

Immune response

Introduction

- Immune response refers to the highly coordinated reactions of the cells of immune system and their products.
- It has two arms:
 - 1) Humoral immune response (antibody mediated immune response)
 - 2) Cell mediated immune response

Cell mediated immune response

Introduction

- Cell-mediated immunity is an immune response that refers to destruction of cells carrying intracellular microbes and other abnormal cells by various specific and non specific cells of immune system

Effector cells of CMI

- Antigen specific :- cytotoxic T cells
- Antigen non-specific :- Nk cells, Macrophages, Neutrophil, Eosinophil

T Cell Activation and Differentiation

- Helper T cell (T_H) activation and differentiation is the key event in immune response

❖ **Activation:** two specific signals

1. Antigen specific signal: Antigen peptide present in MHC-II on antigen presenting cells(APC) binds to TCR present on surface of T_H cells. CD4 molecules interact with Major histocompatibility(MHC)MHC-II

2. Co-stimulatory signal: CD28 molecules binds with B7 molecules on APCs. APCs secrete interleukin-1 which acts on T_H cells

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Signal Transduction

Following induction of signal, its transmission is essential for T_H cell activation. Signal transduction is initiated at CD4 molecule which interacts with CD3 complex, which in turn transmit the signal leading to activation of T_H cells.

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❖ Differentiation

- Activated T_H cells secrete IL-2 which binds to the receptor on same T_H cell and also on other T_H cells
- This induces the naive T cells to proliferate and differentiate
- T_H cells are activated and subsequently differentiate into memory and effector T_H cells

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❖ **Effector T_H cells**

- Derived from naive T_H cells or memory T_H cells following antigenic stimulus
- They differentiate into either
 - 1) TH1(mediates CMI) or
 - 2) TH2 subset(mediates AMI)

Induction of CMI

- Presentation of antigen by Antigen Presenting Cells (APCs) to T lymphocytes
- Recognition of antigen by T cells and activation
- Release of cytokines by T lymphocytes

Presentation of Antigens

For induction of immune responses, recognition of antigens by T cells is essential

1. **Cytosolic pathway:** Here, the endogenous (intracellular) antigens such as viral antigens and tumor antigens are processed and presented along with MHC class I molecules to CD8 T cells.
2. **Endocytic pathway:** In this pathway, the exogenous antigens (extracellular microbes and their products, e.g. toxins) are processed and complexed with MHC class II molecules and presented to T_H cells. The cells involved in endocytic pathway include the APCs such as macrophages, dendritic cells and B cells.

