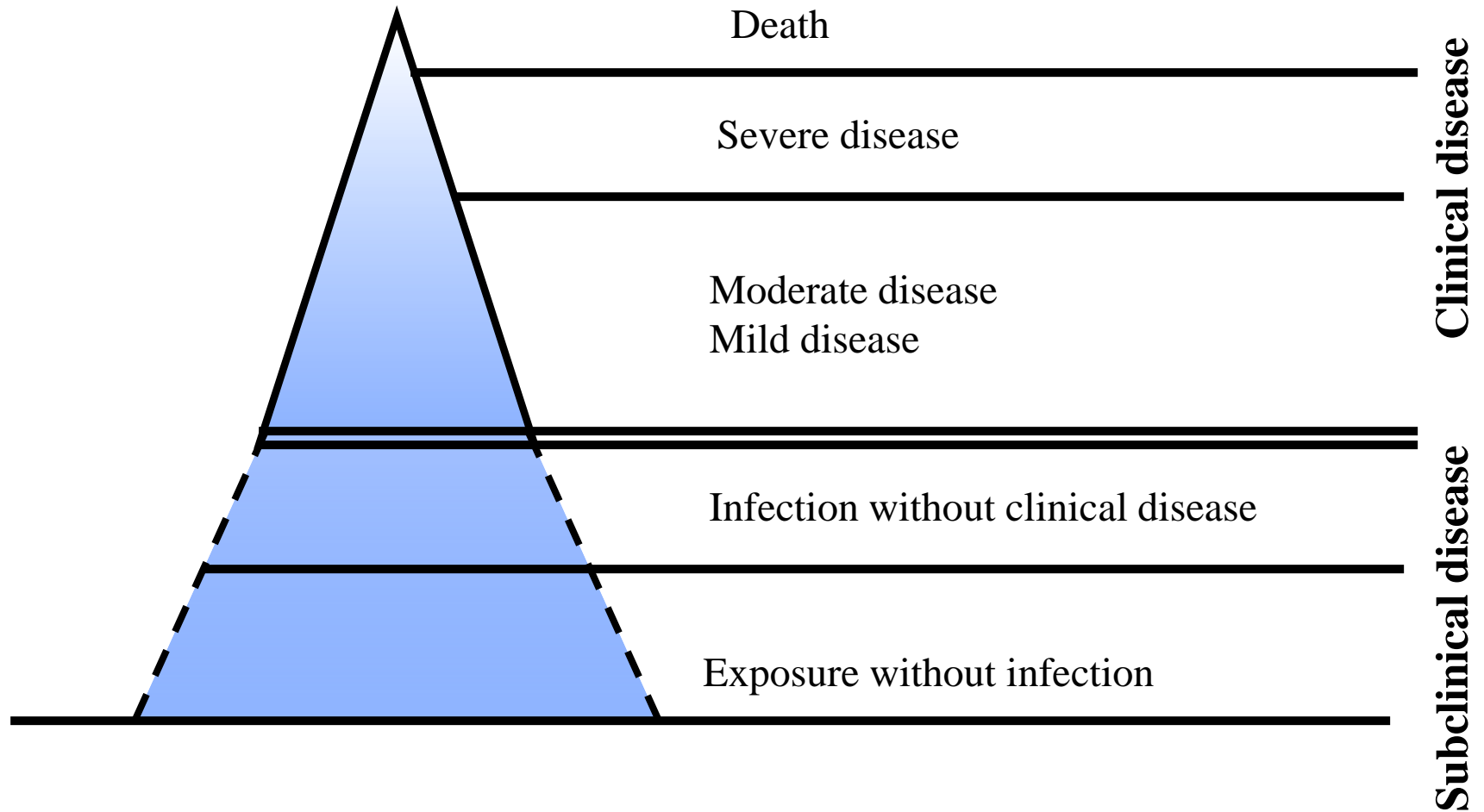
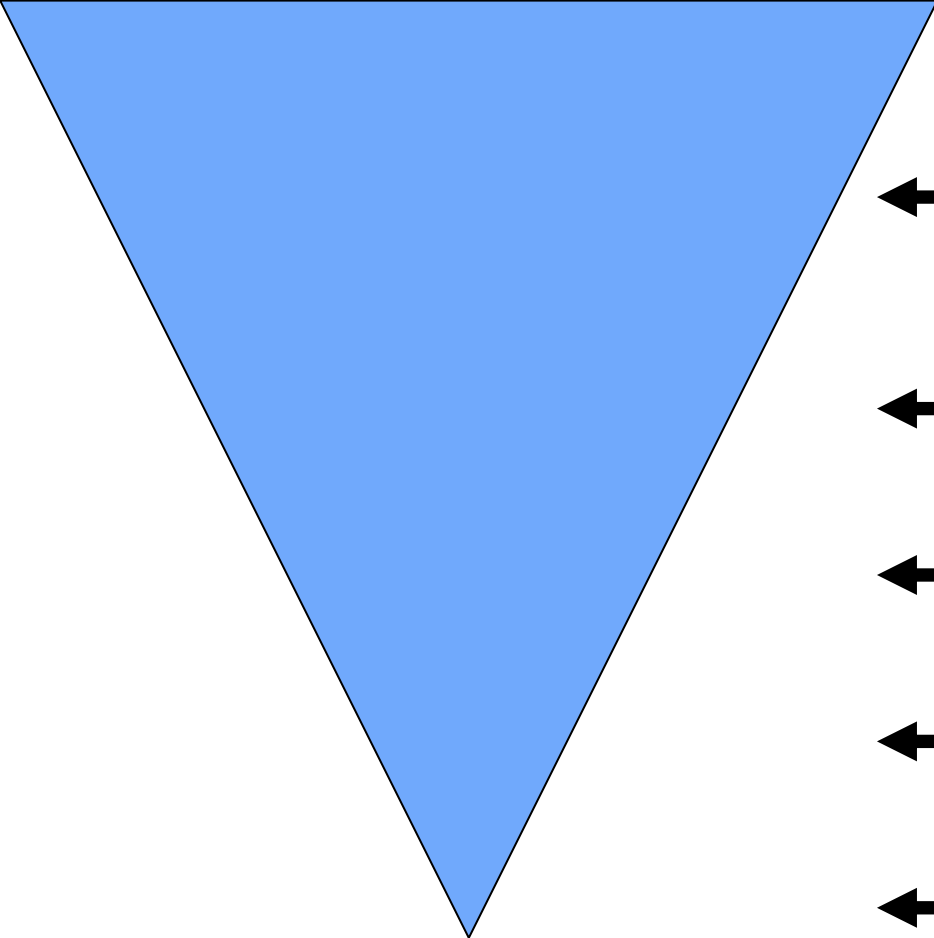


