Hypersensitivity -1

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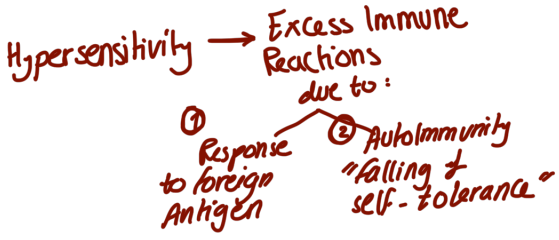
Introduction



- Immune responses are capable of causing tissue injury and disease because of excessive or aberrantly directed immune reactions – (hypersensitivity).
- Hypersensitivity reactions occur due to:

1. Responses to foreign antigens (microbes and environmental antigens) may cause tissue injury when reactions are repetitive or poorly controlled.
2. The immune responses may be directed to against self (autologous) antigens, as a result of the failure of self-tolerance – (autoimmunity).

Classification Overview

Based on Immune Mechanism

- **Four Types of Hypersensitivity**

- **Type I**: IgE + mast cells causing immediate reactions.
- **Type II**: IgG/IgM binding to cell/tissue antigens causing complement or receptor dysfunction.
- **Type III**: circulating immune complexes deposit in vessels leading to vasculitis. "Ag-Ab"
- **Type IV: T-cell mediated** inflammation or cytotoxicity.
- Classification is based on **immune mechanism**, not timing.

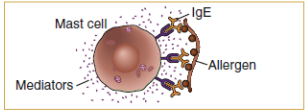
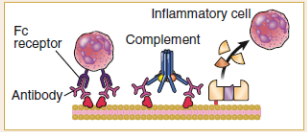
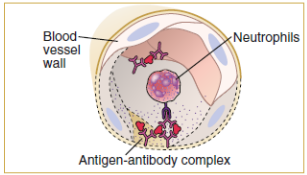
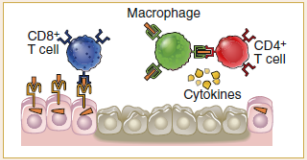
Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	Th2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils)
Antibody-mediated diseases (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function, e.g. hormone receptor signaling
Immune complex-mediated diseases (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes
T cell-mediated diseases (Type IV)	1. Cytokine-mediated inflammation ($CD4^+$ T cells) 2. T cell-mediated killing ($CD8^+$ CTLs) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

Fig. 11.1 Types of hypersensitivity reactions. In the four major types of hypersensitivity reactions, different immune effector mechanisms cause tissue injury and disease. *CTLs*, Cytotoxic T lymphocytes; *Ig*, immunoglobulin; *Th2*, T helper 2 cell.

* First Exposure to Allergen → formation of IgE and they Bind to Mast cells

* Re Exposure to the same Allergen → binds to IgE on Mast Cells → lyses

Type I Hypersensitivity – Immediate Allergic Reactions

- Immediate allergic reactions caused by **IgE antibodies** against environmental antigens, also called atopy or allergy.
  - Trigger mast cell activation on **re-exposure**, not initial contact.
  - Symptoms appear within **minutes** due to vasoactive mediator release
  - **Th2 cytokines (IL-4, IL-5, IL-13)** critical for IgE class-switch & eosinophil recruitment
  - Major diseases: asthma, rhinitis, urticaria, **systemic anaphylaxis.**

Two-Stage Allergy Response

due to first Exposure → Dendritic cell present Antigens to Th2 → release IL4, IL13 → B-cell Activation and Class switching to Release IgE → binds to FcεR1 on Mast cells

- **Sensitization phase**: activation of Th2 response, IgE production and binding to mast cells and basophils.
- **Activation phase**: allergen cross-links IgE bound to FcεRI on mast cells leading to degranulation.

due to Allergen Reexposure

- **Immediate reaction is** mediated by histamine: wheal-and-flare, bronchospasm.
- **Late-phase reaction is** cytokine-driven hours later mediated by eosinophils & monocyte influx.
- Chronic reactions leading to **airway remodeling** and sustained symptoms.

