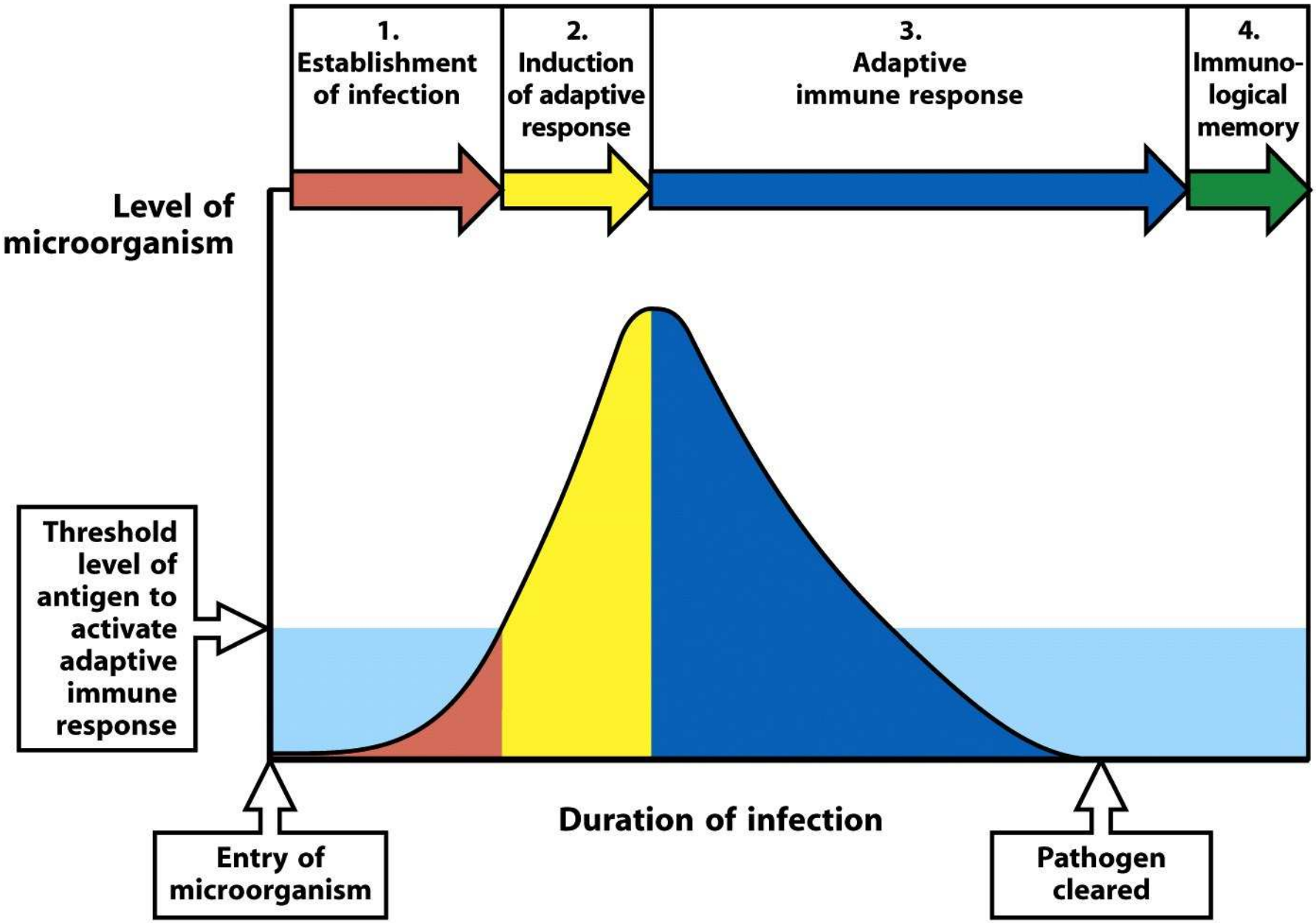


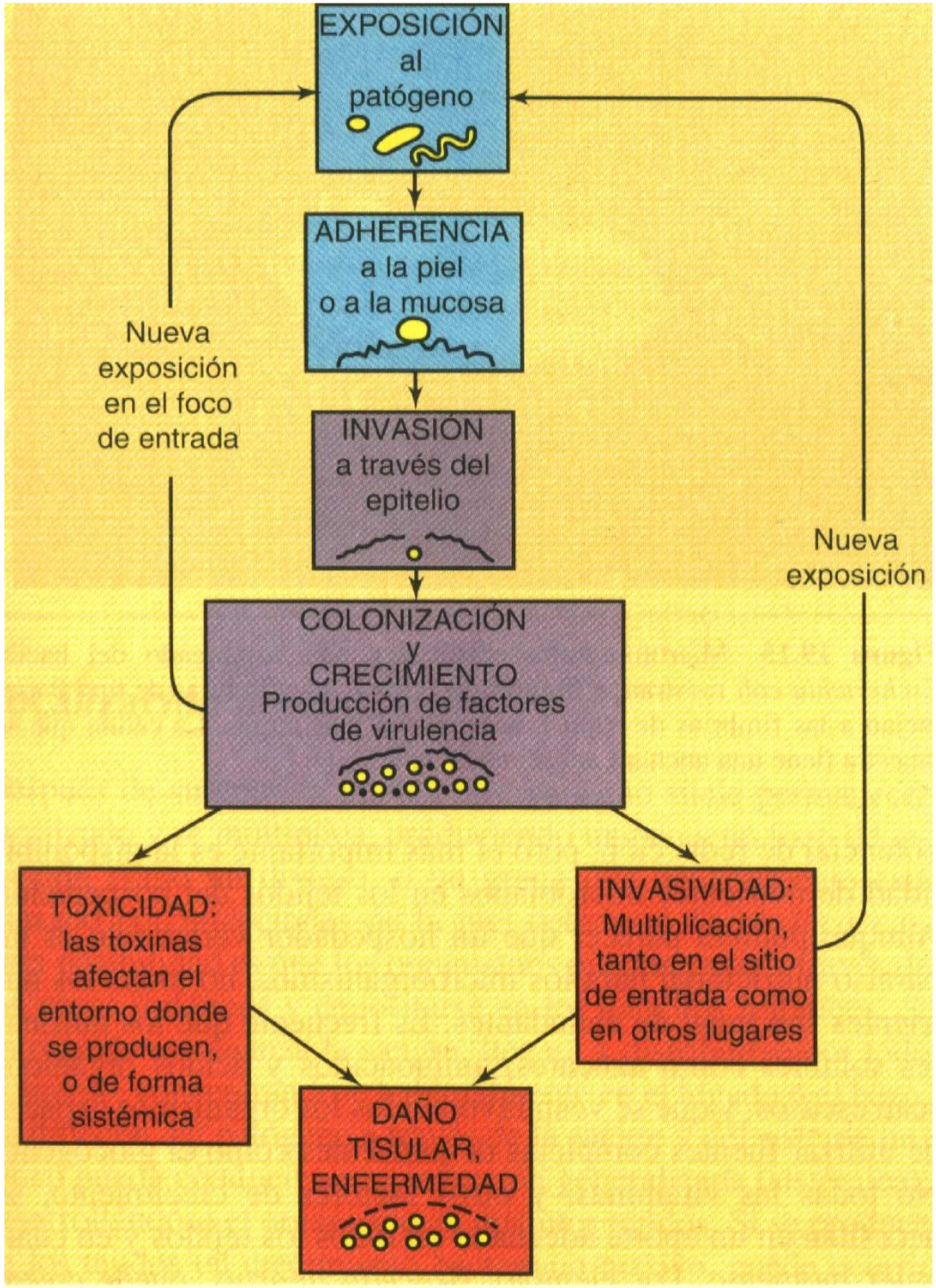
Figure 10-1 Immunobiology, 7ed. (© Garland Science 2008)

Routes of infection for pathogens			
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**
Mucosal surfaces			
Airway	Inhaled droplet	Influenza virus	Influenza
	Spores	*Neisseria meningitidis*	Meningococcal meningitis
		Bacillus anthracis	Inhalation anthrax
Gastrointestinal tract	Contaminated water or food	*Salmonella typhi*	Typhoid fever
		Rotavirus	Diarrhea
Reproductive tract	Physical contact	*Treponema pallidum*	Syphilis
		HIV	AIDS

Figure 2-5 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

ETAPAS DE LA INFECCIÓN

- Exposición
- Adherencia
- Invasión
- Colonización y crecimiento
- Invasividad y/o toxicidad
- Daño tisular
- Enfermedad



BARRERAS NATURALES A LA INFECCIÓN

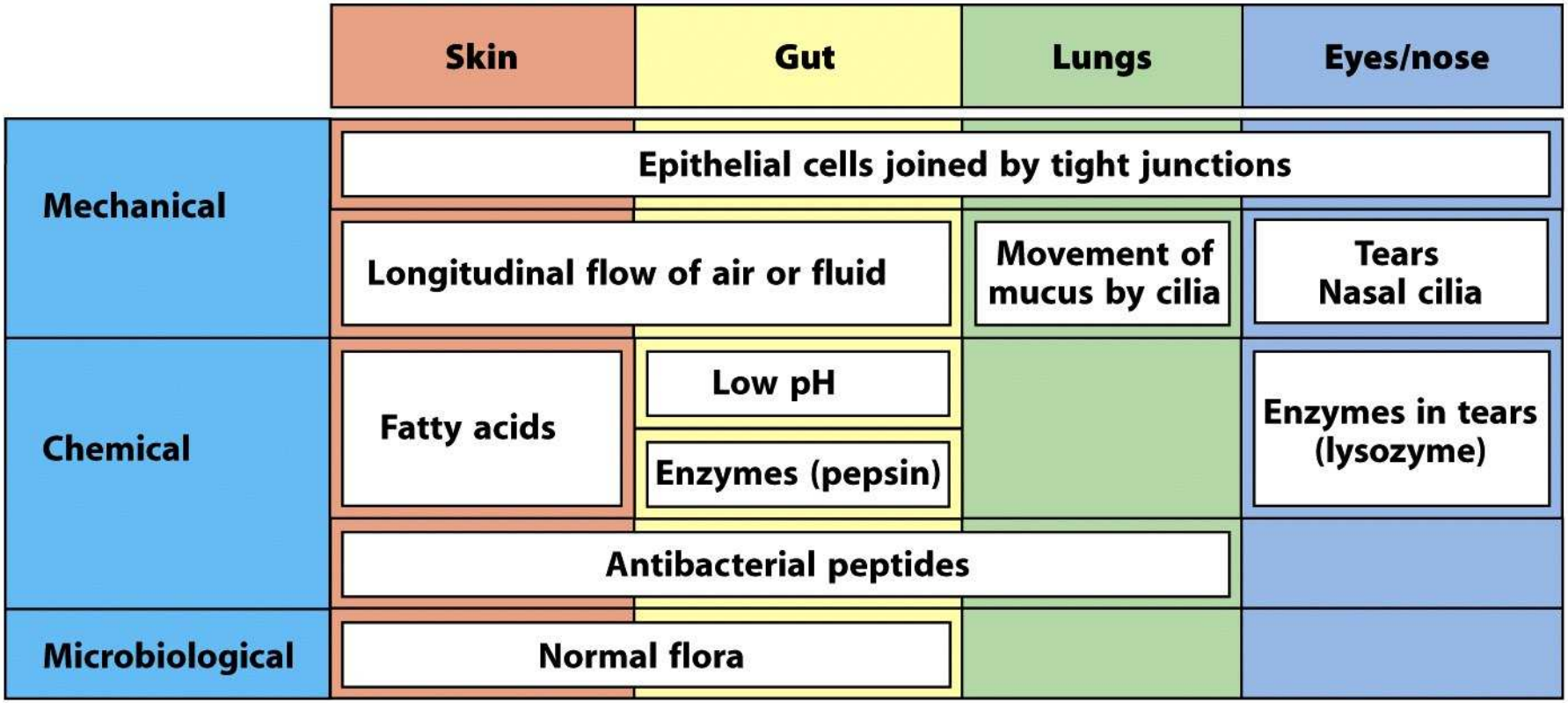
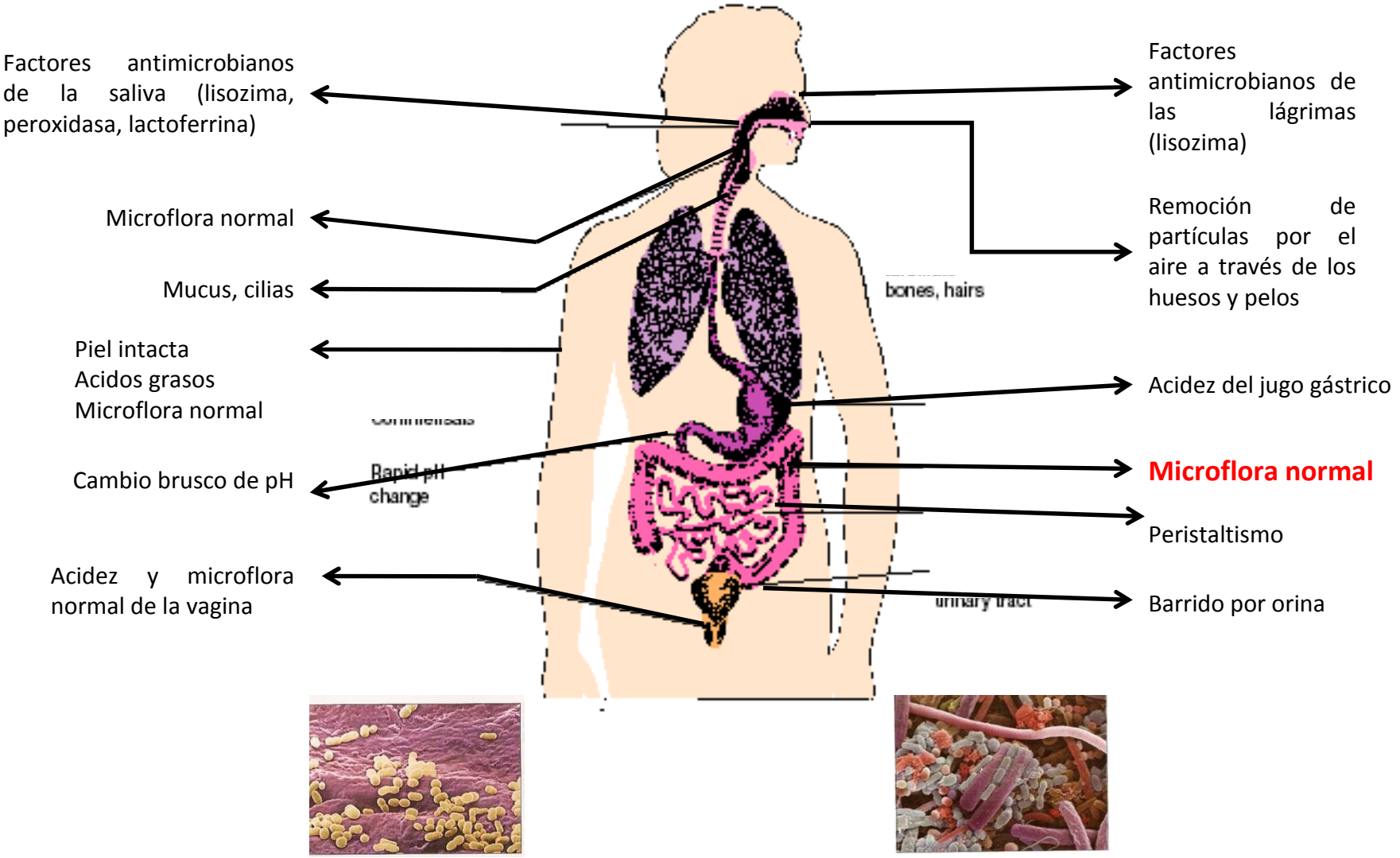
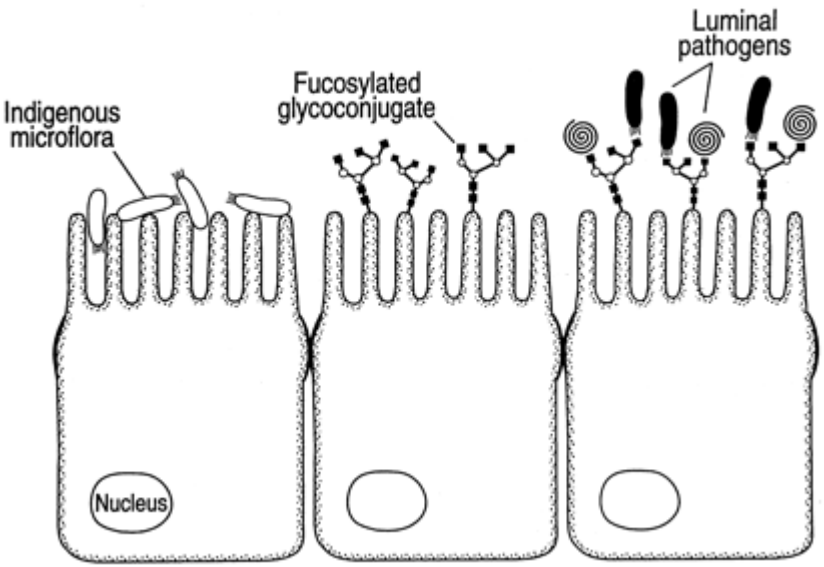


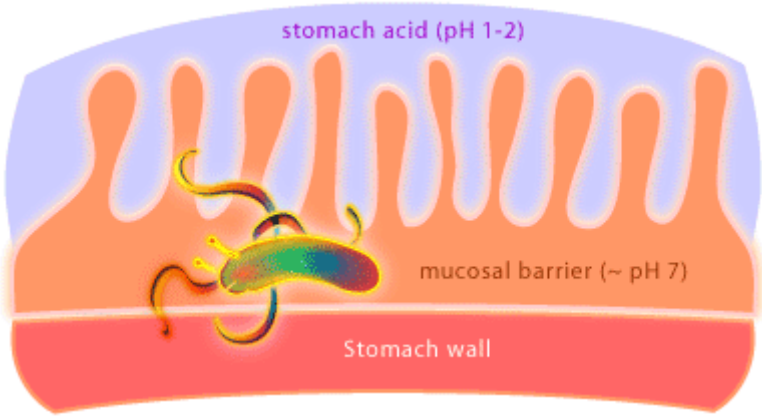
Figure 2-7 Immunobiology, 7ed. (© Garland Science 2008)

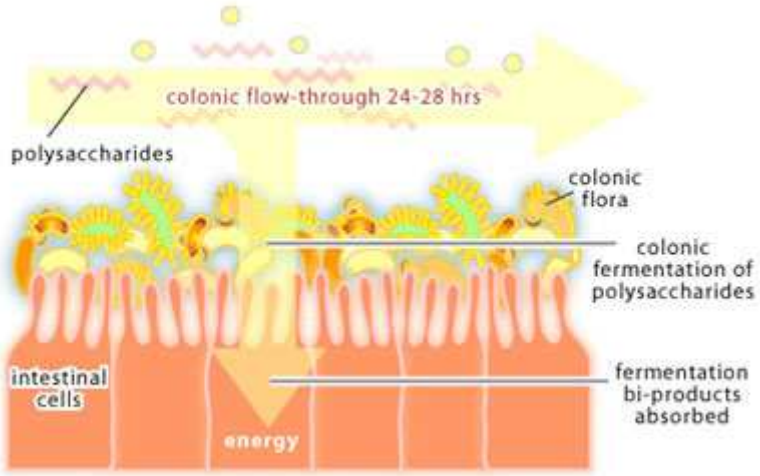
Mecanismos Inespecíficos en piel y mucosas



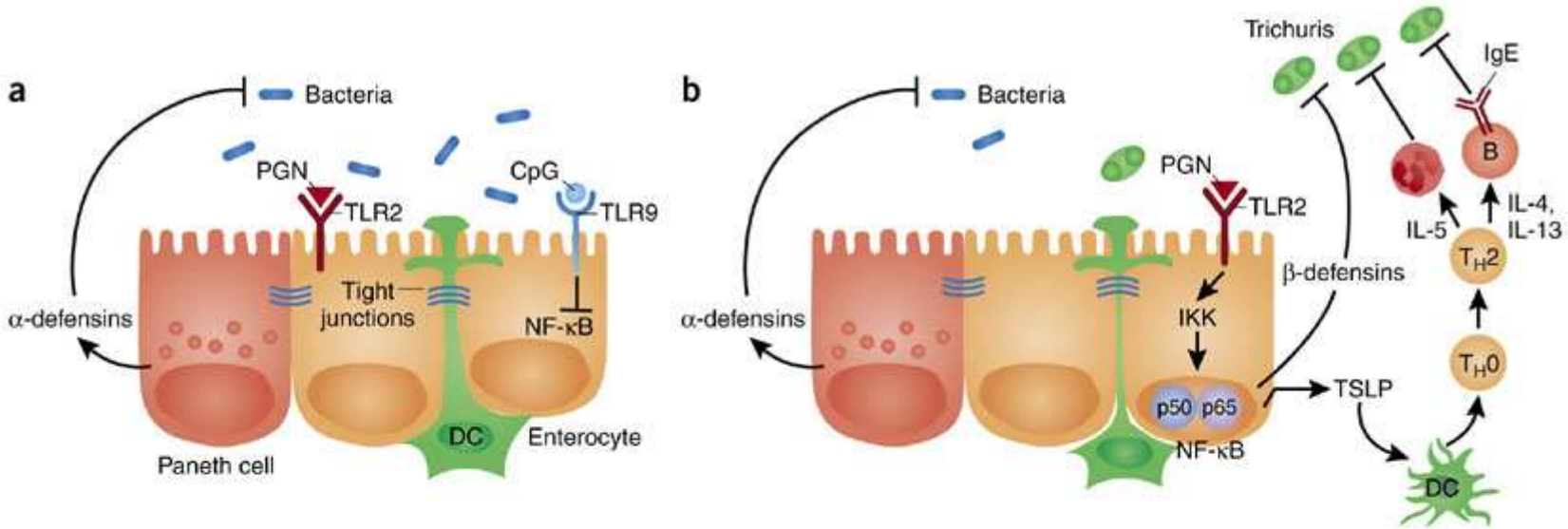
Flora microbiana normal







Crosstalk between intestinal bacteria and the host epithelium. Colonization by indigenous microflora induces the expression of fucosylated glycoconjugates on the host intestinal epithelium. The expression of the glycoconjugates provides lectin-like receptors for the attachment of luminal pathogens and eventually confers susceptibility to pathogen colonization and disease.



(a) During gut homeostasis, while maintaining a polarized configuration (with intact tight junctions), enterocytes are tolerant to TLR stimulation by normal microflora, and NF-κB activation is low. Secretion of α-defensin by Paneth cells helps control the amount of intestinal microflora. PGN, peptidoglycan; CpG, CpG oligo deoxynucleotides; DC, dendritic cell.

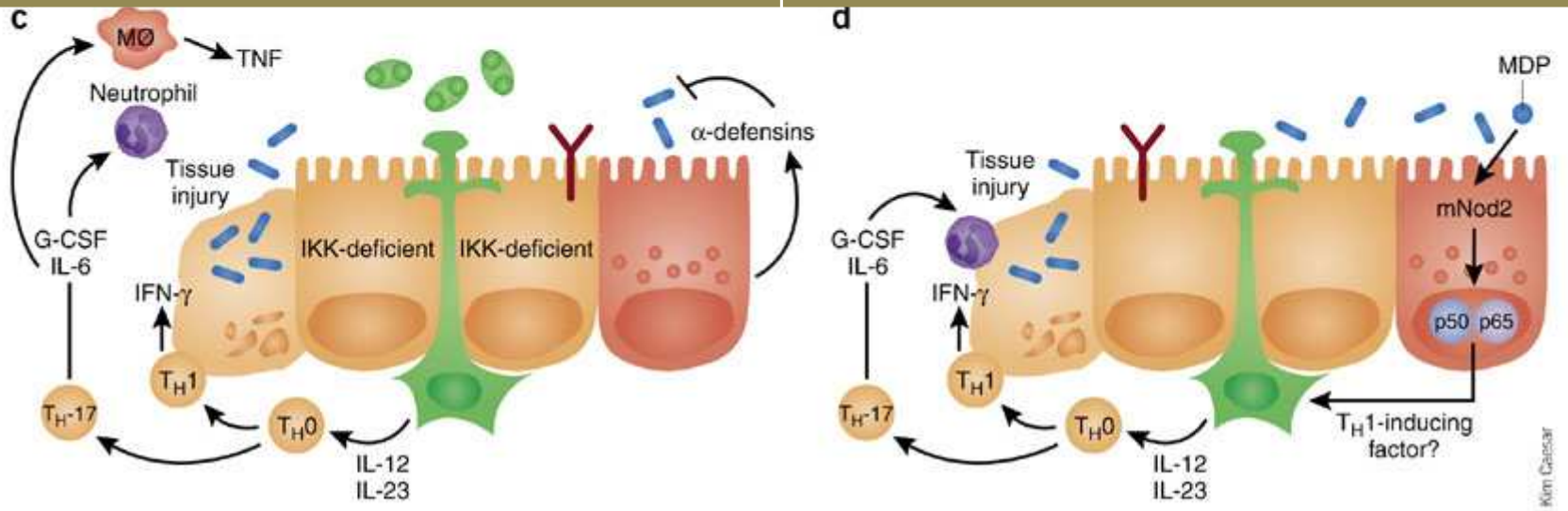
(**b**) Activation of IKK and NF-κB in response to trichuris infection results in TSLP secretion, which 'instructs' dendritic cells to induce a T_H2 response with eosinophils and immunoglobulin E (IgE)–secreting B cells, thus eradicating the parasite. The α-defensins and β-defensins secreted by Paneth cells and enterocytes, respectively, control the microflora. p50 and p65, NF-B subunits.

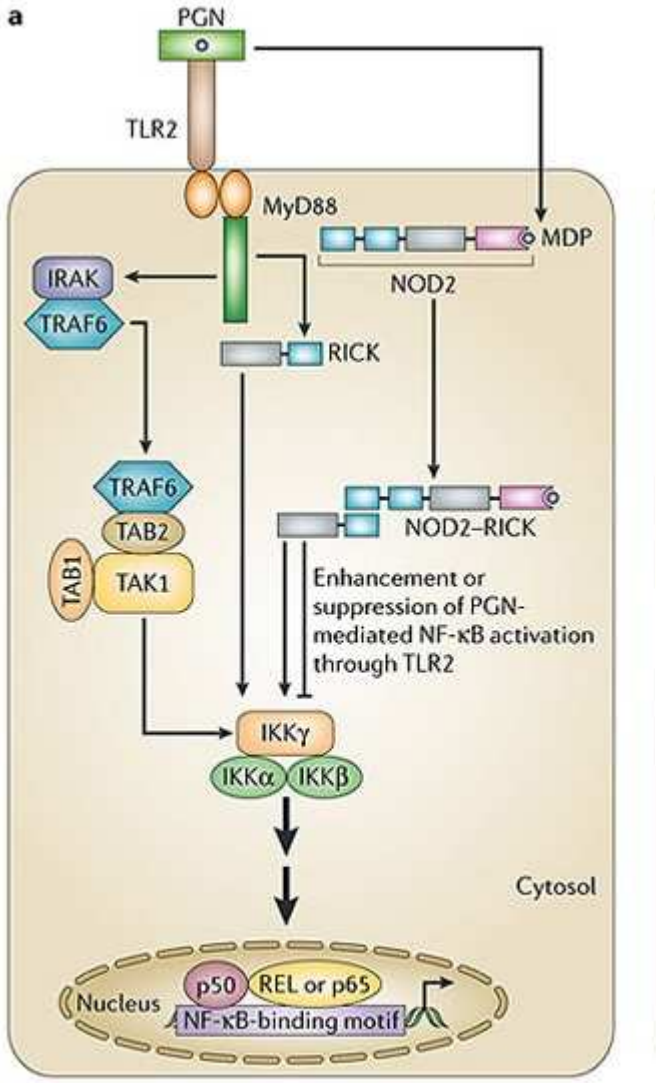
Thymic Stromal LymphoPoietin: TSLP

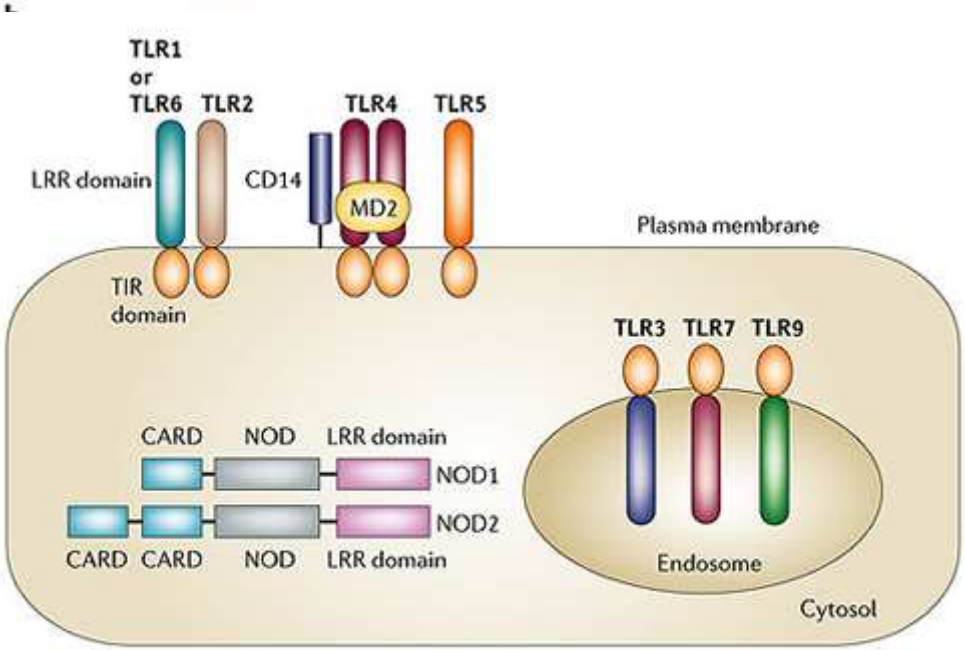
Nature Immunology 8, 479 - 481 (2007)

(**c**) Deficiency in IKK or NEMO (possibly representing ectodermal dysplasia with immune deficiency) leads to a lack of TSLP and α–defensin production, causing dendritic cells to secrete IL-12 and IL-23, which induces a T_H1 and IL-17-secreting T helper (T_H-17) response and, consequently, a chronic inflammatory reaction. Tissue damage ensues, due to the accumulation of neutrophils and other inflammatory cells and the secretion of proapoptotic cytokines such as TNF. MΦ, macrophage; G-CSF, granulocyte colony-stimulating factor.

(**d**) In Paneth cells, gain-of-function mutations in the gene encoding Nod2 (mNod2) with hypersensitivity to muramyl dipeptide (MDP) result in excessive NF-κB activation, with secretion of a hypothetical cytokine that forces DCs to release IL-12 and IL-23. **The outcome is induction of a T_H1 and an IL-17-secreting T helper response that promotes tissue damage and Crohn's colitis.** Alternatively, loss-of-function mutations in the gene encoding Nod2 compromise NF-B activation and the production of a TSLP-like factor, also resulting in T_H1-driven colitis. IFN-γ, interferon-γ.







A reasonable interpretation of these results is that PGN-mediated activation of TLR2 signalling is negatively regulated by MDP-mediated activation of NOD2 signalling and that, in the absence of NOD2, the negative regulation is released.

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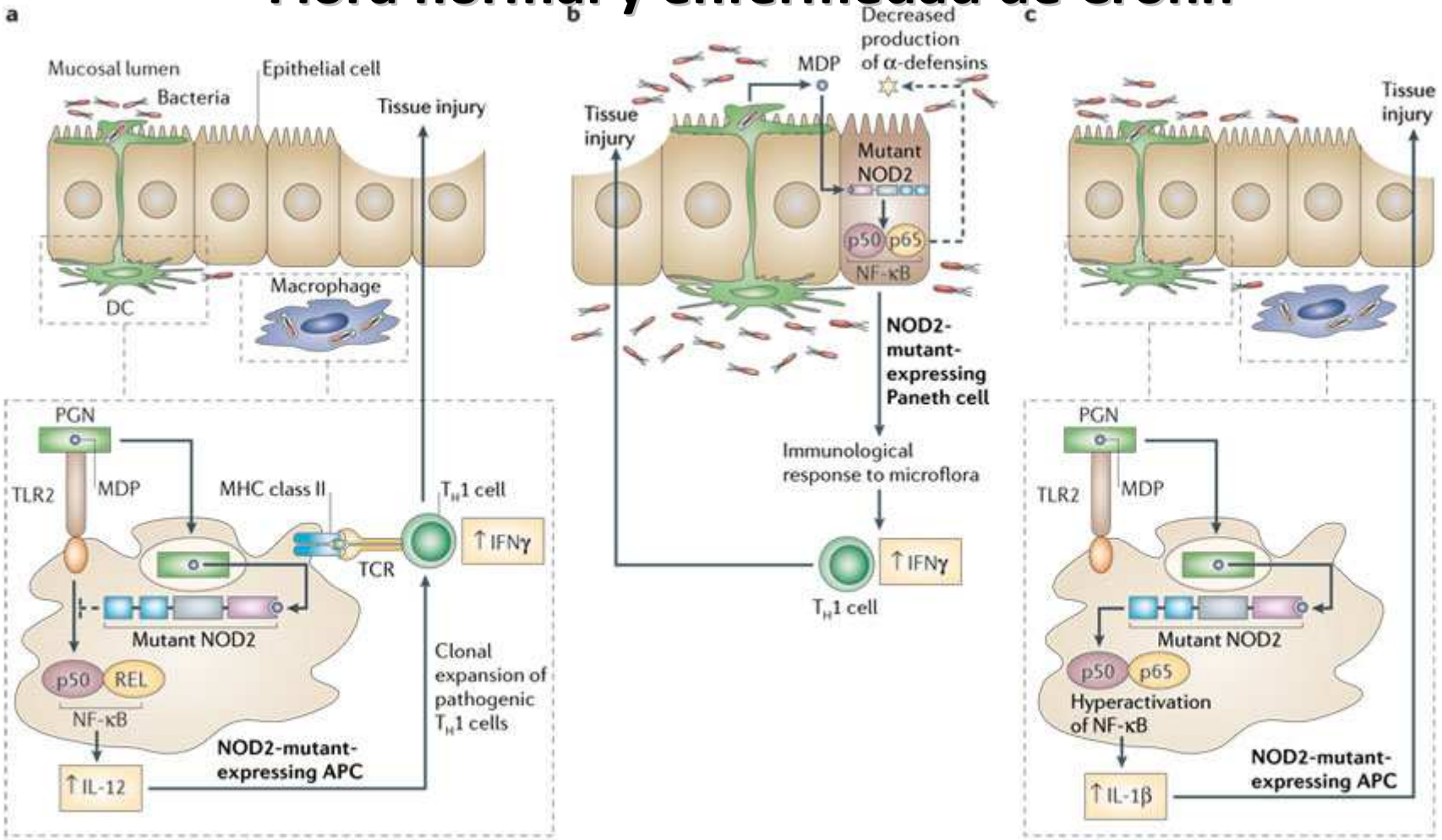
Flora normal y enfermedad de Crohn

Flora normal y enfermedad de Crohn

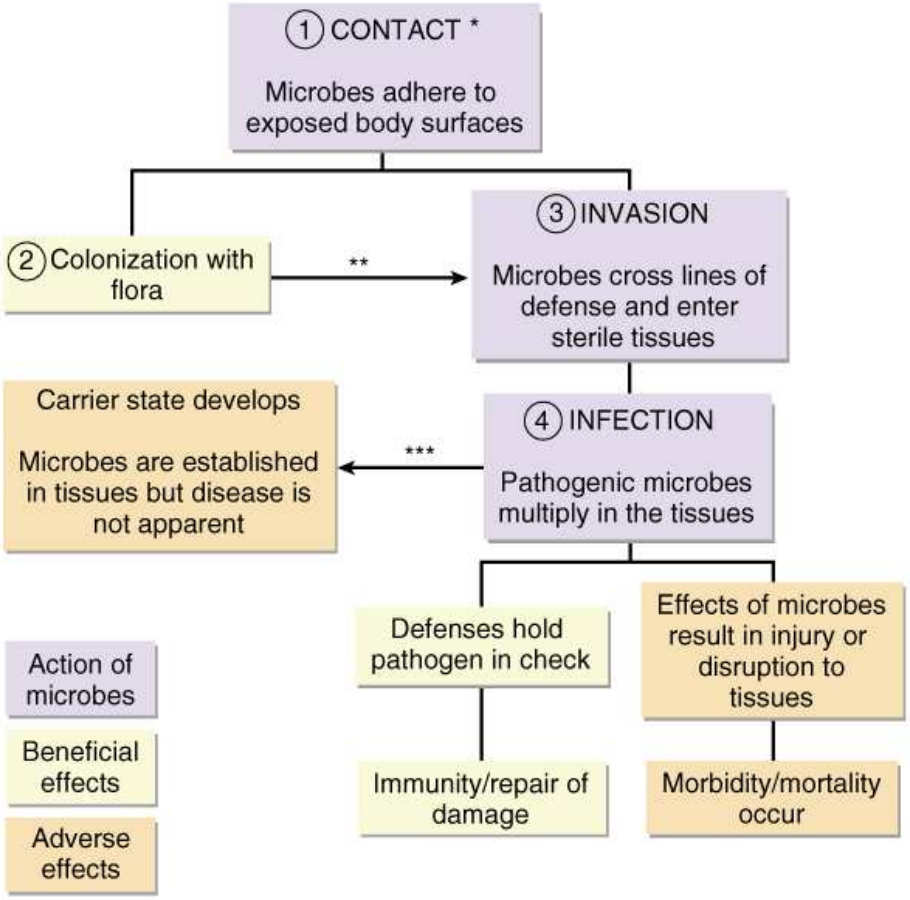


Nature Reviews Immunology 6, 9-20 (January 2006)

Elementos típicos de la INMUNIMIDAD INNATA involucrados en el control de las distintas infecciones

Table 1 | **Typical elements of innate immunity involved in controlling infections**

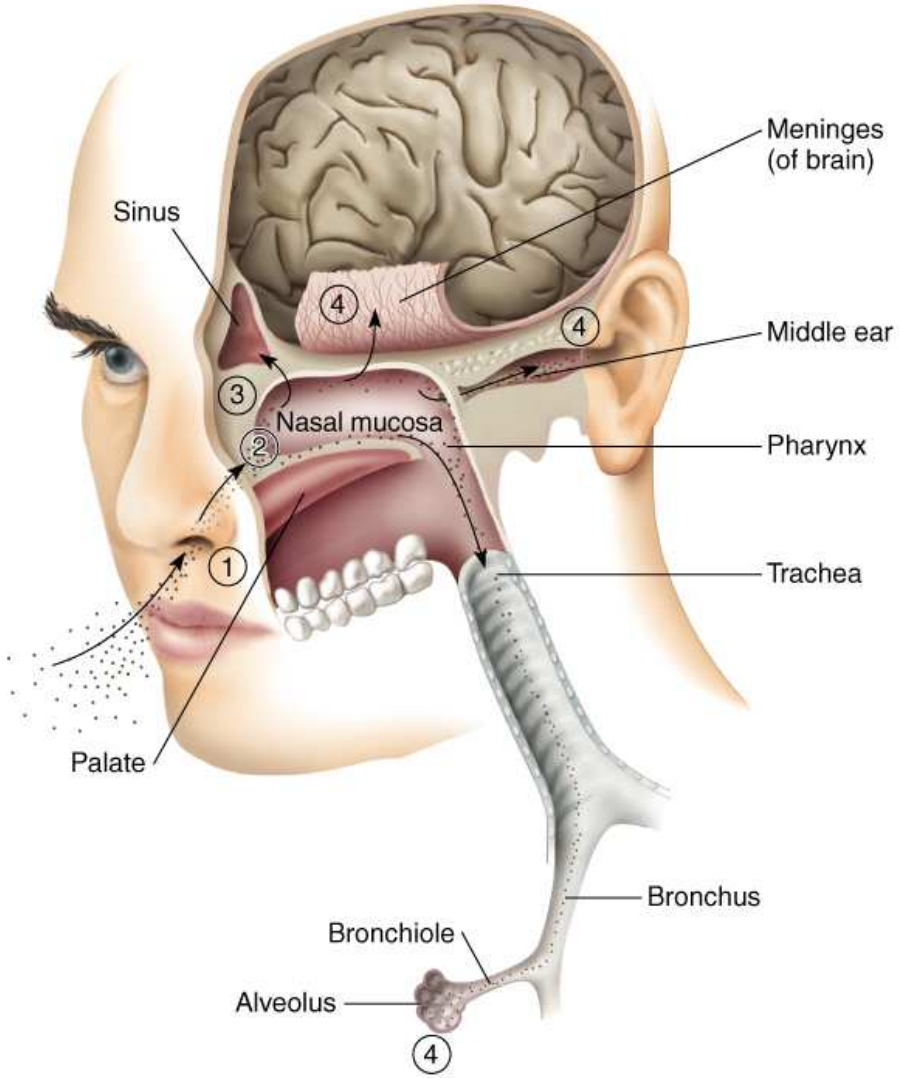
General response	Effects
Pro-inflammatory response	NFκB mediated; activates many agents of inflammation; overstimulation can result in shock
Chemotaxis	Increased endothelial adhesion of phagocytic cells; cell migration to site of infection; diapedesis
Cationic host defence peptides	Increased production of cationic peptides stimulated by bacterial signalling molecules
Phagocytic cell activation	Increased intracellular killing in neutrophils and macrophages (both oxidative and non-oxidative mechanisms are enhanced); increased cytokine production
Extracellular killing mechanisms	Complement activation; antimicrobial peptide secretion; enhanced iron chelation; production of degradative enzymes
Infection containment	Clot formation via fibrinogen activation
Wound repair	Fibroblast growth and adherence; angiogenesis
Activate adaptive immune responses	B- and T-cell activation, often via dendritic cells



* Not all contacts lead to colonization or infection.