ICEBERG CONCEPT OF INFECTIOUS DISEASES



Number of cases



Host death

Severe disease

Mild disease

Infection without clinical disease

Exposure without infection

DEFENSE MECHANISMS



INNATE IMMUNITY

ADAPTIVE IMMUNITY



PRE-EXISTING

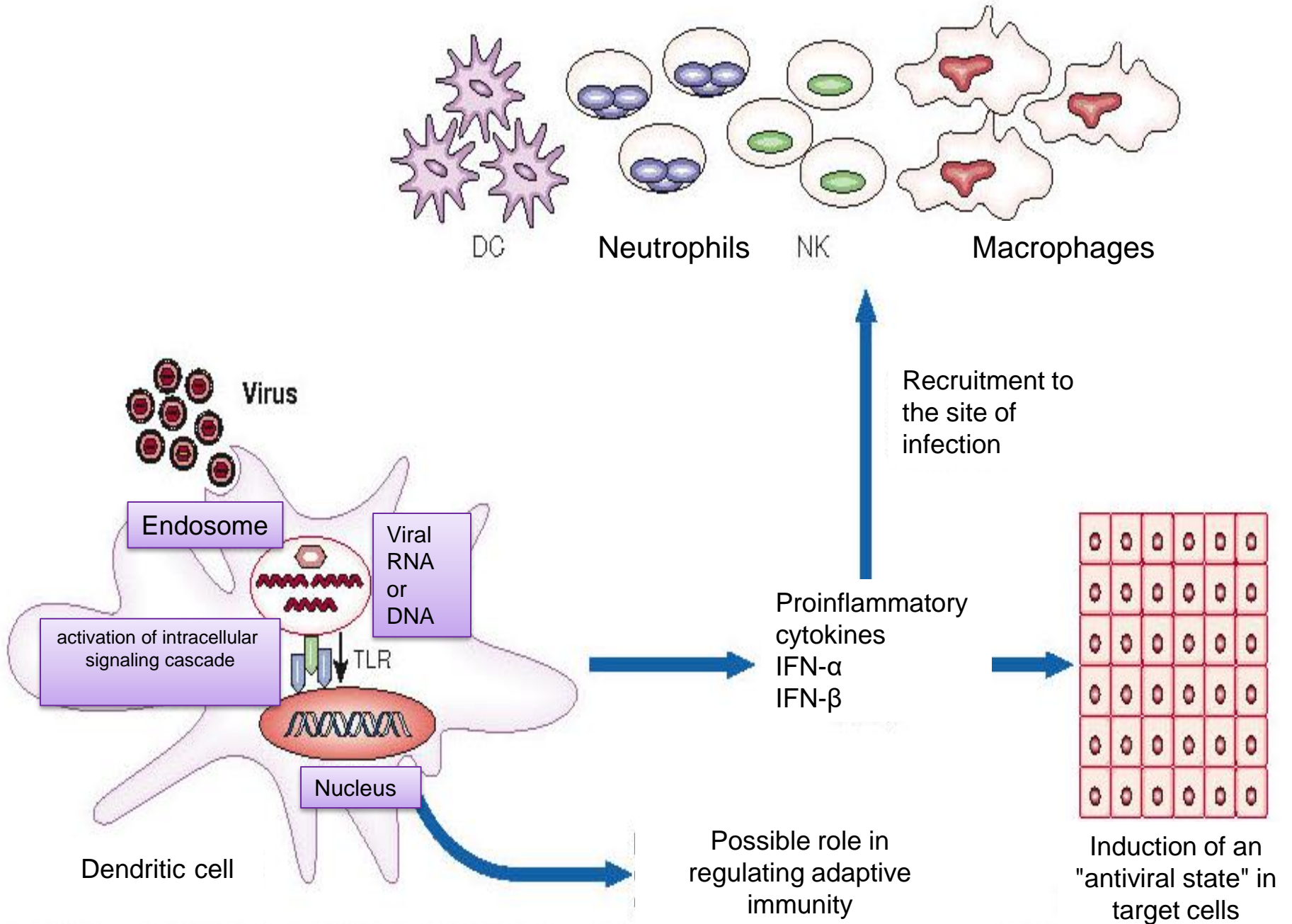
INDUCED

PRE-EXISTING DEFENSE MECHANISMS

- **Mechanical barriers**
- **Nonspecific inhibitors**
- **Phagocytosis**
- **Cytotoxicity**

INDUCED DEFENSE MECHANISMS

- Fever: inhibition of viral replication
- Inflammation:
 - reduced oxygen tension
 - increase in CO₂ concentration
 - high temperature
 - increased organic acid concentrations (↓ pH)
- Viral interference and interferon