Activation phase
- Immediate Reaction within Minutes → due to Histamine Release after Mast cell degranulation
- Late Reaction within hours → due to cytokines Release from Mast cell

Development of IgE

- APCs capture allergen and migrate to LN and present antigens to **naïve CD4+ T cells**.
- IL-4, IL-13 by follicuar TH cells: **isotype switching** in B cells to produce IgE
- IgE binds high-affinity **FcεRI receptors** on mast cells and basophils.
- Sensitization lasts months to years due to **stable IgE–mast cell binding**.
- No clinical reaction until **re-exposure**.

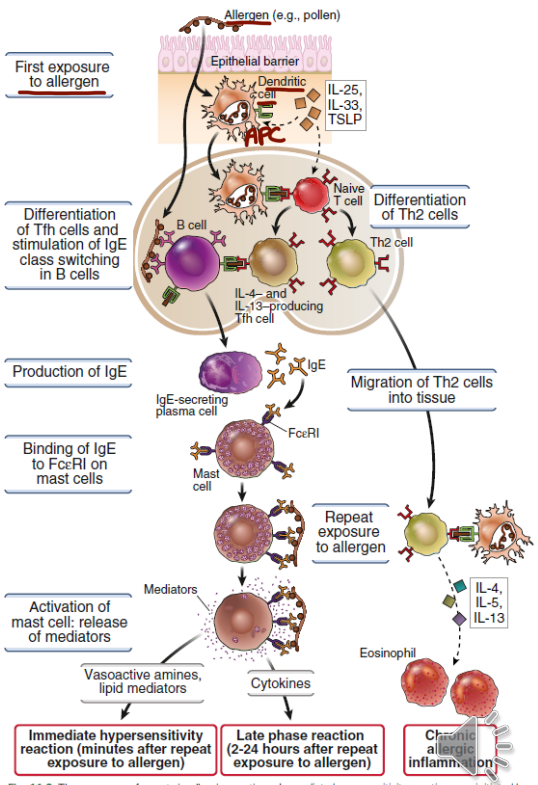


Fig. 11.2 The sequence of events in allergic reactions. Immediate hypersensitivity reactions are initiated by the introduction of an allergen, which, together with cytokines from epithelial cells, stimulates Th2 and IL-4/IL-13–producing Tfh cells. Immunoglobulin E (IgE) produced in response to antigen and Tfh cells binds to Fc receptors (FcεRI) on mast cells, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic reactions of immediate hypersensitivity. Mast cells, Th2 cells, and other cells produce cytokines that elicit inflammation in the late-phase reaction and in chronic allergic di

Mast Cell Activation

After Antigen "Allergen" Reexposure → binds to IgE that present on Mast cell surface → cross-linking leads to Mast cell degranulation

- Cross-linking of IgE receptors leads to **Ca^{2+} influx** and granule exocytosis.
- Seconds–minutes: release of **preformed mediators**. "Histamine"
- Minutes–hours: synthesis of **lipid mediators** (LTs, PGs).
- Hours: secretion of **cytokines** for inflammation propagation.
- Effects vary by organ: skin vs airway vs GI tract.

Immediate Reaction

Late Reaction

Mast Cell Mediators

- **Histamine** : vasodilation, vascular leakage, smooth muscle contraction
- **Proteases:** local tissue damage and complement activation.
- **Leukotrienes C4/D4/E4:** prolonged bronchoconstriction and mucus.
- **Prostaglandin D2:** airway narrowing and vasodilation
- **TNF and IL-5** causing eosinophil recruitment manifesting as late-phase inflammation.

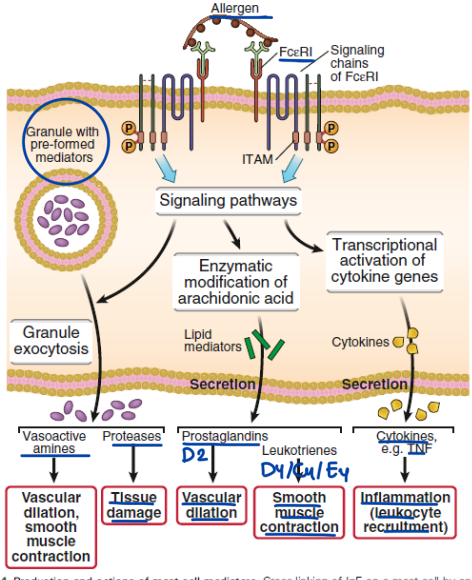


Fig. 11.4 Production and actions of mast cell mediators. Cross-linking of IgE on a mast cell by an allergen stimulates phosphorylation of immunoreceptor tyrosine-based activation motifs *(ITAMs)* in the signaling chains of the IgE Fc receptor *(FcεRI)*, which then initiates multiple signaling pathways. These signaling pathways stimulate the release of mast cell granule contents (amines, proteases), the synthesis of arachidonic acid metabolites (prostaglandins, leukotrienes), and the synthesis of various cytokines. *TNF,* Tumor necrosis factor.