Recognition of antigen by Tcells and activation of Tc

❖ Tcells recognize antigens when presented with MHC molecules

- CD8 cells : antigen + MHC-I
- CD4 cells : antigen + MHC-II

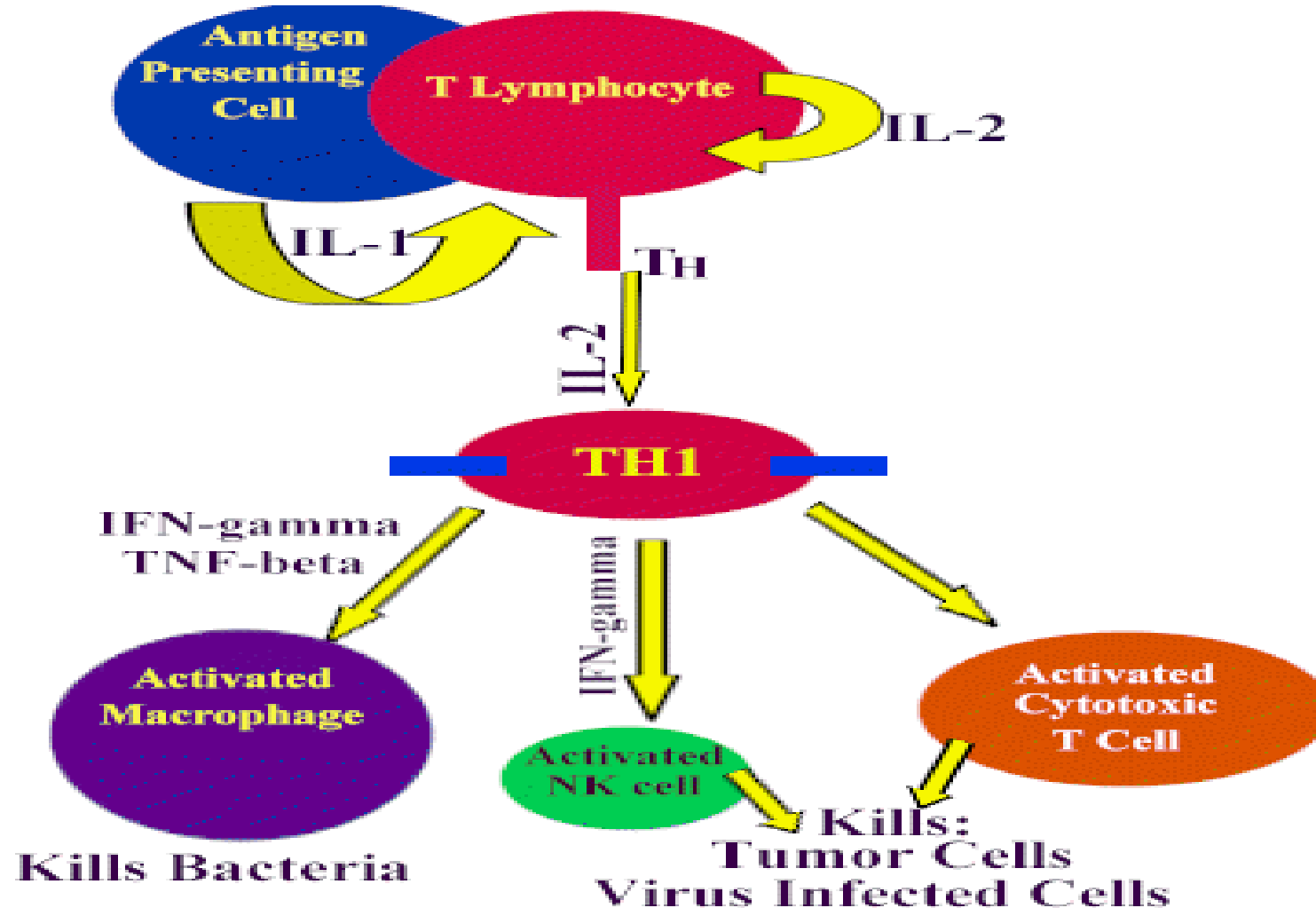
CD8 cytotoxic T lymphocytes (CTL or Tc) are principal effector cells of CMI.

❖ Activation of Tc:

1. Antigen-specific signal: TCR-CD3 complex of naive Tc cells bind to MHC I-peptide complex of target cells. CD8 also interacts with MHC-I
2. Co-stimulatory signal: CD28 of naive Tc cells interacts with target cells
3. Third signal: IL-2 acts on Tc cells

❖ Signal transduction

Release of cytokines by Tc lymphocytes



Functions of CTL

Activated Tc cells produce lethal enzymes

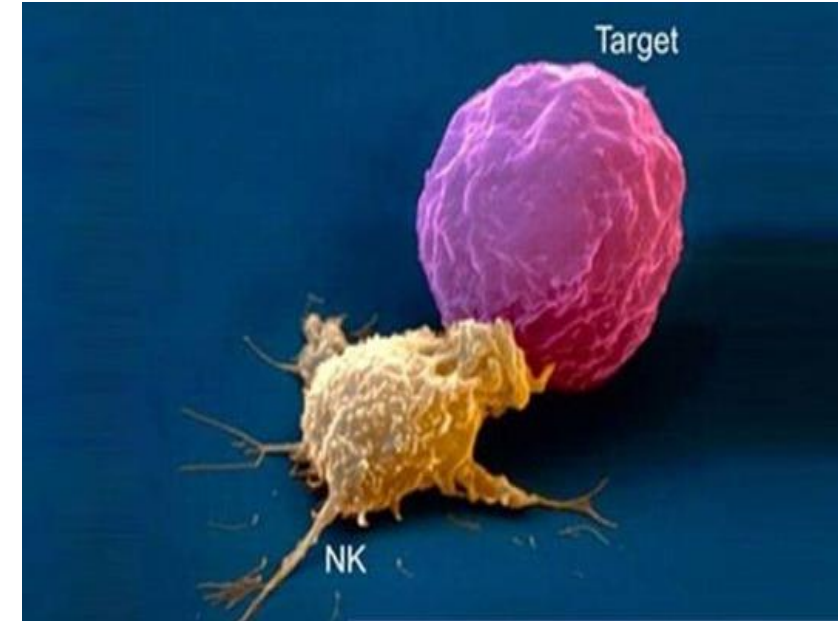
- **Perforins**:- produce pores in target cell membrane
- **Granzymes**:- induce cell death by apoptosis