** Flora may invade, especially if defenses are compromised.

*** Some pathogens may remain hidden in the body



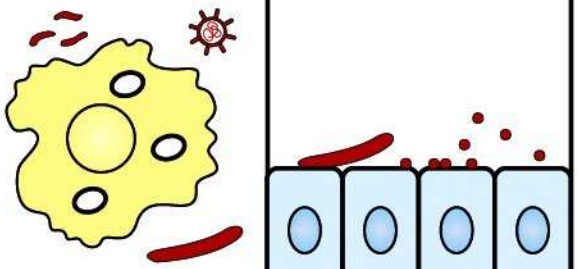
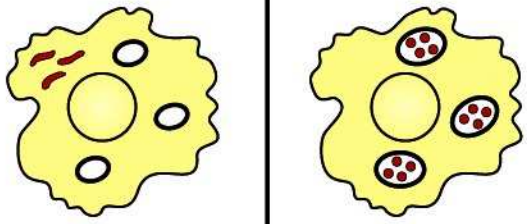
	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
Site of infection				
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Mycoplasma* spp. *Streptococcus pneumoniae* *Vibrio cholerae* *Escherichia coli* *Helicobacter pylori* *Candida albicans* Worms	Viruses *Chlamydia* spp. *Rickettsia* spp. *Listeria monocytogenes* Protozoa	*Mycobacterium* spp. *Salmonella typhimurium* *Yersinia pestis* *Listeria* spp. *Legionella pneumophila* *Cryptococcus neoformans* *Leishmania* spp. *Trypanosoma* spp. *Histoplasma*
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA	NK cells Cytotoxic T cells	T-cell and NK-cell dependent macrophage activation

Figure 2-3 Immunobiology, 7ed. (© Garland Science 2008)

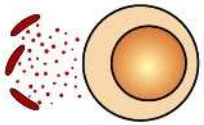
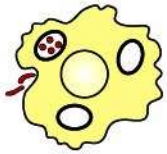
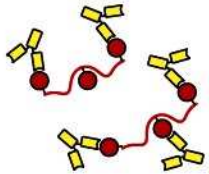
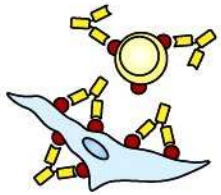
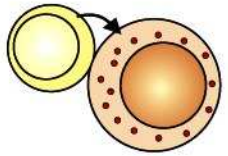
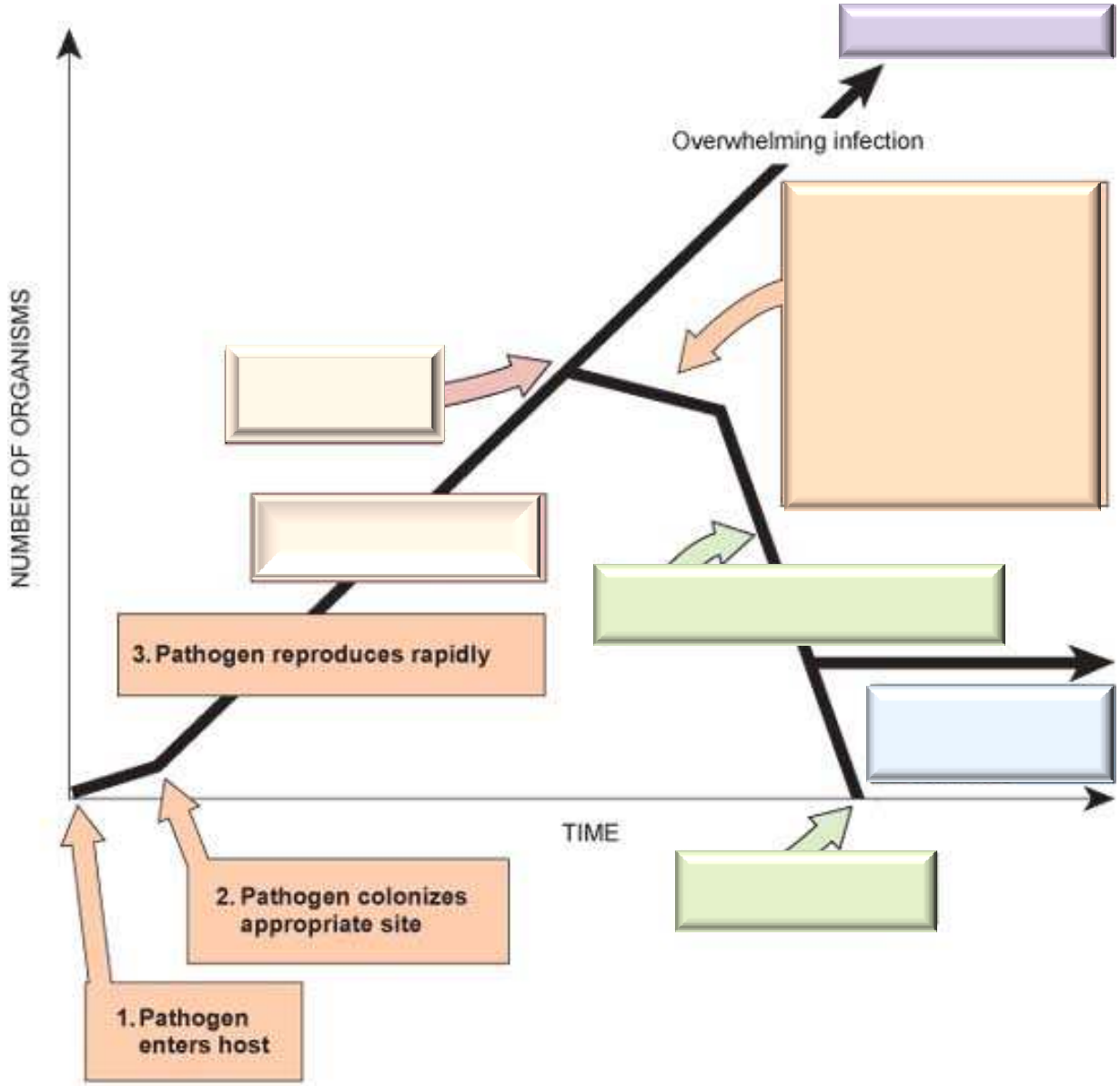
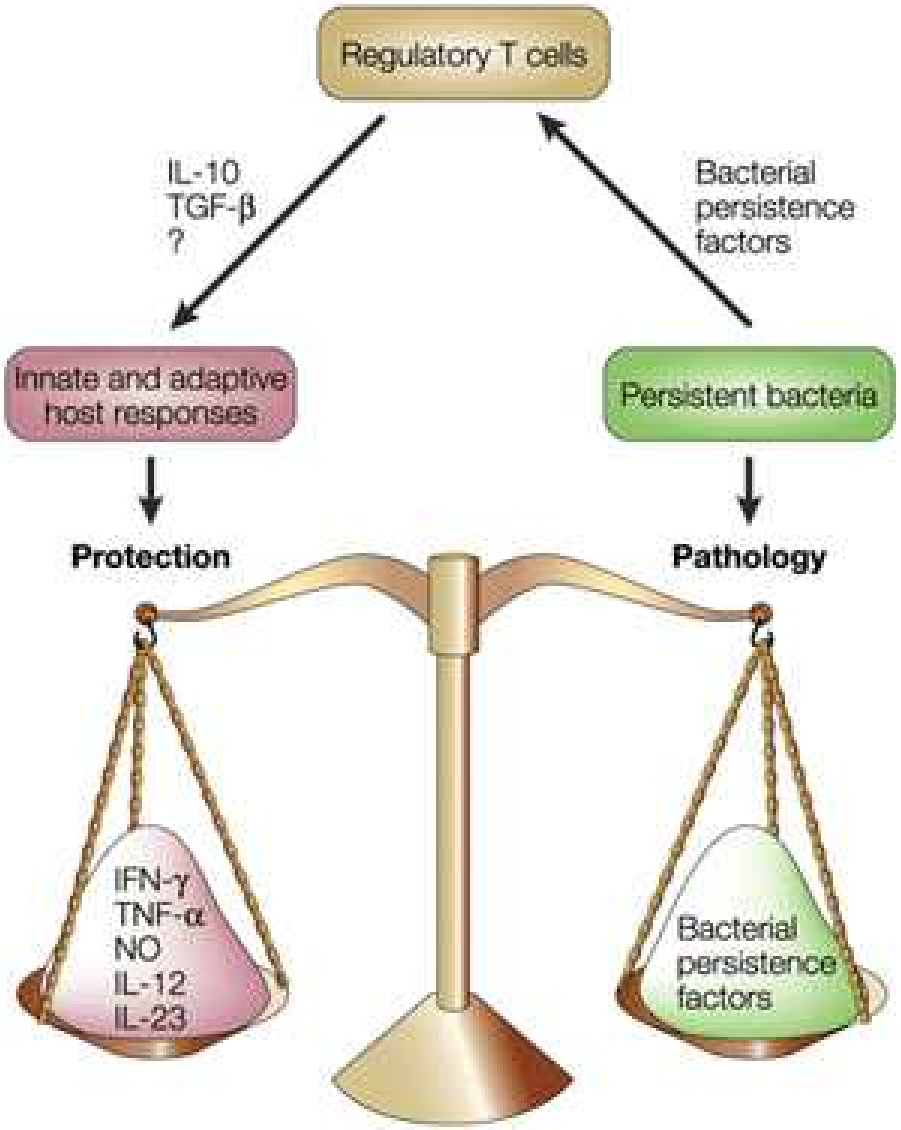
	Direct mechanisms of tissue damage by pathogens			Indirect mechanisms of tissue damage by pathogens		
	Exotoxin production	**Endotoxin**	**Direct cytopathic effect**	**Immune complexes**	**Anti-host antibody**	**Cell-mediated immunity**
Pathogenic mechanism						
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridium tetani* *Vibrio cholerae*	*Escherichia coli* *Haemophilus influenzae* *Salmonella typhi* *Shigella* *Pseudomonas aeruginosa* *Yersinia pestis*	Variola Varicella-zoster Hepatitis B virus Polio virus Measles virus Influenza virus Herpes simplex virus Human herpes virus 8 (HHV8)	Hepatitis B virus Malaria *Streptococcus pyogenes* *Treponema pallidum* Most acute infections	*Streptococcus pyogenes* *Mycoplasma pneumoniae*	*Mycobacterium tuberculosis* *Mycobacterium leprae* Lymphocytic choriomeningitis virus *Borrelia burgdorferi* *Schistosoma mansoni* Herpes simplex virus
Disease	Tonsilitis, scarlet fever Boils, toxic shock syndrome, food poisoning Diphtheria Tetanus Cholera	Gram-negative sepsis Meningitis, pneumonia Typhoid fever Bacillary dysentery Wound infection Plague	Smallpox Chickenpox, shingles Hepatitis Poliomyelitis Measles,subacute sclerosing panencephalitis Influenza Cold sores Kaposi's sarcoma	Kidney disease Vascular deposits Glomerulonephritis Kidney damage in secondary syphilis Transient renal deposits	Rheumatic fever Hemolytic anemia	Tuberculosis Tuberculoid leprosy Aseptic meningitis Lyme arthritis Schistosomiasis Herpes stromal keratitis

Figure 2-4 Immunobiology, 7ed. (© Garland Science 2008)

La infección y los aspectos clínicos…

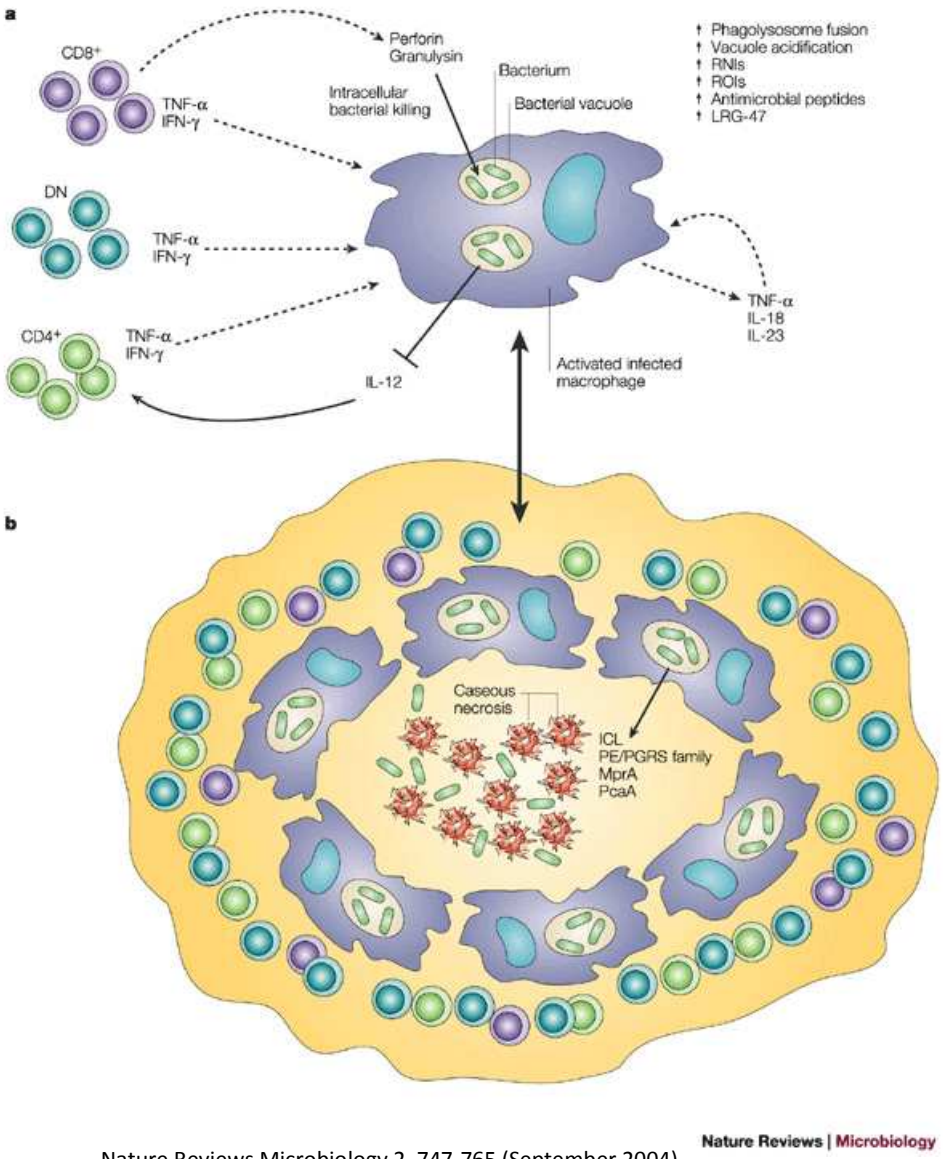


PERSISTENCIA MICROBIANA



The balance between the immune response and infection during persistent infections is important for both the host and the pathogen, with the host switching off the immune response when it becomes more harmful than the presence of the pathogen.

Persistencia de bacterias… Micobaterias….

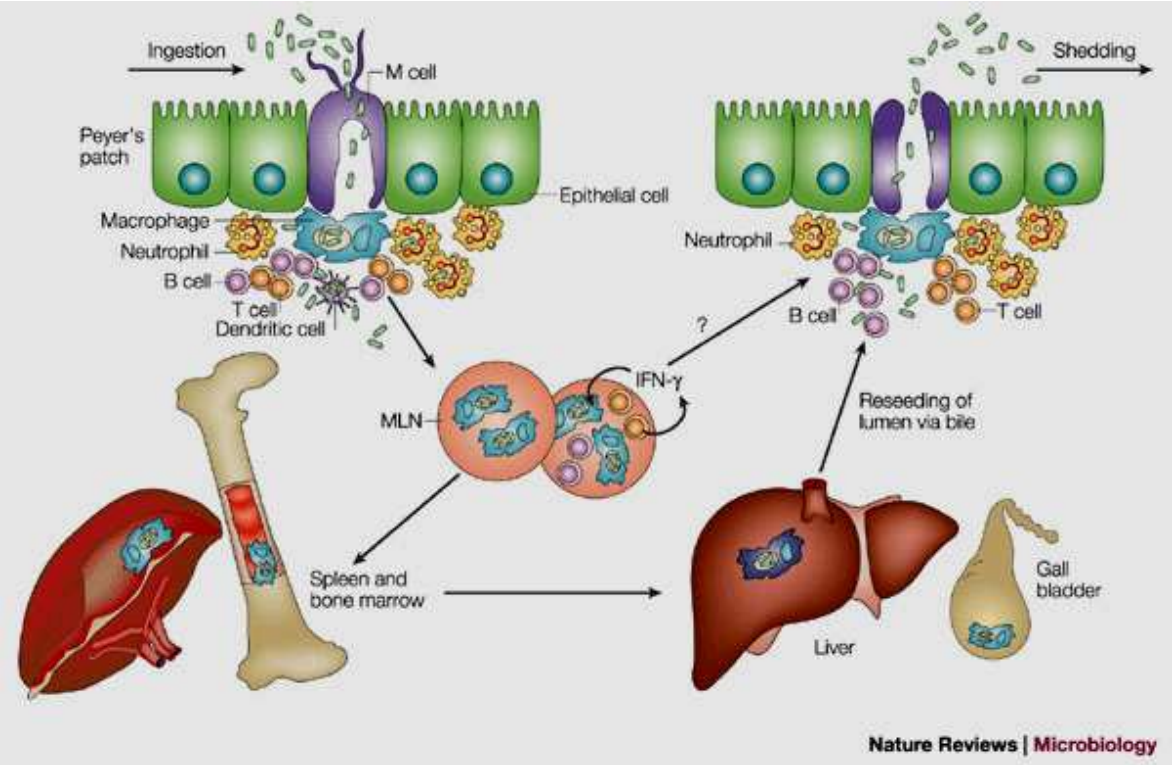


Nature Reviews Microbiology 2, 747-765 (September 2004)

The ability of mycobacteria to inhibit the secretion of IL-12 by infected macrophages might contribute to bacterial survival, as this cytokine normally functions to induce the production of IFN- γ.

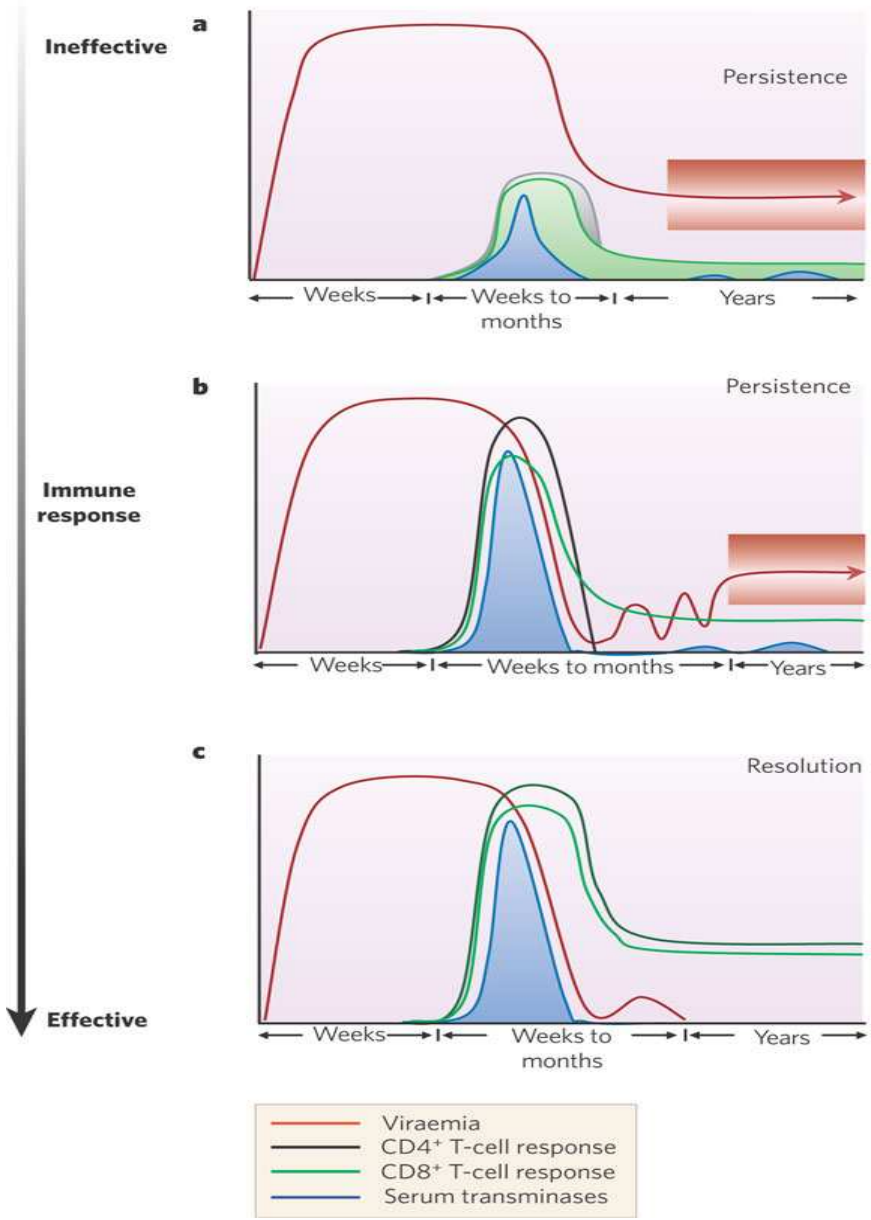
In most persistent mycobacterial infections, the bacteria are initially contained in granulomas. Tuberculous granulomas are thought to arise from aggregates of phagocytic cells that surround individual infected macrophages. These structures contain many T and B lymphocytes, dendritic cells, neutrophils, fibroblasts and extracellular matrix components (for simplicity, only T cells are shown here). Another striking feature of certain tuberculous granulomas is the presence of caseous necrosis in the centre of the granuloma. Some of the genes that are specifically expressed by mycobacteria in granulomas encode the following proteins: isocitrate lyase (ICL), an enzyme essential for the metabolism of fatty acids; outer-membrane proteins of the PE/PGRS family that might have a role in antigenic variation; the transcriptional regulator MprA, which is involved in the regulation of unidentified genes during adaptations that are required for persistence; and PcaA, which encodes a cyclopropane synthase. Mycobacteria that lack PcaA have reduced levels of persistence in the chronic mouse model.

..... Salmonella spp

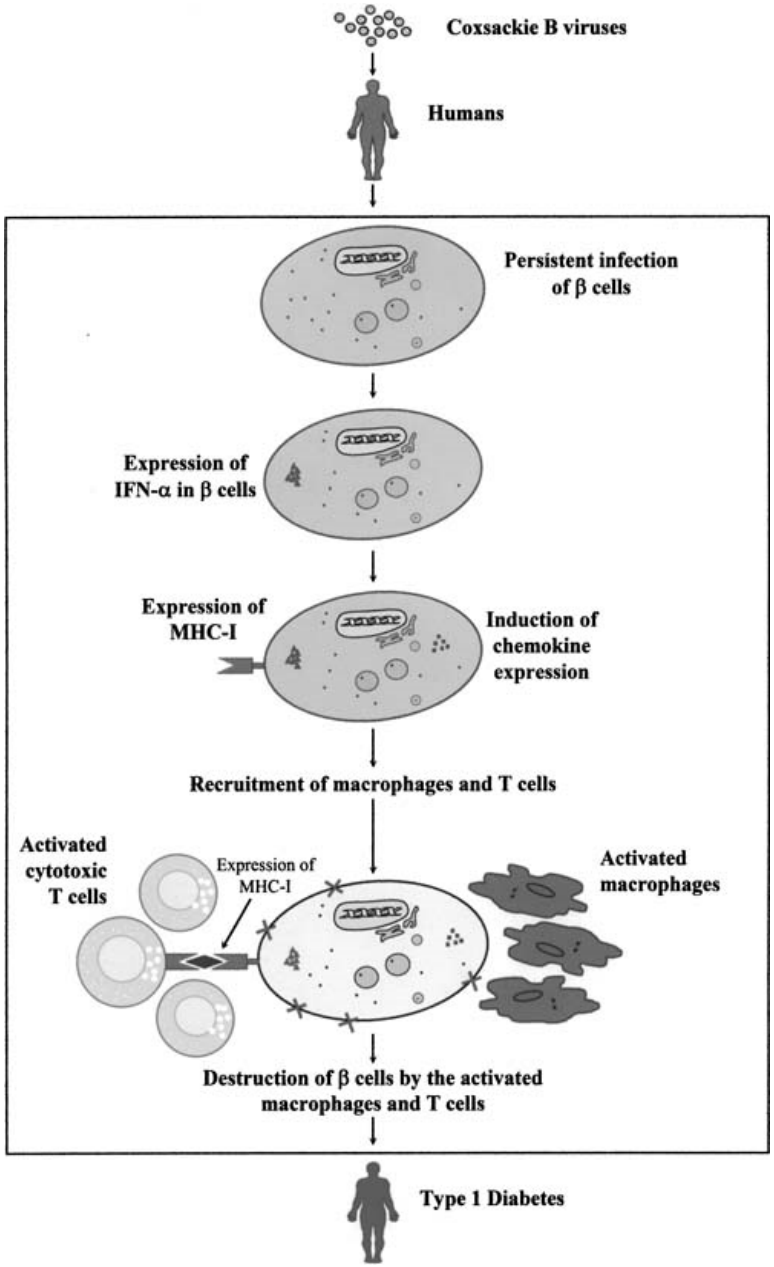


Schematic representation of persistent infection with Salmonella enterica serovar Typhi in humans. Bacteria enter the Peyer's patches of the intestinal tract mucosal surface by invading M cells — specialized epithelial cells that take up and transcytose luminal antigens for uptake by phagocytic immune cells. This is followed by inflammation and phagocytosis of bacteria by neutrophils and macrophages and recruitment of T and B cells. In systemic salmonellosis, such as typhoid fever, Salmonella may target specific types of host cells, such as dendritic cells and/or macrophages that favour dissemination through the lymphatics and blood stream to the mesenteric lymph nodes (MLNs) and to deeper tissues. This then leads to transport to the spleen, bone marrow, liver and gall bladder. **Bacteria can persist in the MLNs, bone marrow and gall bladder for life**, and periodic reseeding of the mucosal surface via the bile ducts and/or the MLNs of the small intestine occur, and shedding can take place from the mucosal surface. **Interferon-γ (IFN-γ), which can be secreted by T cells, has a role in maintaining persistence by controlling intracellular Salmonella replication. Interleukin IL-12, which can increase IFN-γ production and the proinflammatory cytokine tumour-necrosis factor- α (TNF-α) also contribute to the control of persistent Salmonella.**

Infecciones virales…. Persistencia del virus de Hepatitis C



Infecciones virales… persistencia viral y diabetes…



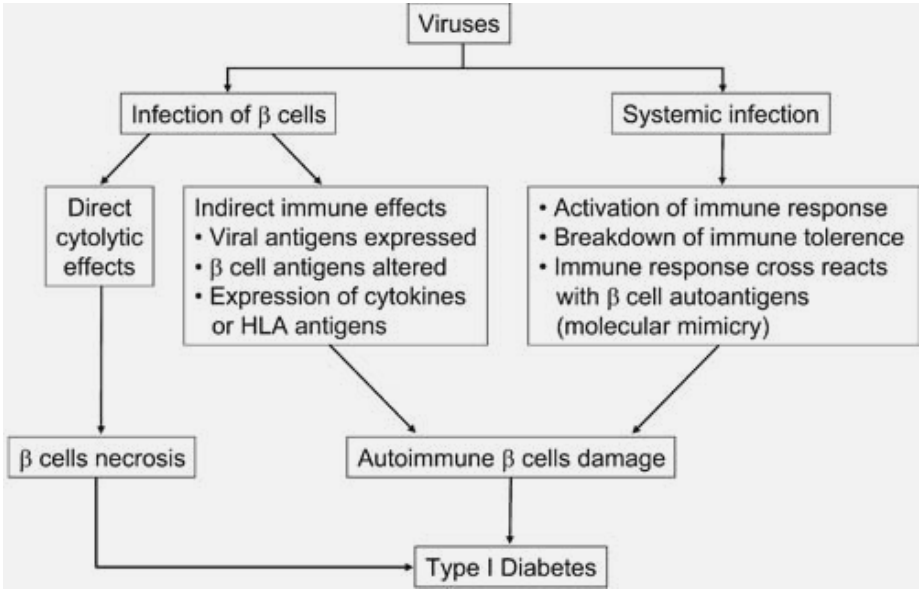


Table 1 Viruses associated with the development of type 1 diabetes mellitus (IDDM) in humans

Virus	Involvement of genetic factors	Remarks
RNA Viruses:		
Picornaviridae		
Coxsackie B virus	Not determined	Evidence from epidemiological studies, anecdotal reports and isolated viruses causing diabetes in infected animals
Retroviridae		
Retrovirus	Not determined	Association of beta cell-specific expression of retroviral gene with development of human autoimmune IDDM
Togaviridae		
Rubella virus	Not determined	Possible association with autoimmune IDDM, especially congenital rubella syndrome
Paramyxoviridae		
Mumps virus	Yes	Possible induction of islet-cell autoantibodies
Reoviridae		
Rotavirus	Not determined	Association with islet autoimmunity
DNA Viruses:		
Herpesviridae		
Cytomegalovirus	Not determined	Association with autoimmune IDDM
Epstein-Barr virus	Not determined	Possible induction of autoimmune IDDM

Infecciones por parásitos….Toxoplasma gondii

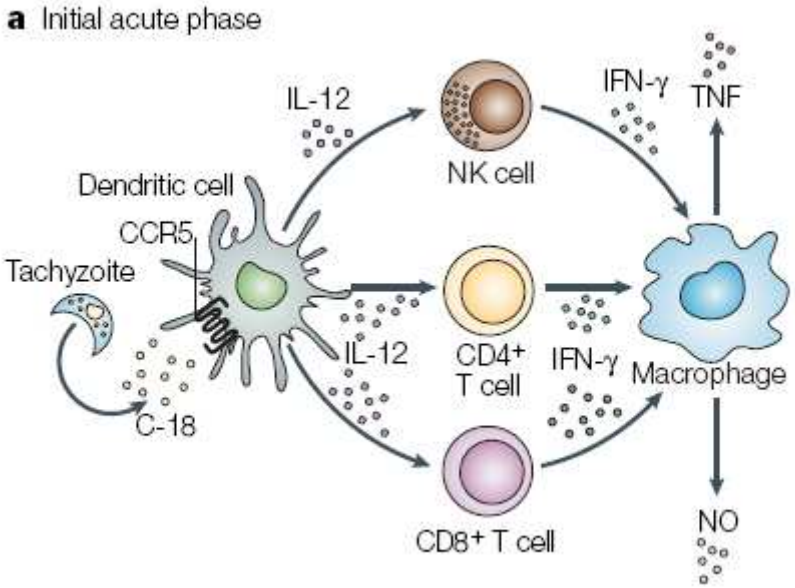
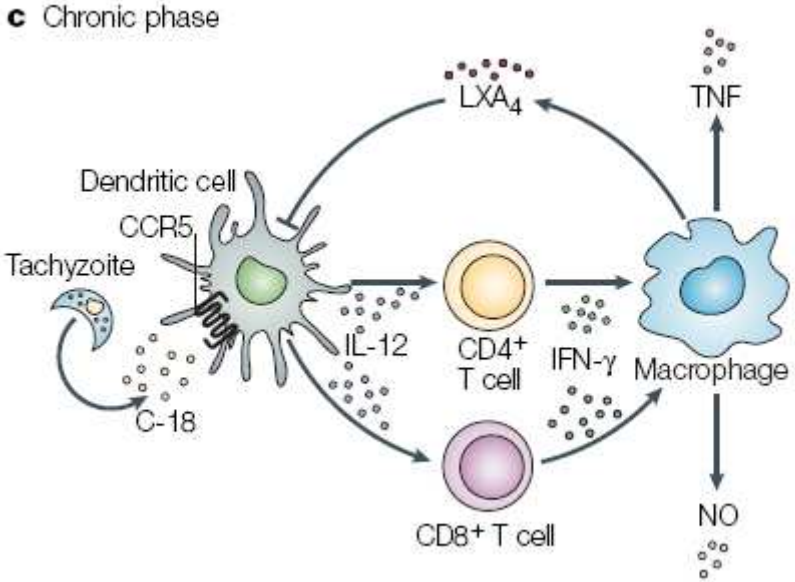


Figure 2 | **Control of pro-inflammatory responses during infection with *Toxoplasma gondii*. a** | Immediately after infection, host dendritic cells (DCs) produce interleukin-12 (IL-12) in response to products secreted by *T. gondii*, including the CC-chemokine receptor 5 (CCR5)-binding protein, cyclophilin-18 (C-18). IL-12 production induces or favours the differentiation and/or proliferation of type 1, interferon-γ (IFN-γ)-producing T cells (both CD4+ and CD8+) and natural killer (NK) cells. IFN-γ, in turn, activates host cells, including macrophages, to exert microbicidal activity, such as the production of nitric oxide (NO) or tumour-necrosis factor (TNF).

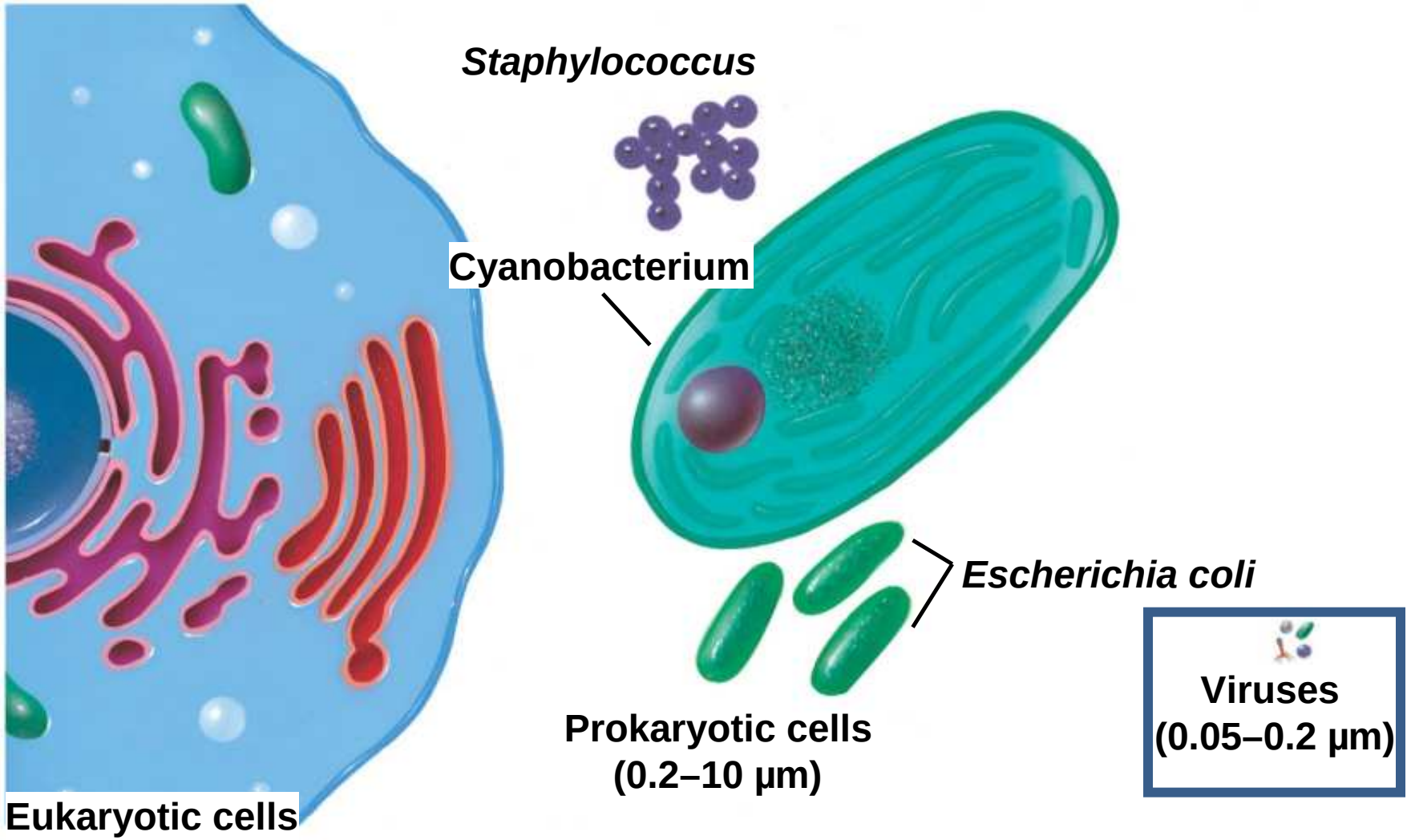


c | With the onset of chronic disease, lipoxin A_4 (LXA_4) is produced and controls pro-inflammatory cytokine responses, mostly at sites where parasite replication might be occurring, such as the central nervous system, without interfering with the microbicidal activity of macrophages.