Immediate vs. Late-Phase Reaction

• Immediate: **5–30 min**, mast cell granules (edema, redness, pruritus).
• Late phase: **2–24 h**: cytokines and leukocyte recruitment.
  • Dominated by **eosinophils & Th2 cells**
  • Causes **epithelial injury** and increased reactivity (e.g., asthma)
• Chronic allergic inflammation: fibrosis, smooth muscle hypertrophy
• Responsible for **chronic asthma and dermatitis pathology.**

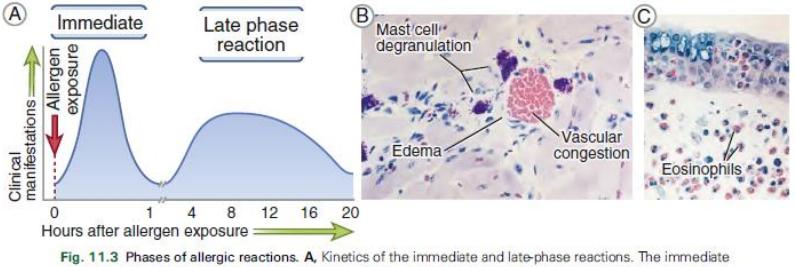


Fig. 11.3 Phases of allergic reactions. A, Kinetics of the immediate and late-phase reactions. The immediate vascular and smooth muscle reaction to allergen develops within minutes after challenge (allergen exposure in a previously sensitized individual), and the late-phase reaction develops 2 to 24 hours later. **B,** Morphology of the immediate reaction is characterized by vasodilation, congestion, and edema. **C,** The late-phase reaction is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells. (Micrographs courtesy the late Dr. Daniel Friend, Department of Pathology, Brigham and Women's Hospital, Boston.)

Th2 Immune Response & Atopy initiation

IL 4 → Activate B cell class switching → IgE production
IL 5 → Eosinophils
IL 13 → ↑ Mucous production

- TH2 cytokines--- IL-4: IgE production; IL-5 : eosinophil survival; IL-13: mucus secretion.
- Thymic stromal lymphopoietin (TSLP), IL-33 from epithelial cells in response to barrier injury enhance Th2 priming.
- Barrier protein defects (e.g., filaggrin protein mutations): increased allergen entry.
- Genetic predisposition: **high IgE** responses to low-dose allergens.
- Environmental "hygiene hypothesis" : proposes that higher levels of exposure to microbes and allergens in early life results in less allergy (and autoimmunity) later.

Eosinophils in Late Phase

IL-5 → Induce degranulation Eosinophil < Basic proteins, Cationic proteins

- IL-5-induced maturation in bone marrow and tissue recruitment.
- Degranulation releases **major basic protein**, eosinophil cationic protein.
- Potent **epithelial cytotoxicity** and tissue remodelling.
- Present in asthma, food allergy, atopic dermatitis.
- Key target for therapy in allergy (anti-IL-5 mAbs).

Organ-Specific Outcomes

- Reaction depends on **allergen entry site.**
- Skin: urticaria; Airway: asthma; GI: vomiting/diarrhea.
- Local reactions can progress to systemic if allergen enters bloodstream.
- Chronicity leads to **irreversible structural changes.**
- Treatment varies based on affected tissue.

Allergic Rhinitis (hay fever)

- Inhaled allergens activate **mucosal mast cells** (itching, sneezing)
- Histamine results in vascular leakage and nasal congestion.
- Leukotrienes: mucus hypersecretion.
- Chronic allergy: **sinusitis** due to obstruction.
- Often associated with **conjunctivitis.**

Inhaled Allergen → Activate the Mucosal Mast Cell → degeneration → Histamine → ↑ vascular leakage
degeneration → Leukotrienes → mucous secretion

Clinical syndrome	Clinical and pathological manifestations
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilation; airway obstruction due to laryngeal edema and bronchial constriction
Atopic dermatitis	Itchy red exudative papules and chronically dry scaly skin

Fig. 11.5 Clinical manifestations of immediate hypersensitivity reactions. Immediate hypersensitivity may be manifested in many other ways, as in development of skin lesions (e.g., urticaria, eczema).

