

# 면역약리학 Immunopharmacology

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# 면역약리학

- 개념

- Immune mechanisms
- Immunosuppressive agents
- Antibodies as immunosuppressants
- Immunomodulating agents
- Mechanisms of drug allergy

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# Immune mechanisms

## 비정상 면역반응

- 과민반응(hypersensitivity)
  - Antibody-mediated(immediate)
  - Cell-mediated(delayed)
- 자가면역 질환(autoimmunity)
  - Self-reactive lymphocytes
- 면역결핍 질환(immunodeficiency)
  - 선천적; DiGeorge's syndrome
  - 후천적; AIDS

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# Immunosuppressive agents의 종류

- Adrenocorticoids
- Selective inhibitors of cytokine production and function
  - Cyclosporine, tacrolimus(FK506), sirolimus
- Antimetabolites
  - Mycophenolate mofetil, azathioprine
- Alkylating agent
  - Cyclophosphamide
- Newer immunosuppressants
  - Etanercept, leflunomide, thalidomide
- Antibodies

# Immunosuppressive agents

## Corticosteroids

- 종류
  - Prednisone, methylprednisolone
- 작용기전
  - Decreases gene expression
    - Prostaglandins, leukotrienes, cytokines
  - Inhibits proliferation of T lymphocytes
    - Dampen cell-mediated and humoral immunity
- 임상적 사용
  - Transplantation
  - 자가면역질환
- 부작용
  - Diabetogenic, hypercholesterolemia, 백내장, 골다공증, 고혈압

# Immunosuppressive agents

- Selective inhibitors of cytokine production and function
  - Cyclosporine
  - Tacrolimus(FK506)
  - Sirolimus(rapamycin)



# Immunosuppressive agents

## Cyclosporine, tacrolimus

- 작용기전
  - Blocks calcineurin and inhibits IL-2 synthesis

NFAT = nuclear factor of activated T cells

# Immunosuppressive agents

## Sirolimus

- 작용기전
  - Blocks IL-2-stimulated cell proliferation
    - T cells
    - B cells
    - Mononuclear cells

# Immunosuppressive agents

## Cyclosporine, tacrolimus, sirolimus

- 임상적 사용
  - Cyclosporine
    - Transplantation
    - 자가면역질환
  - Tacrolimus
    - Liver and kidney transplantation, rescue therapy
  - Sirolimus
    - (+ cyclosporine) kidney and heart transplantation

# Immunosuppressive agents

## Cyclosporine, tacrolimus, sirolimus

- 약동학
  - 경구투여
  - 흡수율 다양함(GI tract CYP3A4); 혈중농도 측정
  - 대사; hepatic CYP3A4
  - 담도계 배설
- 부작용
  - Cyclosporine
    - 신장독성, 간독성, 감염증, lymphoma, anaphylaxis, tremor
  - Tacrolimus
    - 신장독성, 신경독성(tremor, seizure, 환각), post-transplant IDDM
  - Sirolimus
    - Hyperlipidemia, 신장독성(+ cyclosporine), 두통, 오심, 설사, 고혈압, 조혈세포 독성

# Immunosuppressive agents

- Antimetabolites
  - Mycophenolate mofetil
  - Azathioprine

# Immunosuppressive agents

## Mycophenolate mofetil

- 작용기전
  - Mycophenolic acids inhibits purine synthesis
    - suppress B and T lymphocyte activation
- 임상적 사용
  - Renal transplantation(+ low dose cyclosporine)
  - Liver and heart transplantation
- 부작용
  - 비교적 안전하다.
  - 통증, 위장관 장애(설사), leukopenia, 기회 감염증, 패혈증

# Immunosuppressive agents

## Azathioprine

- 작용기전
  - inhibits purine synthesis
    - 6-mercaptopurine(6-MP), thioinosinic acid
    - Inhibit T cell proliferation(B cell)
- 임상적 사용
  - 자가면역질환
  - Renal transplantation
- 부작용
  - Hematotoxicity(골수억제)
    - Increased leukopenia with ACE inhibitor or cotrimoxazole
  - 위장관 자극, increased risk for cancer, allopurinol에 의한 독작용 증가

# Immunosuppressive agents

- Alkylating agent
  - Cyclophosphamide
  - *Cytarabine, dactinomycin, methotrexate, vincristine*



# Immunosuppressive agents

## Cyclophosphamide

- 작용기전
  - Cytotoxic alkylating agent
    - Liver enzyme(cytochrome P450) metabolites inhibit proliferation of B cells(T cells) by alkylation
- 임상적 사용
  - 자가면역질환
  - Transplantation
- 부작용
  - Pancytopenia, GI distress, hemorrhagic cystitis, alopecia, sterility

# Immunosuppressive agents

- Newer immunosuppressants
  - Etanercept
  - Leflunomide
  - Thalidomide

# Immunosuppressive agents

## Etanercept

- 작용기전
  - Recombinant human TNF receptor
    - Binds TNF- $\alpha$ 
      - TNF- $\alpha$ ; proinflammatory, macrophage activation
    - Decrease formation of interleukins and adhesion molecules involved in leukocyte activation
- 임상적 사용
  - Rheumatoid arthritis
- 부작용
  - Injection site reaction, hypersensitivity

# Immunosuppressive agents

## Leflunomide

- 작용기전
  - Arrests lymphocytes in the G<sub>1</sub> phase of the cell cycle
    - Inhibits dihydroorotic acid dehydrogenase(ribonucleotide synthesis)
- 임상적 사용
  - Rheumatoid arthritis
- 부작용
  - Alopecia, rash, diarrhea