Nature Reviews Immunology 5, 162-170 (February 2005)

RESPUESTA INMUNE ANTIVIRAL
Y MECANISMOS DE EVASIÓN DE LA RESPUESTA ANTIVIRAL

EL TAMAÑO DE LOS MICROORGANISMOS



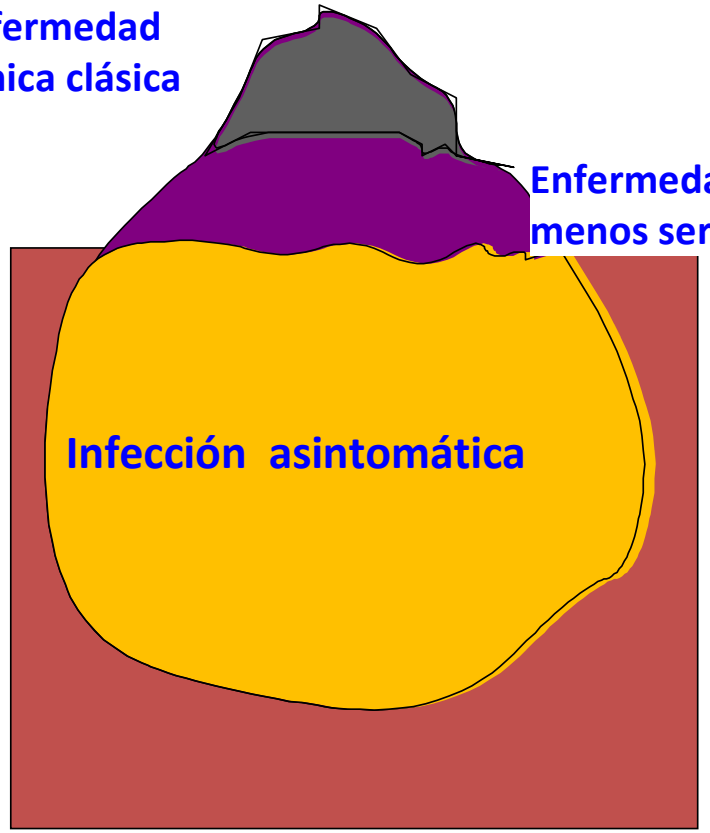
El concepto de iceberg en la infección viral

Poliomielitis en un niño
0.1-1% de las infecciones son clínicamente aparentes

Rubeola
50% de las infecciones son clínicamente aparentes

Espectro de virulencia

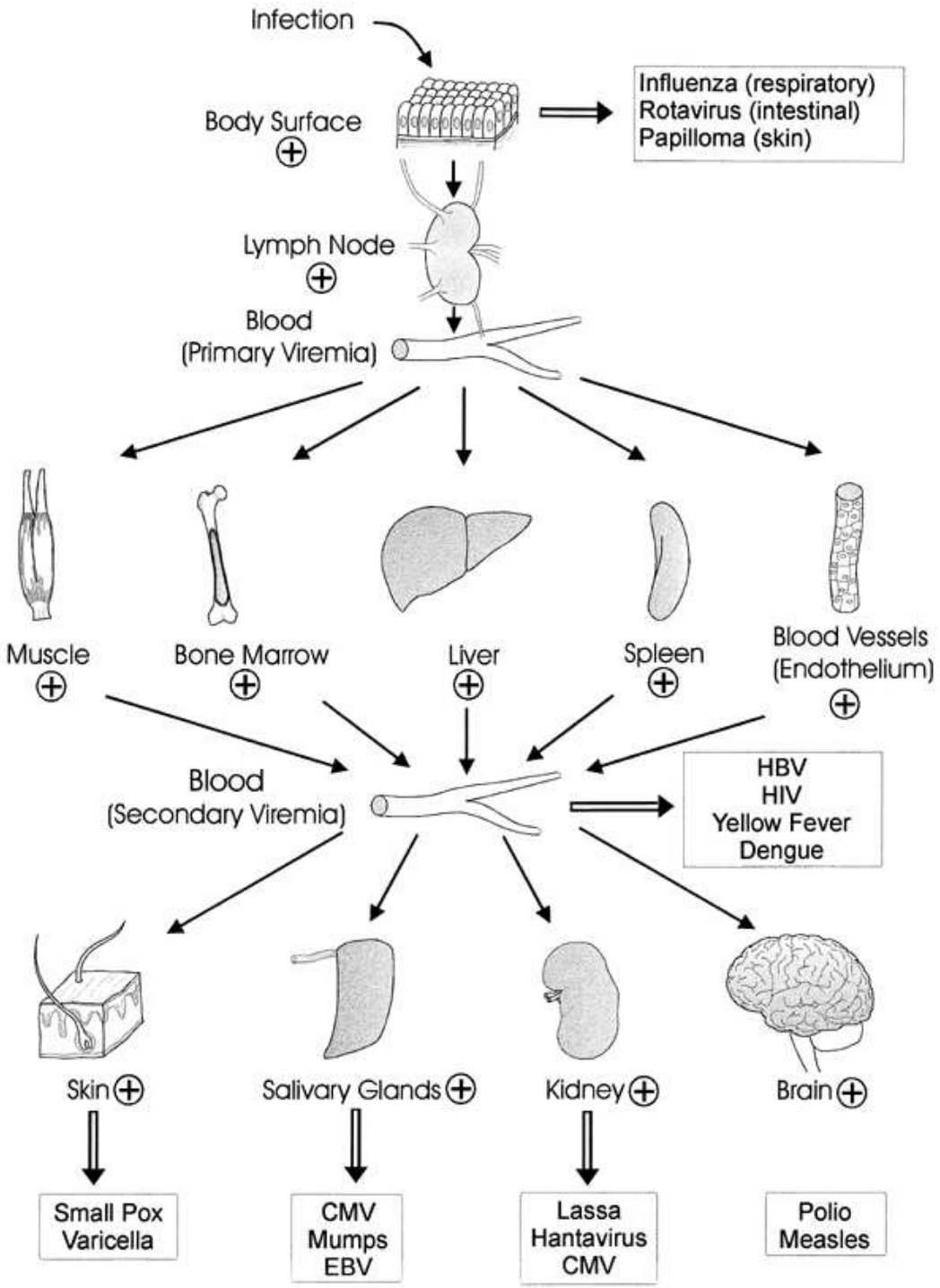
Rabia
100% de las infecciones son clínicamente aparentes



Some common causes of disease in humans

Viruses	DNA viruses	Adenoviruses	Human adenoviruses (e.g., types 3, 4, and 7)
		Herpesviruses	Herpes simplex, varicella zoster, Epstein–Barr virus, cytomegalovirus, HHV8
		Poxviruses	Variola, vaccinia virus
		Parvoviruses	Human parvovirus
		Papovaviruses	Papilloma virus
		Hepadnaviruses	Hepatitis B virus
	RNA viruses	Orthomyxoviruses	Influenza virus
		Paramyxoviruses	Mumps, measles, respiratory syncytial virus
		Coronaviruses	Cold viruses, SARS
		Picornaviruses	Polio, coxsackie, hepatitis A, rhinovirus
		Reoviruses	Rotavirus, reovirus
		Togaviruses	Rubella, arthropod-borne encephalitis
		Flaviviruses	Arthropod-borne viruses, (yellow fever, dengue fever)
		Arenaviruses	Lymphocytic choriomeningitis, Lassa fever
		Rhabdoviruses	Rabies
		Retroviruses	Human T-cell leukemia virus, HIV

Figure 2-2 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)



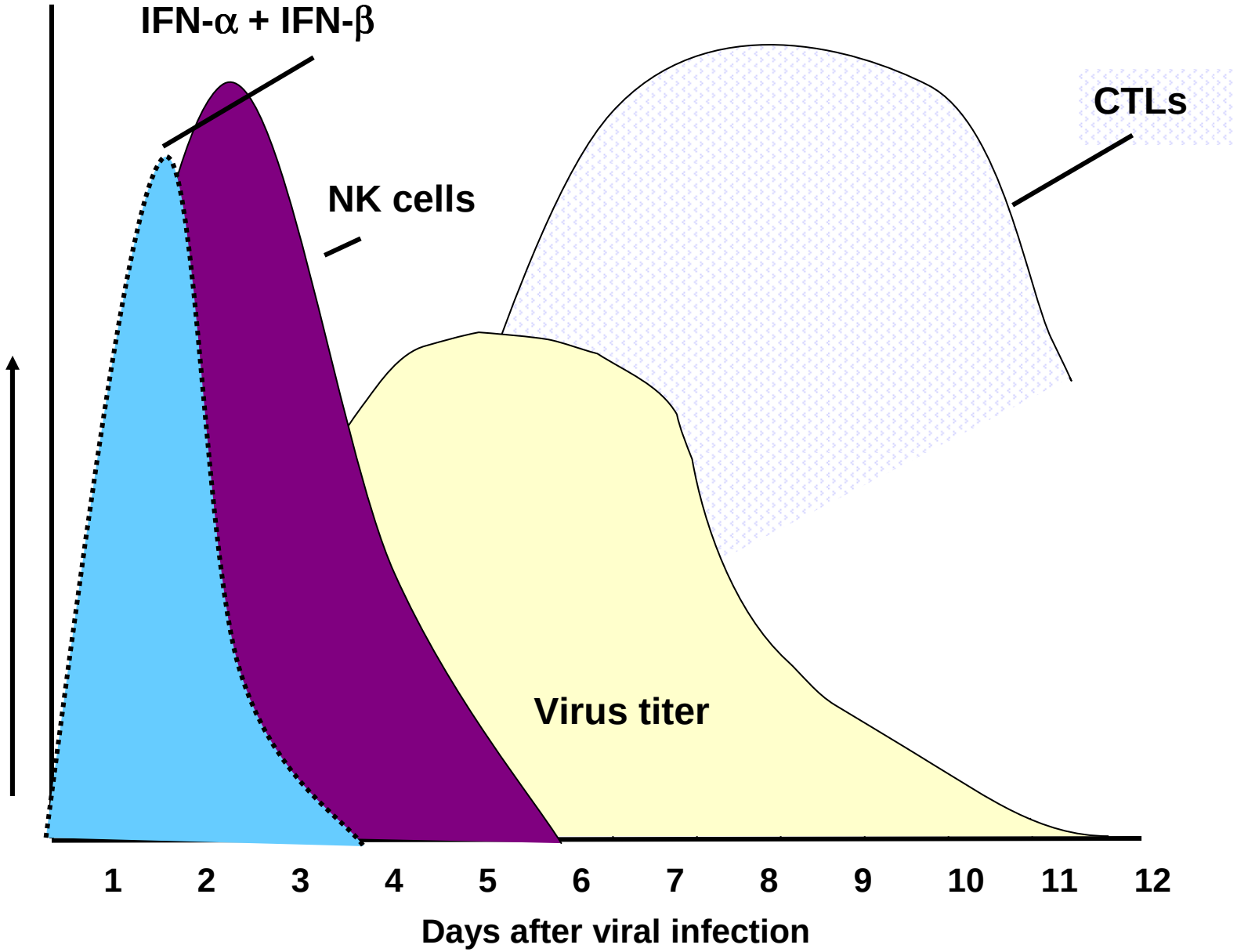
Viral Life Cycle

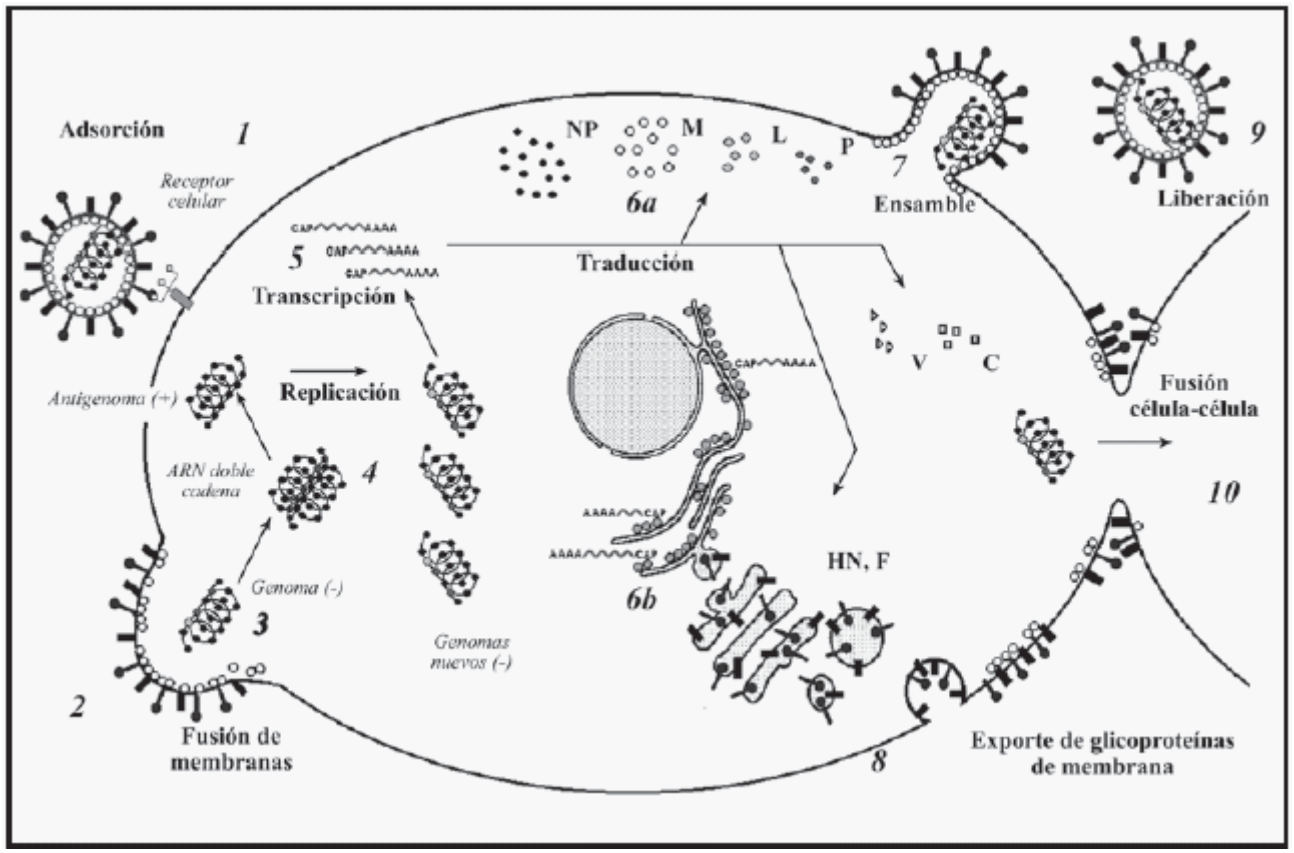
1. **Breach barriers**

2. **Disseminate via lymph nodes**

3. **Viremia to seed target organs**

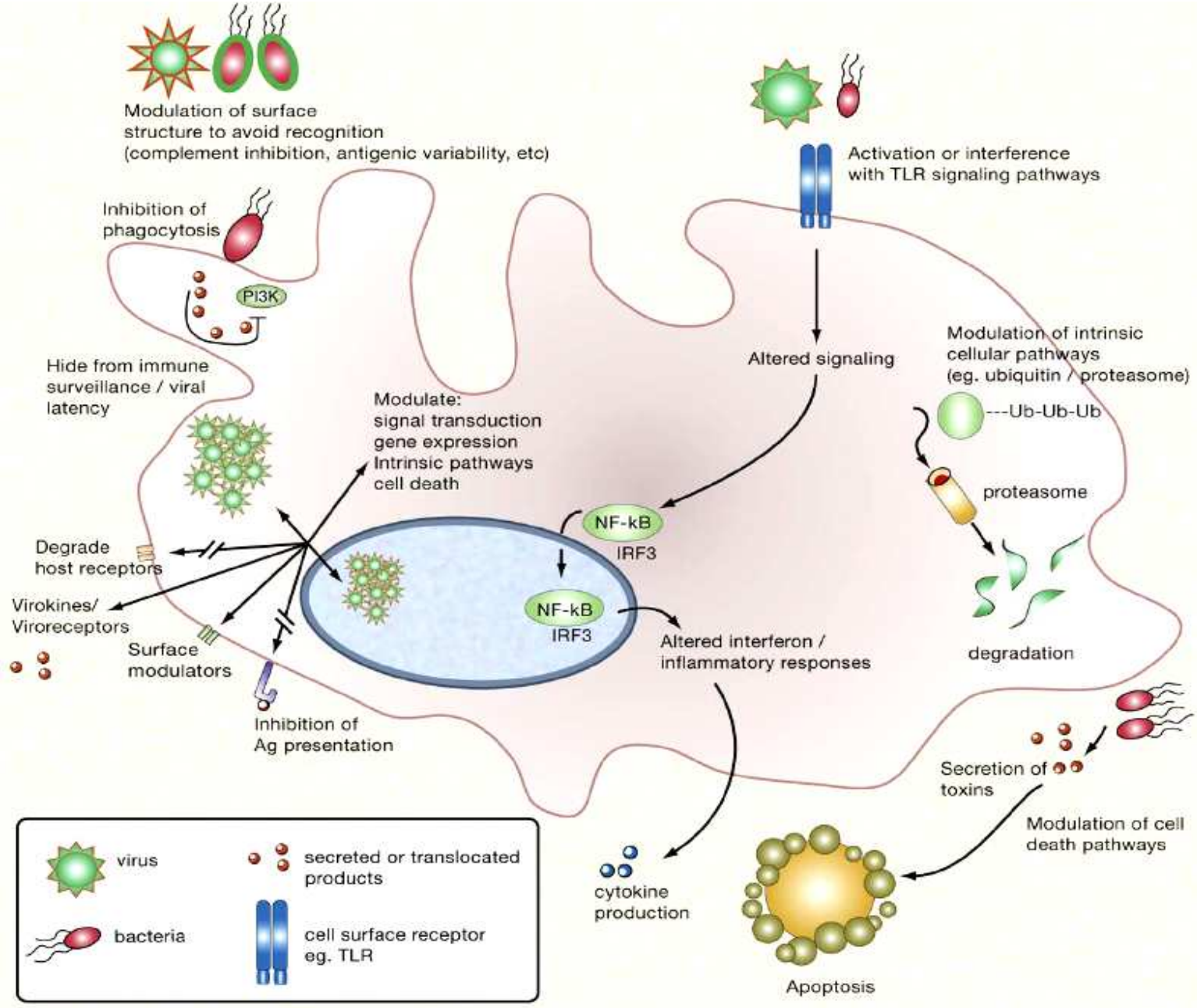
4. **Shedding to new hosts**


IFN-α + IFN-β
NK cells
CTLs
Virus titer
1
2
3
4
5
6
7
8
9
10
11
12
Days after viral infection

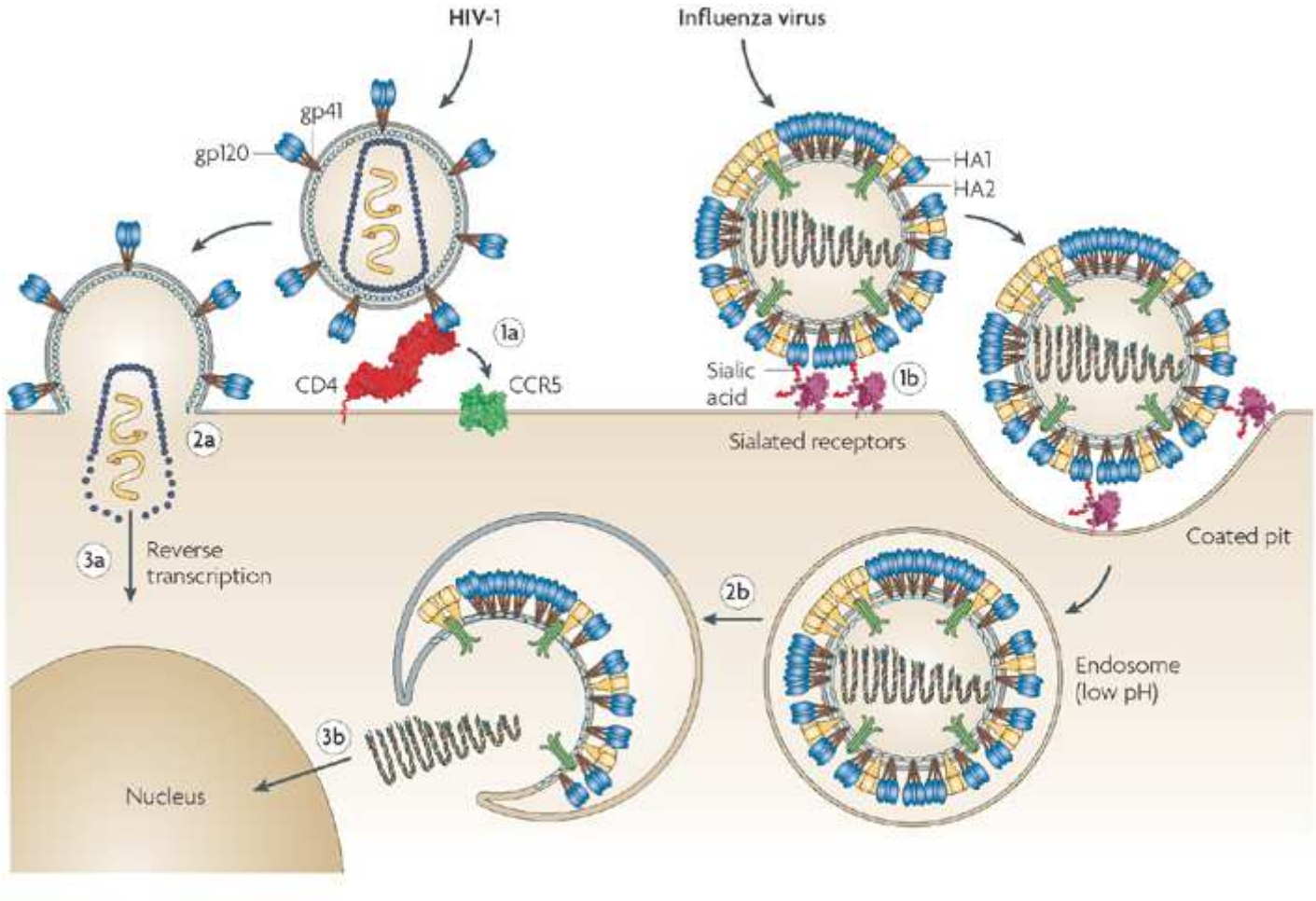

Adsorción
1
Receptor celular
Antigenoma (+)
Replicación
ARN doble cadena
4
Genoma (-)
3
2
Fusión de membranas
5
Transcripción
Traducción
NP
M
L
P
6a
6b
Genomas nuevos (-)
V
C
HN, F
7
Ensamble
8
Exporte de glicoproteínas de membrana
9
Liberación
Fusión célula-célula
10

INMUNIDAD INNATA

1. Defensinas
2. Interferones de tipo I
3. Células NK, NKT, Tγδ
4. Anticuerpos naturales


Modulation of surface structure to avoid recognition (complement inhibition, antigenic variability, etc)
Inhibition of phagocytosis
PI3K
Hide from immune surveillance / viral latency
Modulate: signal transduction gene expression Intrinsic pathways cell death
Degrade host receptors
Virokines/ Viroreceptors
Surface modulators
Inhibition of Ag presentation
Activation or interference with TLR signaling pathways
Altered signaling
NF-kB
IRF3
NF-kB
IRF3
Altered interferon / inflammatory responses
Modulation of intrinsic cellular pathways (eg. ubiquitin / proteasome)
---Ub-Ub-Ub
proteasome
degradation
Secretion of toxins
Modulation of cell death pathways
cytokine production
Apoptosis
virus
bacteria
secreted or translocated products
cell surface receptor eg. TLR

Ingreso del virus a la célula huésped….



Nature Reviews Microbiology 6, 143-155 (February 2008)

Receptores virales expresados en células del sistema inmune

Examples of Viral Receptors Expressed in the Immune System

Receptor family	Host receptor	Virus
Ig superfamily	CD4	HIV
	CD150	measles
complement receptors	CD21	EBV
	CD46	measles, HHV6
	CD55	echoviruses
chemokine receptors	CXCR4, CCR5, etc.	HIV
TNF superfamily	TNFRS14 (HveA)	HSV
C-type lectin receptors	CD209 (DC-SIGN)	HIV, dengue virus
	CD209L (L-SIGN)	SARS coronavirus
Toll receptors	TLR4/CD14	RSV

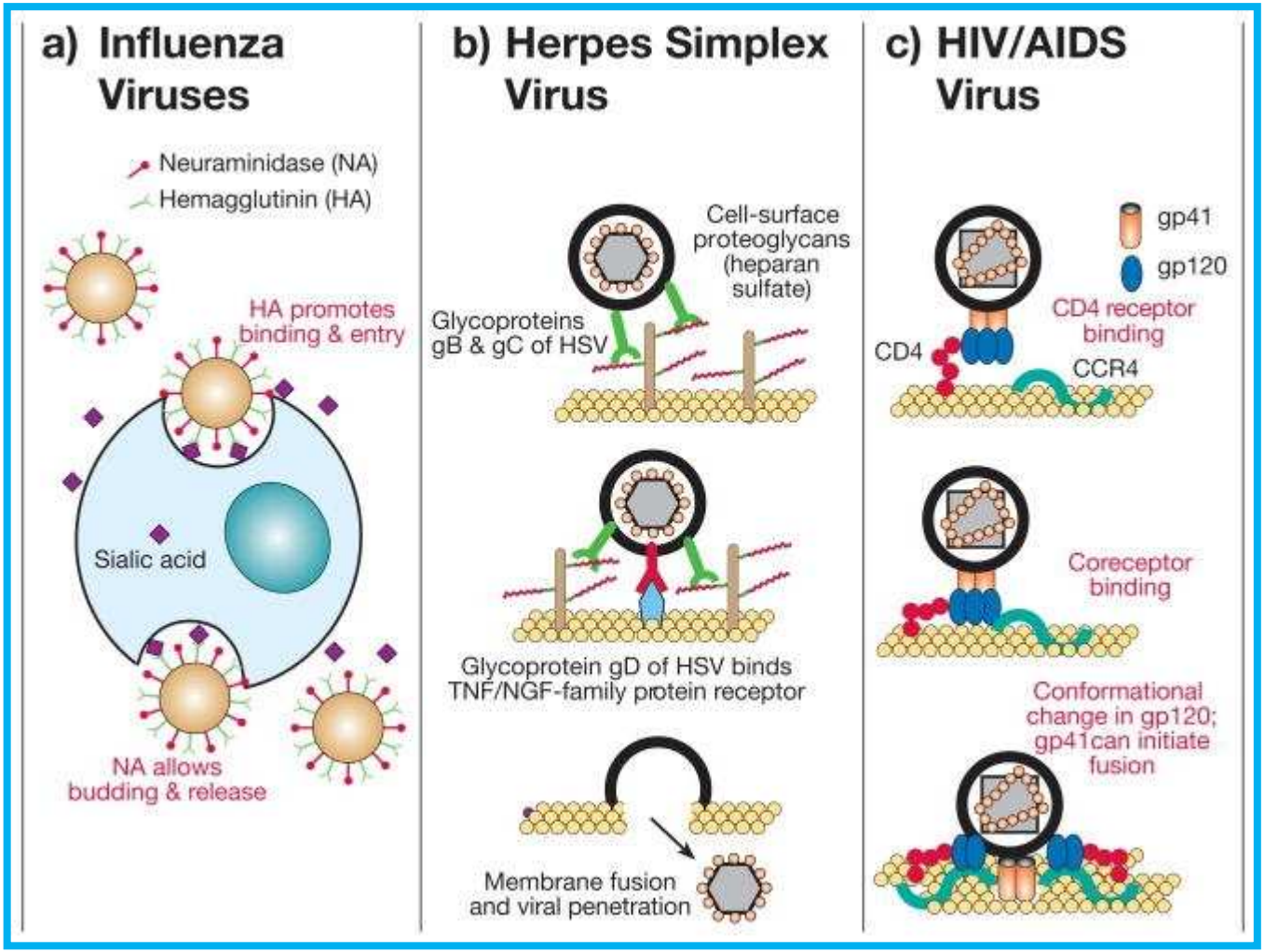
Receptores virales expresados en células del sistema inmune

Table 1 | **The family *Picornaviridae*: genera, some representative species and the diseases that they cause**

Genus	Leader protein	Representative species	Receptor	Disease(s)	Natural host
Enterovirus	No	Poliovirus	CD155	Poliomyelitis	Human
Enterovirus	No	Coxsackievirus	CAR, DAF	Myocarditis, pancreatitis, meningitis	Human
Rhinovirus	No	Rhinovirus	ICAM-1, LDLR	Common cold	Human
Cardiovirus	Yes	Theiler's murine encephalomyelitis virus	?	Encephalomyelitis	Mouse
Aphthovirus	Yes	Foot-and-mouth-disease virus	Integrins	Foot-and-mouth disease	Cloven-hooved ungulates
Erbovirus	Yes	Equine rhinitis B virus	?	Acute respiratory disease	Horses
Kobuvirus	Yes	Aichi virus	?	Gastroenteritis	Human
Teschovirus	Yes	Porcine teschovirus	?	Encephalomyelitis	Pigs
Hepatovirus	No	Hepatitis A virus	HAVcr-1	Hepatitis	Human
Parechovirus	No	Human parechovirus	Integrins	Gastroenteritis, respiratory disease	Human

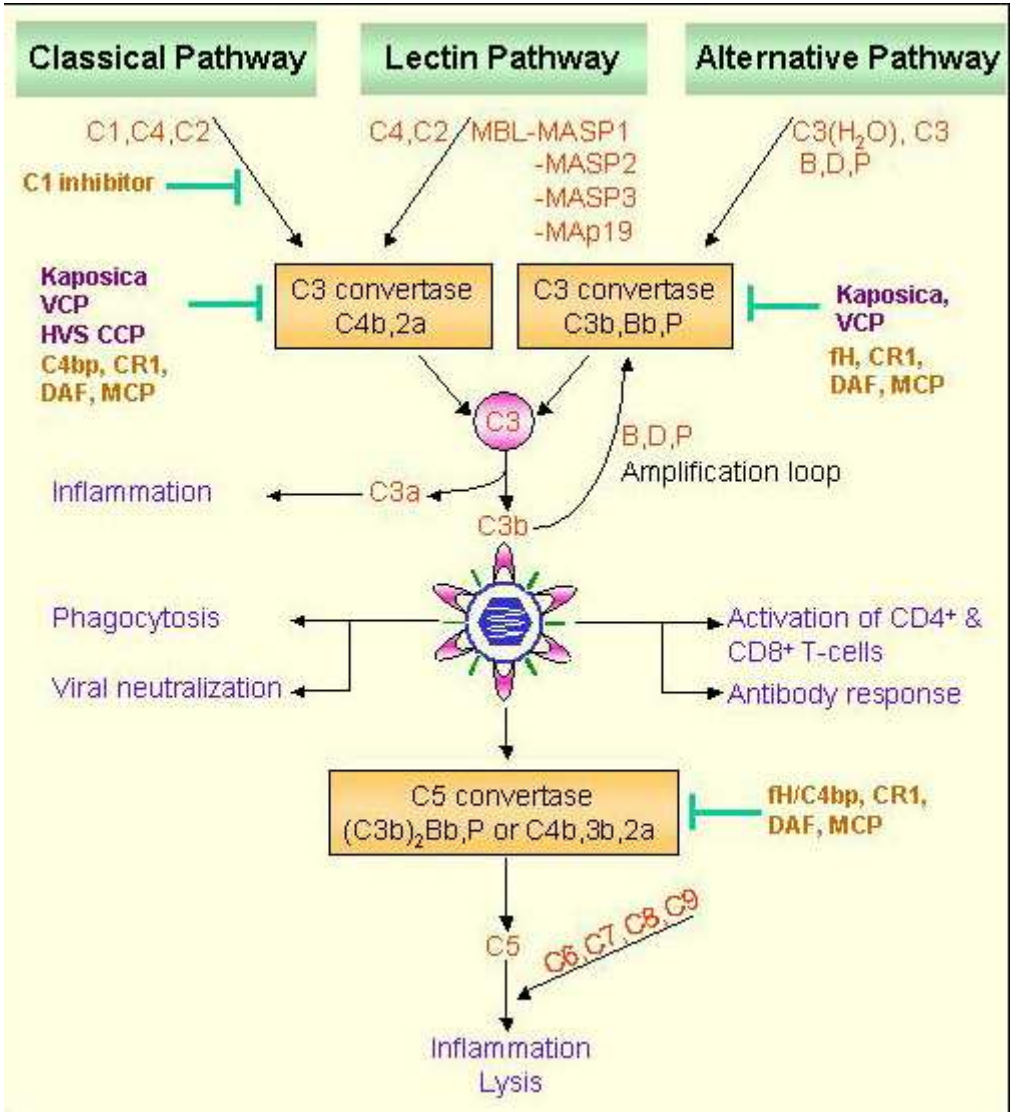
CAR, coxsackievirus and adenovirus receptor; DAF, decay accelerating factor ; ICAM-1, intracellular adhesion molecule 1; LDLR, low-density-lipoprotein receptor.

Influenza virus initiates host cell contact and entry by binding to cell-surface sialic acid receptors through its surface glycoprotein hemagglutinin. After intracellular replication, a cell-surface neuraminidase cleaves sialic acid from the cell membrane allowing viral escape.



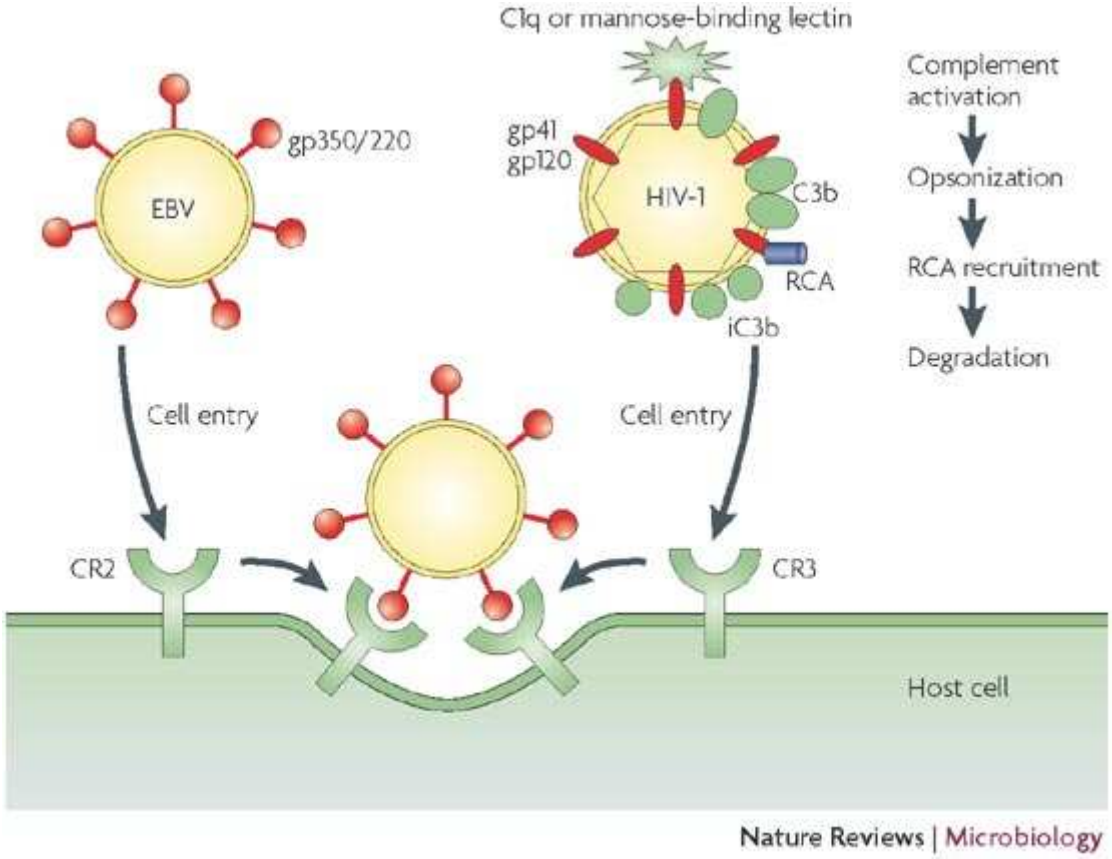
Herpes simplex virus (HSV) engages host cells first through a low-affinity engagement of heparan sulfate proteoglycans via its surface glycoproteins gB and gC. Subsequently, a higher-affinity binding of viral protein gD to a member of the tumor necrosis factor–nerve growth factor (TNF/NGF) receptor family promotes membrane fusion.

Human immunodeficiency virus (HIV) surface glycoprotein gp120 binds sequentially to the CD4 receptor on T cells and then to a coreceptor such as chemokine receptor CCR4. The latter interaction triggers a conformational change in gp120, which exposes gp41, the HIV factor capable of initiating membrane fusion.



VCP, vaccinia virus complement control protein

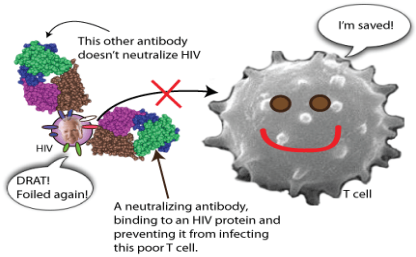
The genome sequencing of vaccinia virus (VV), herpesvirus saimiri (HVS), and Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) have shown that these viruses encode for **complement control protein homologs** (CCPHs)

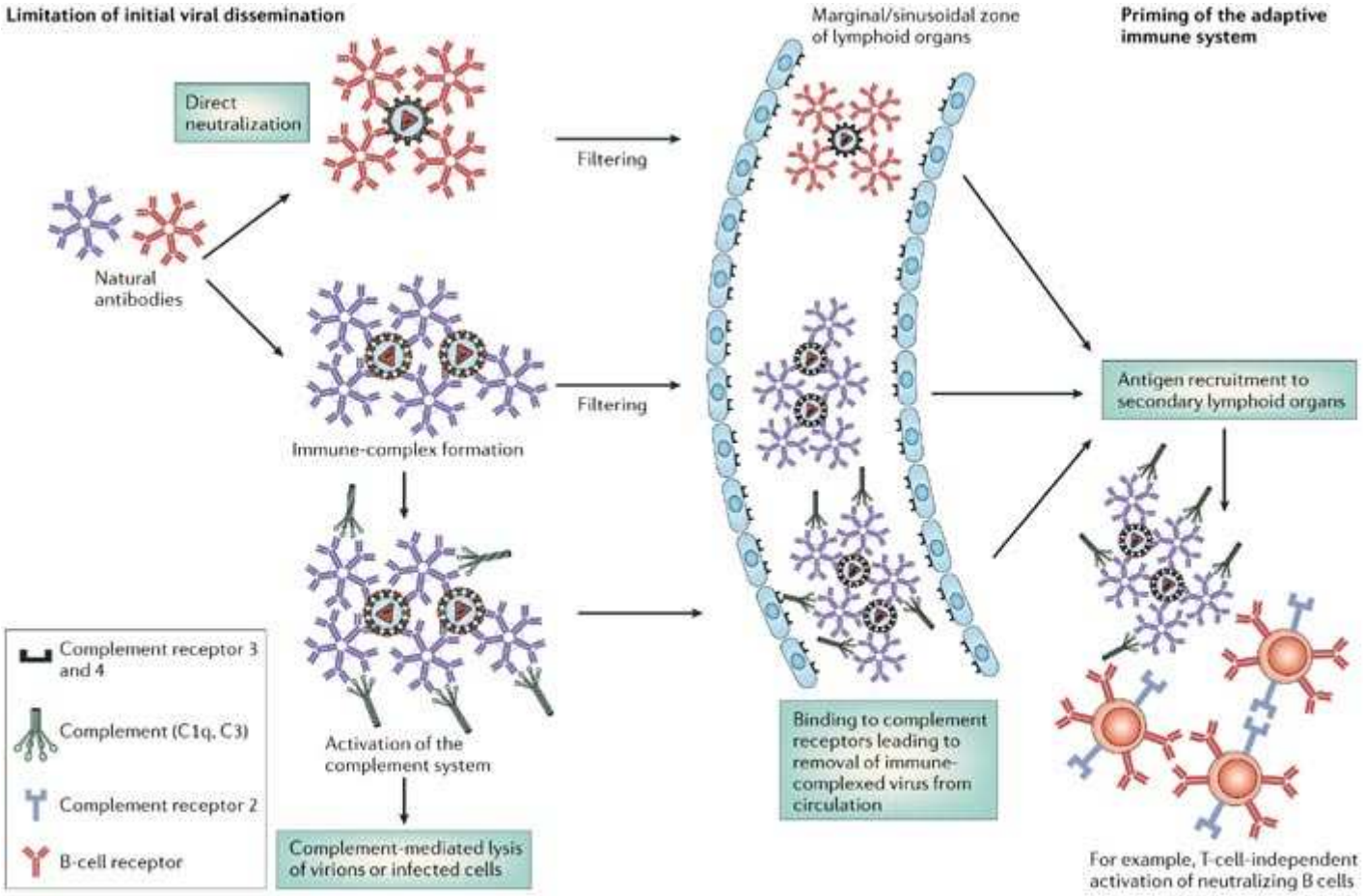


Epstein–Barr virus (EBV) expresses the glycoprotein gp350/220, which specifically interacts with CR2 on B cells and immature T cells, ultimately causing infectious mononucleosis (Pfeiffer's disease). In addition, surface-bound complement regulators serve as targets for the measles virus (haemagglutinin binds to membrane cofactor protein (MCP)), human herpesvirus 6 (glycoprotein H binds to MCP) and some enteroviruses (coxsackievirus and echovirus bind to decay-accelerating factor (DAF).