Allergic Asthma

- Mast cell mediators results in **acute bronchoconstriction.**
- Th2 cytokines cause **airway remodeling** over time.
- Eosinophils cause epithelial injury and airway hyper-responsiveness.
- Goblet cell hyperplasia leading mucus plugs.
- Potentially life-threatening exacerbations.

Basic proteins, Cationic proteins

Asthma Structural Changes

- **Smooth muscle hypertrophy** causing persistent narrowing.
- **Subepithelial fibrosis** from chronic inflammation.
- Hyper-reactive airways respond excessively to stimuli.
- Long-term changes lead to decreased response to bronchodilators.
- Radiologic/biopsy signs reflect chronic damage.

Food Allergy

- Ingested allergens trigger mast cell degranulation.
- Histamine leads to increased peristalsis: diarrhea, cramping, vomiting.
- May cause simultaneous **skin & respiratory symptoms.**
- Severe cases: rapid systemic anaphylaxis.
- Chronic inflammation: eosinophilic GI disease.

Atopic Dermatitis

- Chronic pruritic eczema—flares of itchy red exudative papules.
- Defective skin barrier function (e.g., filaggrin mutations): frequent colonization by *Staphylococcus*.
- Elevated Th2 cytokines → eosinophilic infiltration.
- Children with eczema are at increased risk for developing food allergies and asthma (atopic triad): the sequential development know as atopic march.

Systemic Anaphylaxis

trigger
↳ bee stings
↳ peanut, shellfish
↳ penicillin family
→ systemic distribution of Mast cells → widespread degranulation → bronchospasm and laryngeal edema

- Most severe form of immediate hypersensitivity: widespread mast cell degranulation in response to the systemic distribution of the antigen g **vascular collapse (anaphylactic shock).**
- Bronchoconstriction & laryngeal edema → **airway compromise.**
- Common triggers: bee stings, injected or ingested penicillin-family antibiotics, and ingested nuts or shellfish.
- Rapid onset → requires immediate **IM epinephrine.**

Treatment of Type 1 hypersensitivity

- Therapy for immediate hypersensitivity diseases is aimed at inhibiting mast cell degranulation.

➢ Antihistamines for hay fever. "due to Inhaled Allergen"

➢ Inhaled b-adrenergic agonists, leukotriene and prostaglandin antagonists, and corticosteroids that relax bronchial smooth muscles and reduce airway inflammation in asthma.

➢ Epinephrine in anaphylaxis. "IM"

- Repeated administration of small doses of allergens (desensitization) inducing tolerance in allergen-specific T cells, or by stimulating regulatory T cells (Tregs).
- Monoclonal antibody drugs that block IgE, IL- 4, IL-5, TSLP, and IL-33 receptor binding now approved for the treatment of some forms of asthma and atopic dermatitis.

Syndrome	Therapy	Mechanism of action
Anaphylaxis	Epinephrine	Causes vascular smooth muscle contraction, increases cardiac output (to counter shock), and inhibits bronchial smooth muscle cell contraction
Asthma	Corticosteroids	Reduce inflammation
	Leukotriene antagonists	Relax bronchial smooth muscle and reduce inflammation
	Beta adrenergic receptor antagonists	Relax bronchial smooth muscles
Various allergic diseases	Desensitization (repeated administration of low doses of allergens)	Unknown; may inhibit IgE production and increase production of other Ig isotypes; may induce T cell tolerance
	Anti-IgE antibody	Neutralize and eliminate IgE
	Antihistamines	Block actions of histamine on vessels and smooth muscles
	Cromolyn	Inhibits mast cell degranulation
	Antibodies that block cytokines and their receptors: TSLP, IL-33, IL-4, IL-5R (asthma); IL-4R (atopic dermatitis)	Block cytokine-driven inflammation

Fig. 11.6 Treatment of immediate hypersensitivity reactions. The table summarizes the principal mechanisms of action of currently used therapies for allergic disorders. *Ig,* Immunoglobulin; *IL,* interleukin; *TSLP,* thymic stromal lymphopoietin.