NK Cell-Medicated Cytotoxicity

Natural Killer (NK) cells

- are large granular lymphocytes
- cytotoxic but antigen non-specific
- act against virus infected cells and tumor cells
- lack T cell markers

Mediates ADCC



Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)

Cytotoxic cells bind to antibody coated cells with Fc receptor (FcγRIIIA)



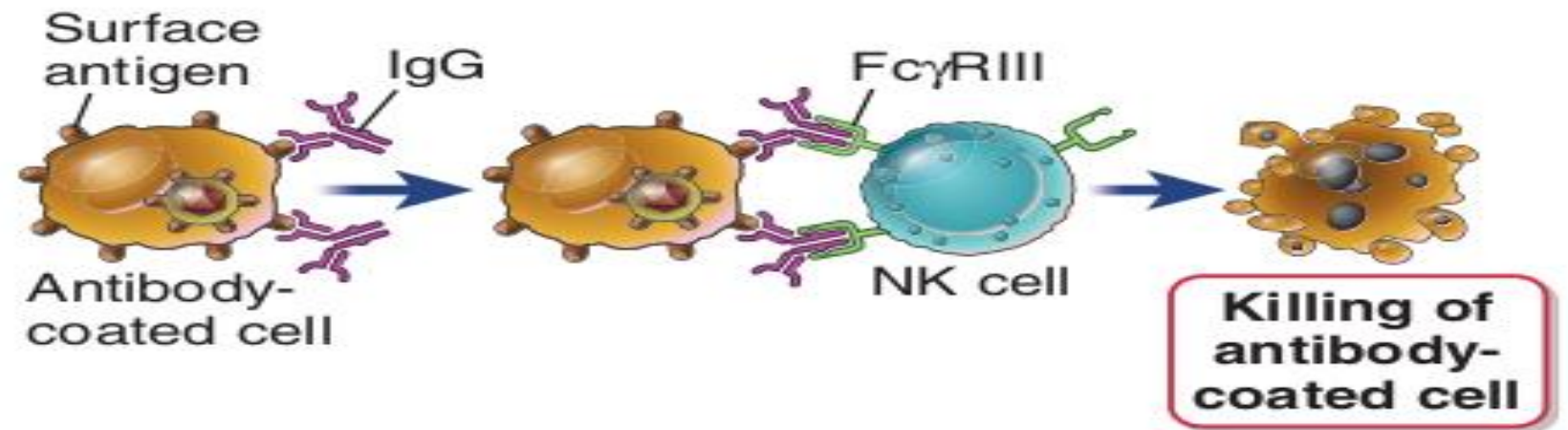
FcγRIIIA (CD16) activates cytotoxic cells



Cytotoxic factors secreted



Lysis of targeted cell



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- ADCC is exhibited by various cells such as NK cells, macrophages, monocytes, neutrophils, and eosinophils

NK cells secrete perforins, and granzymes. Neutrophils release lytic enzymes.

Eosinophils can release lytic enzymes and perforins; play an important role in providing immunity against helminths.

Macrophages produce lytic enzymes and TNF.