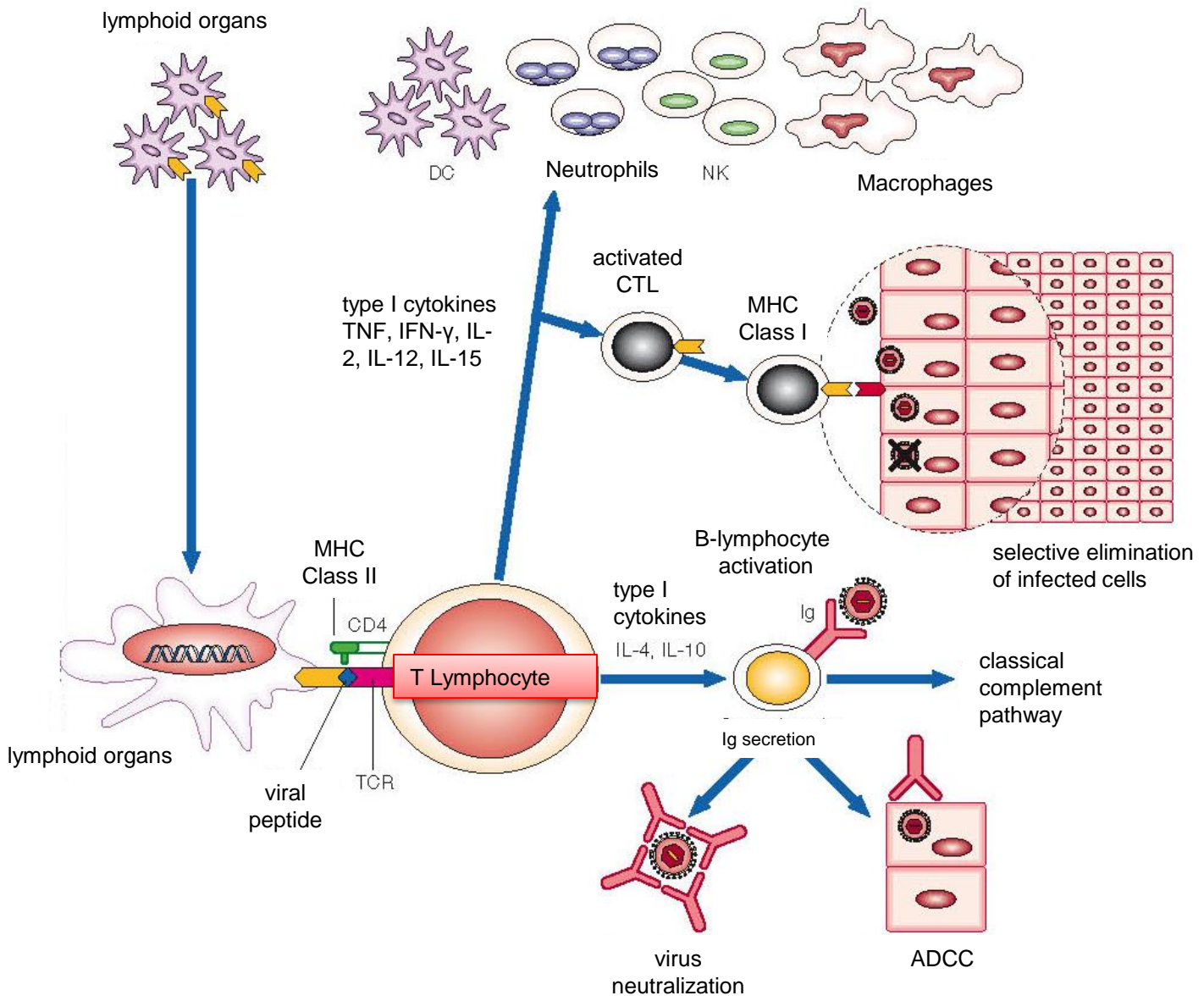
Pattern recognition receptors (PRR) and pathogen-associated molecular patterns (PAMP) involved in innate immune response during viral infection

Family	PRR	PAMP	Effect
Toll-like receptors (TLR)	TLR 2	bacterial and viral DNA	secretion of proinflammatory mediators
	TLR3	viral dsRNA	activation of dendritic cells and macrophages with consequent secretion of proinflammatory mediators
	TLR 7	viral ssRNA	activation of dendritic cells and macrophages with consequent secretion of proinflammatory mediators
	TLR 8	viral ssRNA	activation of dendritic cells and macrophages with consequent secretion of proinflammatory mediators
	TLR 9	bacterial and viral DNA	activation of dendritic cells and macrophages with consequent secretion of proinflammatory mediators
RIG-1-like receptors (RLR)	RIG-1	viral dsRNA	secretion of proinflammatory mediators
	MDA5	viral dsRNA	secretion of proinflammatory mediators
	LGP2	viral dsRNA	secretion of proinflammatory mediators
DNA sensor	DAI	bacterial and viral DNA	secretion of proinflammatory mediators

SPECIFIC DEFENSE MECHANISMS (ADAPTIVE IMMUNITY)

❖ **HUMORAL RESPONSE**

❖ **CELL-MEDIATED RESPONSE**



SPECIFIC IMMUNE RESPONSES

They lead to:

- **Virus removal from body fluids**
- **Destruction of virus-infected cells**
- **Protection of uninfected cells from infection**

SPECIFIC IMMUNE RESPONSES

They lead to:

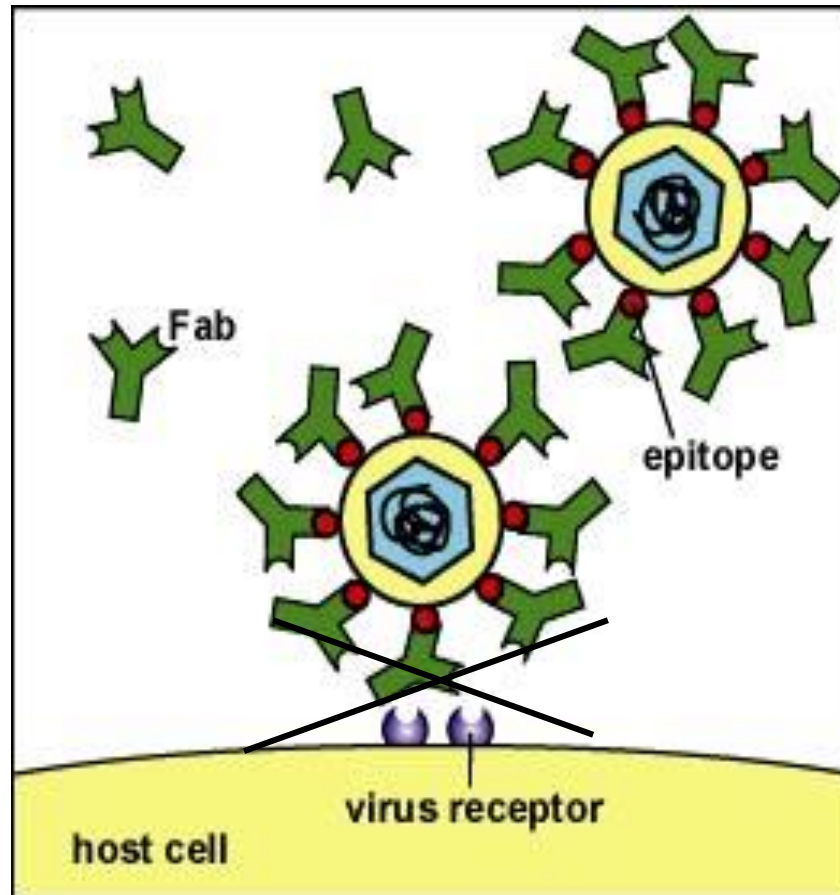
- **Virus removal from body fluids**
- **Destruction of virus-infected cells**
- **Protection of uninfected cells from infection**

Pathology in viral infections is often mediated by the immune response - immunopathology

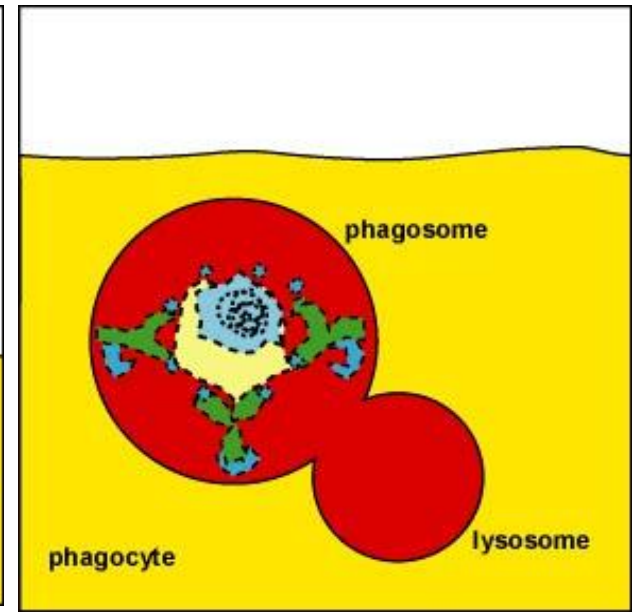
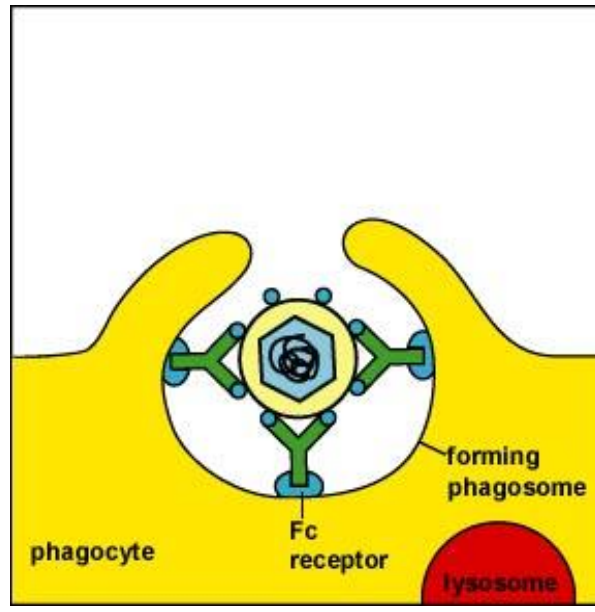
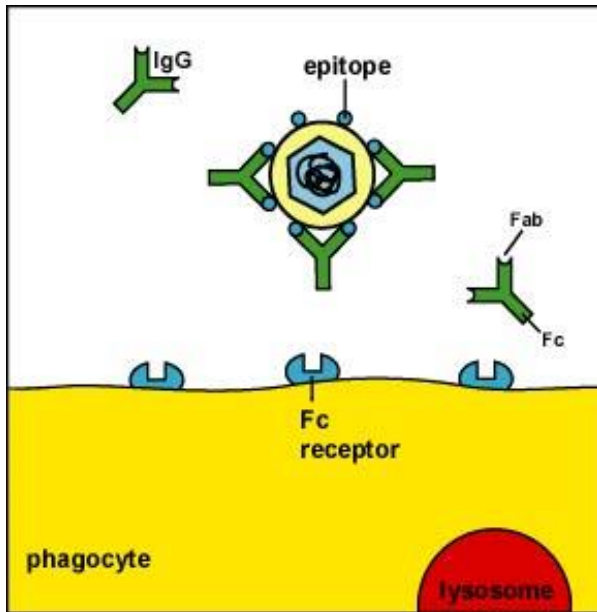
How antibodies prevent the spread of the virus