Type 1 hypersensitivity

2 stages of Response

Sensetization

due to first time exposure to Antigen/Allergen)

The Antigen is presented by APC like dendretic cell To Th2 cell at lymph node

Th2 cell secrete IL4/IL13

Activate class switching of B cell

IgE production

Binds to FCER1 receptor on Mast cell

- no symptoms

Reactivation

due to the Reexposure to the same Antigen

Early Reaction

within seconds – minutes

- Antigen binds to IgE that present on the surface of Mast cell
- Degranulation of Mast cell
- Releasing of preformed Mediators like Histamine
  - ↑ vascular permeability
  - smooth muscle contraction
  - vasodilation

Late Reaction

Minutes – hours

Lipid Mediators

PG → PGD_2 → Broncho constriction

LT ($LT_4/D_4/B_4$)
- Broncho constriction
- ↑ mucous production

within hours

cytokines for Inflammatory Response propagation Like TNF /IL5
- Eosinophilic infiltration as late Inflammatory Reaction
- degranulate to Release Basic proteins and cationic proteins
- epithelial damaging

Out COMES:

the out comes depends on Allergen entery site:

- skin → Uriticaria
- Airways → Asthma
- GI → diarrhea vomiting cramping

Clinical syndroms Result from type 1 hypersensetivity:

Hey syndrom

- Inhaled Allergen
- Mucosal Mast cell degranulation
- 1) Histamine ← Itching, sneezing, nasal congestion
- 2) Leukotriene → ↑ mucous secretion
- **chronic → sinusitis**
- **Associated → conjunctivitis with**
- Anti histamine

Food Allergy

- Ingested Allergen
- Mast cell degranulation
- Histamine
- ↑ peristalis ← vomiting, cramping, diarrhea
- chronic → Eosinophilic GI-disease
- Associated with → skin + RS symptoms
- severe → Anaphylaxis cases

Bronchial Asthma

- Inhaled Allergen
- 1 → Mast cell Mediators → Acute Broncho constriction
- 2 → Eosinophils → epithelial damaging
- 3 → TH2 cytokines → Remodelling
  - Goblet cell hyperplasia → Mucous plugging
  - Smooth Muscle hypertrophy → Airway Narrowing
  - sub epithelial fibrosing

- B_2 Agonist
- corticosteroids
- leukotriene Antagonist
- Monoclonal Antibody

Atopic dermatitis

- Defective skin Barrier
- Repeated colonization of streptococcus
- itchy + exudative papules
- → IL5 → Eosinophils Infiltration
- Associated with → Atopic triad in children
  - Asthma
  - Atopic dermatitis
  - Food Allergies
- If sequentialy develop → "Atopic March"
- Monoclonal Antibody

Most dangerous outcome

↓

Anaphylactic shock

- Epinephrine "IM"

Overview of Type II Hypersensitivity

IgG / IgM binds → Cells → then Complement Activation or phagocyte Recruitment

- **Type II Hypersensitivity Overview**
- Mediated by **IgG or IgM antibodies binding to cell/tissue antigens.**
- Injury from **complement activation**, **phagocyte recruitment**, or **ADCC.**
- Antibodies may also **stimulate or block** receptors to alter tissue function.
- Clinical presentations depend on **where the antigen is expressed.**
- Seen in both **alloimmune** and **autoimmune** conditions.

Mechanisms of Injury

- **Opsonization:** FcγR/C3b-mediated phagocytosis in spleen/liver.
- **Complement : MAC** lysis of target cells in circulation.
- **C3a/C5a** chemoattractants recruit neutrophils/macrophages leading to **local inflammation.**
- **Receptor modulation**: antibodies activate or block signaling pathways
- Tissue injury is **site-specific** vs. Type III systemic disease.