Role of CMI

1) Provides immunity against intracellular microbes

- It is the only effective response against obligate intracellular microbes like viruses, MTB, Rickettsia
- It also provides protection against facultative intracellular organisms like Listeria, Salmonella

2) It provides protection against tumor cells and other damaged and altered cells

3) It mediates type IV hypersensitivity

4) It plays key role in transplantation immunity

**Humoral immune response(antibody
mediated immune response)**

Humoral Immunity

Antibody-mediated immune response (AMI) provides protection to the host by **secreting antibodies**; that prevent invasion of microbes present on the surface of the host cells and in the extracellular environment, but has no role against intracellular microbes. AMI occurs through the following three sequential steps:

1. Activation of B cells following contact with the microbial antigen (B cells act as APCs).
2. Proliferation and differentiation of B cells into effector cells (antibody producing plasma cells) and memory cells.
3. Effector function: Production of secreted antibodies by plasma cells which in turn counter act with the microbes in many ways, such as neutralization, opsonization, complement activation, etc.

Activation of B-cells

- Thymus dependent antigens(proteins) activate B-cells indirectly via activated Tcells
- Thymus independent antigens(capsule, nucleic acids, polysaccharides) are not processed by antigen presenting cells and they directly activate B-cells

1)Signal induction

2)Signal transduction

Signal induction

1. **Signal 1:** It is induced by the cross linking of IgM on B cell membrane with the microbial antigen.
2. **Signal 2:** It is an additional signal provided by binding of CD40 on B cell with CD40L (ligand) on activated T_H cells.
3. **Signal 3:** It is usually a cytokine stimulus. Cytokines produced by the activated T_H cells bind to specific cytokine receptor on B cells.

Signal transduction

- Signal transduction is initiated by the B-cell receptor(BCR)
- Following antigen cross linkage to membrane Ig, Ig- α ,/Ig- β heterodimer is activated and in turn transmits the signal, ultimately leading to activation of B cells.

Proliferation and differentiation of B cells

- Following the antigenic exposure, the naive B cells are activated and then they proliferate
- Eventually, the primary lymphoid follicles transform into secondary lymphoid follicles.
- Secondary lymphoid follicles bear a germinal center which in turn has two areas; dark zone and light zone
- In dark zone, centroblasts undergoes somatic hypermutation and affinity maturation resulting to survival of centrocytes with high affinity membrane Ig
- In light zone, class switch over takes place to produce other classes of Ig

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- Different cytokines induce production of different classes of Ig by switching mechanism

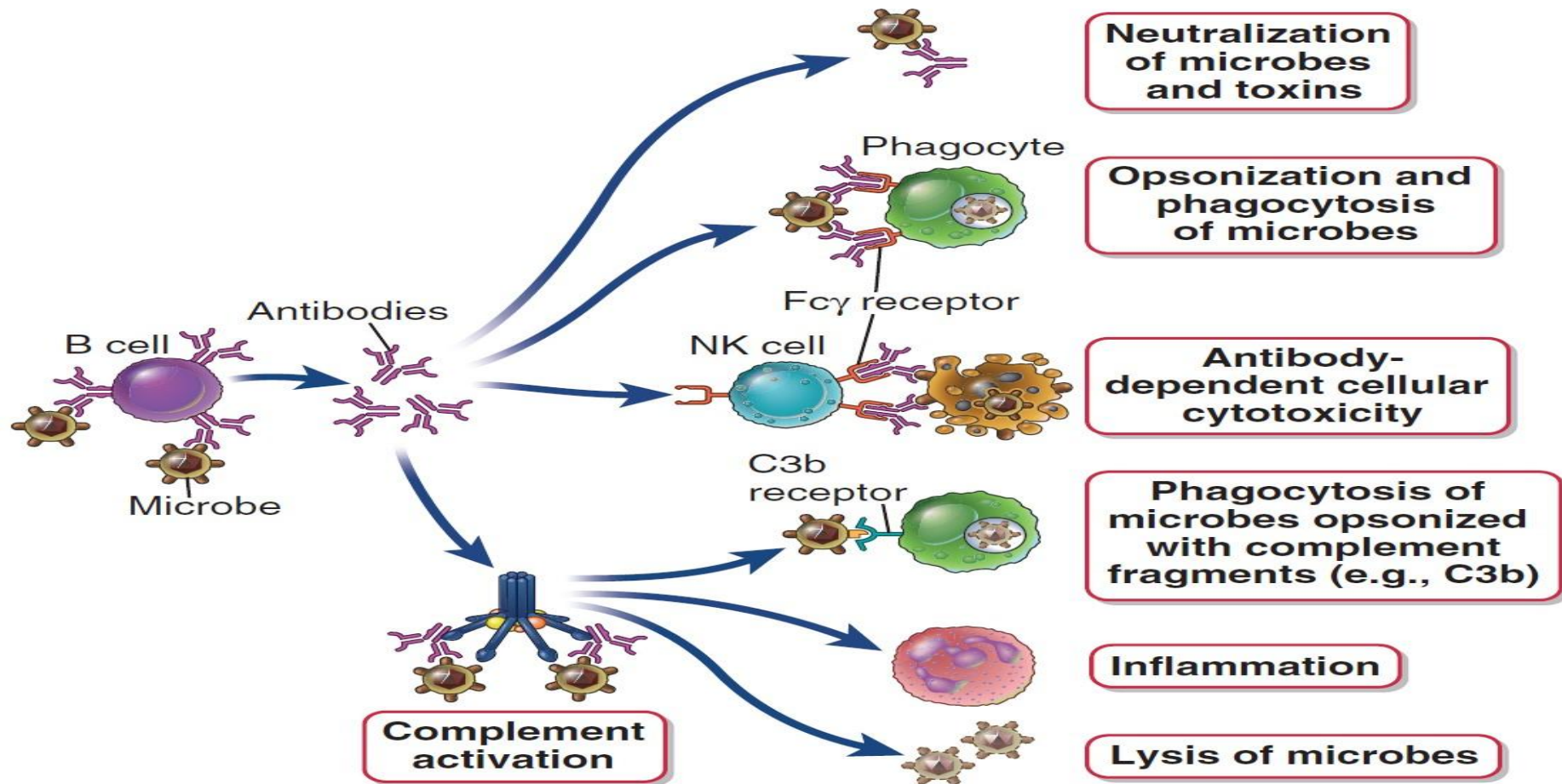
TABLE 15.6: Cytokines secreted by T_H cells and the respective Ig class/subclass they induce