- ✓ **Neutralization of virus infectivity**
- ✓ **Virus aggregation**
- ✓ **Complement fixation:**
 - **lysis of virus**
 - **lysis of infected cells**
- ✓ **Elimination of infected cells (ADCC, complement, Cytotoxic T Lymphocytes)**

Virus neutralization by neutralizing antibodies



Virus removal by phagocytosis



Removal of virus-infected cells by:

- 1) ANTIBODIES
- 2) CTL
- 3) NK

Protection of uninfected cells from infection

1. Neutralizing antibodies against viruses
2. Interferons

VIRUSES ESCAPE HOST RESPONSES

**Some viruses can establish infection in sites
not accessible to the immune system**

(eg: HSV, Papillomavirus)

VIRUSES ESCAPE HOST RESPONSES

- **Restricted pattern of viral gene expression (latency)**
Herpesvirus in the dorsal root ganglion
- **Mutation**
HIV, Influenza A virus
- **Immune escape through “masking strategies”**
Paramixovirus, picornavirus

VIRUSES ESCAPE HOST RESPONSES

- Viruses can directly or indirectly inhibit host defenses

Downregulation of surface molecules required for T cell recognition

MHC I: Adeno, CMV, HSV, HIV;

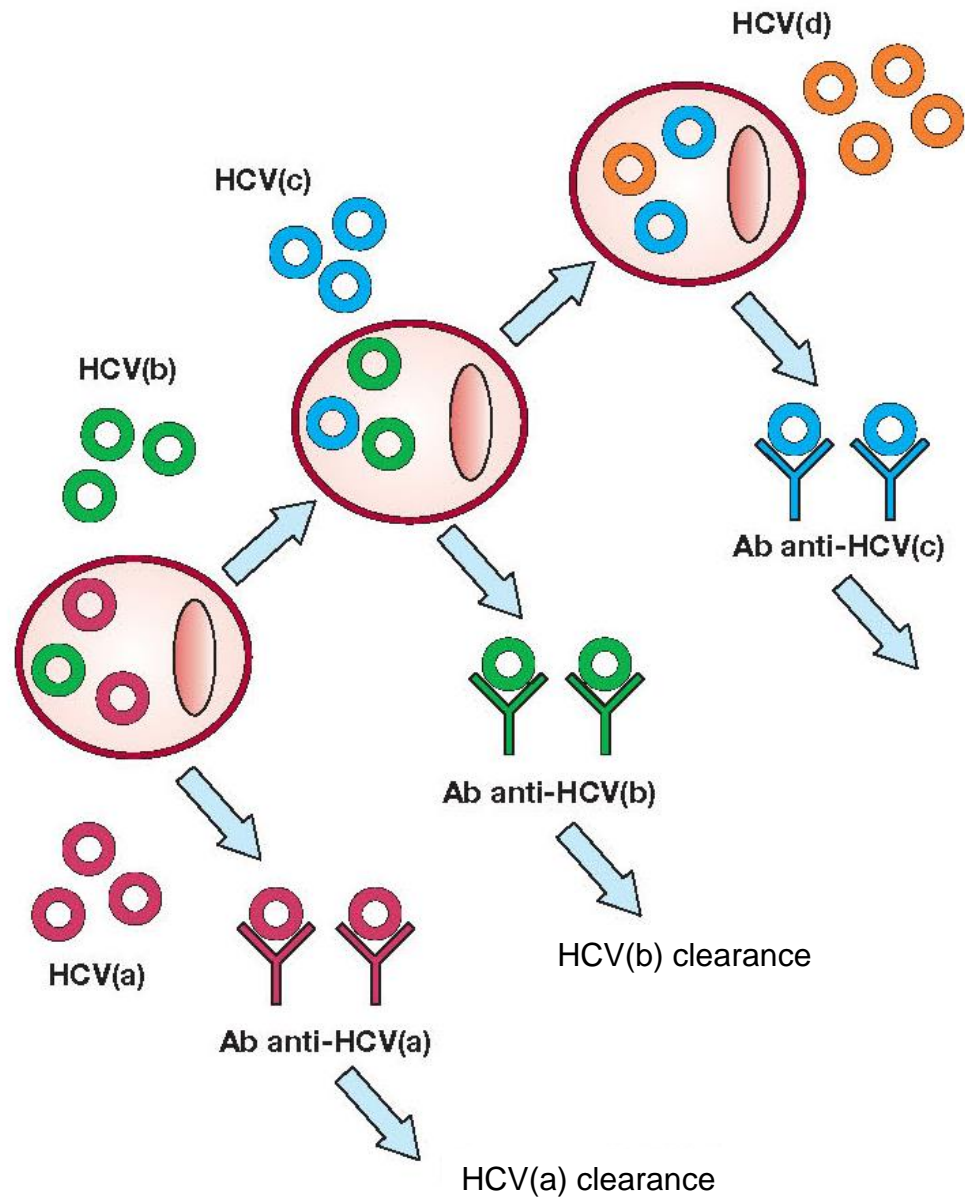
MHC II: CMV, HIV, Measles;

ICAM 1: EBV

Interference with endogenous antigen processing

Adeno/retain MHC I in the ER;