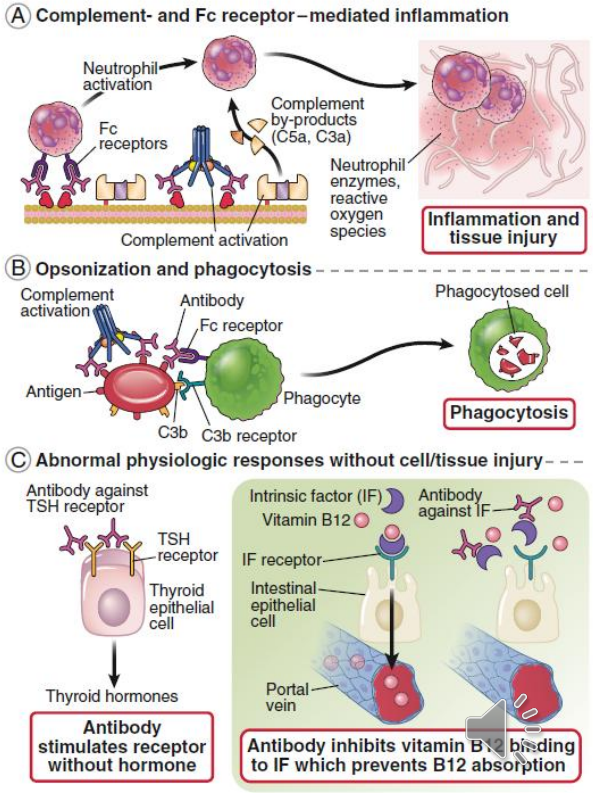


Fig. 11.7 Pathogenesis of diseases caused by antibodies specific for tissue or cell antigens. Antibodies can cause disease by **(A)** inducing inflammation at the site of deposition, **(B)** opsonizing cells (such as red cells) for phagocytosis, and **(C)** interfering with normal cellular functions, such as hormone receptor signaling or absorption of a necessary dietary factor. *TSH,* Thyroid-stimulating hormone.

Cytotoxic Antibody-Driven Diseases

- Autoimmune hemolytic anemia: **RBC opsonization** by antibodies leading to extravascular hemolysis.
- Immune thrombocytopenia: platelet destruction leading to mucocutaneous bleeding.
- Rh incompatibility: **hemolytic disease of newborn** (erythroblastosis fetalis).
- Drug-induced hemolysis: **hapten** formation triggers new antigenicity.
- Evidence: **positive direct Coombs test.**

Inflammatory Antibody Injury

- Antibodies against **basement membrane** leading to complement activation and necrotizing inflammation.
- Prototypical example: **Goodpasture syndrome** (lung and kidney involvement).
- Neutrophils degranulate when frustrated on fixed surfaces.
- **Fibrinoid necrosis** seen histologically in damaged tissue.
- Damage location: **antigen distribution** determines organ involvement.

Receptor Dysfunction in Type II

- **Graves disease** — antibodies activate **TSH receptor** leding to increased T3/T4 production.
- **Myasthenia gravis** — AChR blockade → impaired neuromuscular transmission.
- No cell destruction: **functional** disease mechanism.
- Symptoms improve with **immunosuppression** or **receptor blockade.**
- Proves Type II can cause disease **without cytotoxicity.**

by Receptor Dysfunction

Antibody-mediated disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune (idiopathic) thrombocytopenic purpura	Platelet membrane proteins (gpIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Goodpasture's syndrome	Protein in basement membranes of kidney glomeruli and lung alveoli	Complement and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Graves' disease (hyperthyroidism)	Thyroid stimulating hormone (TSH) receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetycholine binding, complement-mediated damage to neuro-muscular junction	Muscle weakness, paralysis
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated disruption of intercellular adhesions	Skin vesicles (bullae)
Pernicious anemia	Intrinsic factor, gastric parietal cells	Neutralization of intrinsic factor and damage to gastric parietal cells causing decreased absorption of vitamin B_{12}	Anemia due to abnormal erythropoiesis, nerve damage
Rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis

Fig. 11.8 Human antibody-mediated diseases (type II hypersensitivity). The figure lists examples of human diseases caused by antibodies. In most of these diseases, the role of antibodies is inferred from the detection of antibodies in the blood or the lesions, and in some cases by similarities with experimental models in which the involvement of antibodies can be formally established by transfer studies. In some of these diseases, concurrent T cell–mediated tissue damage also occurs. *TSH*, Thyroid-stimulating hormone.

More reading..

- Abbas, A. K., Lichtman, A. H., & Pillai, S. (2023). *Basic Immunology: Functions and Disorders of the Immune System* (7th ed.). Elsevier Health Sciences.
- Abbas, A. K., Lichtman, A. H., Pillai, S., & Henrickson, S. (2025). *Cellular and Molecular Immunology* (11th ed.). Elsevier.