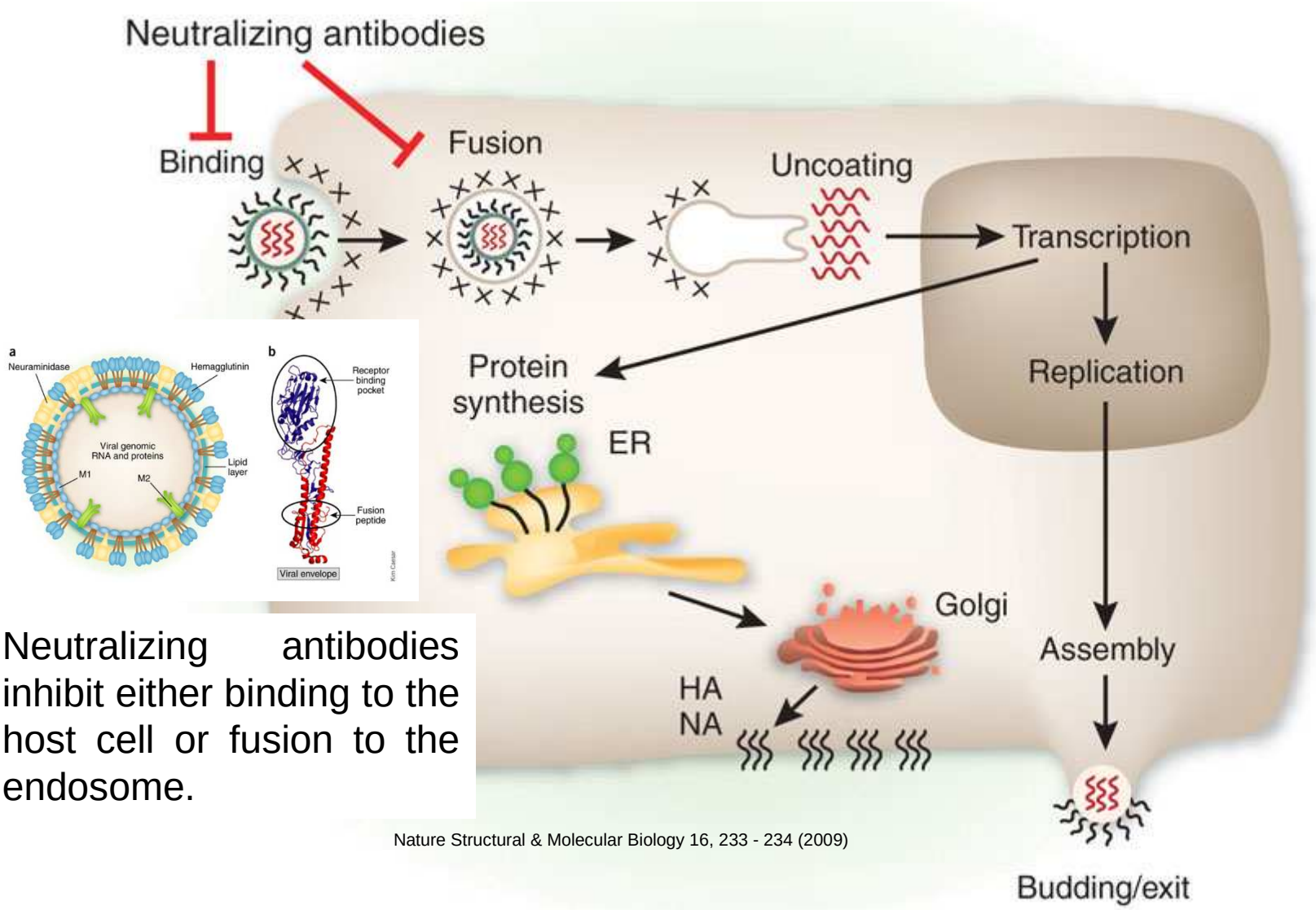
Nature Reviews Microbiology 6, 132-142 (February 2008)

Anticuerpos naturales





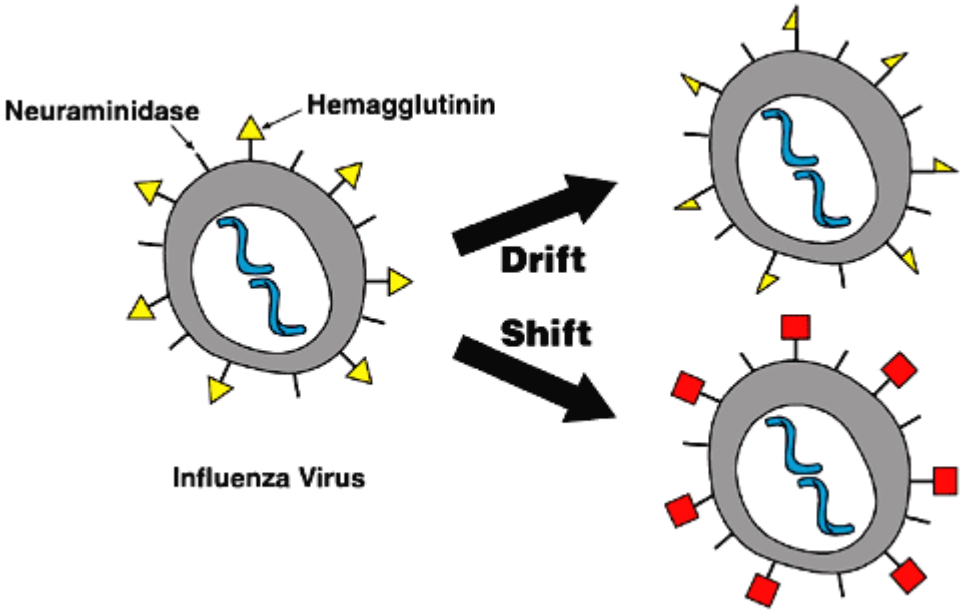
Virus influenza



Neutralizing antibodies inhibit either binding to the host cell or fusion to the endosome.

Nature Structural & Molecular Biology 16, 233 - 234 (2009)

Variación antigénica

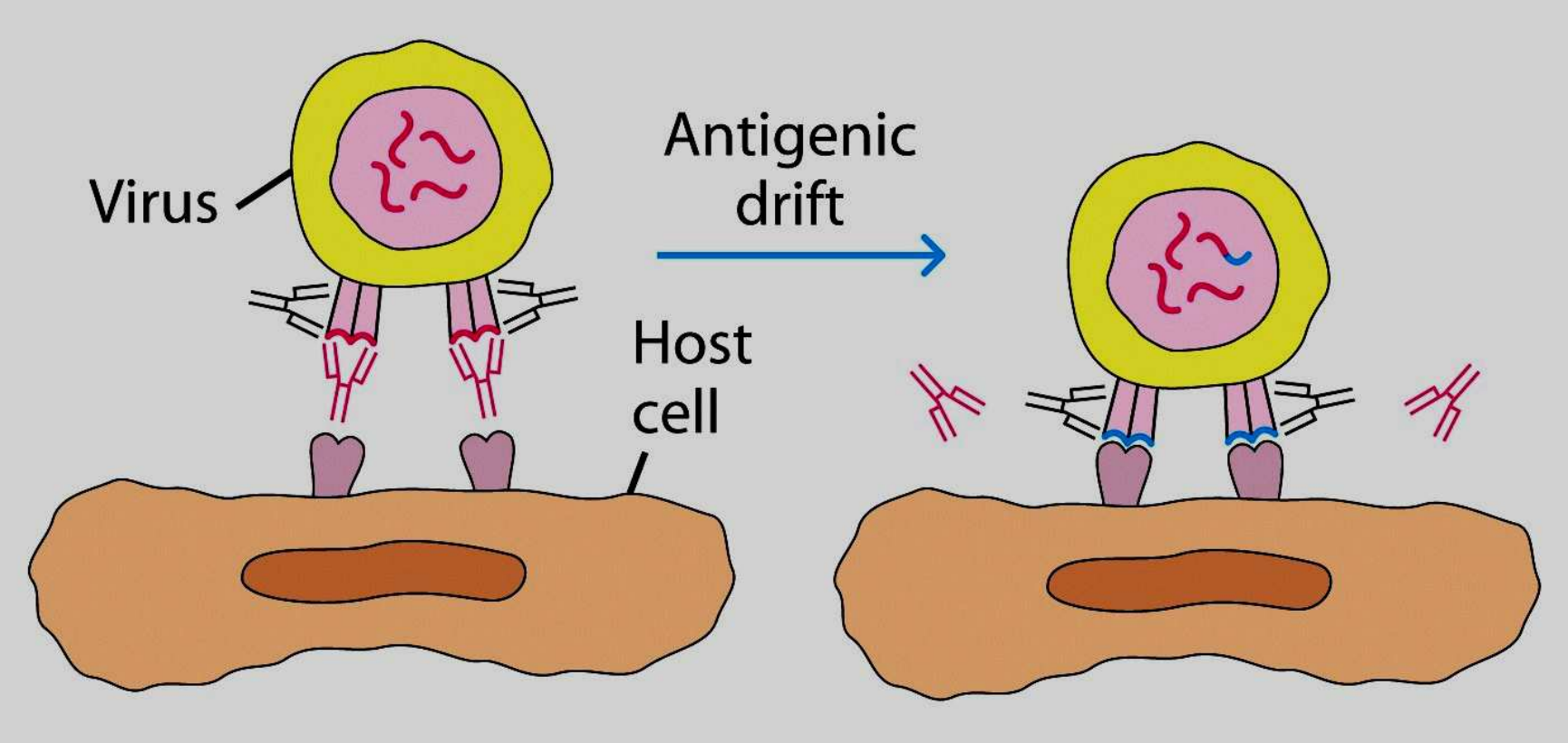


Mutations can cause small changes in the hemagglutinin and neuraminidase antigens on the surface of the virus. This is called **antigenic drifts**, which creates an increasing variety of strains over time until one of the variants eventually achieves higher fitness, becomes dominant, and rapidly sweeps through the human population—often causing an **epidemic.**

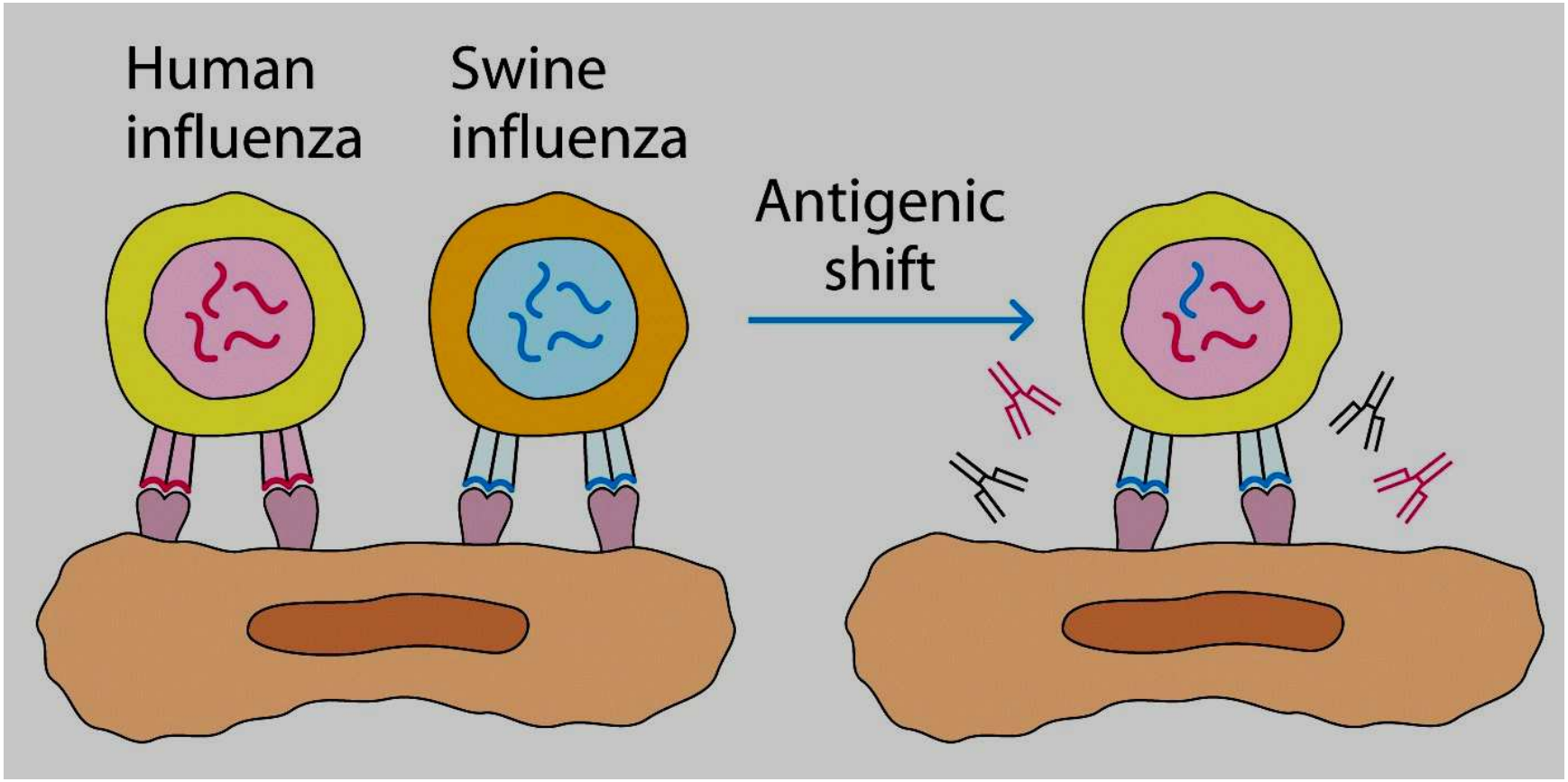
In contrast, when influenza viruses reassort, they may acquire new antigens—for example by reassortment between avian strains and human strains; this is called **antigenic shift**. If a human influenza virus is produced with entirely novel antigens, everybody will be susceptible, and the novel influenza will spread uncontrollably, causing a **pandemic.**

Los virus pueden modificar sus antígenos mediante mutaciones puntuales, o en el caso de los RNA virus, mediante reordenamientos de sus genomas de RNA.

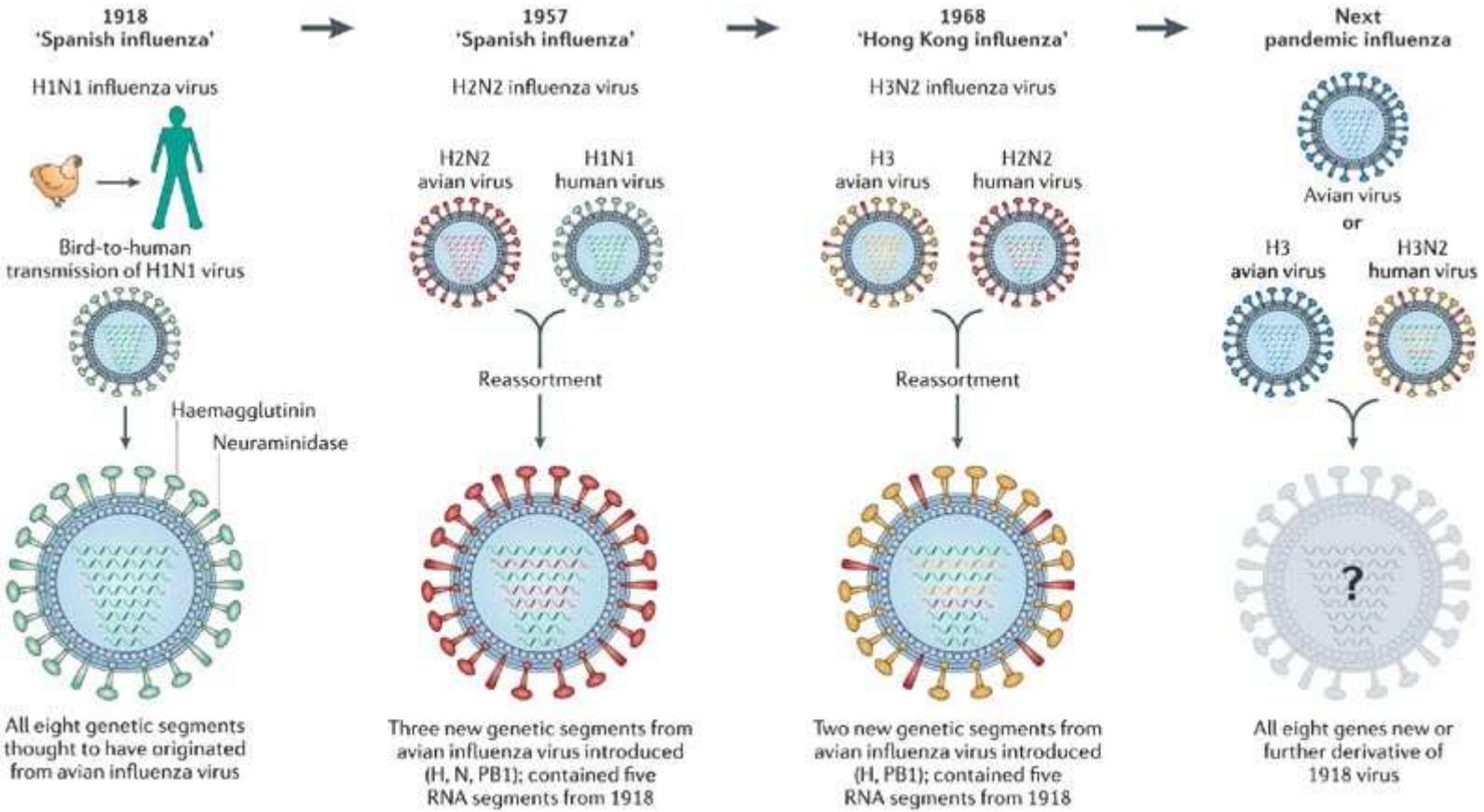
Virus de la influenza: “deriva antigénica”



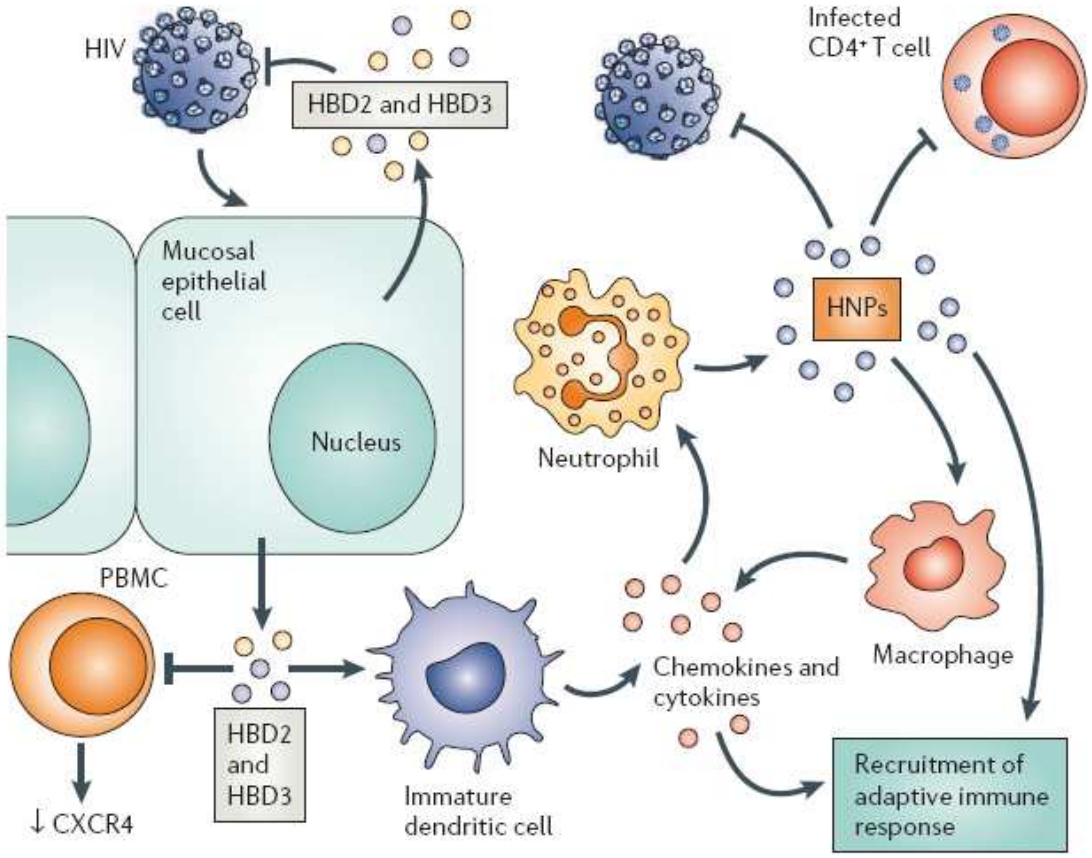
Virus de la influenza: “cambio antigénico”



“Antigenic shift”

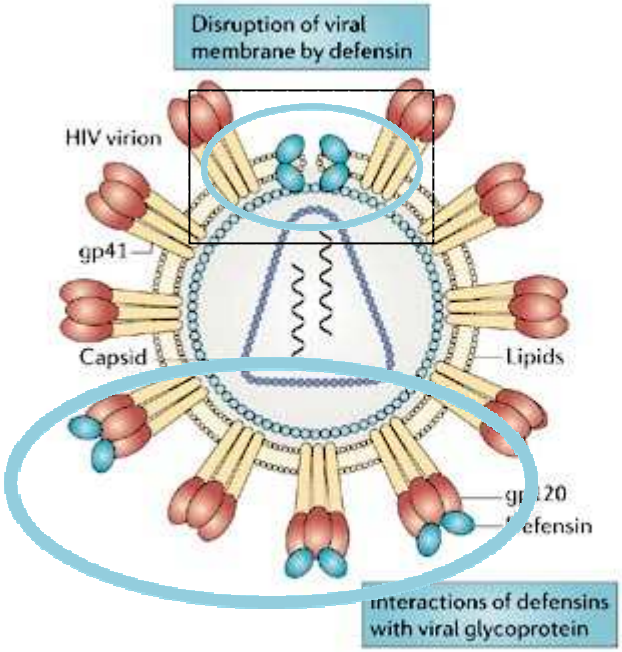


Síntesis de defensinas tras la infección viral



Virus HIV

Induce virólisis….



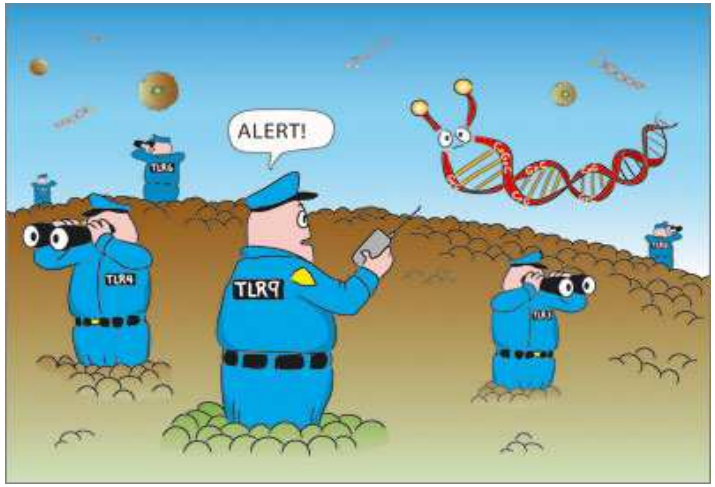
In the absence of serum (such as at mucosal surfaces), defensins inactivate enveloped virus particles by disrupting viral envelopes or by interacting with viral glycoproteins, such as HIV gp120.

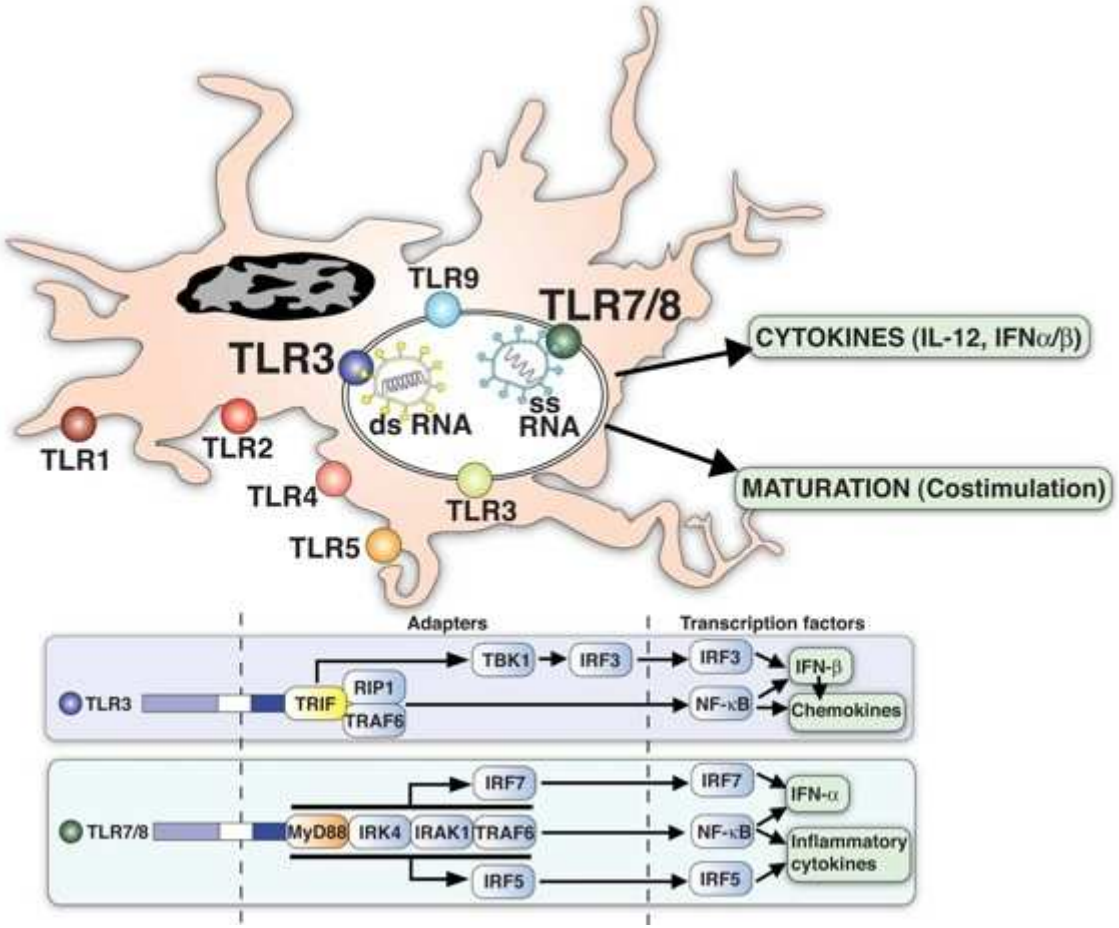
Inhiben la unión a los receptores celulares….

Actividades antivirales de las defensinas y otros péptidos antimicrobianos

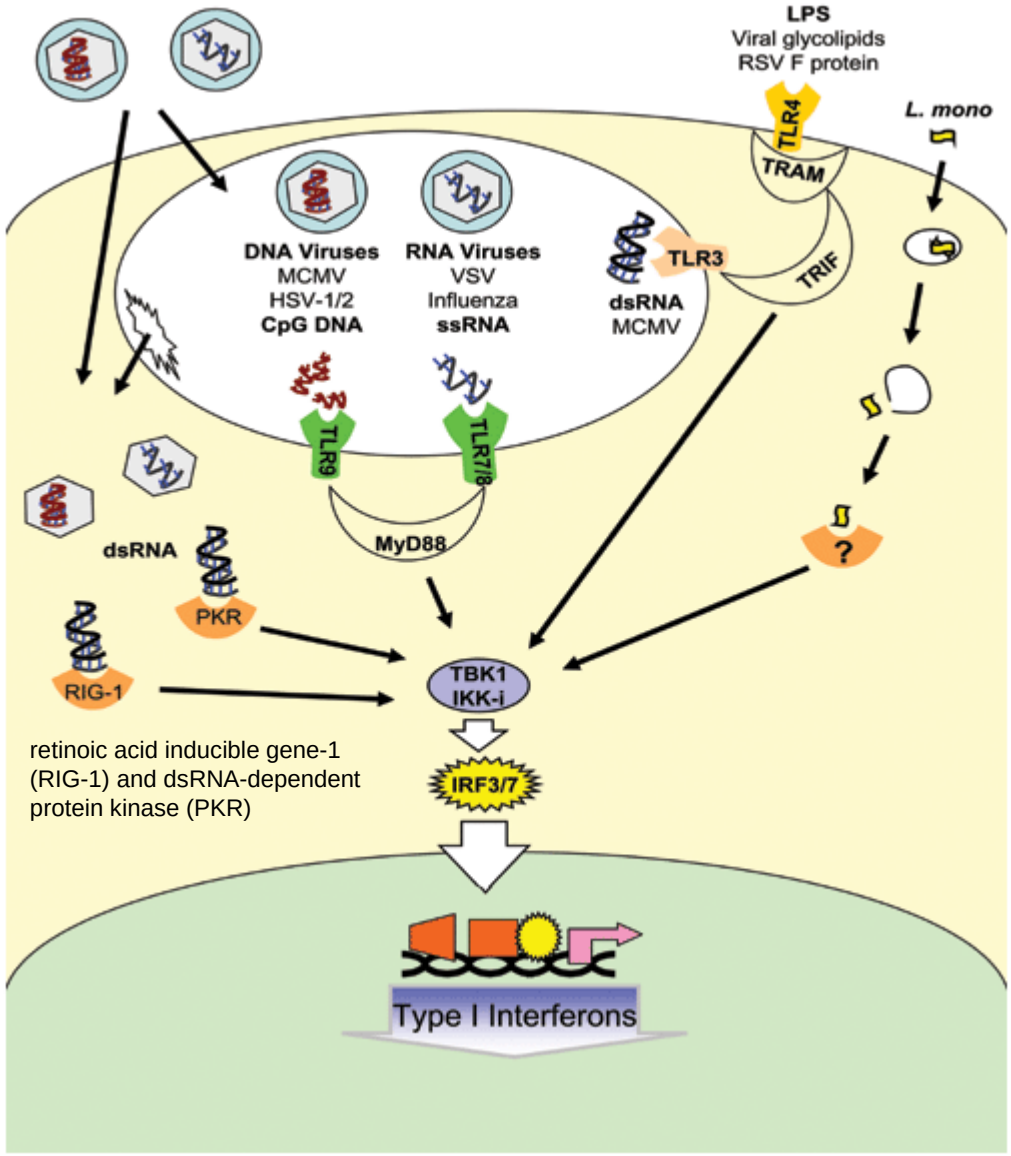
Defensins	Viruses	Effect	References
α-Defensins			
HNP1, HNP2 and HNP3	HIV-1, HSV-1, HSV-2, VSV, influenza virus, CMV, adenovirus and papillomavirus	Inhibitory	9,28,64,70–72, 74,75,84,87,88
HNP1	Echovirus, reovirus and vaccinia virus	None	9,107
HNP4	HIV-1	Inhibitory	72
HD5	Papillomavirus	Inhibitory	87
RMAD4	HIV-1	Inhibitory	77
Guinea pig NP1	HIV-1	Inhibitory	69
Rat NP1	HIV-1	Inhibitory	69
Rabbit NP1	HIV-1 and HSV-2	Inhibitory	69,83
Cryptdin-3	HIV-1	Enhanced	77
β-Defensins			
HBD1	HIV-1 and vaccinia virus	None	47,78,107
HBD2	HIV-1 and adenovirus	Inhibitory	47,78,88
	Rhinovirus and vaccinia virus	None	34,107
HBD3	HIV-1 and influenza virus	Inhibitory	47,78,81
HBD6	PIV-3 (*in vivo*)	Enhanced	86
Sheep BD4	PIV-3 (*in vivo*)	Inhibitory	85
θ-Defensins			
Retrocyclin-1 and retrocyclin-2	HIV-1, HSV-2 and influenza virus	Inhibitory	20,46,74, 79,81,84
RTD1, RTD2 and RTD3	HIV-1 and HSV-2	Inhibitory	74,79,84
Other antimicrobial peptides			
LL37	Vaccinia virus	Inhibitory	107
CRAMP	Vaccinia virus (*in vitro*, *in vivo*)	Inhibitory	107
Indolicidin	HIV-1	Inhibitory	108
Dermaseptin S4	HIV-1	Inhibitory	109
Caerin 1.1 and caerin 1.9	HIV-1	Inhibitory	110
Maculatin 1.1	HIV-1	Inhibitory	110

BD4, β-defensin-4; CMV, cytomegalovirus; CRAMP, cathelicidin-related antimicrobial peptide; HBD, human β-defensin; HNP, human neutrophil peptide; HSV, herpes simplex virus; NP1, neutrophil peptide 1; PIV, parainfluenza virus; RMAD, rhesus macaque myeloid α-defensin; RTD, rhesus θ-defensin; VSV, vesicular stomatitis virus.


ALERT!
TLR6
TLR4
TLR9
TLR1

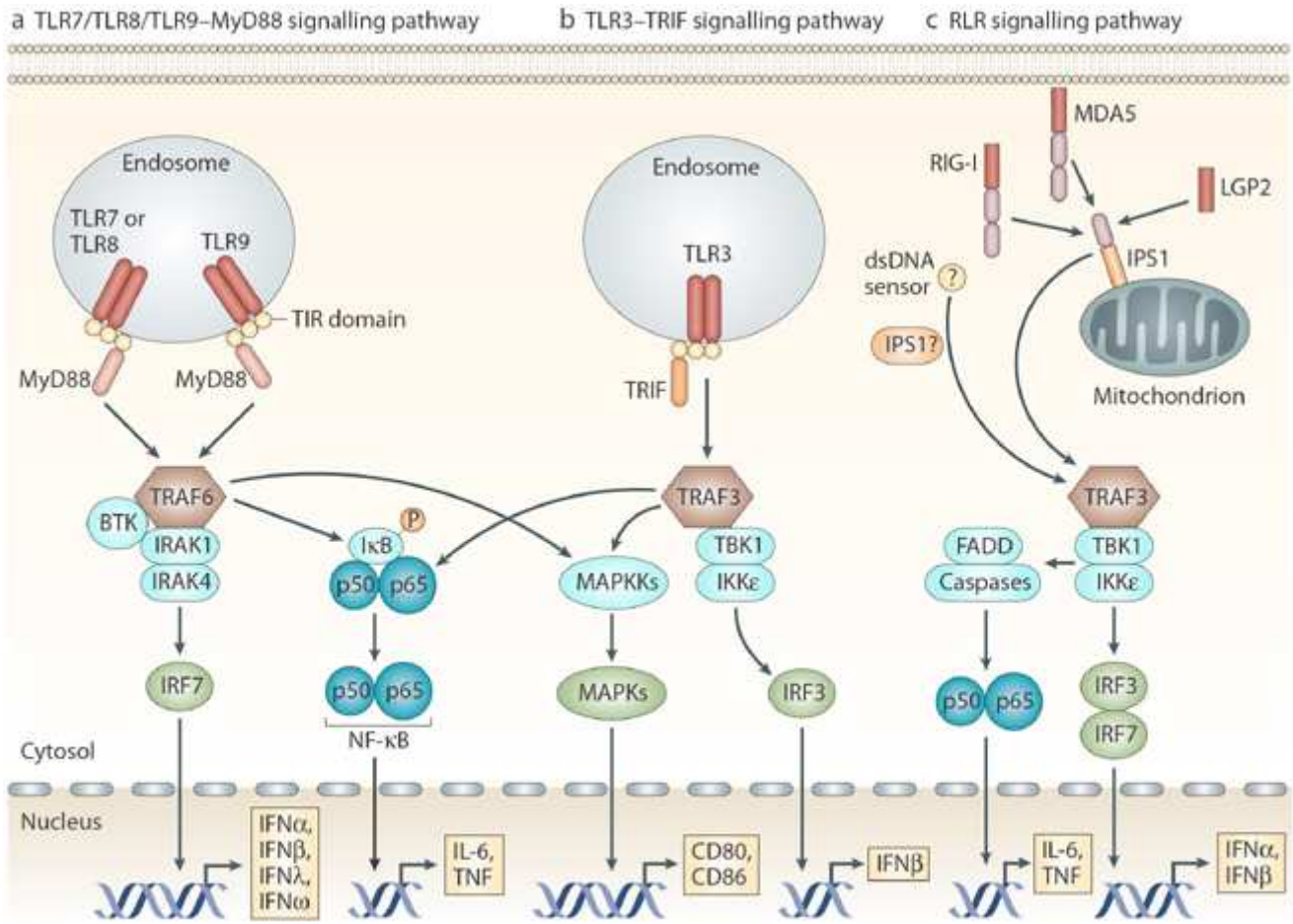

TLR9
TLR7/8
TLR3
ds RNA
ss RNA
CYTOKINES (IL-12, IFNα/β)
MATURATION (Costimulation)
TLR1
TLR2
TLR4
TLR3
TLR5
Adapters
Transcription factors
TLR3
TRIF
RIP1
TRAF6
TBK1
IRF3
IRF3
IFN-β
NF-κB
Chemokines
TLR7/8
MyD88
IRK4
IRAK1
TRAF6
IRF7
IRF7
IFN-α
NF-κB
Inflammatory cytokines
IRF5
IRF5

VIRUS Y TLR



Pathways involved in activation of type I IFN production. Recognition of viral and bacterial components by host pattern recognition receptors (PRR) trigger signaling pathways that induce production of type I IFN. Viruses enter cells either by fusion at the plasma membrane or by endocytosis followed by fusion with the endosomal membrane, and entry into the cytoplasm. Viruses that reach the cytoplasmic compartment produce dsRNA during replication, which is recognized by the PRRs retinoic acid inducible gene-1 (RIG-1) and dsRNA-dependent protein kinase (PKR). Viruses that enter endocytic compartments are recognized by Toll-like receptors (TLR), TLR3, TLR7, TLR8, and TLR9. TLR9 recognizes CpG motifs of DNA viruses including murine cytomegalovirus (MCMV), herpes simplex virus (HSV) -1, and HSV-2. TLR7 and TLR8 recognize ssRNA from RNA viruses including vesicular stomatitis virus (VSV), and influenza virus. TLR3 recognizes dsRNA motifs of both types of viruses including MCMV. TLR4 is able to recognize the LPS component of Gram-negative bacteria, viral glycolipids, and the F protein of respiratory syncytial virus (RSV). *Listeria monocytogenes* (*L. mono*) enters cells by phagocytosis, and subsequently lyses the phagosomal membrane to escape into the cytoplasm. An unknown PRR recognizes intracellular *L. mono*. All of these PRRs can activate production of type I IFNs, likely through activation of the kinases TANK-binding kinase-1 (TBK1) and/or the inducible IκB kinase (IKK-i,). TLR9 and TLR7 utilize the adaptor protein myeloid differentiation factor-88 (MyD88), while TLR3 and TLR4 utilize Toll/IL-1 receptor domain-containing adaptor inducing IFN β (TRIF) to transmit signals to TBK1/IKK-i. TBK1 and IKK-i activate the transcription factors interferon regulatory factor (IRF)-3 and IRF7, which induce the transcription of type I IFNs. Type I IFNs have pleiotropic effects and activate multiple components of host innate and adaptive immune responses.

Señalización a través de TLR

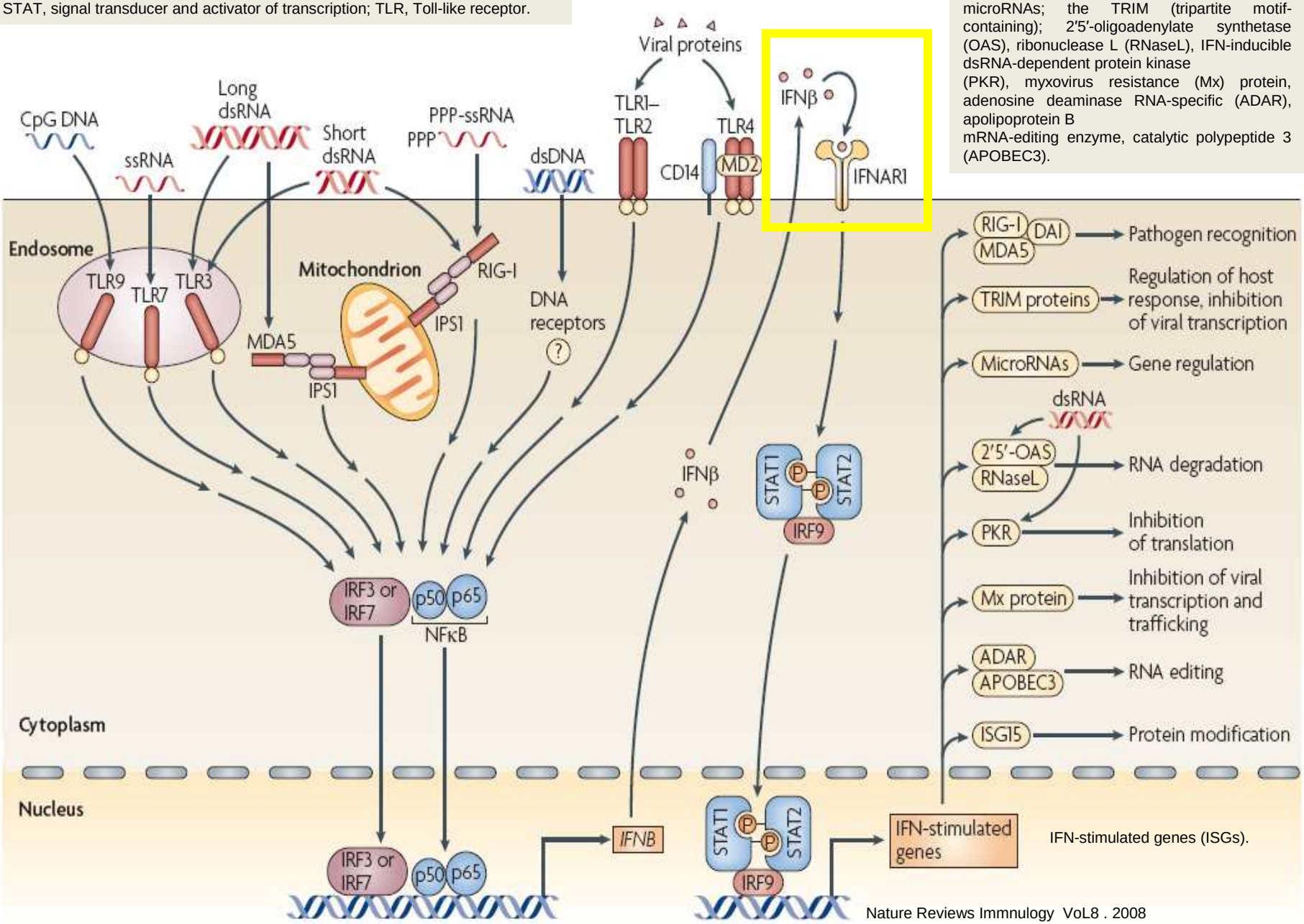


Nature Reviews Immunology 8, 594-606 (August 2008)

Nature Reviews | Immunology

IFNAR1,interferon-α receptor; IPS1, *IFNB-promoter stimulator 1;*
*ISG15, IFN-stimulated protein of 15 kDa; MD2, myeloid*differentiation protein 2;
PPP, 5′ triphosphate; ssRNA, single-stranded RNA;
STAT, signal transducer and activator of transcription; TLR, Toll-like receptor.