HSV blocks transport of viral peptides into ER

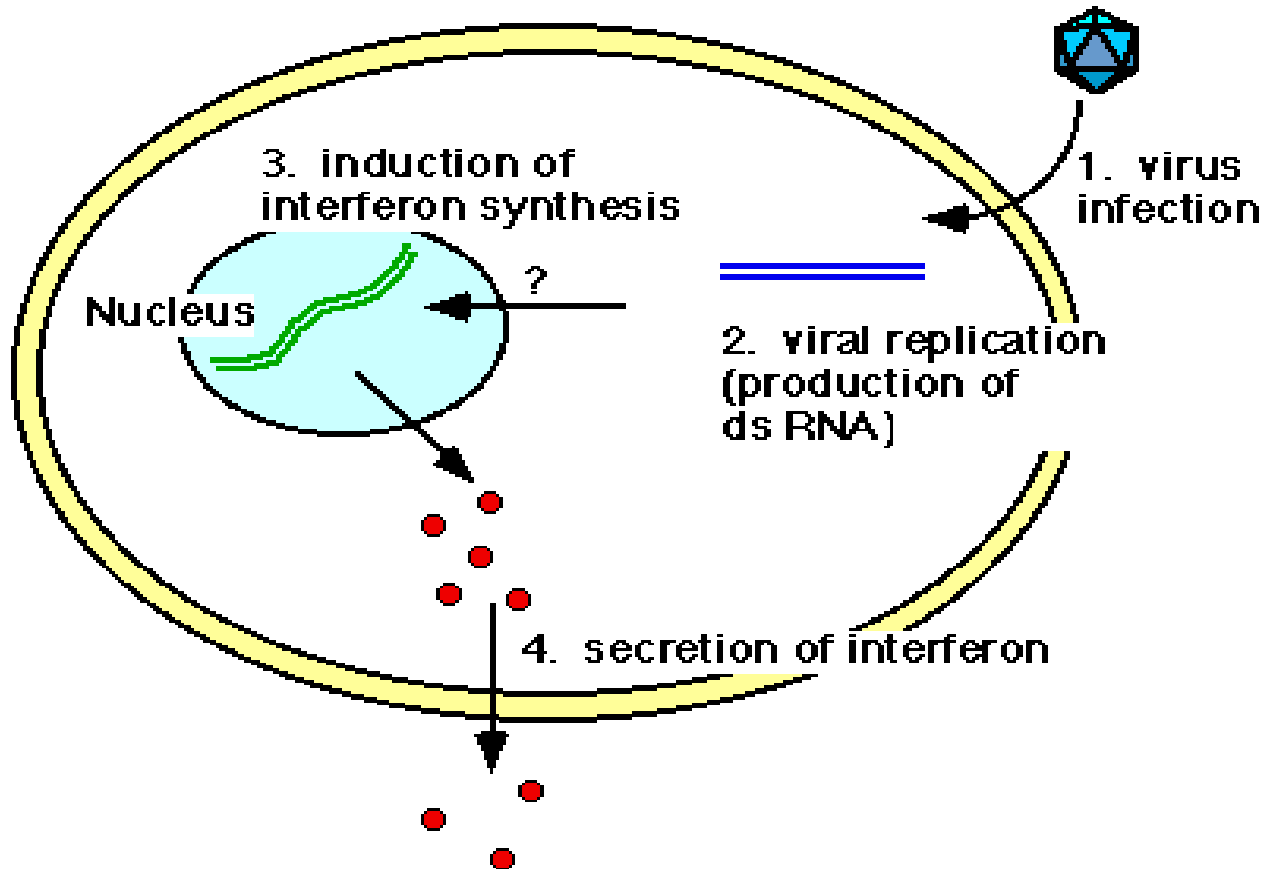


INTERFERONS

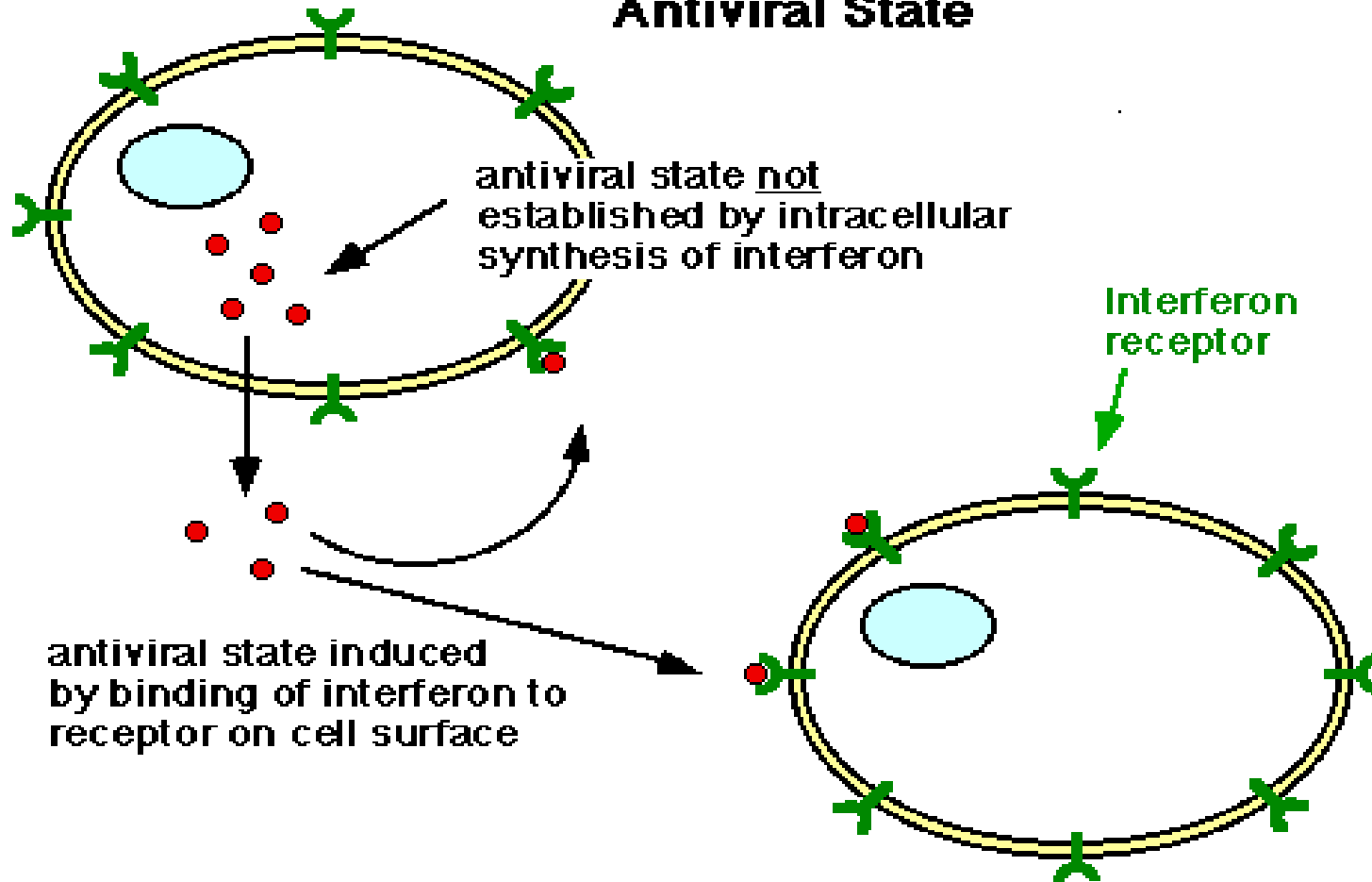
characteristics of human interferons

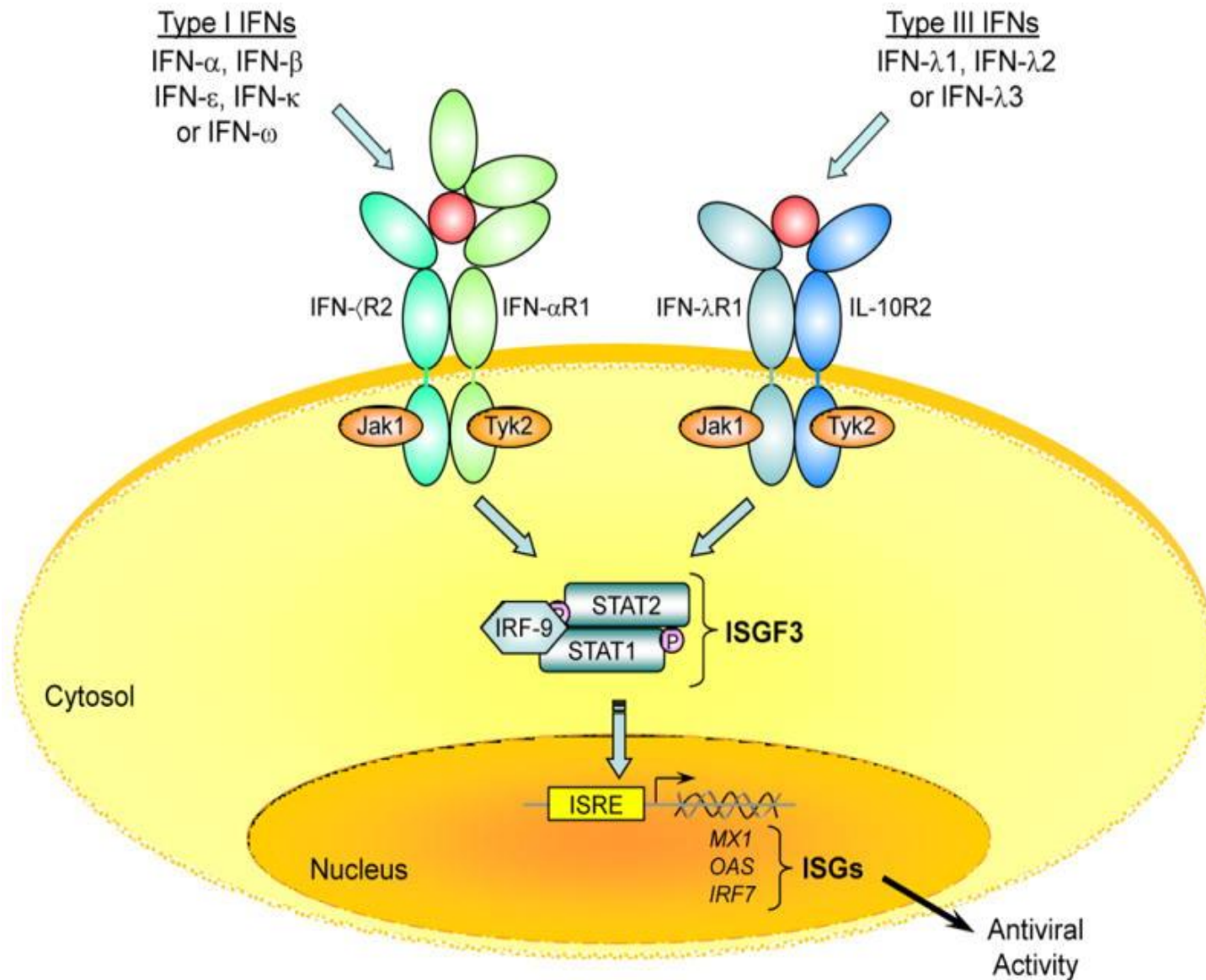
Type	Subtype	Receptor	chromosomal location	number of amino acids	Molecular weight (kilodalton)	Gene expression
I	IFN- α	IFNR-1/IFNR2	9p21	165-166	15-23	ubiquitous
	IFN- β	IFNR-1/IFNR2	9p21	166	15-23	ubiquitous
	IFN- ϵ	IFNR-1/IFNR2	9p21	208	24.4	uterus, ovaries
	IFN- κ	IFNR-1/IFNR2	9p21	180	24.5	epidermal keratinocytes
	IFN- ω	IFNR-1/IFNR2	9p21	172	20-23	leukocytes
II	IFN- γ	IFNGR-1/IFNR2	12q24.1	146	34	lymphocytes T, NK cells
III	IFN- λ 1	IL-28R α /IL-10R β	19q13.13	200	20-33	ubiquitous
	IFN- λ 2	IL-28R α /IL-10R β	19q13.13	200	22	ubiquitous
	IFN- λ 3	IL-28R α /IL-10R β	19q13.13	196	22	ubiquitous