Cytokine(s)	Ig class produced
IFN- γ	IgG2a or IgG3
IL-5 + TGF- β	IgA or IgG2b
IL-4	IgE or IgG1 or IgG4
IL-2,4,5	IgM
IL-4,5,6 + IFN- γ	IgG

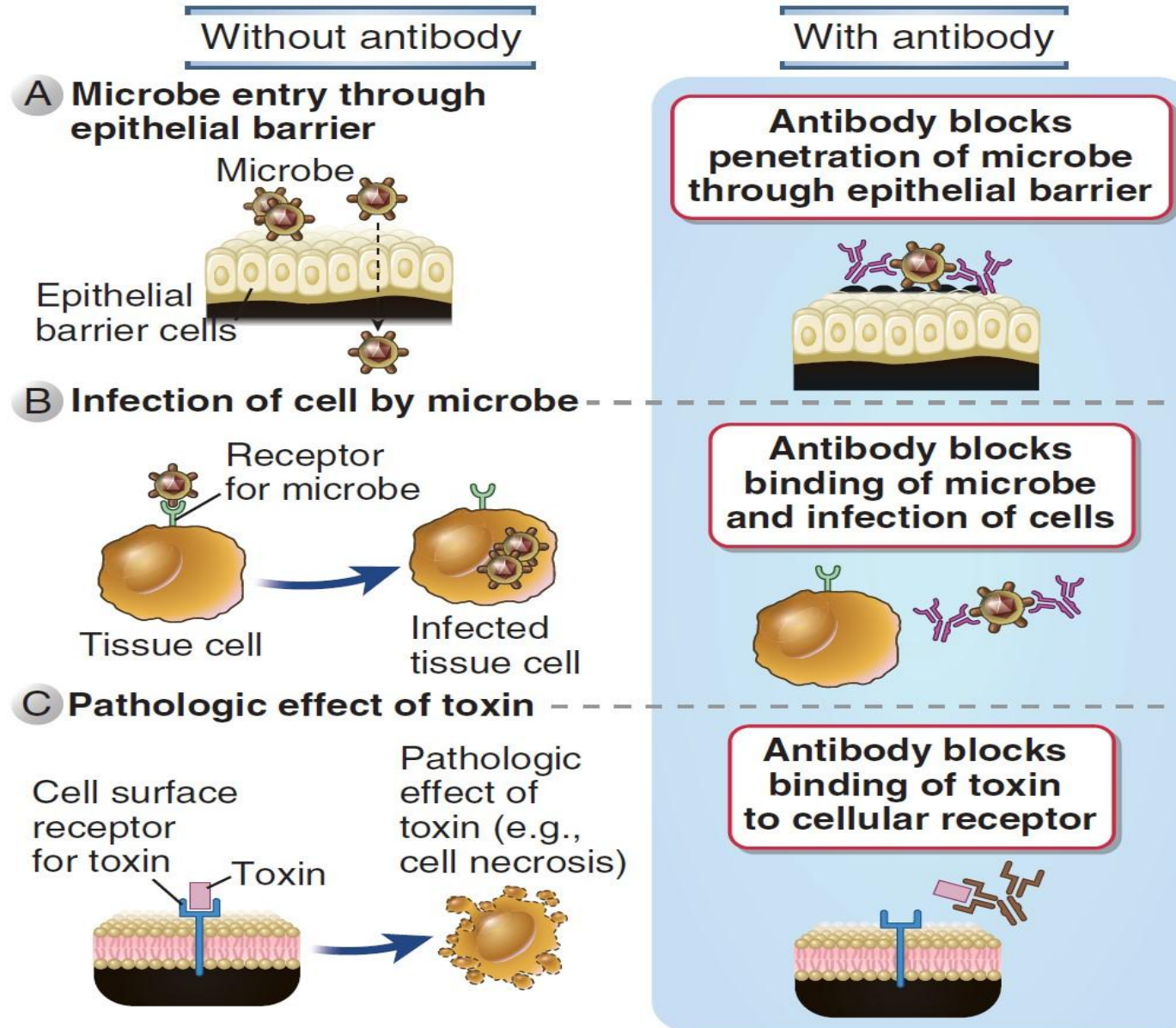
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- In light zone, centrocytes differentiate into plasma cells and memory cells
 - Plasma cells are large antibody-secreting cells; produce secretory Ig enormously, but do not synthesize