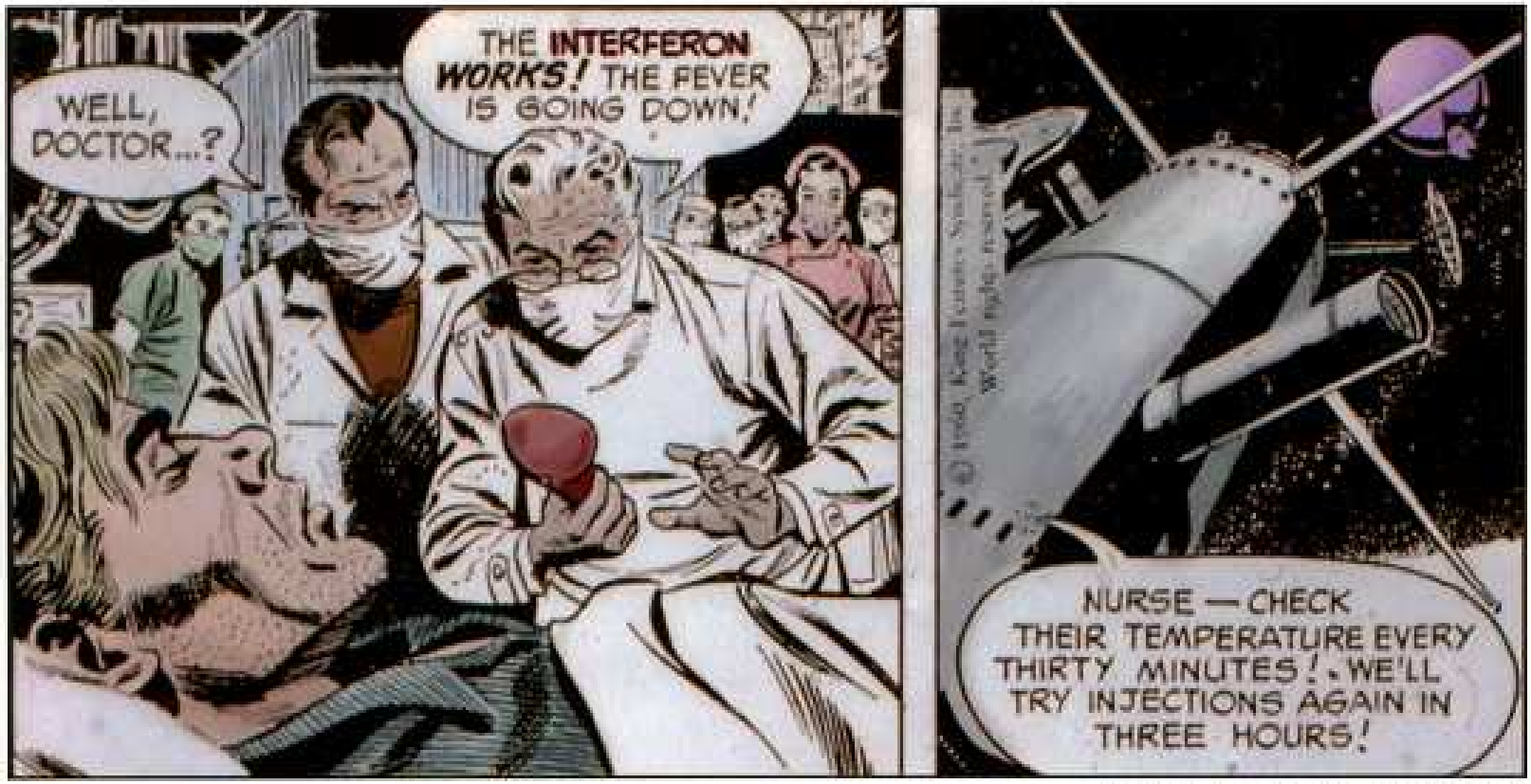
RIG-I (retinoic-acid-inducible gene I), MDA5 (melanoma differentiation-associated gene 5), DAI (DNA-dependent activator of IRFs), microRNAs; the TRIM (tripartite motif-containing); 2′5′-oligoadenylate synthetase (OAS), ribonuclease L (RNaseL), IFN-inducible dsRNA-dependent protein kinase
(PKR), myxovirus resistance (Mx) protein, adenosine deaminase RNA-specific (ADAR), apolipoprotein B
mRNA-editing enzyme, catalytic polypeptide 3 (APOBEC3).



IFN-stimulated genes (ISGs).

Nature Reviews Immnulogy VoL8 . 2008

SECRECIÓN DE INTERFERONES



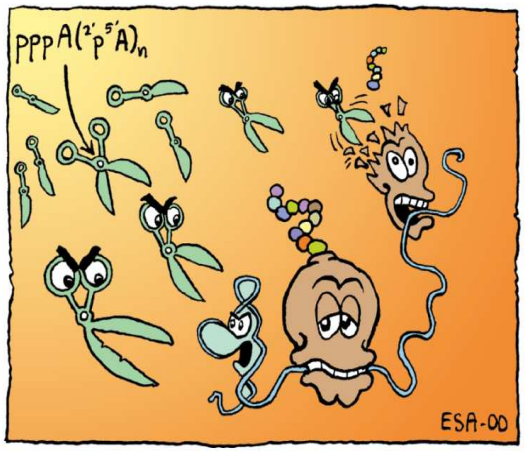
Agente antivírico sintetizado por células vivas como resultado de una infección vírica, bacteriana, parasitaria o por contacto de esas células con ciertos compuestos inductores.

INTERFERÓN

- Glicoproteínas (15– 30.000 daltons)
- Resistencia moderada al calor.
- Estables a pH ácido.
- Degradables por tripsina.

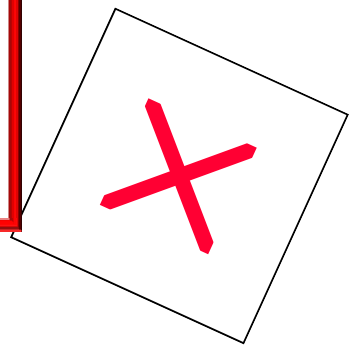
INDUCCIÓN DE INTERFERÓN

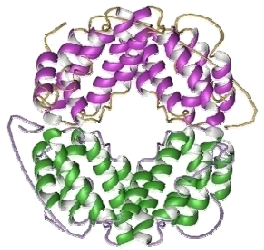
- **IFN α-β**
  - Infección vírica, ARN doble cadena, ciertos componentes bacterianos.
  - Fuertes propiedades antivíricas.
- **IFN γ**
  - Antígenos bacterianos, virales, tumorales.
  - Fuertes propiedades antitumoral



INTERFERONES

IFN-α,leucocitos
IFN-β,fibroblastos
IFN-ω,leucocitos
IFN-κ,keratinocitos
IFN-λ,leucocitos



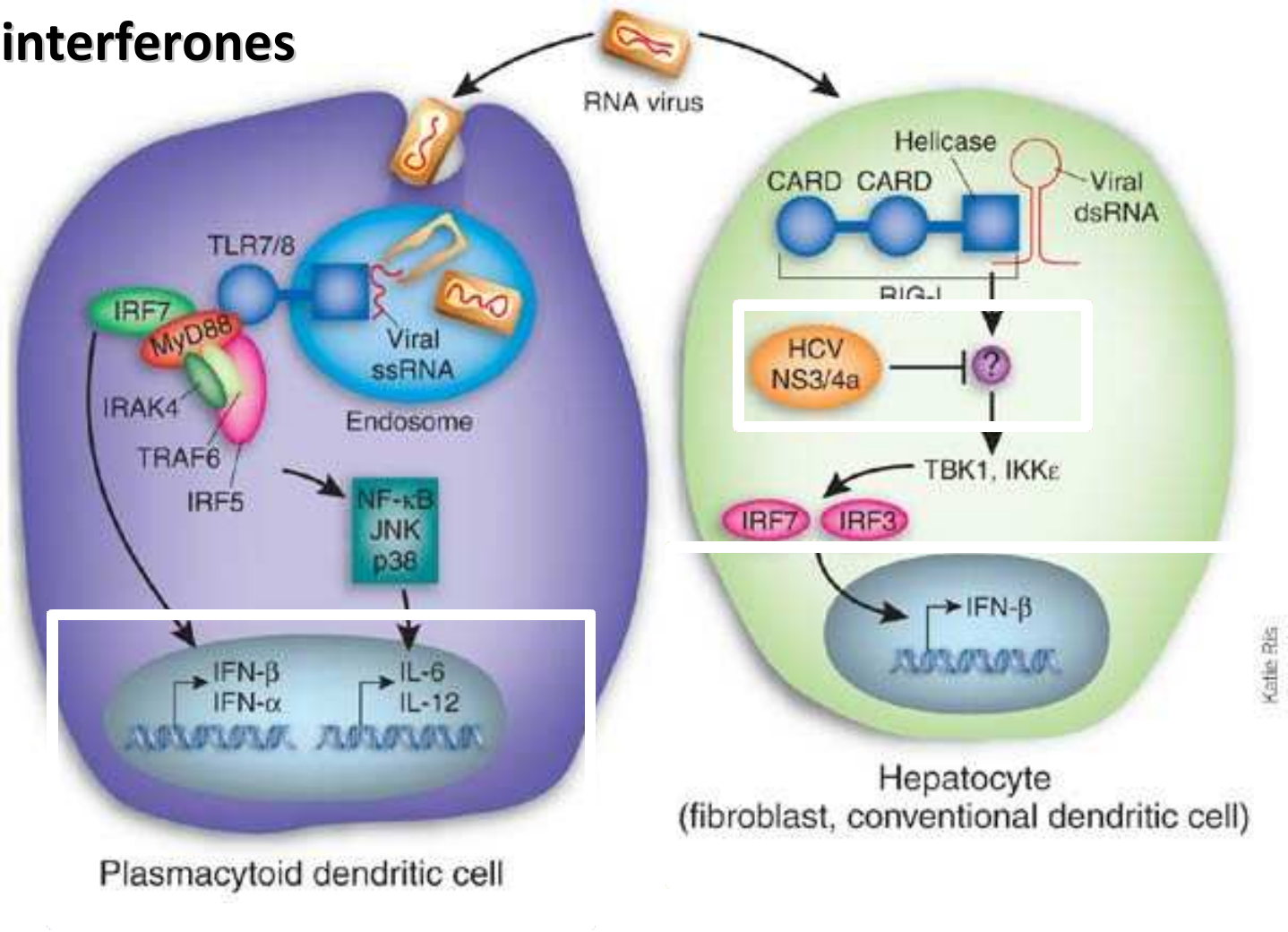


Type I (α1, α2.., β, δ, ε, τ, κ)

Type II (γ)

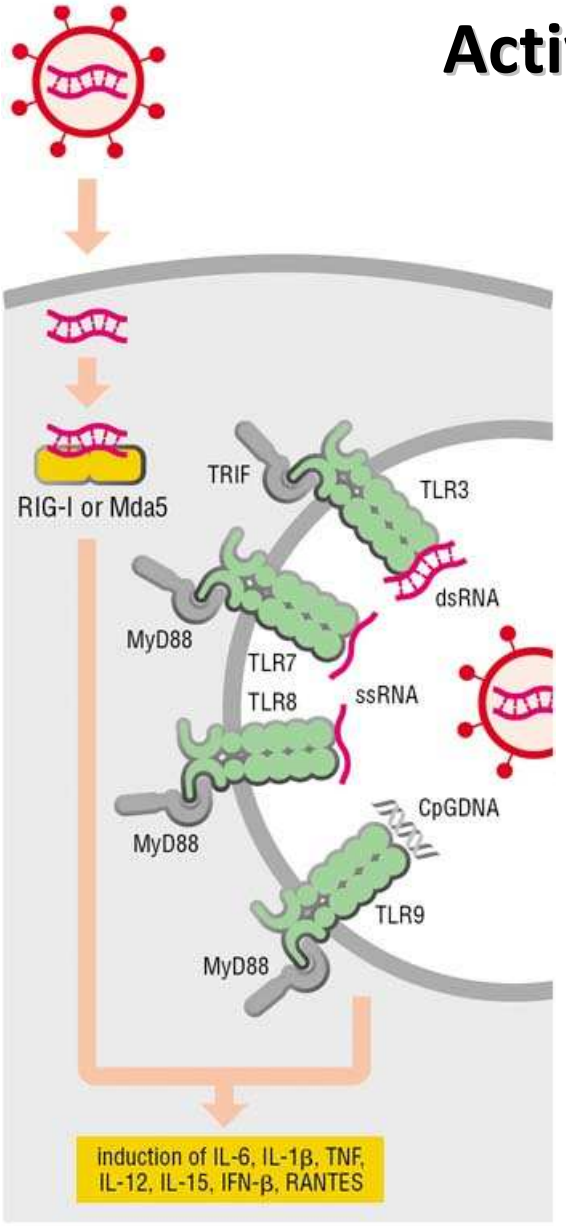
Size	~ 18 kDa	21 kDa
Cell Source	Most Nucleated cells	Activated T Cells, NK Cells
Target Cells	All	Monocytic Cells and others
Effect	Mainly Antiviral	Antiviral and Antitumor
Receptor	IFNAR	IFNGR

Virus e interferones



Nature Medicine 11, 929 - 930 (2005)

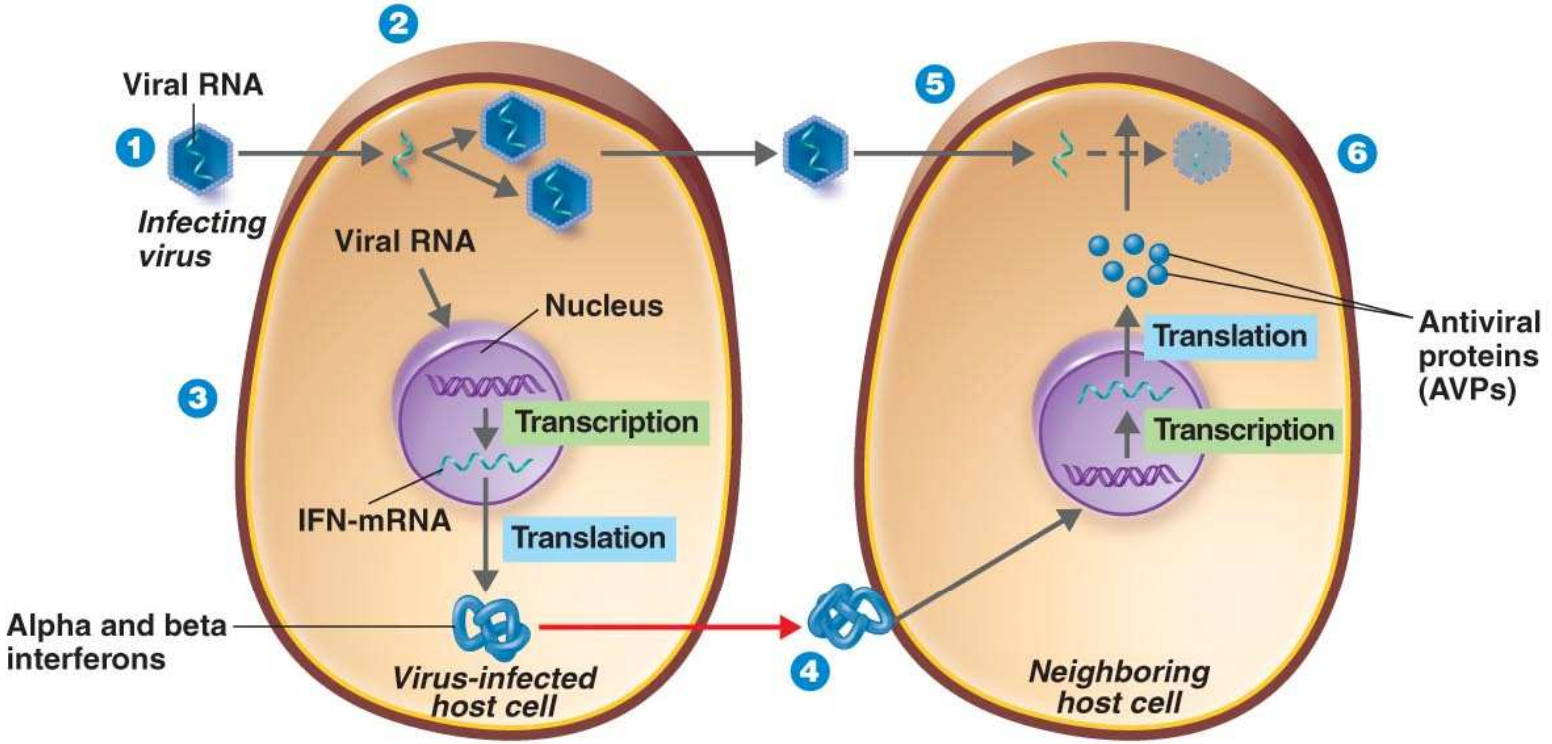
Activación de PRRs por los virus



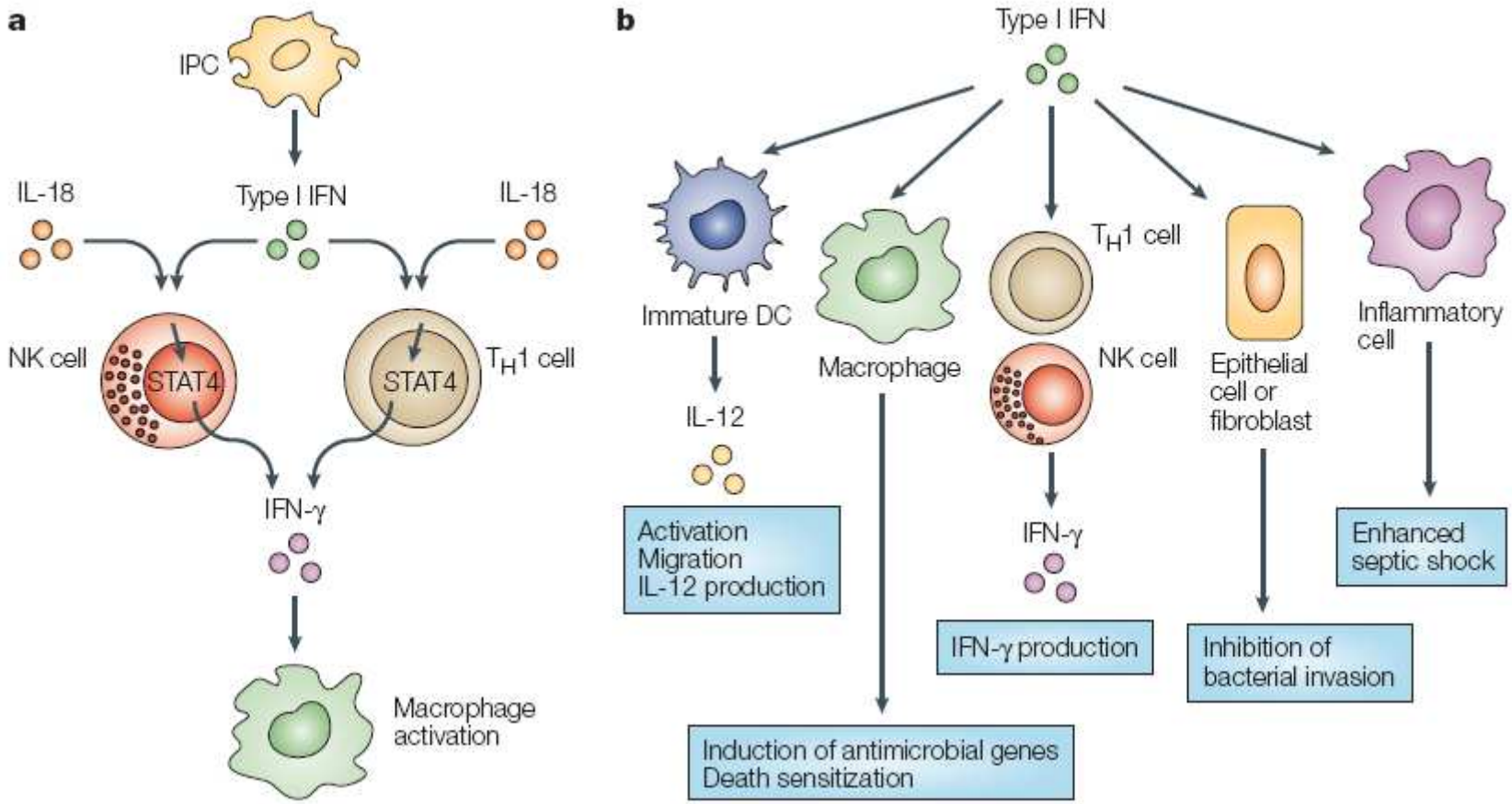
Interferones tipo I

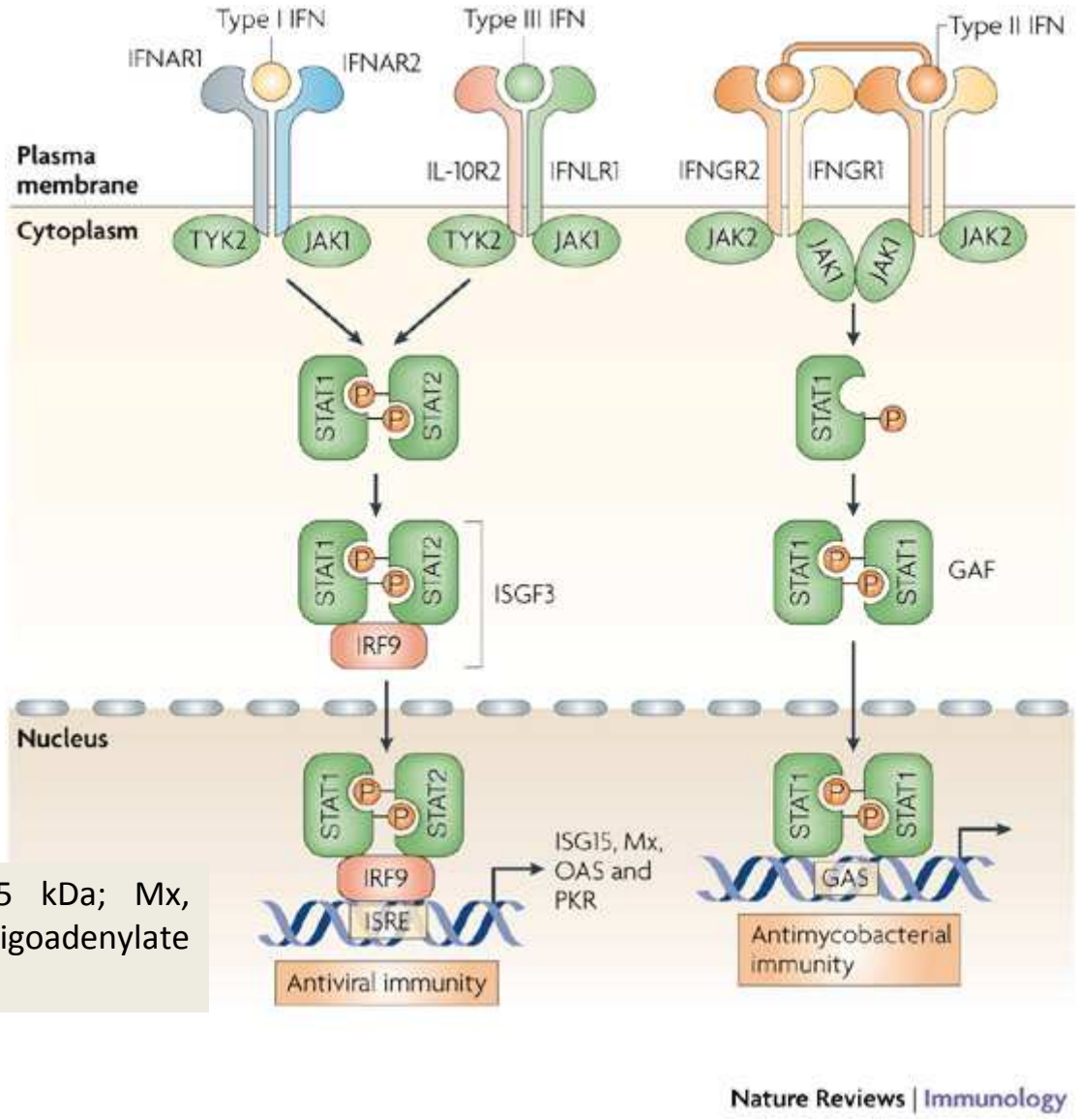
- Producidos fundamentalmente por pDC; actúan como un factor de supervivencia de dichas células,
- utilizan el mismo receptor e interactúan con éste en la superficie de las células infectadas y en las células vecinas,
- inhiben la replicación viral,
- **modulan la función de diferentes células: activación de NK, diferenciación de TCD4$^+$ en un perfil Th1, activación de TCD8$^+$, incremento de la expresión de MHC I/II.**

Acción antiviral de los interferones(IFNs)



1. Viral RNA from an infecting virus enters the cell.
2. The infecting virus replicates into new viruses.
3. The infecting virus also induces the host cell to produce interferon mRNA (IFN-mRNA), which is translated into alpha and beta interferons.
4. Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase and protein kinase.
5. New viruses released by the virus-infected host cell infect neighboring host cells.
6. AVPs degrade viral mRNA and inhibit protein synthesis—and thus interfere with viral replication.

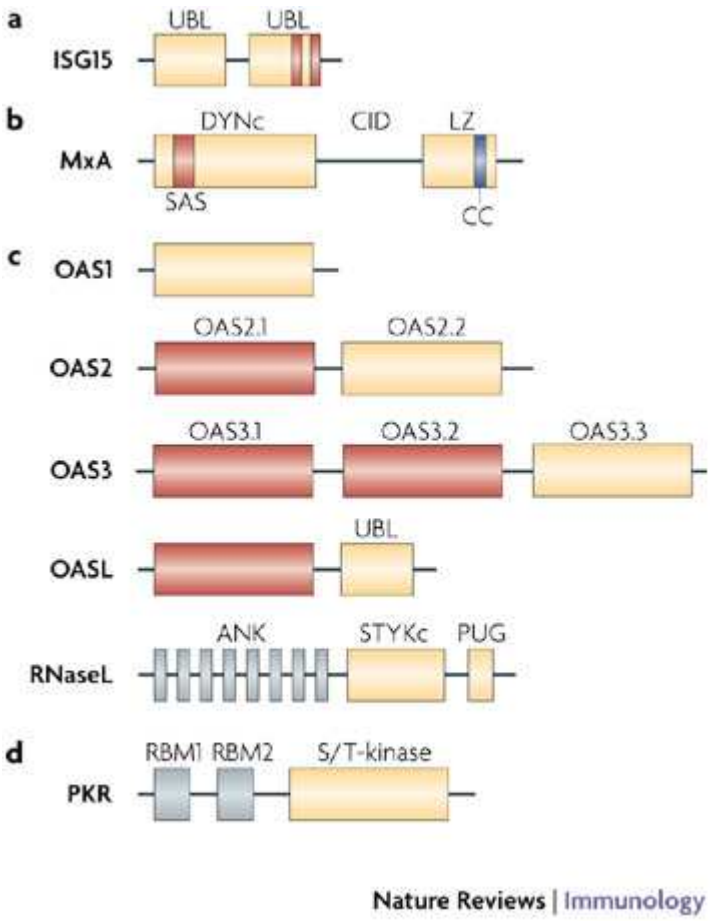

a
IPC
IL-18
Type I IFN
IL-18
NK cell
STAT4
STAT4
TH1 cell
IFN-γ
Macrophage activation
b
Type I IFN
Immature DC
Macrophage
TH1 cell
NK cell
Epithelial cell or fibroblast
Inflammatory cell
IL-12
Activation
Migration
IL-12 production
IFN-γ
Enhanced septic shock
IFN-γ production
Inhibition of bacterial invasion
Induction of antimicrobial genes
Death sensitization

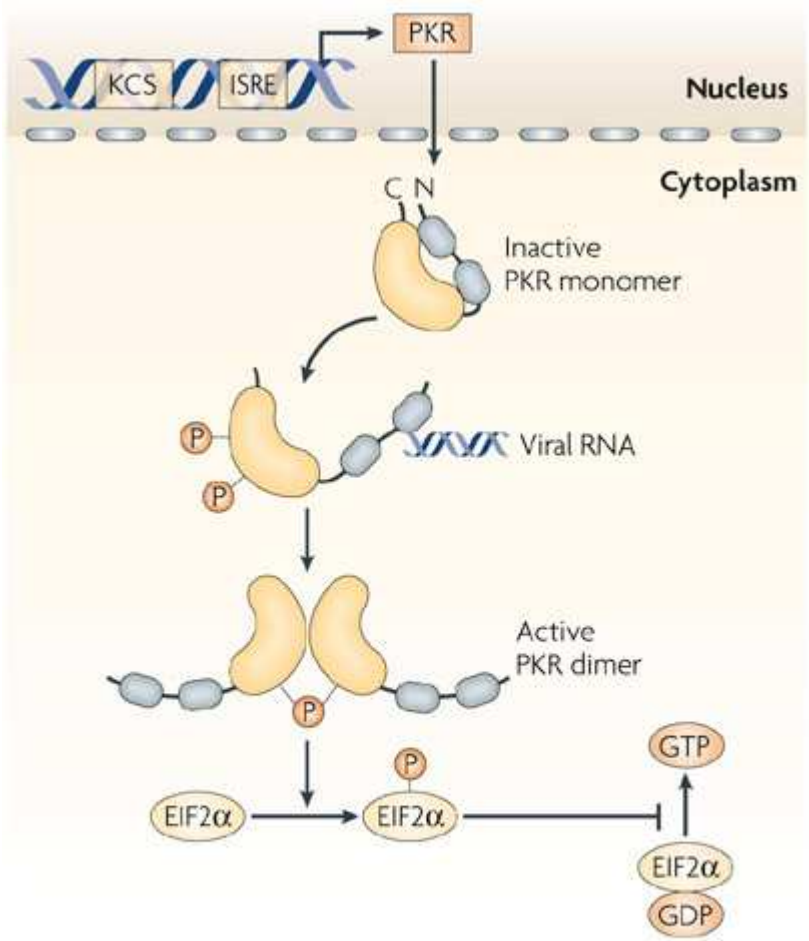


ISG15, IFN-stimulated protein of 15 kDa; Mx, myxovirus resistance; OAS, 2',5'-oligoadenylate synthetase; PKR, protein kinase R.

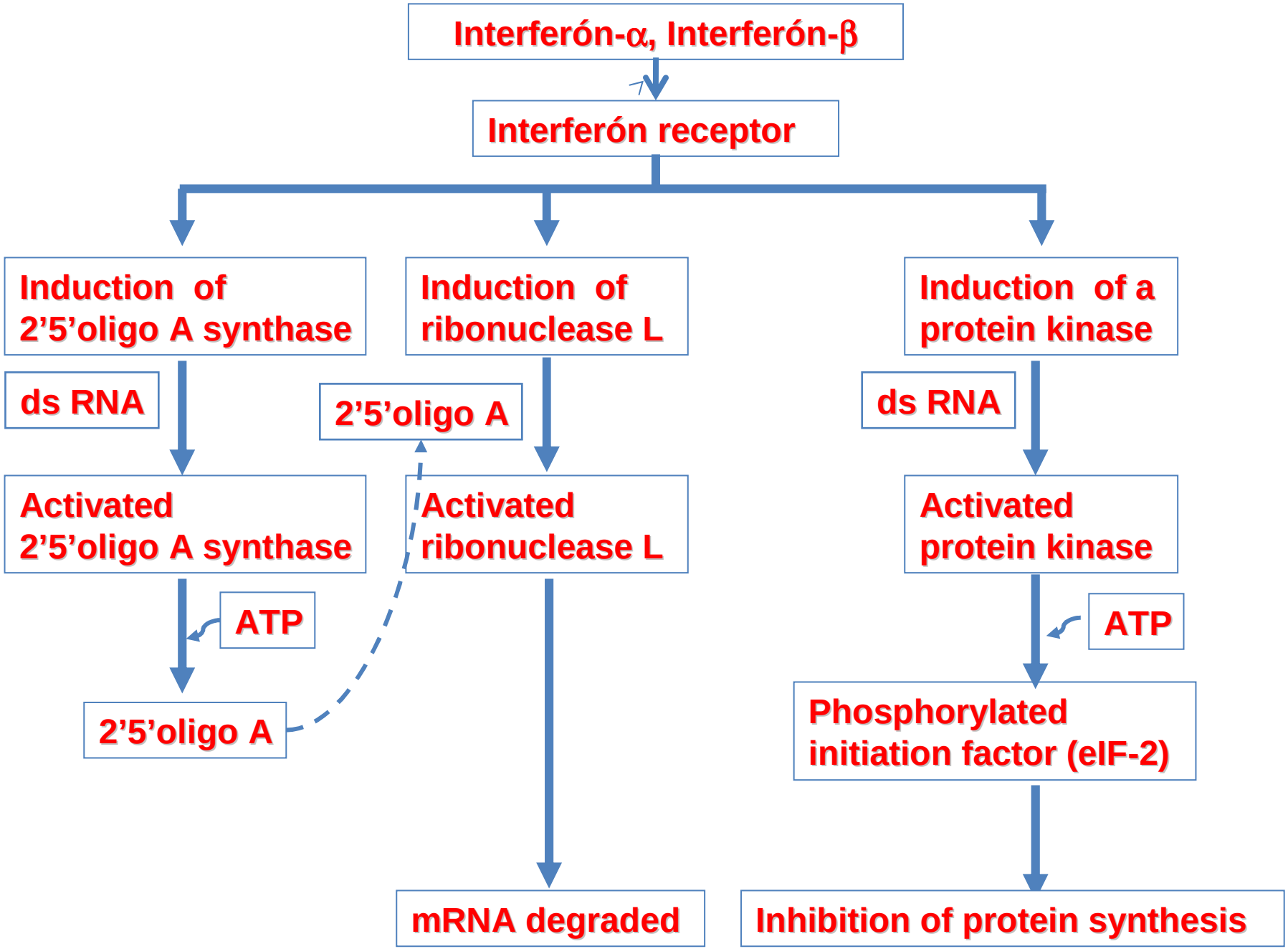
Nature Reviews Immunology 8, 559-568 (July 2008)

PROTEÍNAS ANTIVIRALES INDUCIDAS POR EL VIRUS





Activated PKR regulates several cell signalling pathways through mechanisms that have not been fully explained, but a crucial function of PKR in viral defence is the inhibition of translation by phosphorylation of eukaryotic translation initiation factor 2α (EIF2α).