Induction of interferons

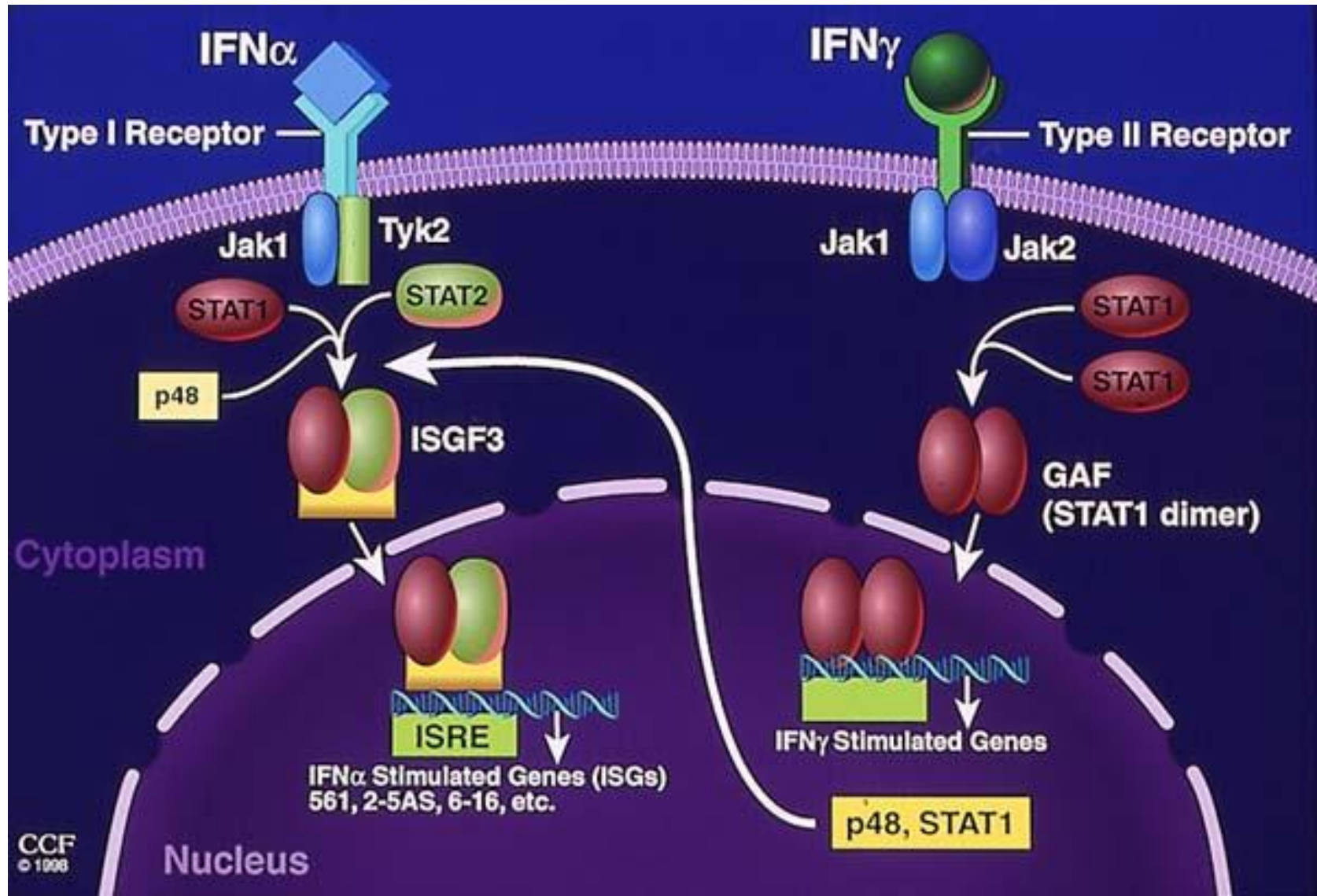


Induction of the Antiviral State





SIGNAL TRANSDUCTION PATHWAY OF IFNs



SPECIFIC AND NON SPECIFIC DEFENSE MECHANISMS ENHANCED BY INTERFERON

- **Production of antibodies**
- **Cell-mediated immune response**
- **Expression of surface molecules in lymphocytes and other cells**
- **Phagocytosis**
- **NK activity**

MECHANISMS TO ESCAPE THE IFN SYSTEM	VIRUS
Inhibition of IFN synthesis	Influenza A and B virus, Ebola virus, herpes simplex virus, adenovirus, hepatitis C virus, SARS-coronavirus, reovirus, papillomavirus 16, herpesvirus 8, poxvirus
Inhibition of toll like receptors signaling	Hepatitis C virus, hepatitis C virus
Inhibition of RIG-1 and Mda-5 signaling	Hepatitis C virus, paramixovirus
Synthesis of IFN receptor homologs	Poxvirus
Inhibition of IFN signaling	Adenovirus, Ebola virus, Epstein-Barr virus, hepatitis C virus, citomegalovirus, parainfluenza virus 1 and 2, papillomavirus 16, Influenza A and B virus, Dengue virus
Inhibition of IFN –induced proteins: PKR 2'-5'oligoadenylate synthetase/RNase L Mx	Hepatitis C virus, Influenza A virus, reovirus, rotavirus, herpes simplex virus, herpesvirus 8, HIV, adenovirus, Epstein-Barr virus, poliovirus, vaccinia virus, papillomavirus Reovirus, rotavirus, HIV, herpes simplex virus, vaccinia virus, Influenza A virus Hepatitis B virus