membrane Ig. They do not have MHC-II molecules and do not undergo further class switch over.
 - Memory cells bear high affinity membrane Ig molecules of all classes as compared to naive B cell that bear only low affinity IgM or IgD membrane Ig. They are long lived cells which respond to the secondary antigenic stimulus.

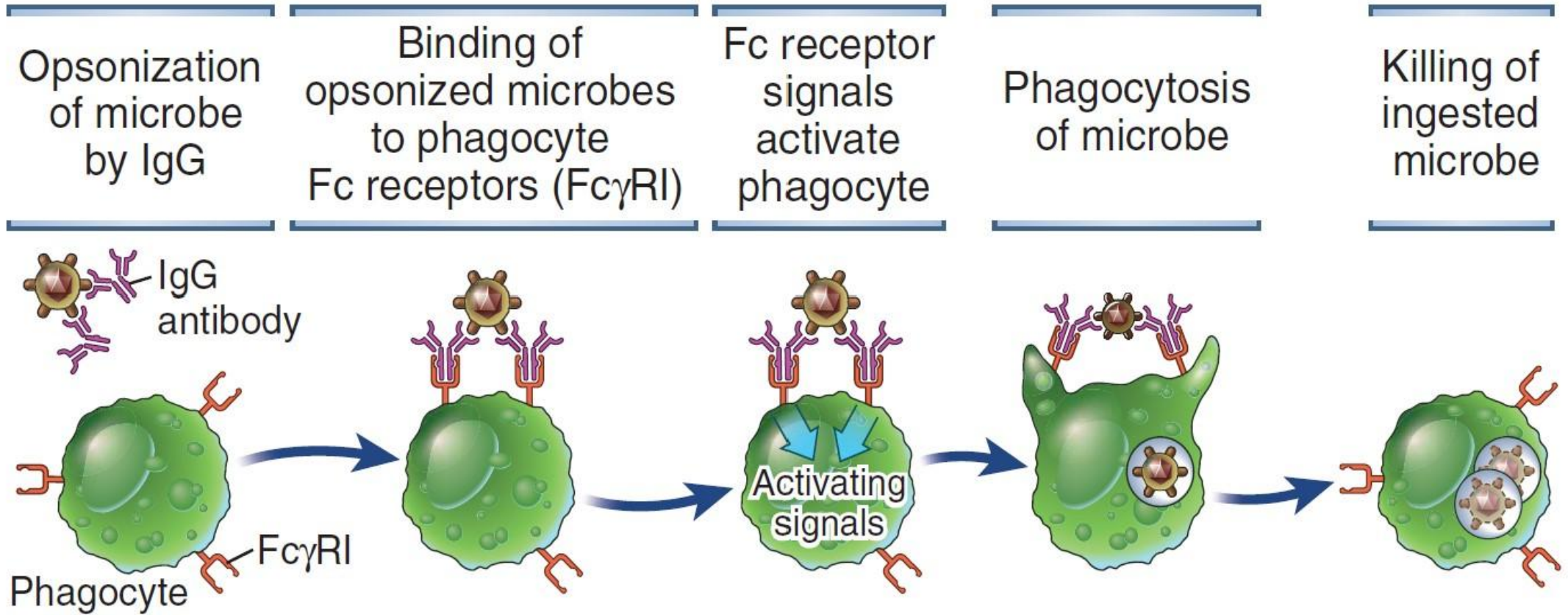
Effector functions of humoral immune response