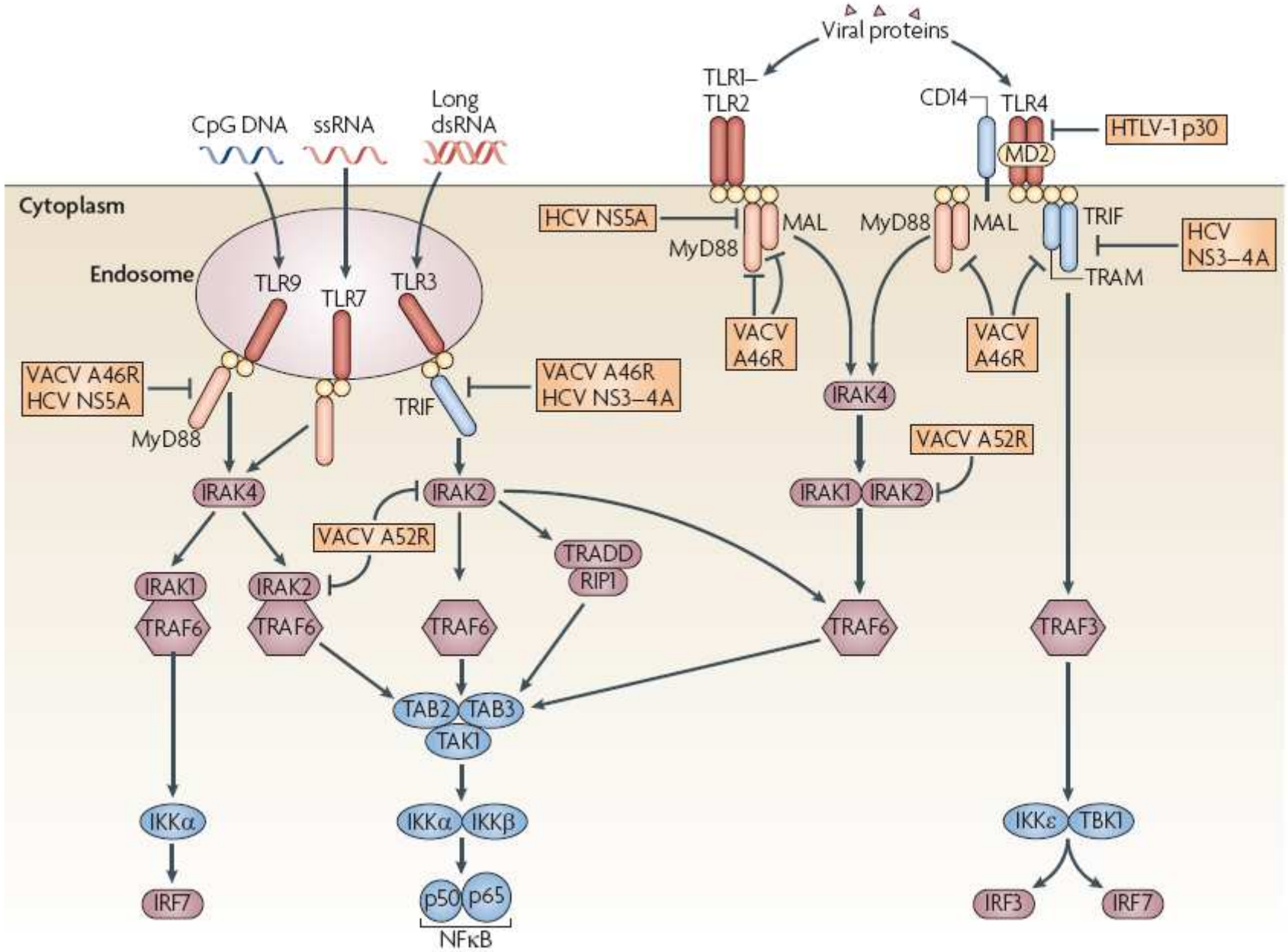

Interferón-α, Interferón-β
Interferón receptor
Induction of 2'5'oligo A synthase
Induction of ribonuclease L
Induction of a protein kinase
ds RNA
2'5'oligo A
ds RNA
Activated 2'5'oligo A synthase
Activated ribonuclease L
Activated protein kinase
ATP
ATP
2'5'oligo A
Phosphorylated initiation factor (eIF-2)
mRNA degraded
Inhibition of protein synthesis

Proteínas virales que interfieren con las vías de señalización a través de PRR

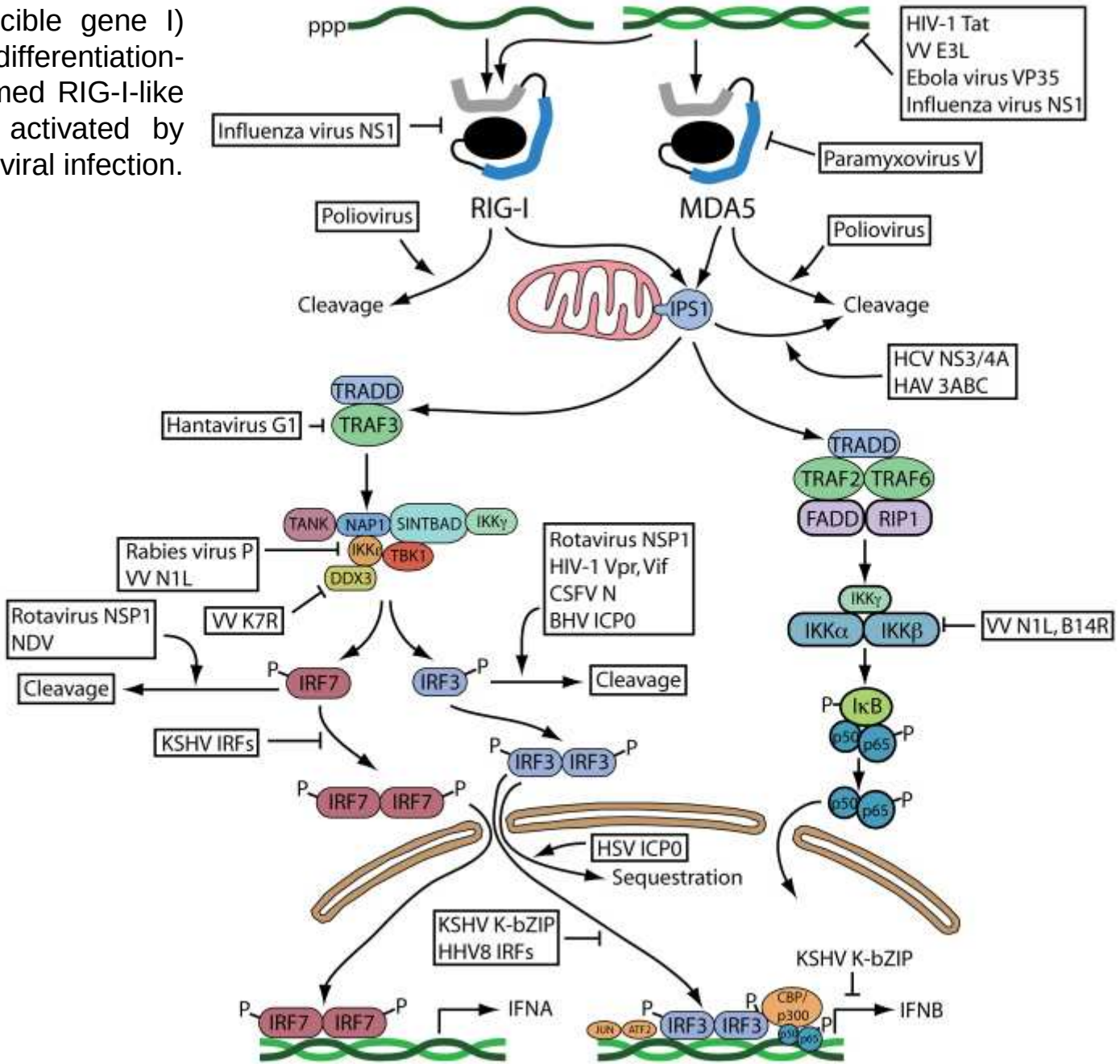
Table 1 | **Representative viral proteins that interfere with PPR signalling pathways at multiple points**

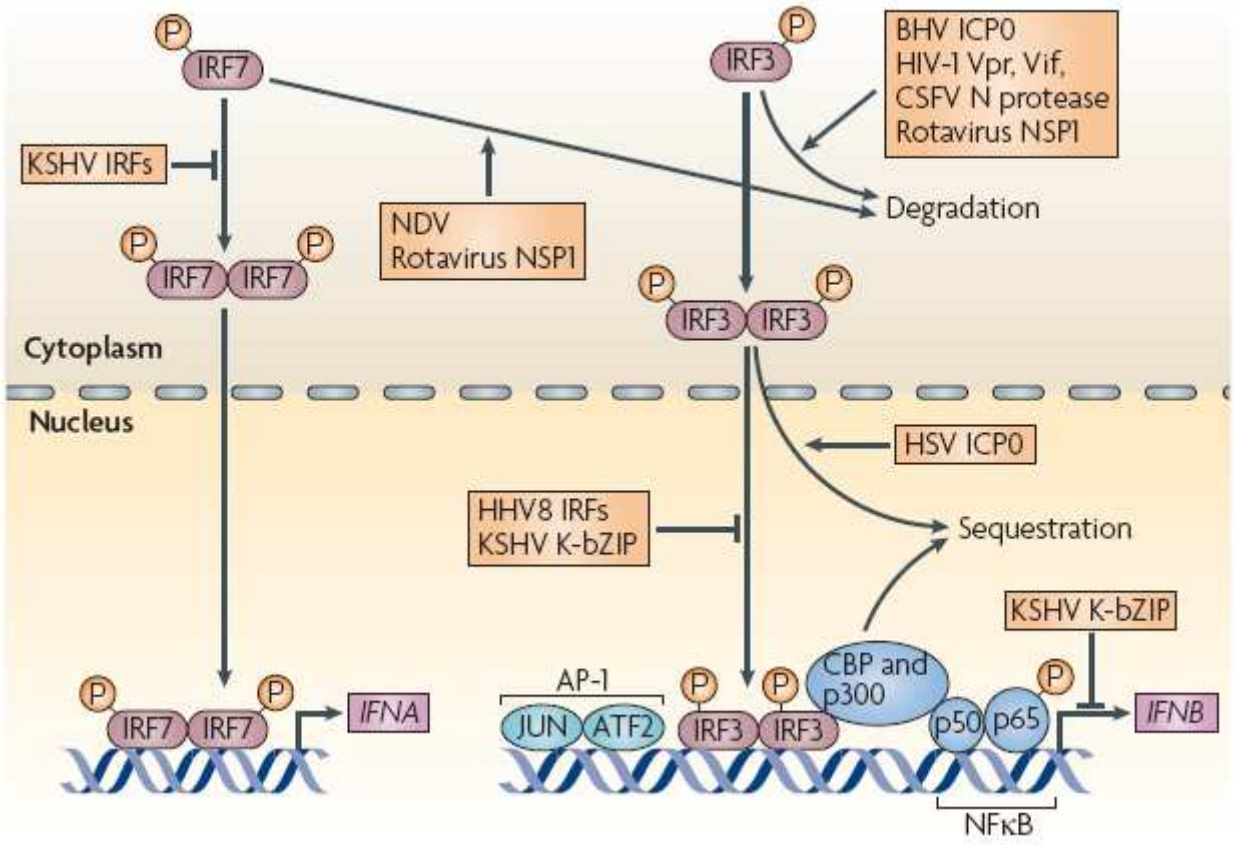
Protein	Virus	Assigned functions in evading or subverting PRR signalling pathways	Refs
VP35	Ebola virus	Sequesters viral dsRNA	112
		Inhibits IRF3 activation downstream of IPS1	112
NS3–4A	Hepatitis C virus	Degrades TRIF to inhibit TLR3 signalling	35
		Cleaves IPS1 from its mitochondrial tether to disable RLR signalling pathways	48,69,70
		Inhibits IRF3 phosphorylation by disrupting the TBK1–IRF3 interaction	75
NS5A	Hepatitis C virus	Inhibits PKR through direct binding	113
		Inhibits OAS through direct binding	114
		Inhibits TLR signalling by binding MyD88	36
E3L	Vaccinia virus	Sequesters viral dsRNA	115
		Inhibits PKR through direct binding	116
		Prevents DAI from interacting with DNA	5
		Binds to and disables ISG15	93
A52R	Vaccinia virus	Inhibits TLR-induced NFκB activation by binding IRAK2	38
		Enhances TLR-induced IL-10 production by binding TRAF6	106
NS1	Influenza A virus	Sequesters viral dsRNA	117
		Binds to RIG-I and suppresses RIG-I signalling	51

DAI, DNA-dependent activator of IRFs; ds, double stranded; IFN, interferon; IL-10, interleukin-10; IL-1R, IL-1 receptor; IPS1, *IFNB*-promoter stimulator 1; IRAK2, IL-1R-associated kinase 2; IRF3, IFN-regulatory factor 3; ISG15, IFN-stimulated protein of 15 kDa; MyD88, myeloid differentiation primary-response gene 88; NFκB, nuclear factor-κB; NS1, nonstructural protein 1; OAS, 2′, 5′-oligoadenylate synthetase; PKR, IFN-inducible dsRNA-dependent protein kinase; PPR, pattern-recognition receptor; RLR, retinoic-acid-inducible gene I (RIG-I)-like receptor; TANK, TRAF-family-member-associated NFκB activator; TBK1, TANK-binding kinase 1; TLR, Toll-like receptor; TRAF6, TNFR-associated factor 6; TRIF, TIR-domain-containing adaptor protein inducing IFNβ.

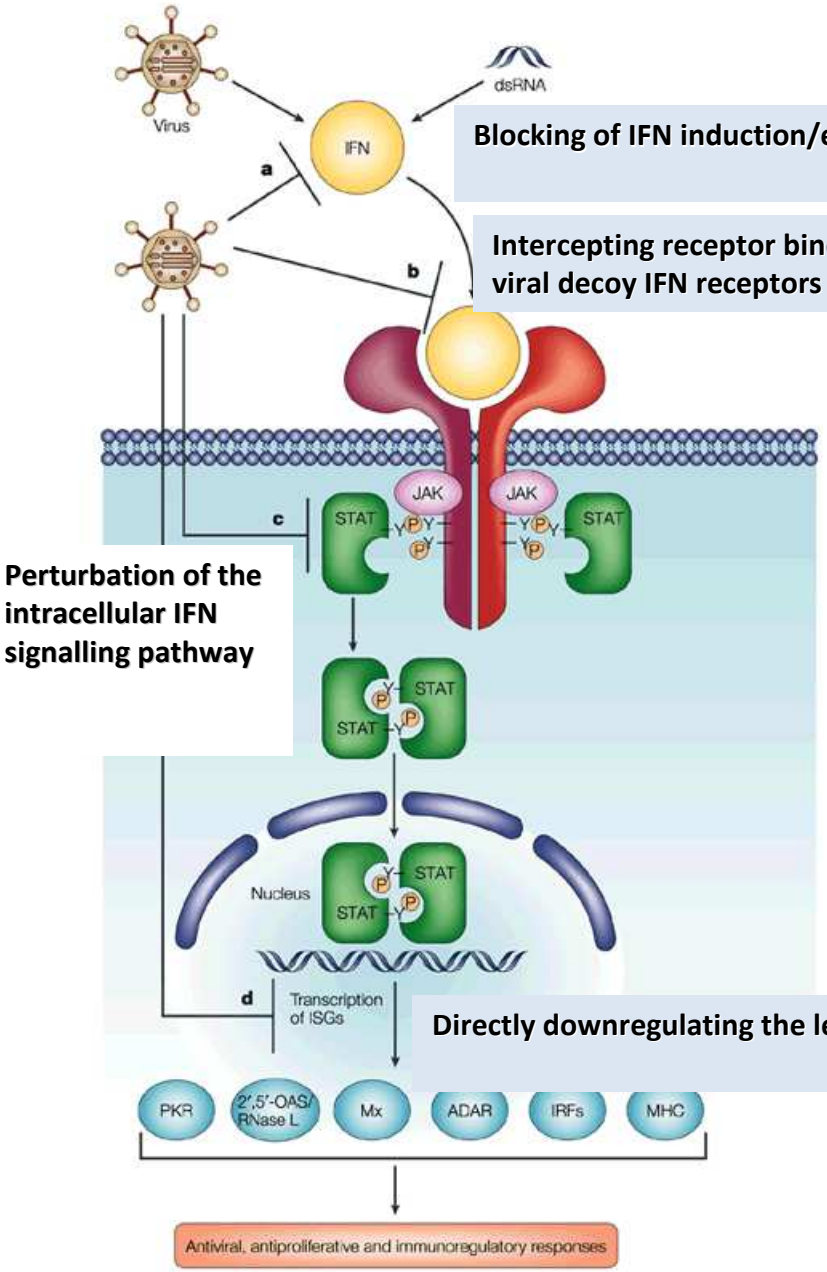

Viral proteins
TLR1–
TLR2
CD14
TLR4
HTLV-1 p30
MD2
CpG DNA
ssRNA
Long
dsRNA
Cytoplasm
HCV NS5A
MAL
MyD88
MyD88
MAL
TRIF
HCV
NS3–4A
TRAM
Endosome
TLR9
TLR7
TLR3
VACV
A46R
VACV
A46R
VACV A46R
HCV NS5A
VACV A46R
HCV NS3–4A
MyD88
TRIF
IRAK4
VACV A52R
IRAK4
IRAK2
IRAK1
IRAK2
VACV A52R
TRADD
RIP1
IRAK1
IRAK2
TRAF6
TRAF6
TRAF6
TRAF6
TRAF3
TAB2
TAB3
TAK1
IKKα
IKKα
IKKβ
IKKε
TBK1
IRF7
p50
p65
NFκB
IRF3
IRF7

RIG-I (retinoic-acid-inducible gene I) and MDA5 (melanoma differentiation-associated gene 5), termed RIG-I-like receptors (RLRs), are activated by cytoplasmic RNA during viral infection.




P
IRF7
KSHV IRFs
P
IRF7
IRF7
P
NDV
Rotavirus NSP1
P
IRF3
BHV ICP0
HIV-1 Vpr, Vif,
CSFV N protease
Rotavirus NSP1
Degradation
P
IRF3
IRF3
P
Cytoplasm
Nucleus
HSV ICP0
HHV8 IRFs
KSHV K-bZIP
Sequestration
KSHV K-bZIP
P
IRF7
IRF7
P
IFNA
AP-1
JUN
ATF2
P
IRF3
IRF3
P
CBP and
p300
p50
p65
P
IFNB
NFκB

Influenza virus e interferone



Blocking of IFN induction/expression

Intercepting receptor binding of IFNs through viral decoy IFN receptors

Perturbation of the intracellular IFN signalling pathway

Directly downregulating the level of expression of ISGs

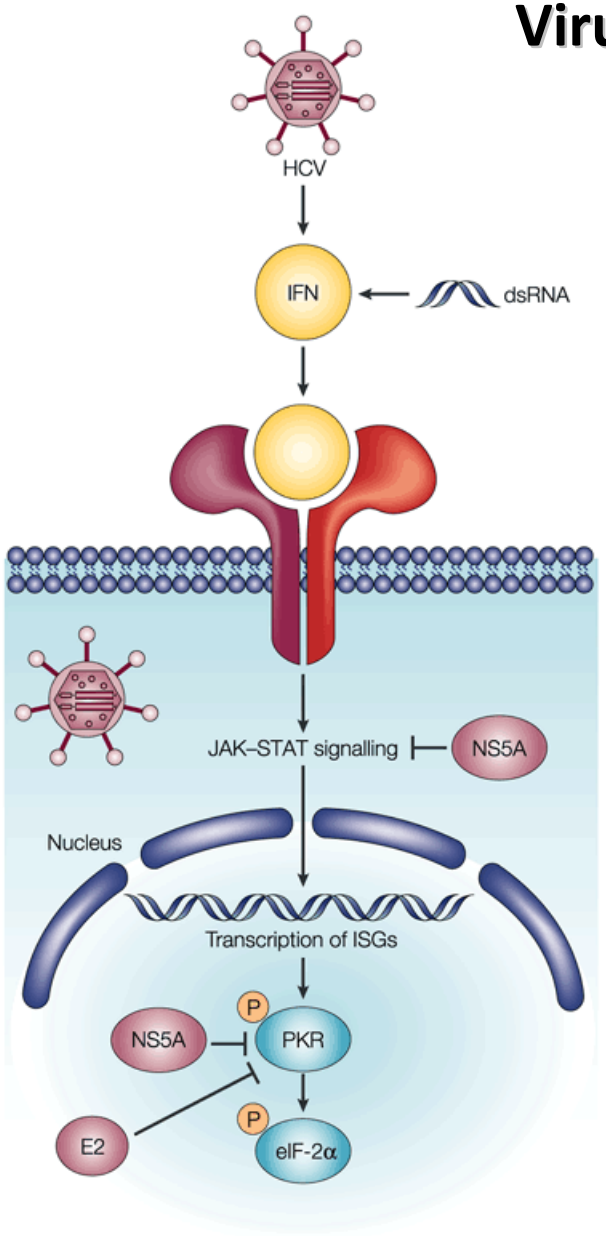
Type I interferons (IFNs) are a group of antiviral cytokines that are induced during viral infection by viral-replication products, such as double-stranded (ds)RNA. IFNs exert their biological functions by binding to specific cell-surface receptors. In turn, this triggers the intracellular IFN signalling pathway — mainly the JAK–STAT pathway— which eventually induces the expression of a large number of IFN-stimulated genes (ISGs). **The ISGs, the workhorses of the IFN response, set up an antiviral, antiproliferative and immunoregulatory state in the host cells**. However, most, if not all, viruses have evolved a broad spectrum of strategies to block and interfere with the IFN pathway.

ADAR, RNA-specific adenosine deaminase; IRF, IFN-regulatory factor; JAK, Janus kinase; Mx, myxovirus-resistance proteins; OAS, oligoadenylate synthetase; PKR, protein kinase; STAT, signal transducer and activator of transcription.

IFN-stimulated genes (ISGs).

Nature Reviews Immunology 2, 675-687 (September 2002)

Virus de HEPATITIS C y HERPES SIMPLE



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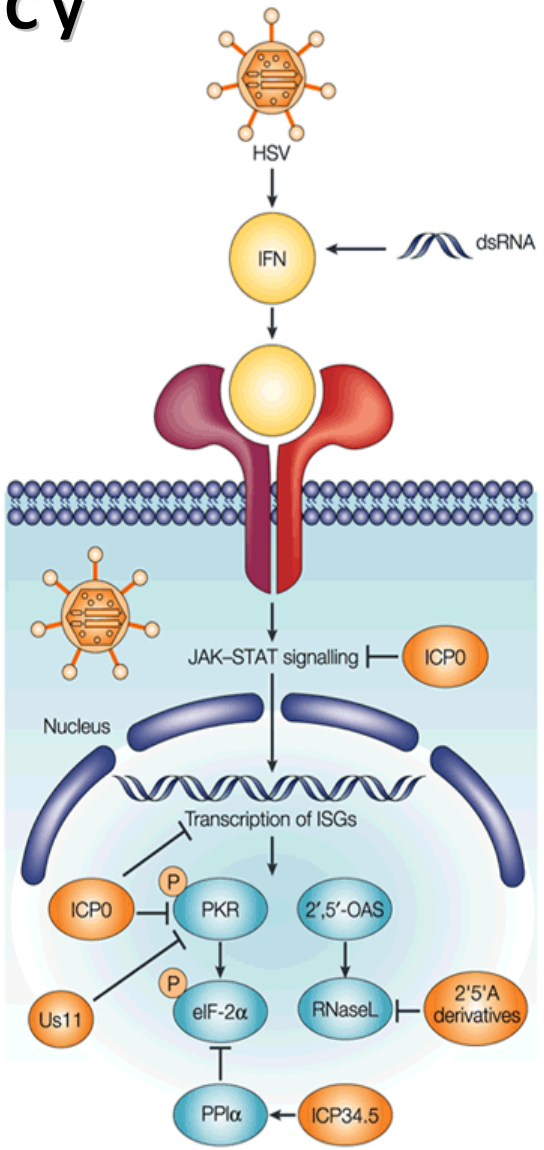

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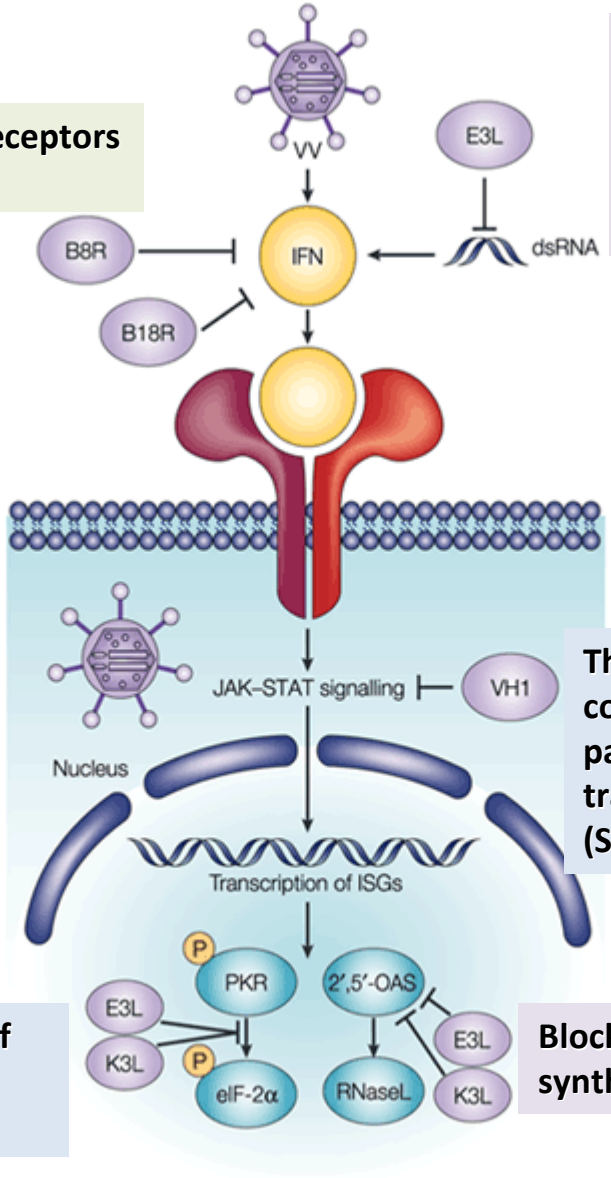
Virus Vaccinia y otros poxvirus

Soluble interferon receptors

The vaccinia virus E3L gene product is a double-stranded (ds) RNA-binding protein that inhibits activation of the protein kinase PKR and blocks IFN responses by sequestering dsRNA molecules



The vaccinia virus VH1 phosphatase, a virion component, intercepts the IFN signalling pathway through dephosphorylation of signal transducer and activator of transcription 1 (STAT1)

Inhibit activation of the protein kinase PKR

Block the IFN-induced 2',5'-oligoadenylate synthetase (OAS) antiviral pathway

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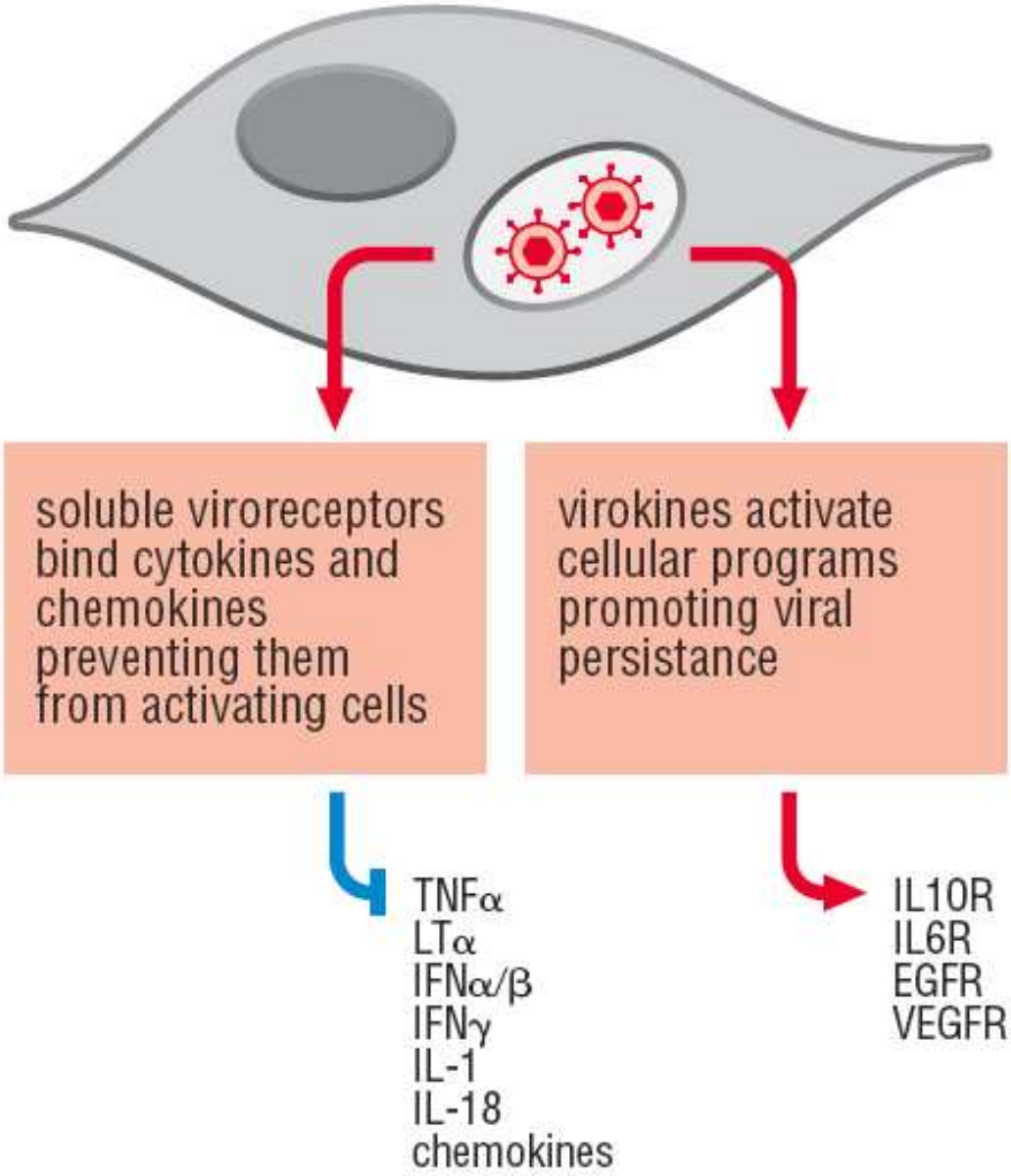
USO TERAPEÚTICO DE LOS INTERFERONES

- ANTI-VíRICO
  - e.j. interferón-α uso aprobado para algunos casos de VHC y VHB agudos y crónicos.
  - Herpes, HPV, Rinovirus, VIH.
- ACTIVACIÓN MACRÓFAGOS
  - interferón-γ se ha usado en e.j. lepra lepromatosa, leishmaniasis, toxoplasmosis.
- ANTI-TUMORAL
  - e.j. melanoma, Sarcoma de Kaposi, CML
- ESCLEROSIS MÚLTIPLE
  - interferón-β

Virus de DNA largos (herpesviruses, poxviruses) codifican proteínas adicionales para "distraer" al sistema inmune del huésped….

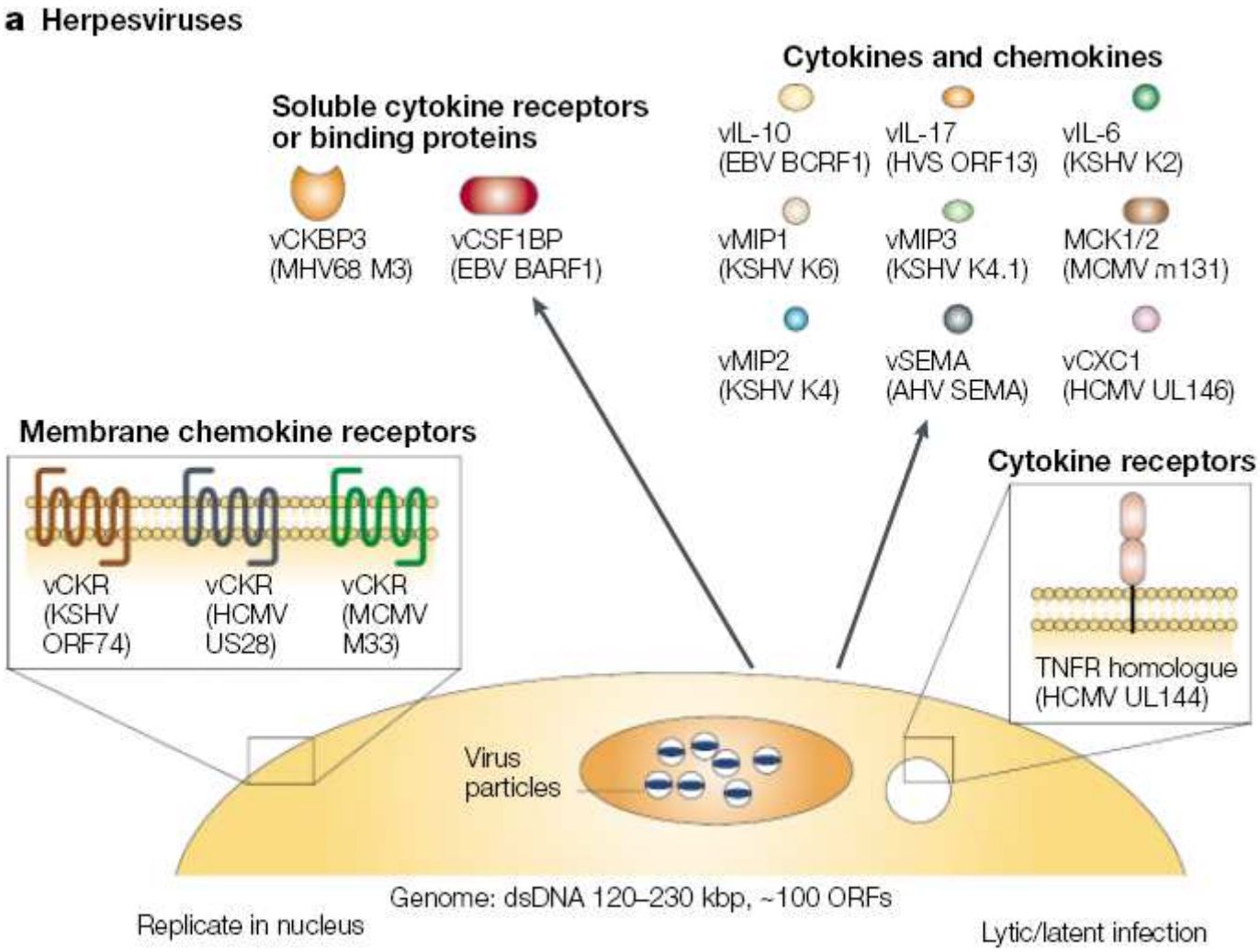


LOS VIRUS SECRETAN CITOCINAS Y QUIMIOCINAS….

Table 1 | **Viral cytokines and chemokines**

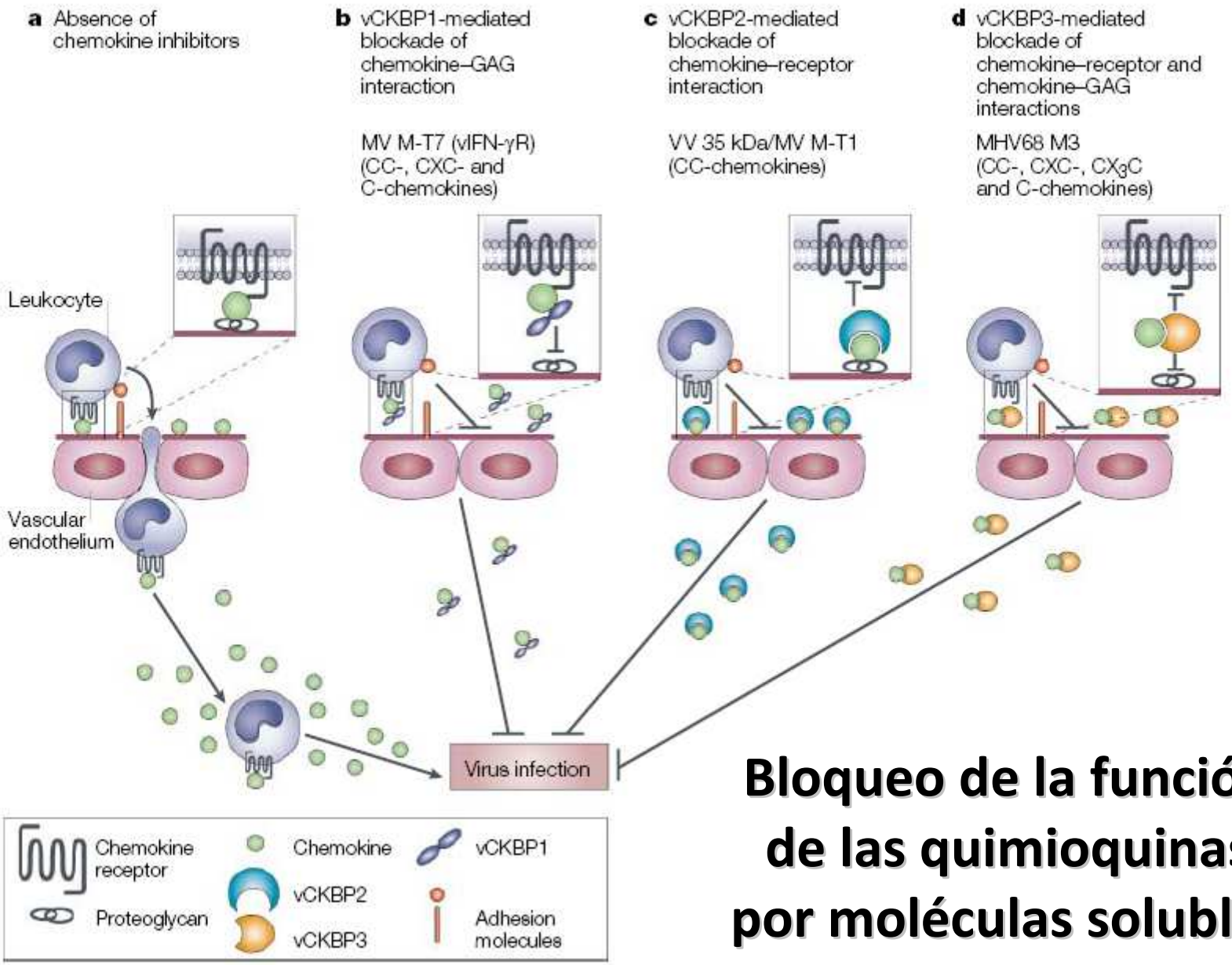
Viral function	Gene/protein	Virus	Mechanism of action
Viral cytokines			
vEGF	VGF/C11R	VV	Stimulates cell growth; virulence factor
vVEGF	A2R	OV	Binds to VEGFR2; angiogenic factor
vIL-10	BCRF1 UL111a	EBV HCMV	Downregulates T_H1 response; B-cell growth factor Low sequence similarity to other vIL-10s
vIL-17	ORF13	HVS	T-cell mitogen
vIL-6	K2	KSHV	Angiogenic factor, B-cell growth factor
vSEMA	A39R	VV	Binds semaphorin receptor VESPR
vTGF-β	FPV080	FPV	TGF-β homologue; unknown function
vβ-NGF	FPV072, FPV076	FPV	β-NGF homologues; unknown function

Nature Reviews Immunology 3, 36-50 (January 2003)



Nature Reviews Immunology 3, 36-50 (January 2003)

Viral chemokines			
vCK	vMIP1/K6	KSHV	CCR8 agonist, T_H2 chemoattractant; angiogenic activity
vCK	vMIP2/K4	KSHV	C-, CC-, CXC- and CX_3C-chemokine antagonist, T_H2 chemoattractant; angiogenic activity
vCK	vMIP3/K4.1	KSHV	CCR4 agonist, T_H2 chemoattractant; angiogenic activity
vCK	U83	HHV6	CC-chemokine agonist, monocyte chemoattractant
vCK	MCC1/MC148	MCV	CC- and CXC-chemokine antagonist, specific CCR8 antagonist, interferes with monocyte function
vCK	MCK1/2, m131/129	MCMV	CC-chemokine agonist, promotes monocyte-associated viraemia *in vivo*
vCK	vCXC1/UL146	HCMV	CXCR2 agonist, neutrophil chemoattractant
vCK	MDV003	MDV	CXC-chemokine
vCK	Tat	HIV	Partial chemokine similarity, monocyte chemoattractant
vCK	Glycoprotein G	RSV	Partial chemokine similarity, CX_3CL1 activity



Bloqueo de la función de las quimioquinas por moléculas solubles

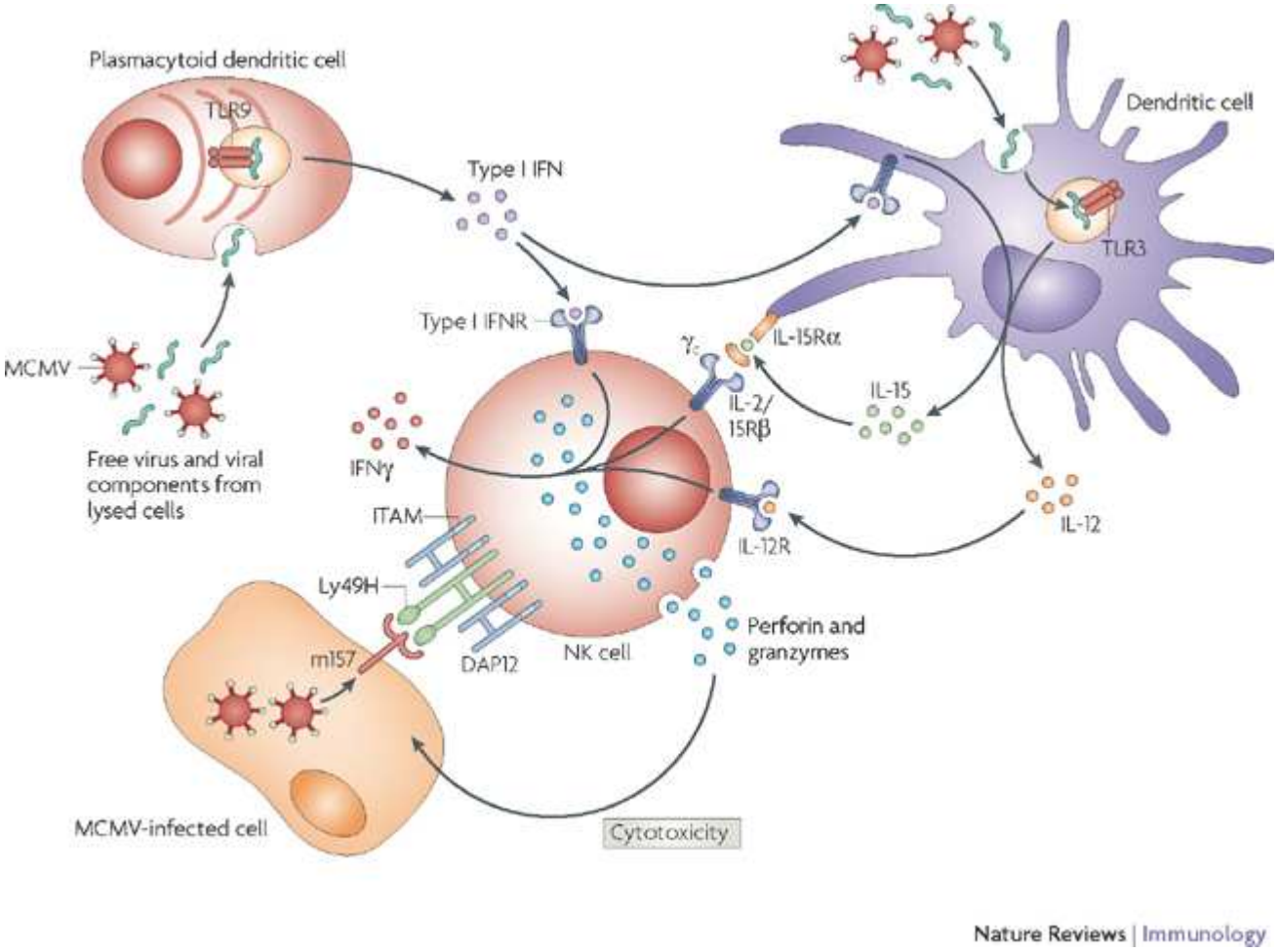
LOS VIRUS EXPRESAN RECEPTORES DE CITOCINAS /QUIMIOCINAS….

Table 2 | **Viral cytokine and chemokine receptors or binding proteins**

Viral function	Gene/protein	Virus	Mechanism of action
Viral cytokine receptors or binding proteins			
vTNFR	CrmB/H4R M002R/L (M-T2)	CPV MV	Secreted TNF inhibitor, virulence factor in MV
vTNFR	CrmC/A53R	CPV	Secreted TNF inhibitor
vTNFR	CrmD/K2R	CPV	Secreted TNF inhibitor
vTNFR	CrmE/K3R	CPV	Secreted TNF inhibitor, also expressed at the cell surface
vTNFR	UL144	HCMV	Membrane TNFR homologue; unknown function
vTNFR	ORF167L	LCDV1	Homology to domain of TNFR; unknown function
vCD30	E13	EV	Secreted; blocks binding of CD30 to CD30L and induces reverse signalling in cells that express CD30L
vIL-1βR	B16R	VV	*B15R* gene in VV strain WR; secreted, blocks febrile response
vIFN-γR	M007R/L (M-T7) B8R	MV VV	Secreted; the VV protein binds IFN-γ from various species and it is a virulence factor in MV
vIFN-α/βBP	B19R	VV	*B18R* gene in VV strain WR; secreted and cell surface, binds IFN-α/β from various species, virulence factor in VV
vCSF1BP	BARF1	EBV	Secreted; binds CSF1
vGM-CSF/IL-2BP	GIF	OV	Secreted; sequence similarity to the VV 35 kDa protein (vCKBP2)
vIL-18BP	MC54	MCV	Secreted; inhibits IL-18-induced IFN-γ production
vIL-18BP	E19	EV	Secreted; inhibits IL-18-induced IFN-γ production and NK-cell response
vIL-18BP	MC51, MC53	MCV	Secreted IL-18BP homologues; unknown ligand
vIFN-γ/IL-2/IL-5BP	Gene not identified	TPV	35 kDa; secreted

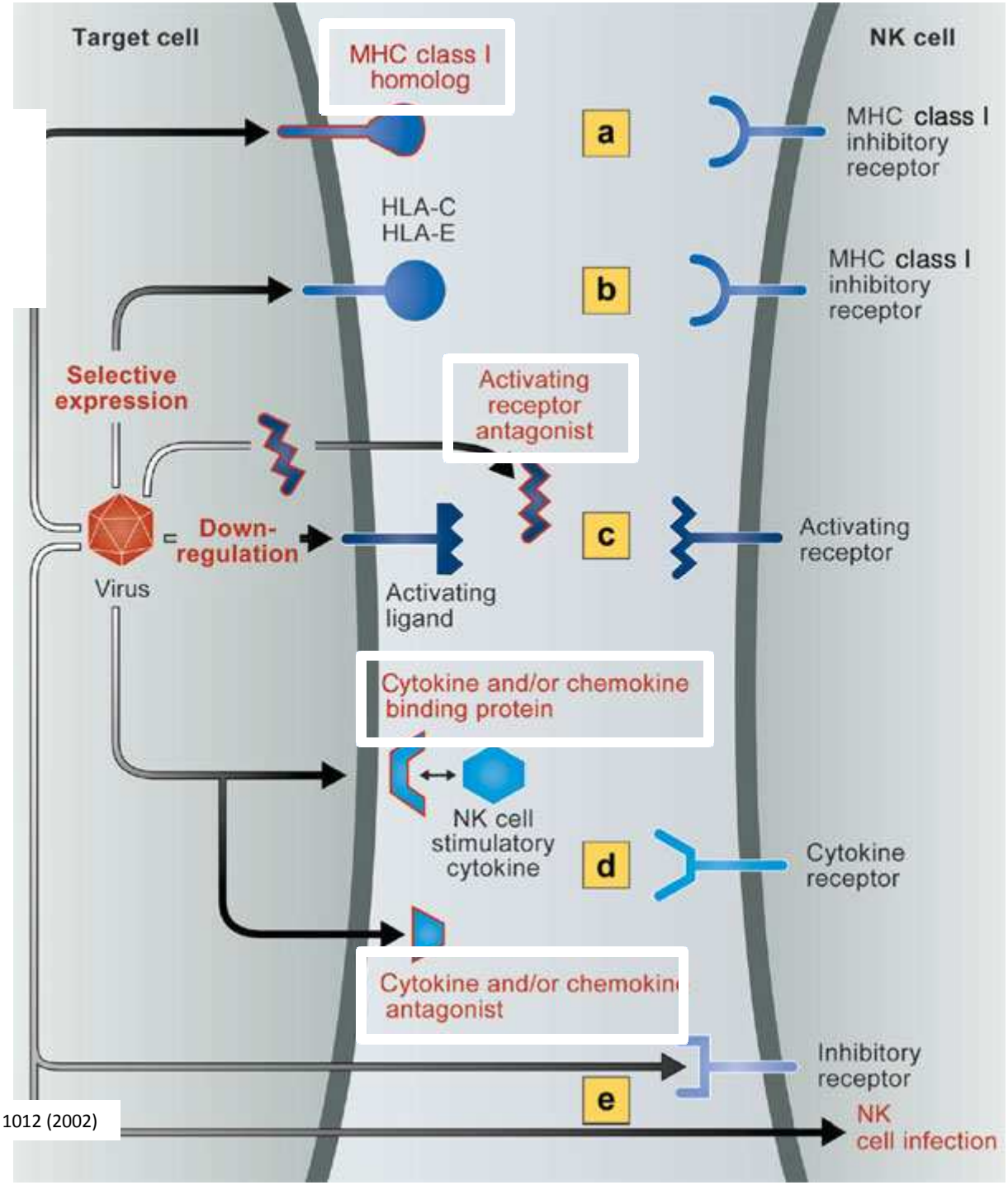
NK, NKT…

Células NK y virus



Nature Reviews Immunology 8, 259-268 (April 2008)

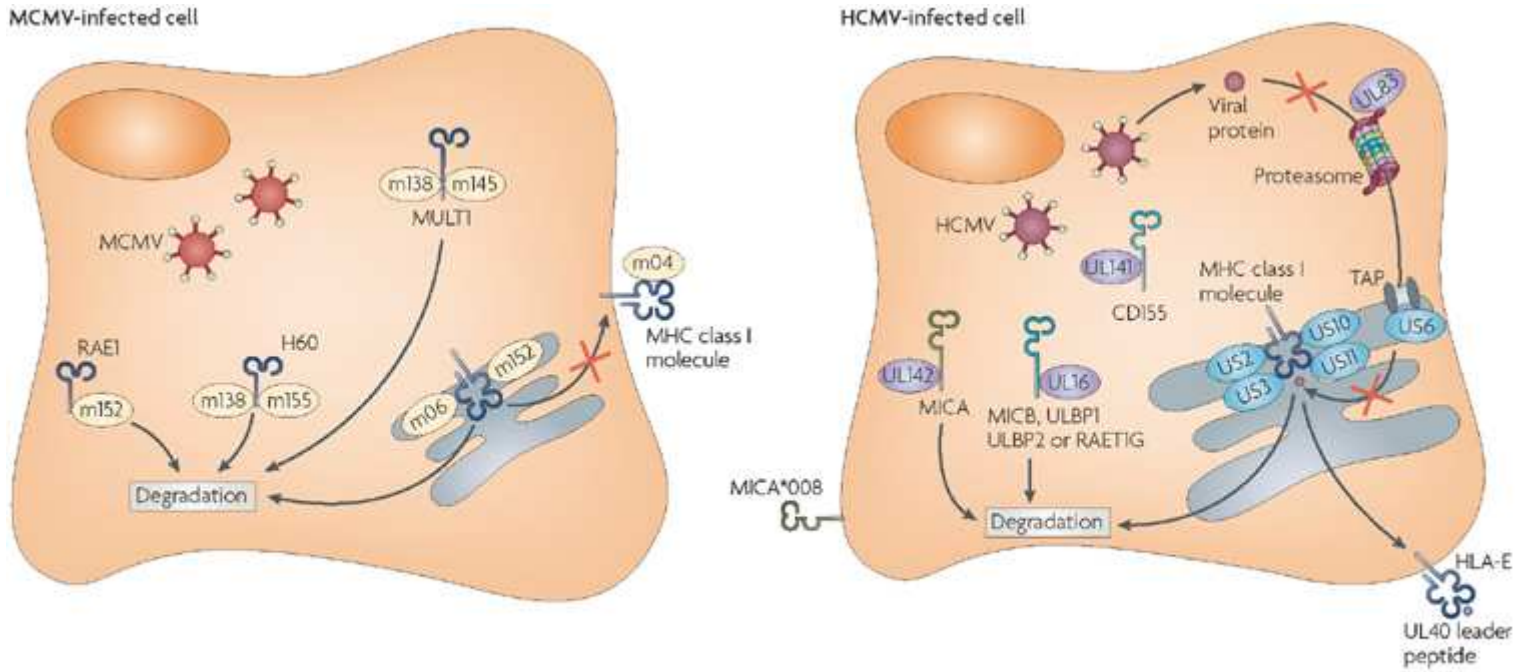
NK y virus



Nature Immunology **3**, 1006 - 1012 (2002)

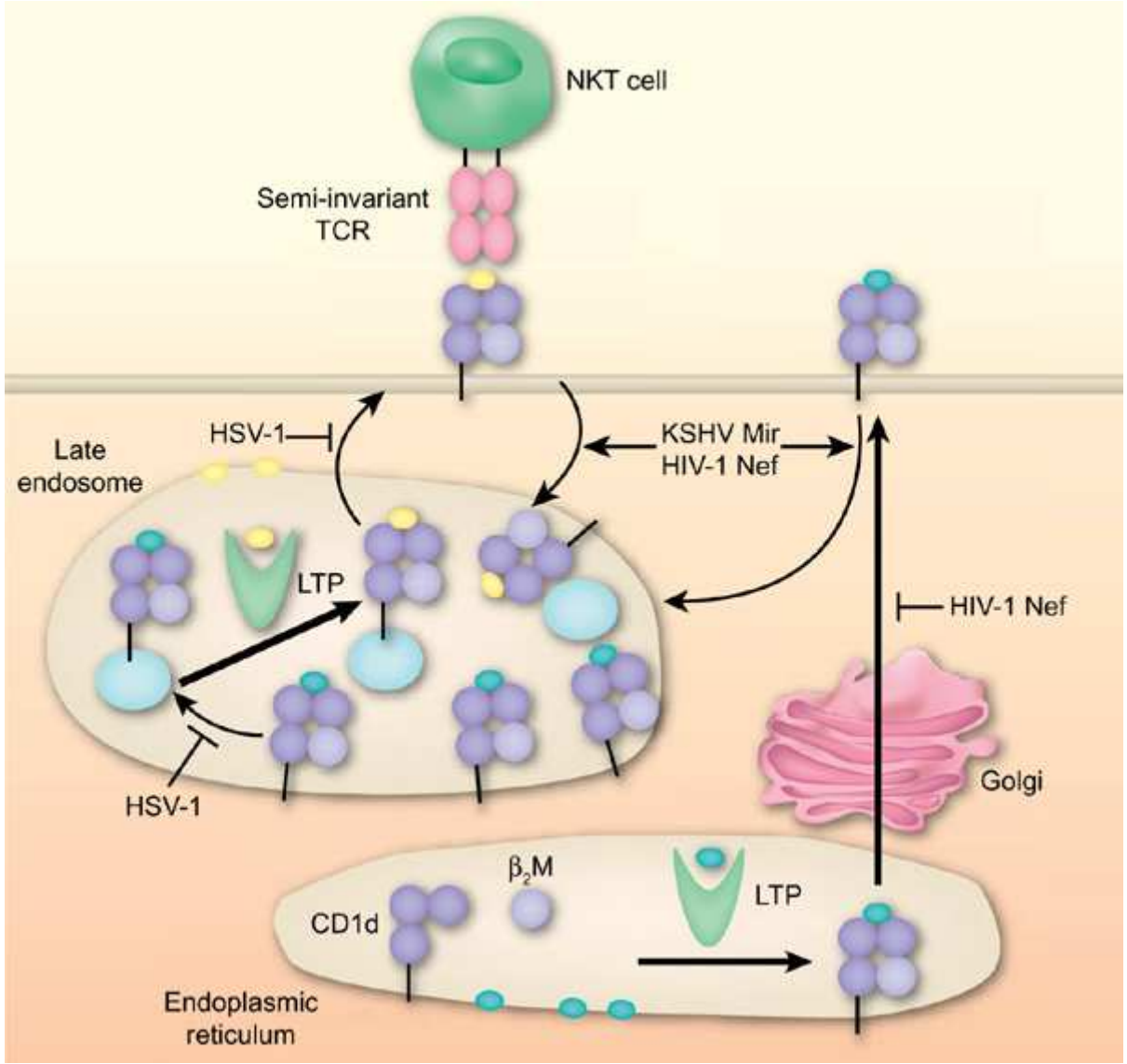
- The strategies by which viruses evade NK cells fall into five categories and are depicted in the interaction between a virus infected target cell (left) and an NK cell (right).
- (**a**) NK cells can be inhibited by a viral MHC class I homolog with structural similarity to endogenous host class I that binds to inhibitory class I receptors on NK cells.
- (**b**) Viruses can inhibit expression of HLA-A and HLA-B, resulting in a relative increase in HLA-C and HLA-E on the surface of the target cell; these inhibit NK cells through the class I inhibitory receptors CD94-NKG2A and KIR, respectively. Alternatively, viral gene expression can result in selectively increased expression of HLA-E, which inhibits NK cells through CD94-NKG2A.
- (**c**) Virus-encoded proteins can function as cytokine binding proteins that block the action of NK cell activating cytokines. In addition, viruses can produce homologs, or increase host production of cytokines that inhibit NK cells.
- (**d**) NK cell activities can also be avoided by decreased expression of NK cell−activating ligands in virus-infected target cells, which prevent signal transduction *via* NK cell−activating receptors. To achieve the same end, viruses can encode antagonists of the activating receptor−ligand interaction.
- (**e**) Viruses can also directly inhibit NK cells by infecting them or using envelope proteins to ligate NK cell inhibitory receptors. Proteins outlined in red are virally encoded. Each mechanism corresponds to the similarly numbered section of the text where additional details and examples are provided.

Citomegalovirus evade al sistema inmune…



The HCMV proteins US2, US3, US10 and US11 interact with the MHC class I heavy chains on their own or with the heavy chains complexed with β_2-microglobulin, ultimately resulting in their degradation, whereas US6 blocks TAP (transporter associated with antigen processing) function and UL83 inhibits protein entry into the proteasome. UL40 provides a leader peptide that binds to HLA-E allowing its expression on the surface of HCMV-infected cells, presumably for interactions with the inhibitory CD94–NKG2A (NK group 2, member A) receptor on NK cells. Both MCMV and HCMV inhibit expression of the NKG2D ligands in infected cells

Nature Reviews Immunology 8, 259-268 (April 2008)



Newly synthesized CD1d heavy chains and β2-microglobulin (β2M) bind phospholipids in the lumen of the endoplasmic reticulum, with the assistance of lipid-transfer proteins (LTP). These CD1d-lipid complexes exit the endoplasmic reticulum and are transported to the cell surface by exocytosis. Cell surface CD1d molecules are then endocytosed by a clathrin-dependent mechanism into late endosomes, many of which contain intracellular vesicles. In this compartment, with the assistance of lipid-transfer proteins, CD1d molecules are loaded with antigenic glycolipids, after which they are displayed at the cell surface for presentation to CD1d-restricted NKT cells. This diagram shows the location where viruses and their products are thought to affect CD1d trafficking. TCR, T cell receptor; KSHV, Kaposi sarcoma–associated herpesvirus; HIV, human immunodeficiency virus.

Nature Immunology 7, 795 - 797 (2006)

RESPUESTA ADAPTATIVA EN LA INFECCIÓN VIRAL

TABLE 17-1 Mechanisms of humoral and cell-mediated immune responses to viruses

Response type	Effector molecule or cell	Activity
Humoral	Antibody (especially, secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM, and IgA antibody	Blocks fusion of viral envelope with host-cells plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex
Cell-mediated	IFN-γ secreted by T_H or T_C cells	Has direct antiviral activity
	Cytotoxic T lymphocytes (CTLs)	Kill virus-infected self-cells
	NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

INMUNIDAD ADAPTATIVA

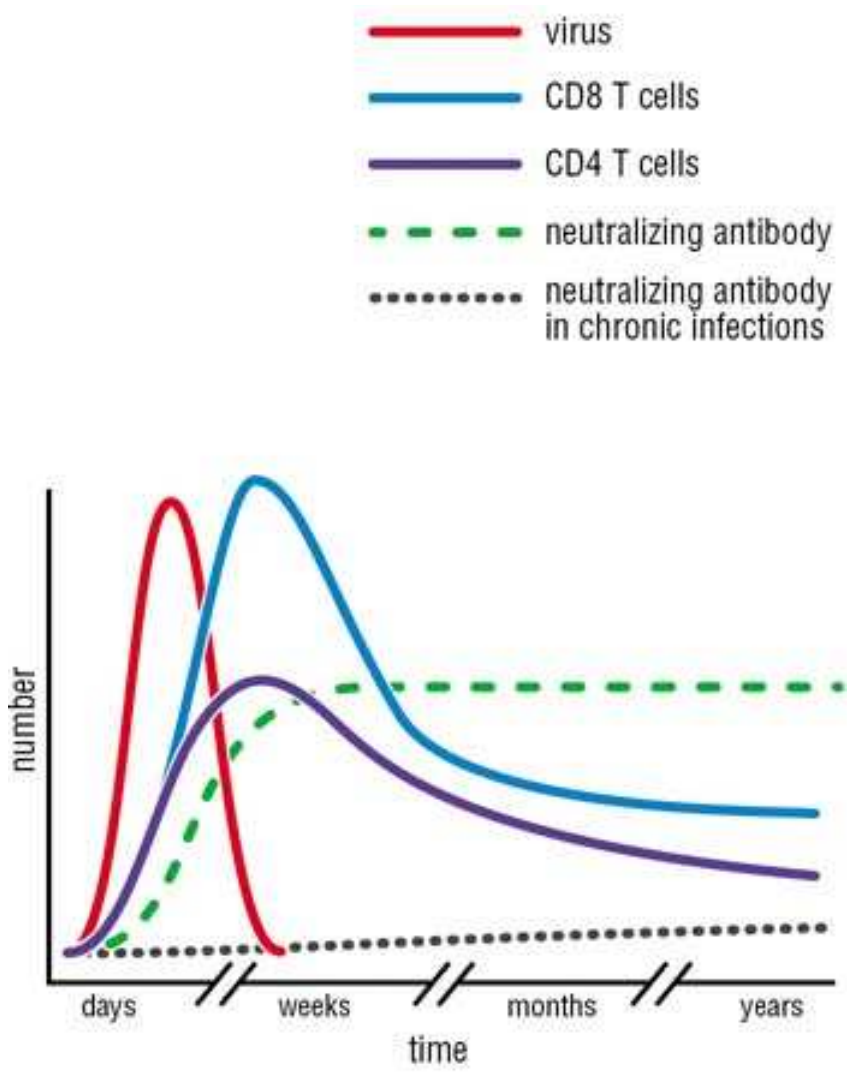
Linfocitos TCD8^{+}:

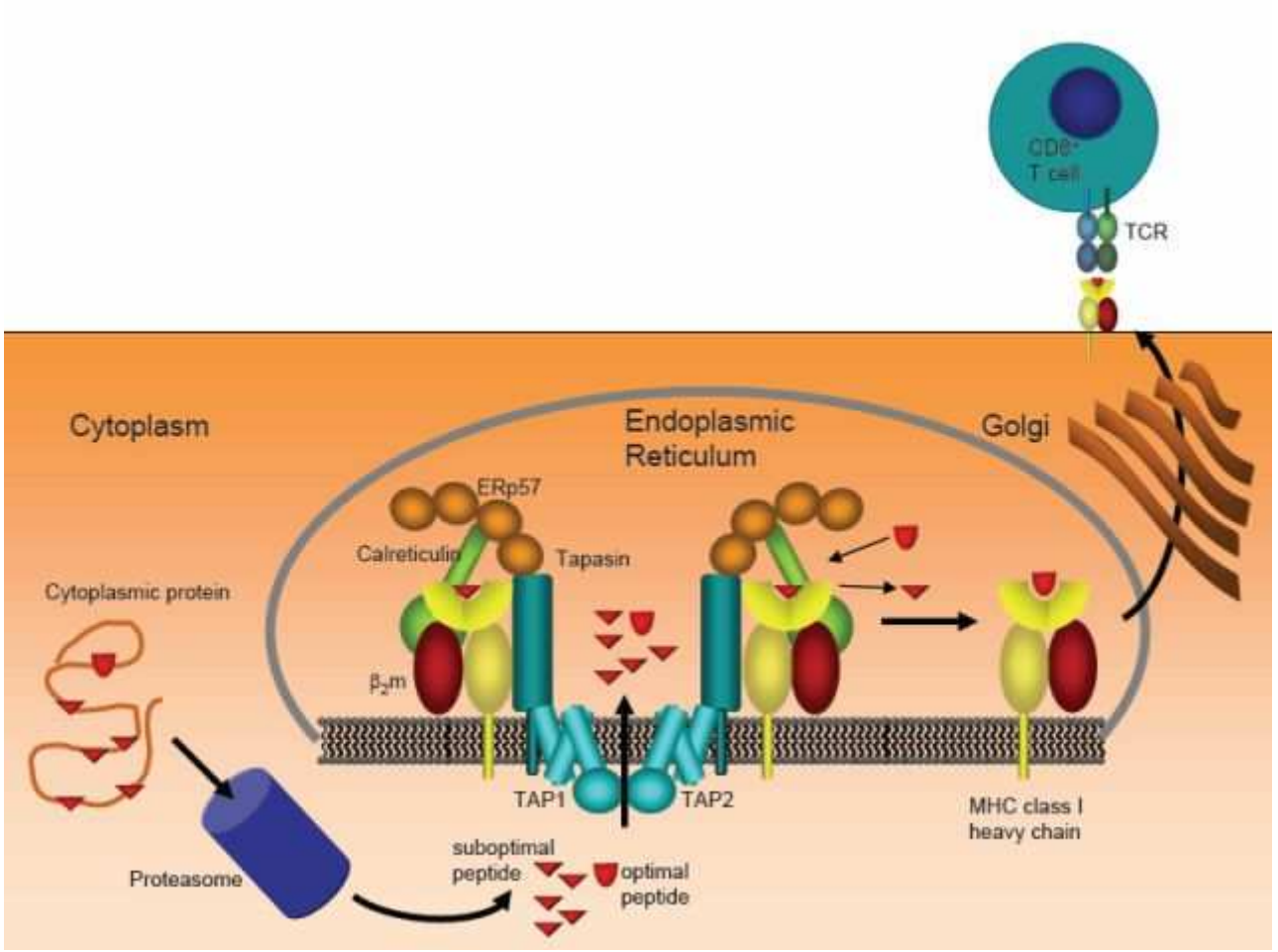
- Destrucción de células infectadas,
- lesiones hísticas en el caso de virus no citopáticos

Anticuerpos neutralizantes:

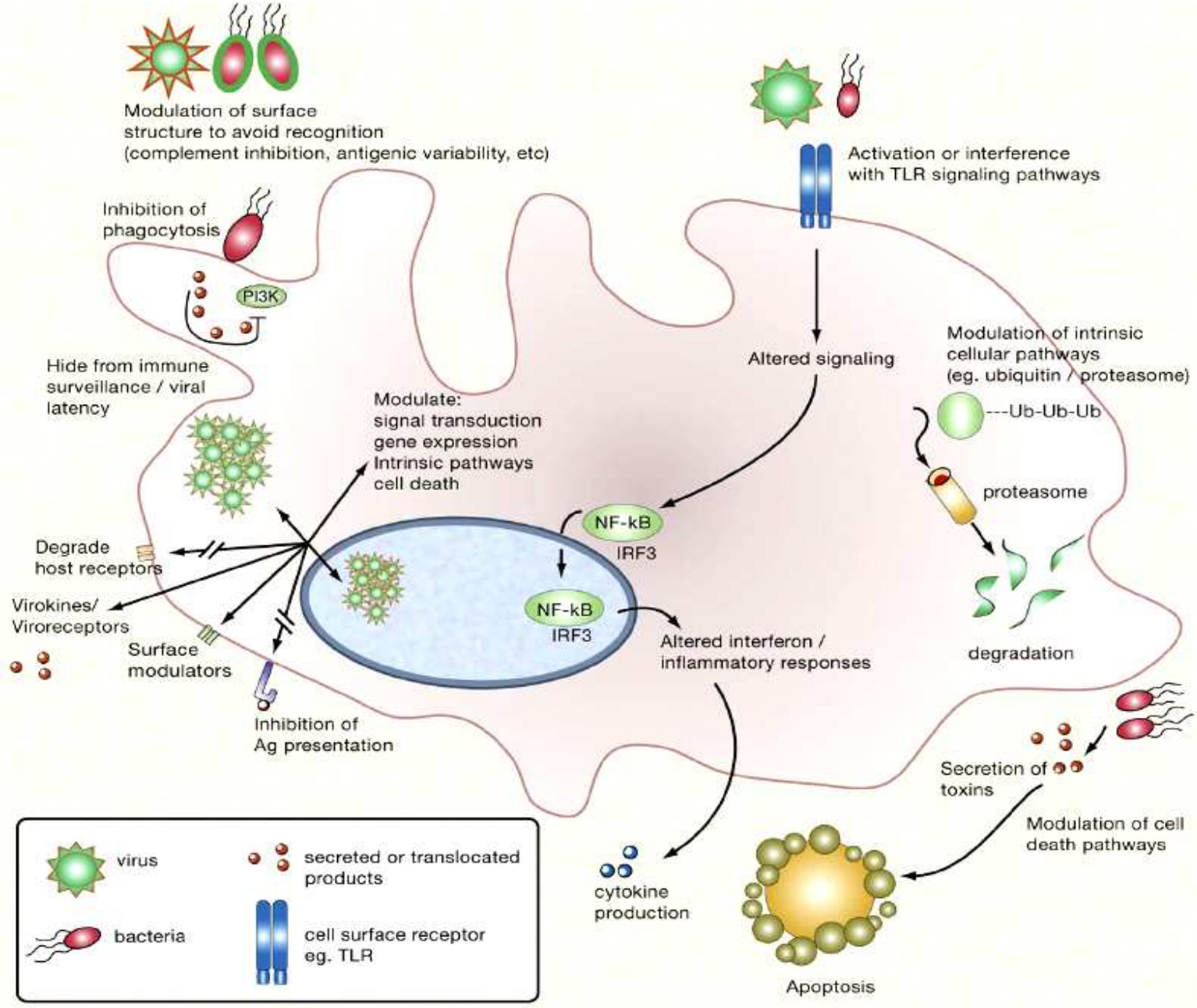
- Bloqueo de la unión del virus al receptor en la célula diana**,**
- bloqueo de la unión de la proteína de fusión al correceptor.

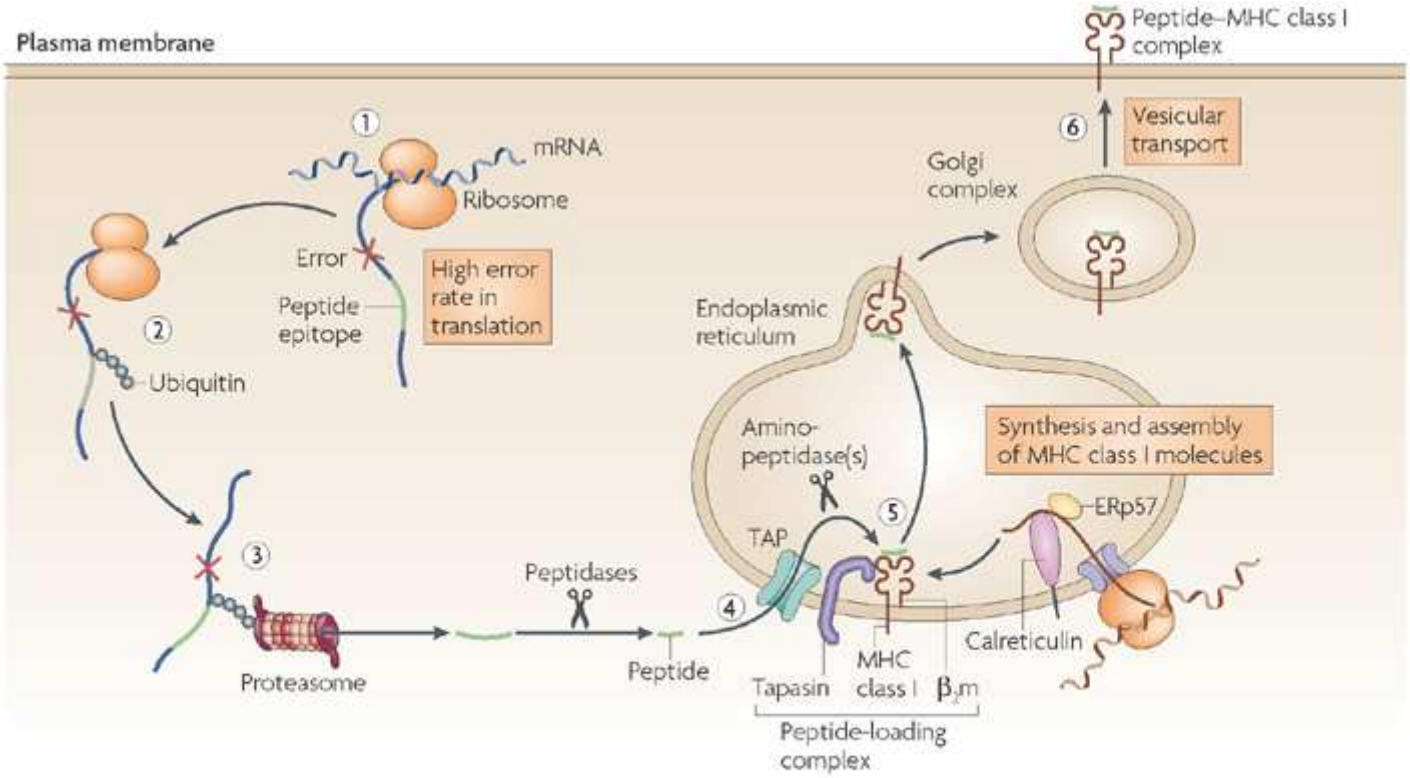
La respuesta adaptativa en la infección viral





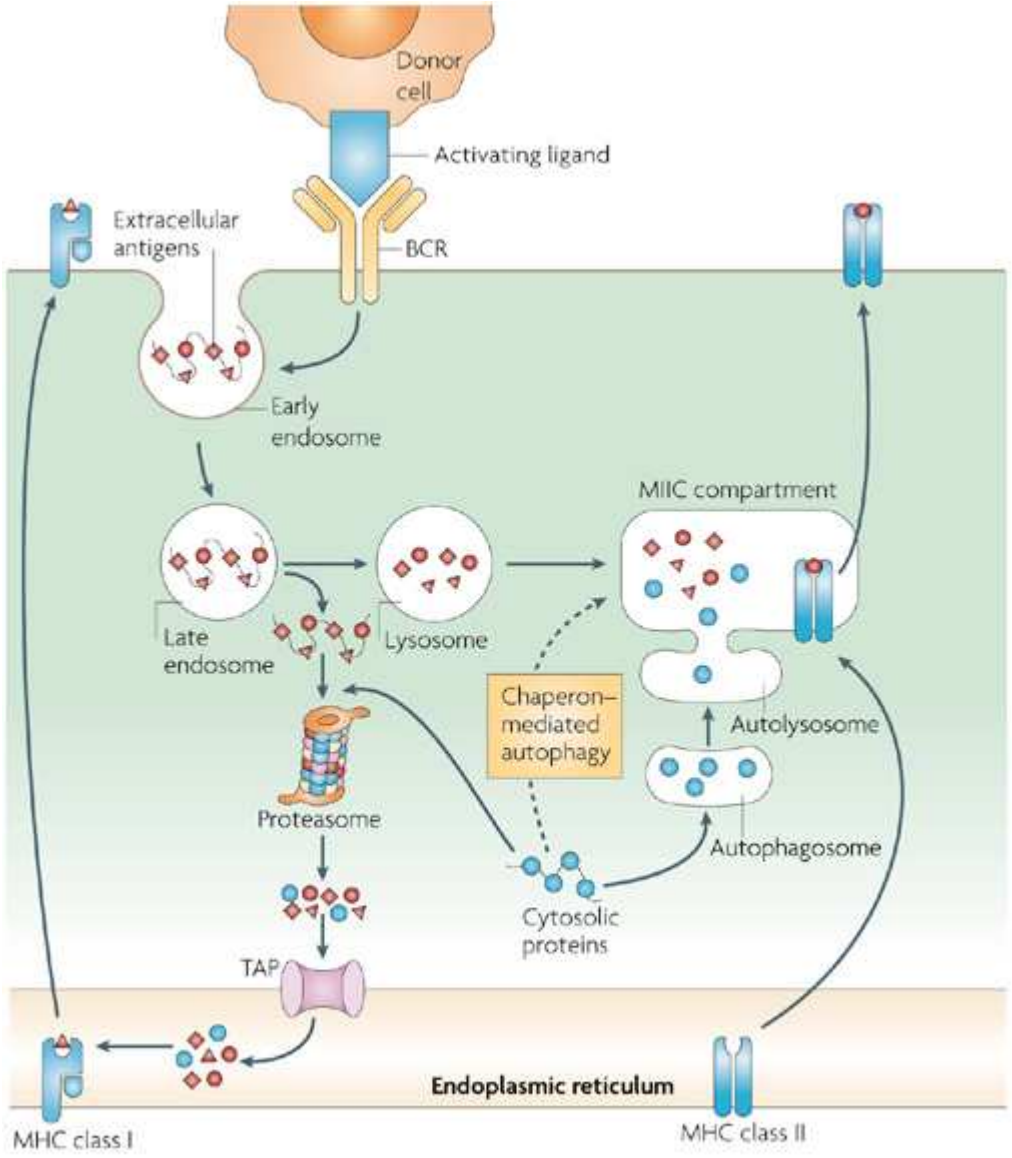
Inhibición del PROCESAMIENTO Y PRESENTACIÓN ANTIGÉNICA


Modulation of surface structure to avoid recognition (complement inhibition, antigenic variability, etc)
Inhibition of phagocytosis
PI3K
Hide from immune surveillance / viral latency
Modulate: signal transduction gene expression Intrinsic pathways cell death
Degrade host receptors
Virokines/ Viroreceptors
Surface modulators
Inhibition of Ag presentation
Activation or interference with TLR signaling pathways
Altered signaling
NF-kB
IRF3
NF-kB
IRF3
Altered interferon / inflammatory responses
Modulation of intrinsic cellular pathways (eg. ubiquitin / proteasome)
---Ub-Ub-Ub
proteasome
degradation
Secretion of toxins
Modulation of cell death pathways
cytokine production
Apoptosis
virus
bacteria
secreted or translocated products
cell surface receptor eg. TLR

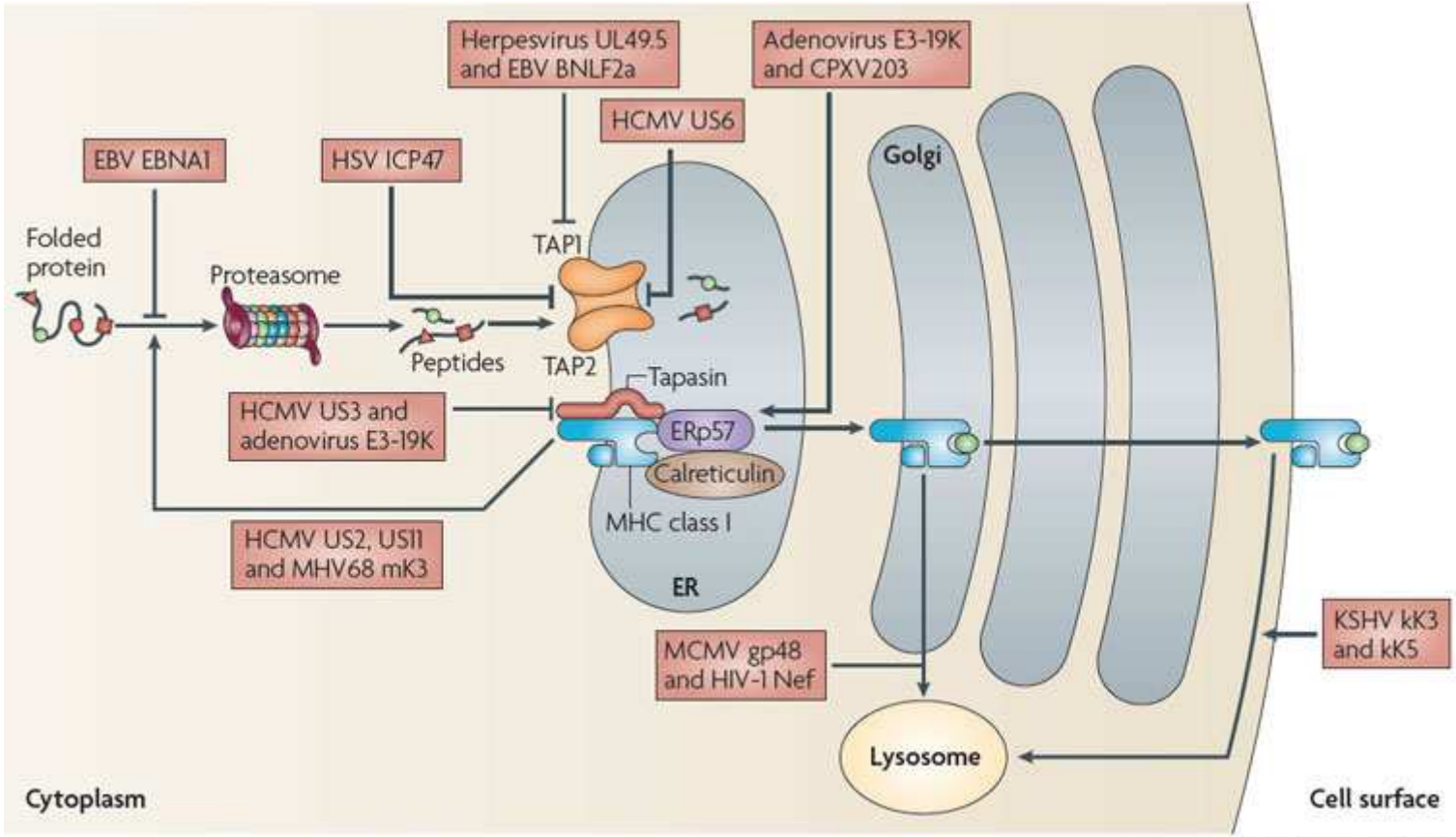


Nature Reviews | Immunology

Nature Reviews Immunology 8, 607-618 (August 2008)

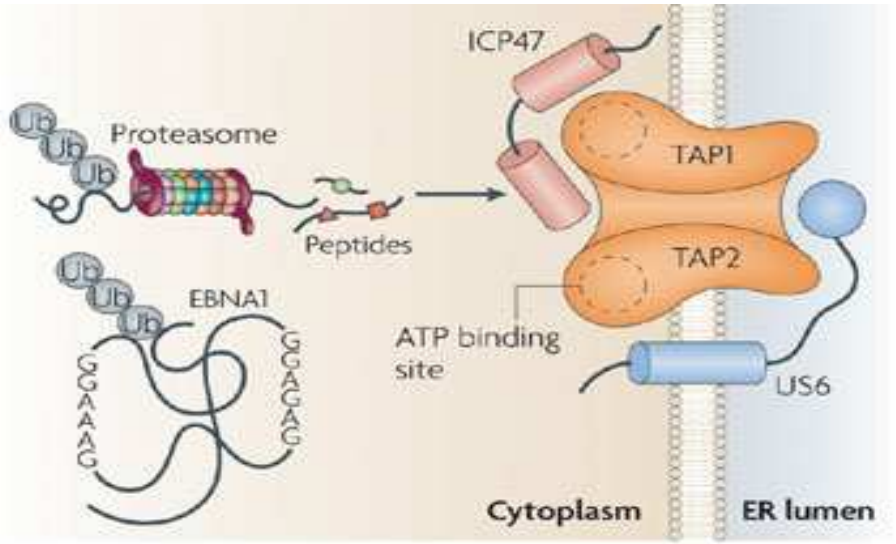


Nature Reviews Immunology 7, 942-953 (December 2007)



Nature Reviews | Immunology

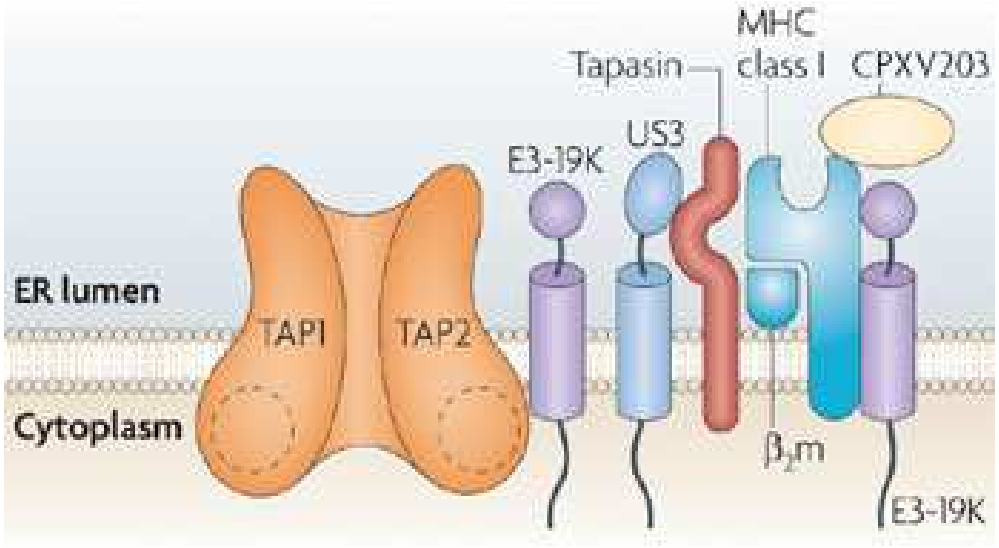
The ability of EBNA1 to escape proteasomal processing is due to long repeats of glycine and alanine residues in the protein. How these repeats confer inhibitory properties to EBNA1 is unclear, but they do not prevent ubiquitylation of the protein.