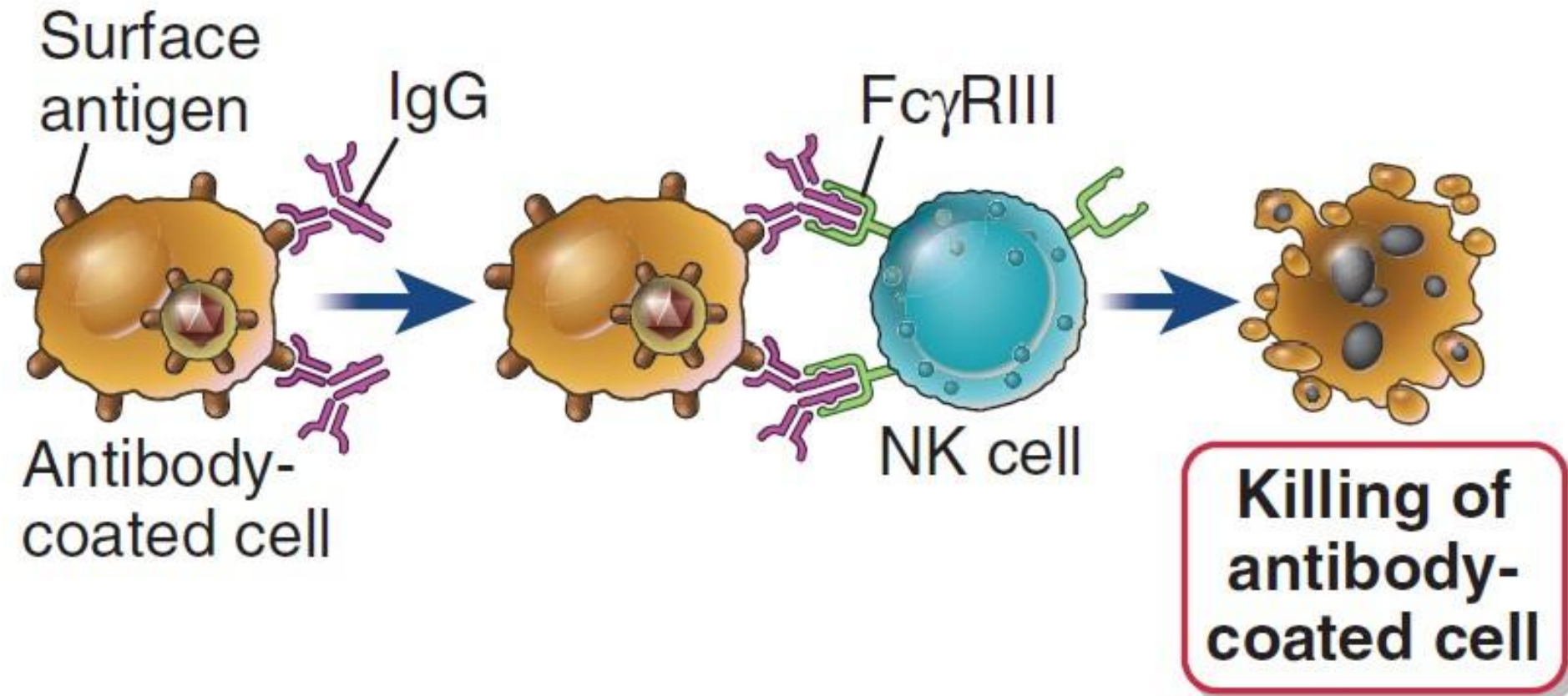
Neutralization of Microbes and Toxins



Antibody-Mediated Opsonization and Phagocytosis

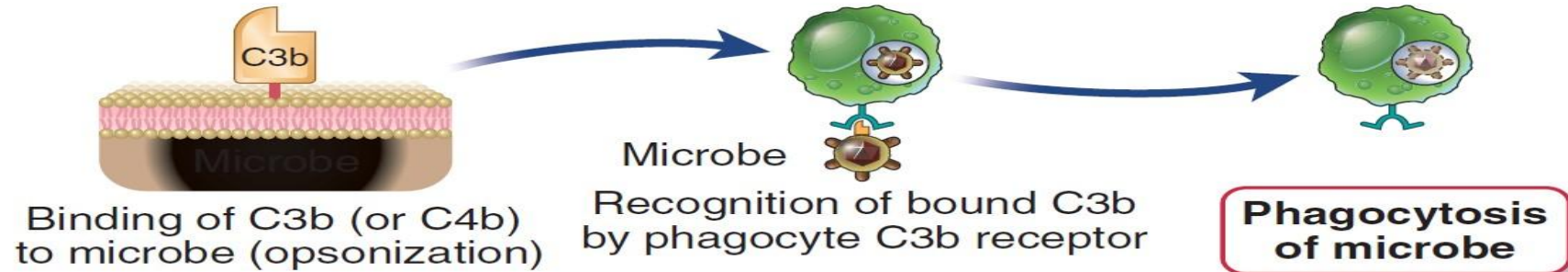


Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)

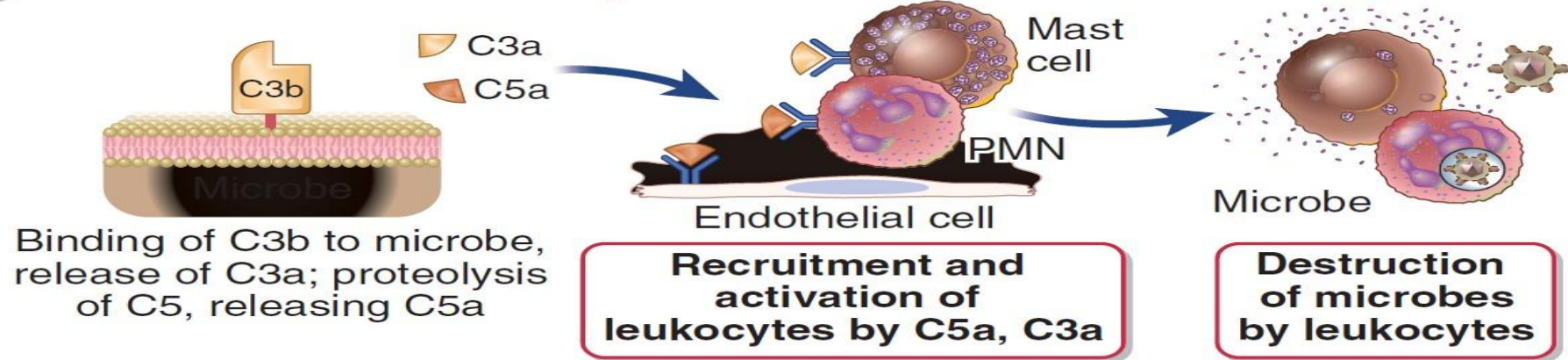


Complement Activation

A Opsonization and phagocytosis



B Stimulation of inflammatory reactions



C Complement-mediated cytotoxicity