Nature Reviews | Immunology

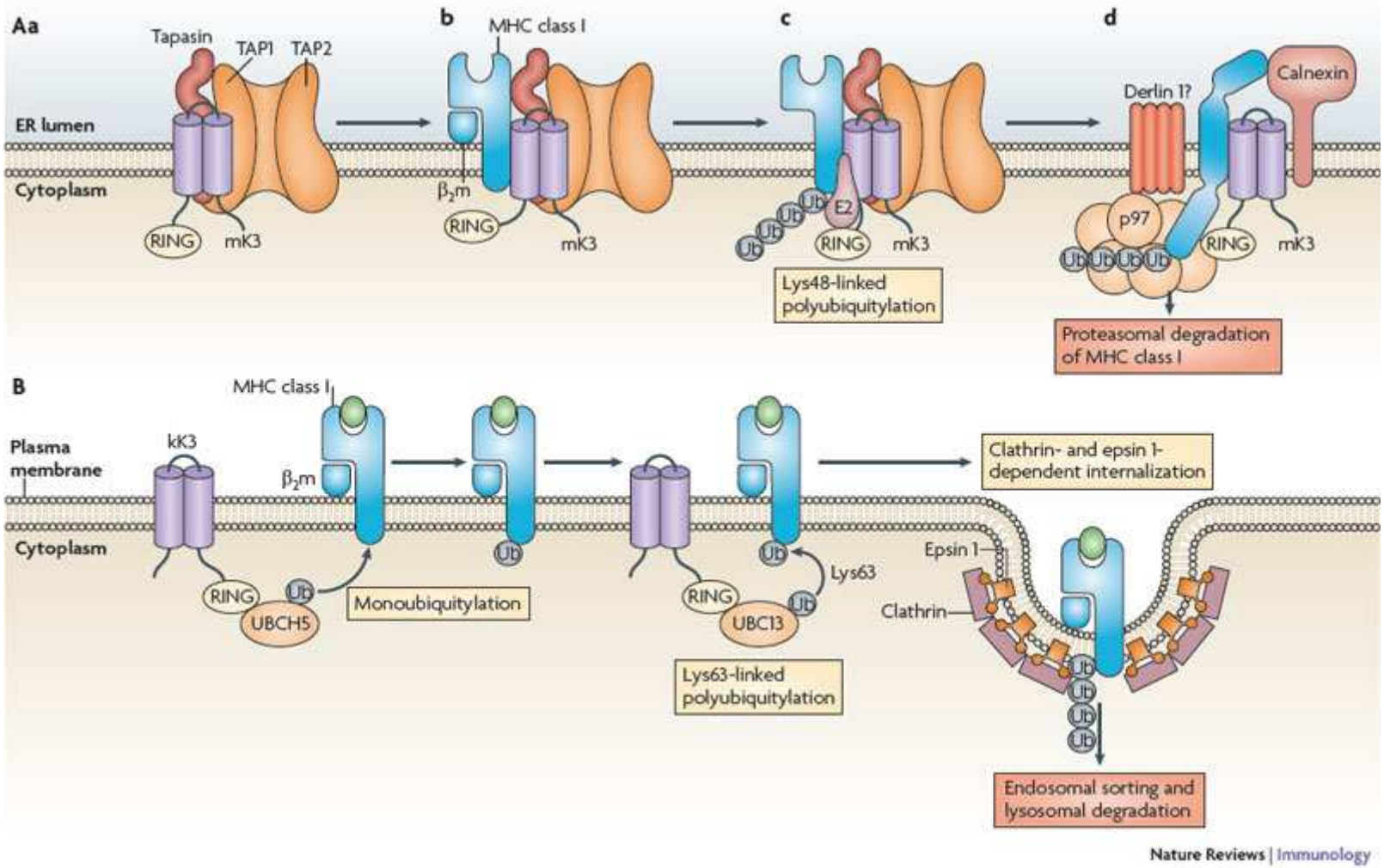
The proteasome is the central unit for the degradation of ubiquitylated proteins into peptides, which are then translocated into the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP). A remarkable property of Epstein–Barr virus nuclear antigen 1 (EBNA1) is to evade proteasomal processing, such that no EBNA1-derived peptides are generated. The ability of EBNA1 to escape proteasomal processing is due to long repeats of glycine and alanine residues in the protein. How these repeats confer inhibitory properties to EBNA1 is unclear, but they do not prevent ubiquitylation of the protein. ICP47 from herpes simplex virus inhibits peptide binding to the cytoplasmic face of the TAP complex. By contrast, US6 from human cytomegalovirus binds to the ER-luminal side of TAP but, remarkably, prevents ATP binding to TAP on the cytoplasmic side. The molecular mechanisms by which ICP47 and US6 block peptide transport are not completely defined, but they seem to exploit the conformational flexibility of TAP that is normally required to transport peptides. Ub, ubiquitin.

Modulación de la función de tapasina y retención de moléculas de MHC class I proteínas virales



Nature Reviews | Immunology

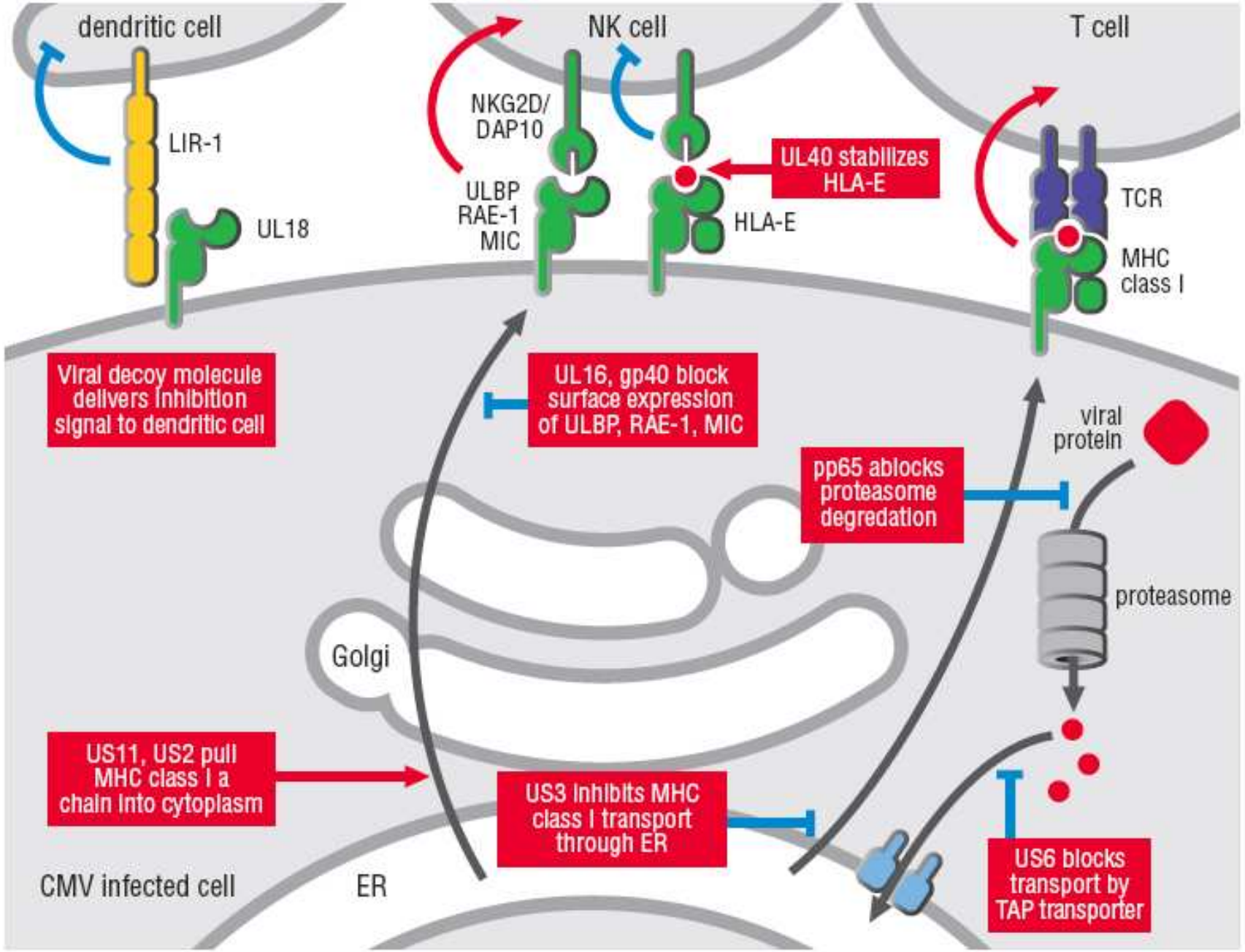
The US3 protein from human cytomegalovirus binds to tapasin and inhibits its ability to facilitate the binding of kinetically stable peptides to MHC class I molecules (known as peptide optimization), and E3-19K from adenovirus binds to transporter associated with antigen processing (TAP) and inhibits the ability of tapasin to recruit TAP to the PLC. The newly identified cowpox virus protein 203 (CPXV203) uses a retention strategy that is similar to that of E3-19K to suppress the presentation of viral peptides.



Nature Reviews Immunology 9, 503-513 (July 2009)

- A | Mouse herpesvirus 68 protein mK3 ubiquitylates MHC class I molecules, which results in their degradation by the proteasome through the endoplasmic reticulum (ER)-associated degradation (ERAD) pathway. mK3 binds to its primary binding partner, transporter associated with antigen processing (TAP), which is associated with the MHC class I specific chaperone tapasin (a). After assembling with β2-microglobulin (β2m), the MHC class I heavy chain binds the TAP–tapasin complex to await a suitable peptide ligand. TAP orients the mK3 catalytic RING domain such that it is in proximity with the tail of MHC class I molecules (b). The association of mK3 with TAP–tapasin induces the recruitment of an E2 ligase, which results in the polyubiquitylation of the MHC class I tail. β2m also dissociates from the heavy chain (c), perhaps leading to the recruitment of the ER chaperone calnexin into the multimeric complex. Polyubiquitylation with lysine 48 linkages of the MHC class I heavy chain initiates partial denaturation of the heavy chain and the recruitment of the ATPase p97. p97 then facilitates the retro-translocation of the heavy chain to the cytoplasm by a putative dislocation channel that may include derlin 1 and mK3. The MHC class I heavy chain undergoes proteasome-mediated degradation in the cytoplasm mediated by the p97, resulting in the generation of ubiquitin (Ub) monomers and peptides (d). B | Kaposi's sarcoma-associated virus protein kK3 induces polyubiquitylation and internalization of MHC class I molecules. kK3 associates with MHC class I molecules in a post-ER compartment. Initially, kK3 induces the recruitment of the E2 ligase ubiquitin-conjugating enzyme H5 (UBCH5), which adds the first ubiquitin moiety to the tail of the MHC class I heavy chain, and then induces the recruitment of UBC13, which elongates the ubiquitin chain with lysine 63 linkages. The modified MHC class I heavy chain is then endocytosed in an epsin 1-dependent manner. Epsin 1 recruits clathrin, promotes vesicle formation and binds polyubiquitin chains on substrates. The targeted MHC class I molecule is ultimately directed to multivesicular bodies and degraded in the lysosomes. This pathway establishes a paradigm for how MARCH (membrane-associated RING-CH) proteins regulate the expression of MHC class II molecules. Image is modified, with permission, from EMBO Journal Ref. 130

Citomegalovirus bloquea la respuesta antiviral….



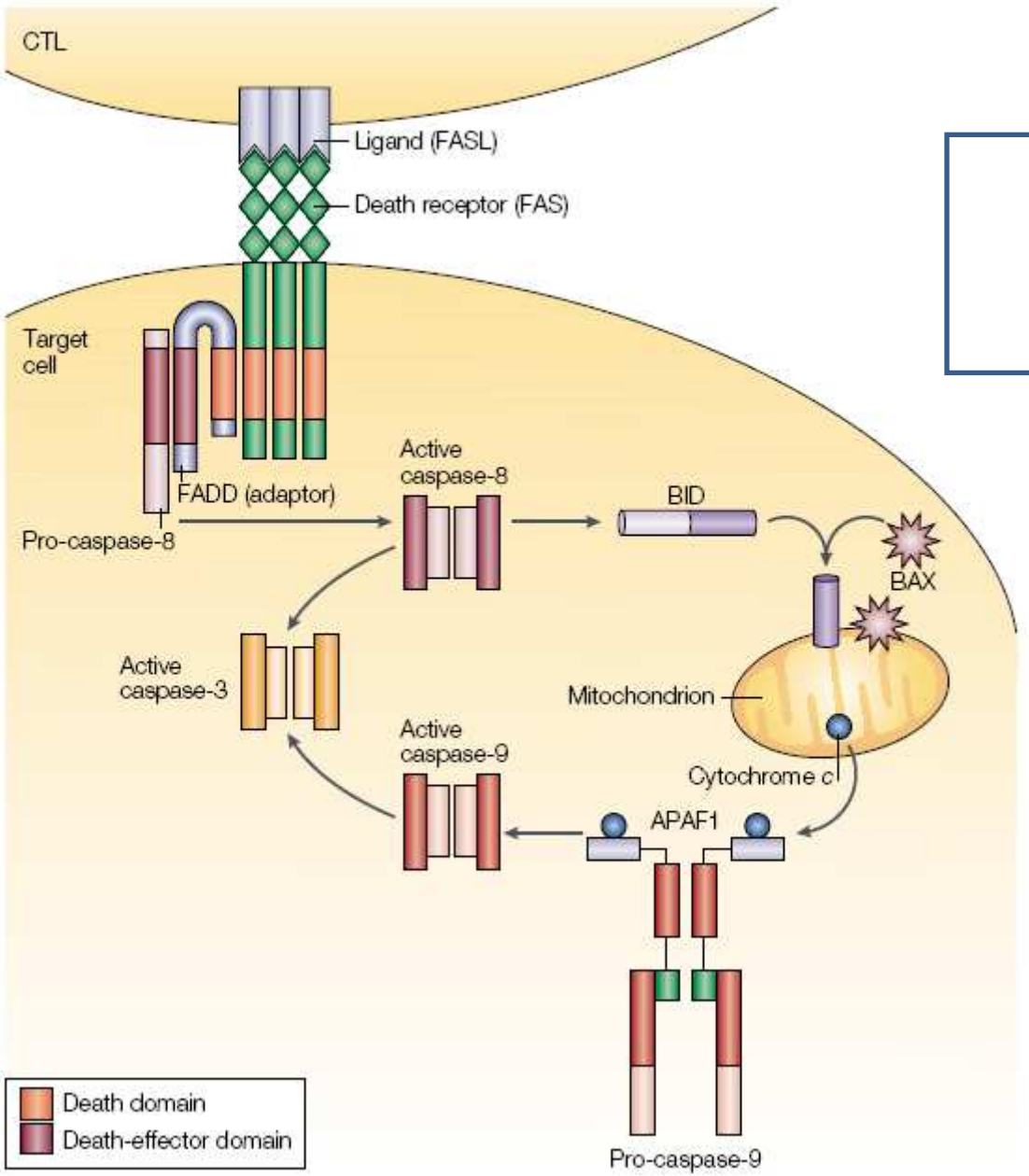
Inhibición de la apoptosis

a. Inhibición de receptores de muerte
b. Inhibición de caspasas
c. Homólogos de Bcl-2
d. Inhibidores de p53
e. Inhibidores de la apoptosis inducida por TNF
f. Inhibición del stress oxidativo

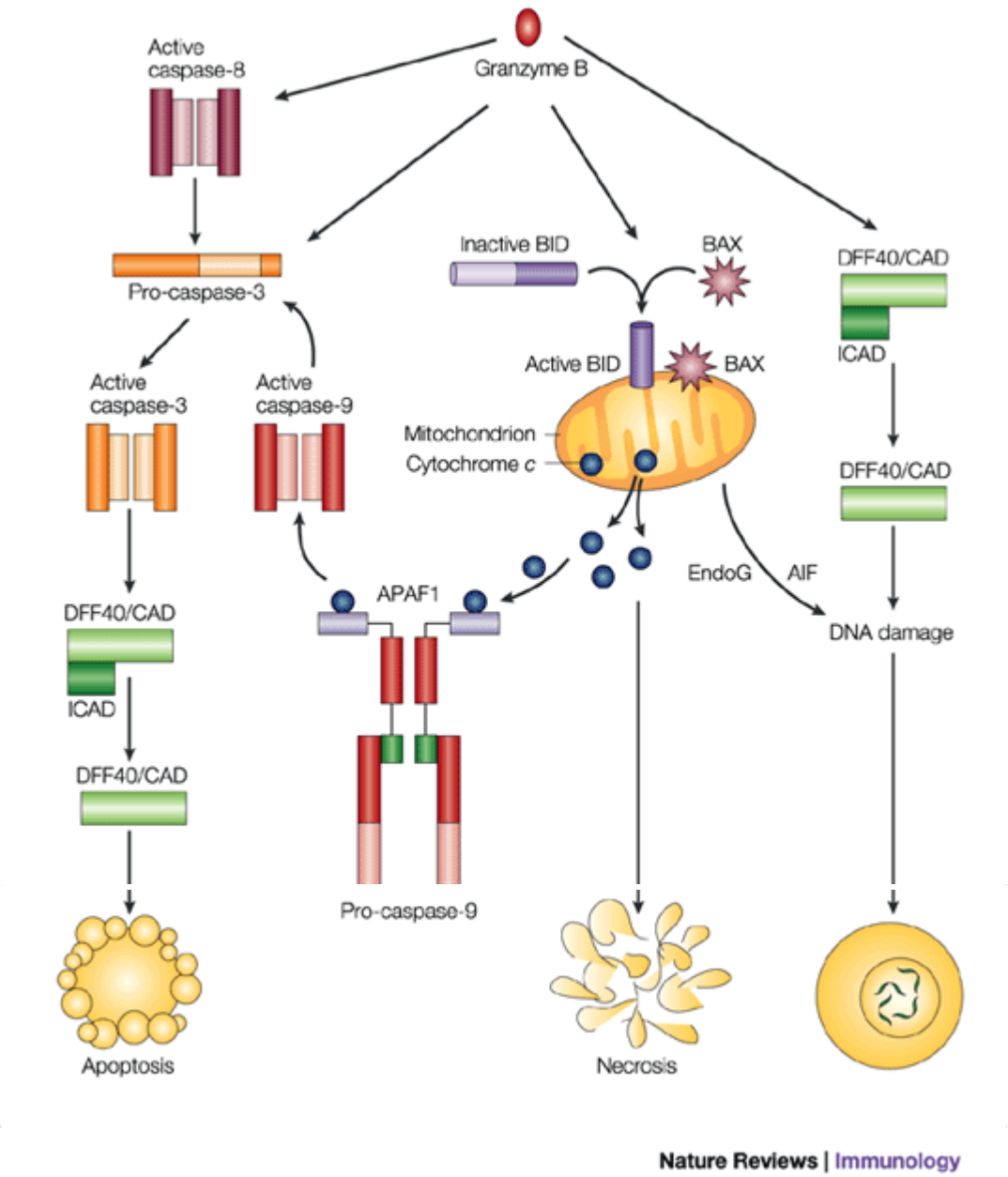
Viral Inhibition of Apoptosis

Cellular target/homolog	Viruses
Fas	adenovirus
death-domain receptors	HHV8, HVS, EHV-2, MCV, BHV4
caspases	cowpox, vaccinia, baculoviruses, adenovirus
Bcl-2 homologs	EBV, HHV8, AFSV, HVS, MHV, adenovirus
p53	adenovirus, SV40, HPV
transcription (inhibits TNF-induced apoptosis)	CMV, Marek's disease virus
oxidative stress	MCV

Inducción de APOPTOSIS

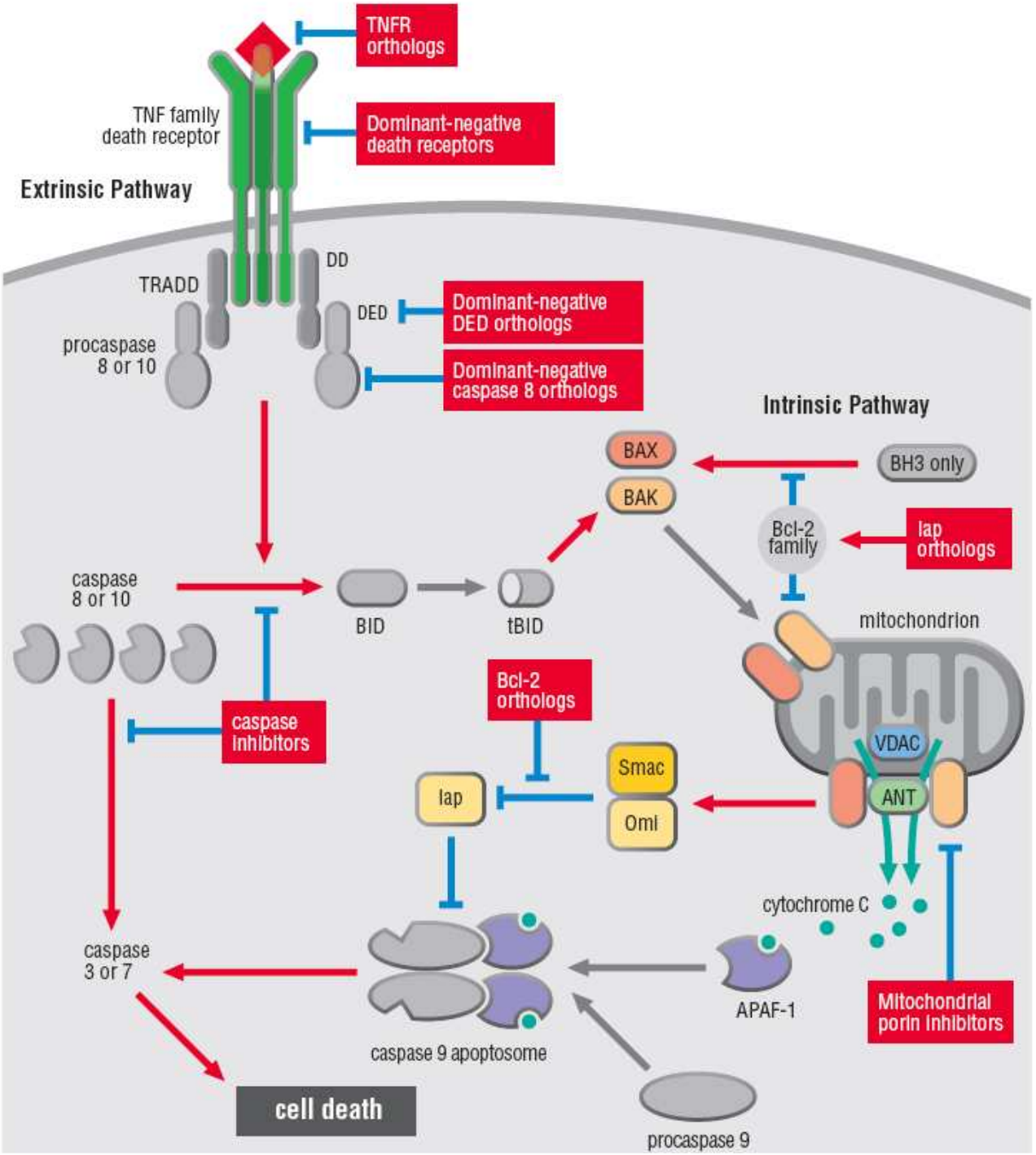


Nature Reviews Immunology 2, 401-409 (June 2002)



Once released into the cytoplasm, granzyme B can initiate apoptotic cell death through the direct cleavage of pro-caspase-3 or, indirectly, through caspase-8. In addition, cleavage of BID results in its translocation, with other members of the pro-apoptotic BCL2-family such as BAX, to the mitochondria. This prompts cytochrome c release and the activation of caspase-9 through interaction with the adaptor molecule apoptotic protease-activating factor 1 (APAF1). Alternatively, mitochondrial dysfunction can lead to necrotic death and the release of factors such as apoptosis-inducing factor (AIF) and endonuclease G (EndoG), which mediate caspase-independent cell death. Finally, studies have shown a direct activation of DFF40/CAD (DNA fragmentation 40/caspase-activated deoxynuclease) — which damages DNA and leads to cell death — by granzyme-B-mediated proteolysis of the inhibitor ICAD.

BLOQUEO de APOPTOSIS



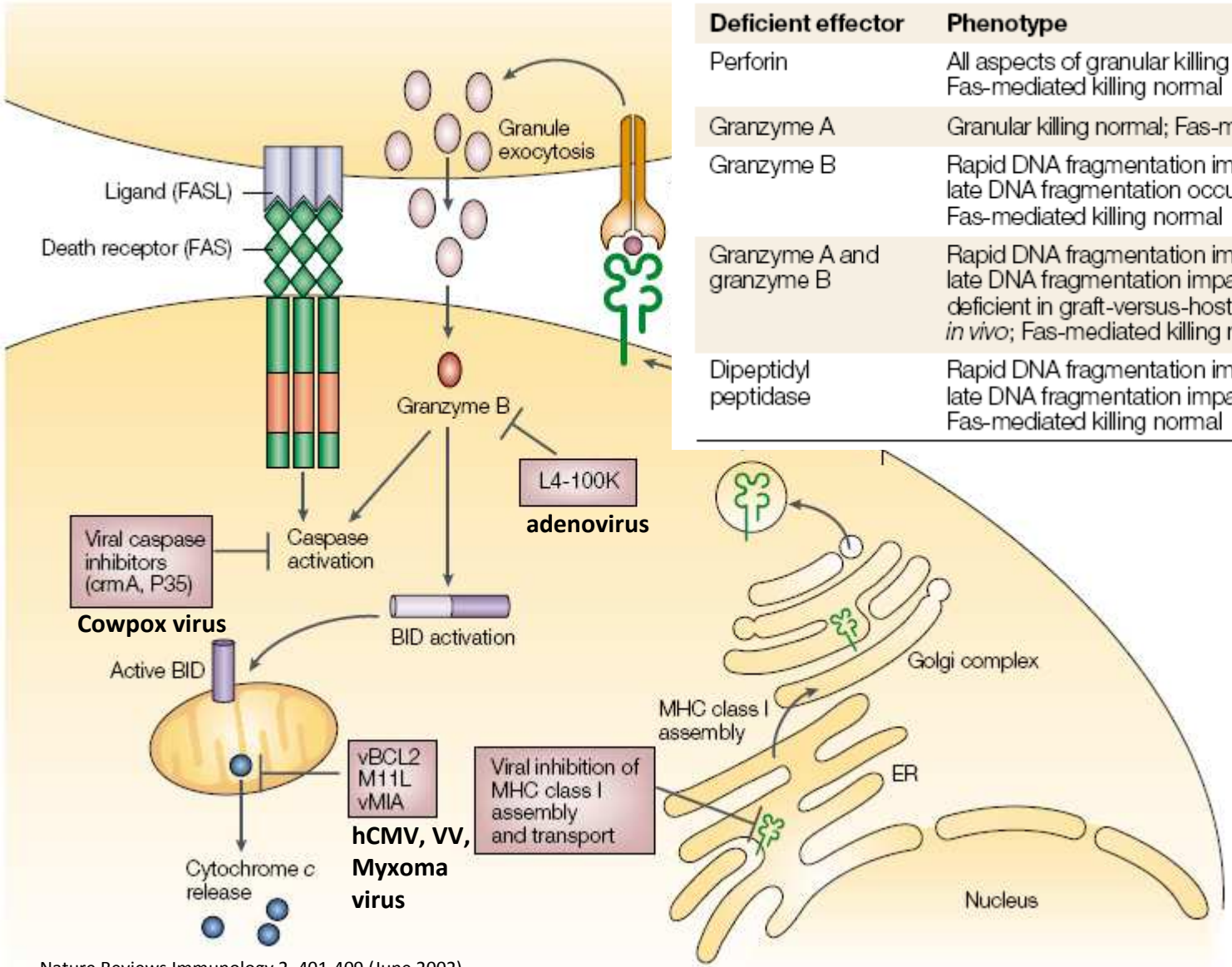


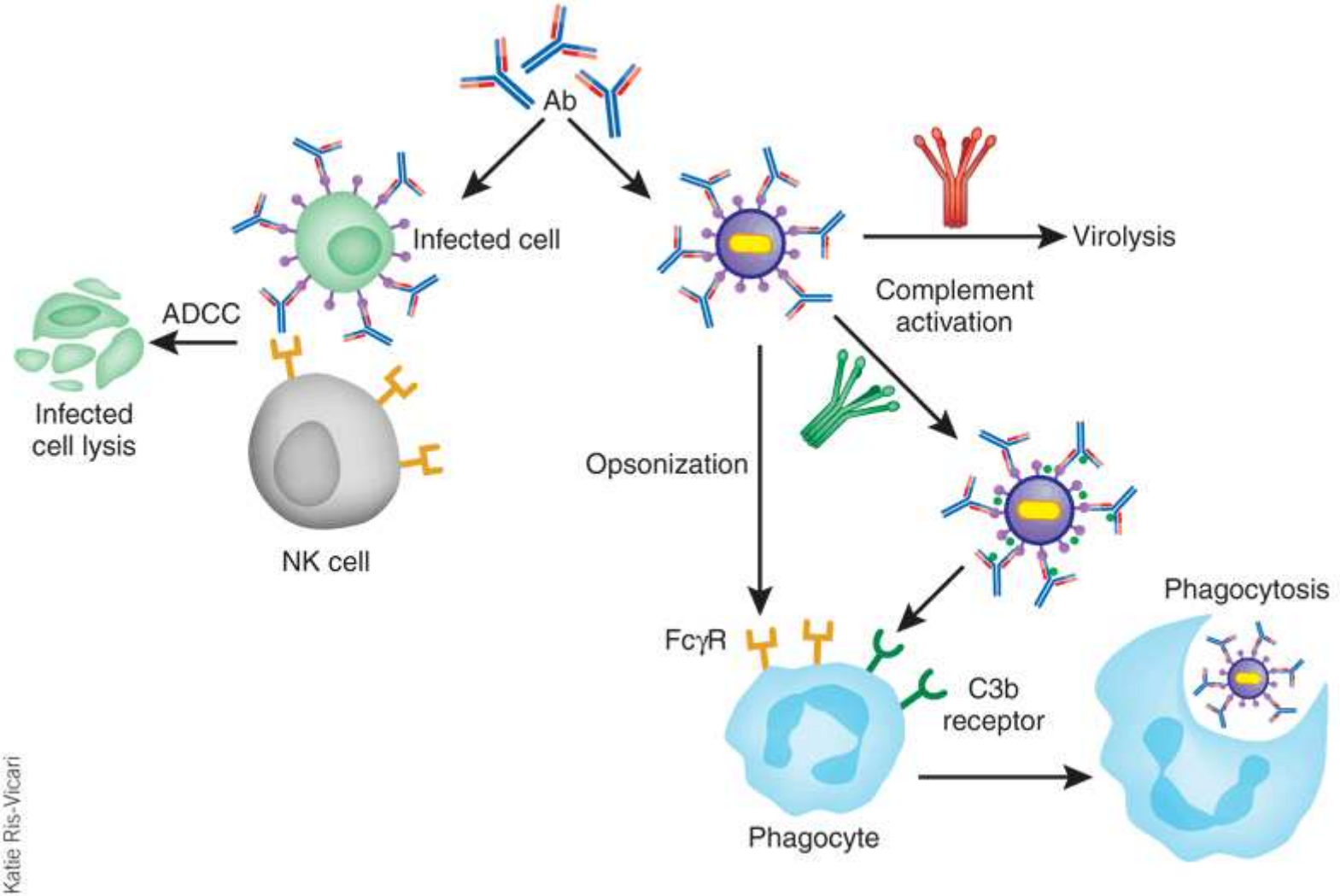
Table 2 | **Effector-deficient cytotoxic T cells**

Deficient effector	Phenotype
Perforin	All aspects of granular killing impaired; Fas-mediated killing normal
Granzyme A	Granular killing normal; Fas-mediated killing normal
Granzyme B	Rapid DNA fragmentation impaired; late DNA fragmentation occurs; Fas-mediated killing normal
Granzyme A and granzyme B	Rapid DNA fragmentation impaired; late DNA fragmentation impaired; deficient in graft-versus-host disease *in vivo*; Fas-mediated killing normal
Dipeptidyl peptidase	Rapid DNA fragmentation impaired; late DNA fragmentation impaired; Fas-mediated killing normal

Nature Reviews Immunology 2, 401-409 (June 2002)

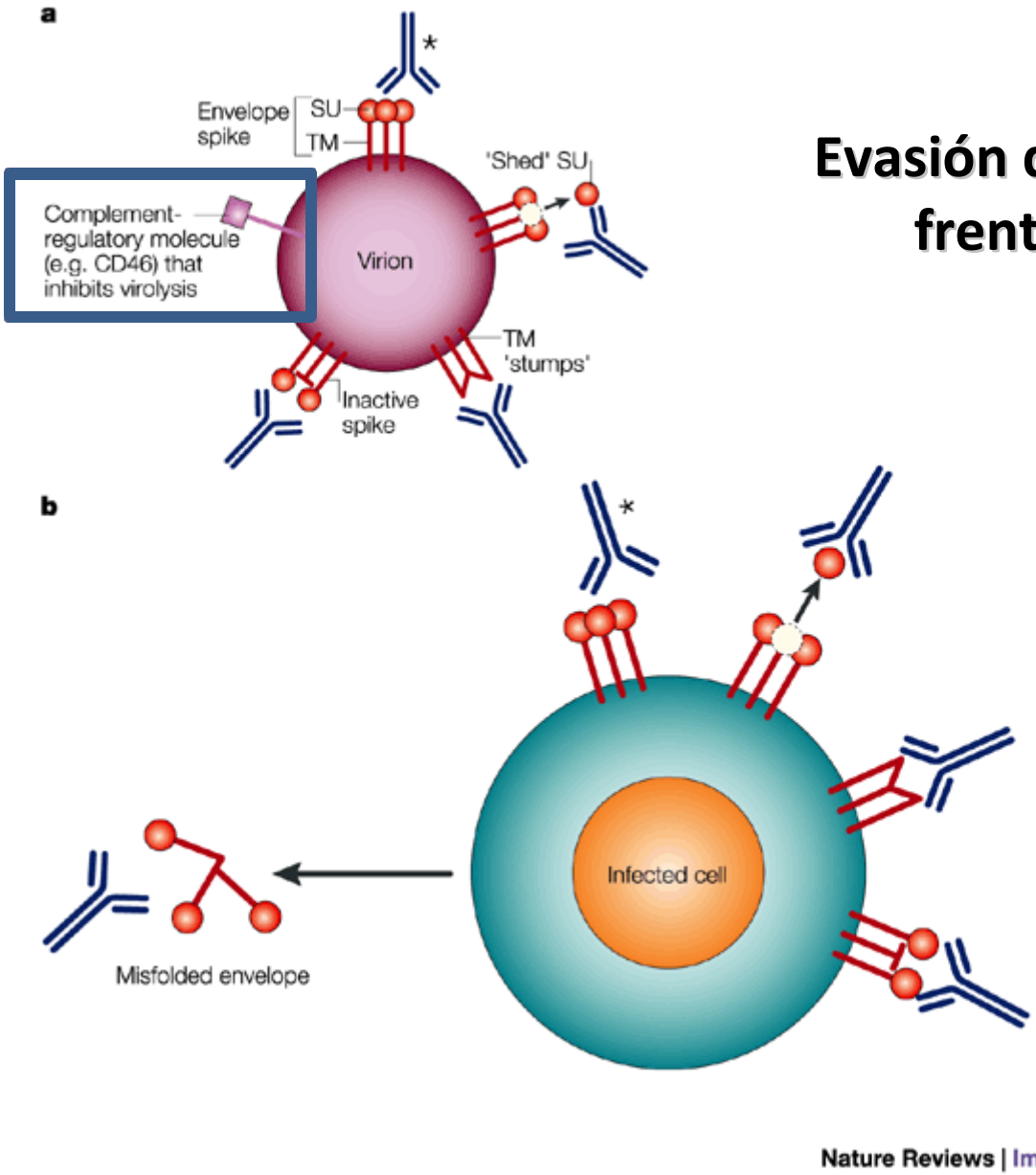
- **Viruses can inhibit CTL-mediated apoptosis and necrosis by interfering with the expression of cell-surface MHC class I molecules. This can occur by means of the endocytosis of cell-surface MHC class I, retention and degradation of MHC class I in the endoplasmic reticulum (ER), or the modulation of the transporter for antigen processing that is necessary for the transport of viral peptides into the ER.** Virus-encoded caspase inhibitors, such as crmA and P35, inhibit apoptosis by blocking caspase activity. In addition, virus-encoded BCL2-like proteins (vBCL2) and novel mitochondria-localized proteins, such as M11L from myxoma virus and the immediate-early glycoprotein UL37 (vMIA) from human cytomegalovirus, also inhibit apoptosis by blocking the release of cytochrome c from the mitochondria. The L4-100K protein of adenovirus inhibits granzyme B directly. CTL, cytotoxic T lymphocyte; TCR, T-cell receptor.

ROL DE LOS ANTICUERPOS NEUTRALIZANTES



Nature Biotechnology 25, 1421 - 1434 (2007)

Evasión de la respuesta inmune frente a los anticuerpos neutralizantes



Nature Reviews | Immunology

Mecanismos de evasión de la respuesta inmune por Virus

Mecanismo de Evasión Respuesta Inmune	Ejemplo
Variación génica.	Influenza, HIV, HVC
Inhibición del procesamiento del antígeno: •Inhibición del transportador TAP •Bloqueo de MHC-I	Herpes virus, Citomegalovirus.
Inhibición de la apoptosis.	Poxvirus.
Producción de homólogos de citoquinas, quimioquinas o sus receptores.	Poxvirus (IL-1, INF-γ), herpesvirus, citomegalovirus (quimiocina)
Síntesis de citoquinas inmunosupresoras	Virus de Epstein Barr (IL-10)
Infección de células inmunocompetentes	HIV
Bloqueo de anticuerpos neutralizantes	Dengue virus

"El verdadero optimista está consciente de los problemas, pero reconoce las soluciones; sabe de las dificultades, pero cree que pueden superarse; ve lo negativo pero acentúa lo positivo; está expuesto a lo peor, pero espera lo mejor; tiene razón para quejarse, pero prefiere sonreír."

Willian A. Ward

SEA PERSEVERANTE

"El valor de la perseverancia es parte del perfil de formación de nuestra gente". **Eduardo Echeverry q.e.p.d**