# Immunosuppressive agents

## Thalidomide

- 작용기전
  - Suppress TNF production
    - TNF- $\alpha$ ; proinflammatory, macrophage activation
- 임상적 사용
  - 자가면역질환
  - Leprosy reactions
  - AIDS; aphthous ulcer, wasting syndrome
- 부작용
  - Teratogenicity
    - Amelia, phocomelia

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# Antibodies as immunosuppressants

- Polyclonal antibodies
  - Lymphocyte immune globulin(LIG)
  - Rh<sub>0</sub>(D) immune globulin(Rh<sub>0</sub>GAM)
- Monoclonal antibodies
  - Muromonab-CD3
  - Daclizumab
  - Infliximab

# Antibodies as immunosuppressants

## Lymphocyte immune globulin(LIG)

- 작용기전
  - Destruction of T lymphocytes
    - Suppress cell-mediated immunity
    - Horse serum against human thymus cells
- 임상적 사용
  - Allograft rejection의 hyperacute phase 치료
- 부작용
  - Injection site reaction, hypersensitivity, lymphadenopathy, 감염증



# Antibodies as immunosuppressants

## Rh<sub>0</sub>(D) immune globulin(Rh<sub>0</sub>GAM)

- 작용기전
  - Human IgG against RBC Rh<sub>0</sub>(D) Ag.
  - Feedback immunosuppression
- 임상적 사용
  - 신생아 Rh 용혈성 빈혈 예방

# Antibodies as immunosuppressants

## Monoclonal antibodies

- Muromonab-CD3
- Daclizumab
- Infliximab

# Antibodies as immunosuppressants

## Muromonab-CD3

- 작용기전
  - Destruction of T lymphocytes
    - Blocks killing action of cytotoxic T cells by binding to CD3 on T cells
- 임상적 사용
  - Renal allograft acute rejection
  - Steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients
- 부작용
  - 과민반응
  - 발열, 오한, 호흡곤란, 폐부종

# Antibodies as immunosuppressants

## Daclizumab

- 작용기전
  - Blocks the IL-2 receptor (basiliximab)
    - Prevent activation of T cells by IL-2
      - IL-2; T cell proliferation, activation of T<sub>H</sub>1, NK and LAK cells
- 임상적 사용
  - Renal transplantation(+ immunosuppressants)
- 부작용
  - Well tolerated, 위장관 장애

# Antibodies as immunosuppressants

## Infliximab

- 작용기전
  - Binds to TNF- $\alpha$ 
    - TNF- $\alpha$ ; proinflammatory, macrophage activation
- 임상적 사용
  - 자가면역질환
    - Remissions in treatment-resistant Crohn's disease
    - Rheumatoid arthritis(+ methotrexate)
    - Inflammatory bowel disease
- 부작용
  - Infusion reactions, infection

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# Immunomodulating agents

- 임상적 사용
  - 면역결핍 질환
  - 만성 감염 질환
  - 암
- 종류
  - Aldesleukin
  - Interferons(IFNs)
    - IFN- $\alpha$ -2a, IFN- $\beta$ -1b, IFN- $\gamma$ -1b
  - BCG
  - Thymosin

# Immunomodulating agents

## Aldesleukin

- 작용기전
  - Recombinant IL-2
    - IL-2; T cell proliferation, activation of  $T_H1$ , NK and leukocyte-activated killer(LAK) cells
- 임상적 사용
  - 보조요법
    - Renal cell carcinoma



# Immunomodulating agents

## Interferons

- 종류
  - Interferon- $\alpha$ ,  $\beta$ ; activates NK cells, antiviral, oncostatic
  - Interferon- $\gamma$ ; activates  $T_H1$ , NK, CTL and macrophages, antiviral, oncostatic
- 임상적 사용
  - Interferon- $\alpha$ -2a
    - Hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, Kaposi's sarcoma, hepatitis B, C
  - Interferon- $\beta$ -1b
    - Relapsing multiple sclerosis
  - Interferon- $\gamma$ -1b
    - Chronic granulomatous disease(defect in phagocytes)
      - 감염증 발생률 감소

# Immunomodulating agents

- BCG(Bacille Calmette-Guerin)
  - 작용기전
    - Activation of macrophage
  - 임상적 사용
    - 결핵 예방접종, superficial bladder cancer
- Thymosin
  - 작용기전
    - Hormone from thymus
      - Stimulates the maturation of pre-T cells
      - Promotes the formation of T cells from ordinary lymphoid stem cells
  - 임상적 사용
    - DiGeorge's syndrome(thymic aplasia)

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# Mechanisms of drug allergy

- Type I drug allergy
  - 발현 시간; 2-30 min.
    - Immediate(즉시형)
  - IgE
  - mast cell degranulation
  - 종류
    - Penicillins, sulfonamides

# Mechanisms of drug allergy

- Type II drug allergy
  - 발현 시간; 5-8 hrs.
  - IgG, IgM, cytotoxic
  - 종류
    - 자가면역질환
      - Methyldopa
        - » 용혈성 빈혈
      - Hydralazine, clozapine, procainamide
        - » SLE
      - Quinidine
        - » Thrombocytopenic purpura

# Mechanisms of drug allergy

- Type III drug allergy
  - 발현 시간; 2-8 hrs.
  - IgG, IgM, immune complex, complement activation
  - 종류
    - Drug-induced serum sickness, vasculitis
    - Sulfonamides;
      - Stevens-Johnson syndrome

# Mechanisms of drug allergy

- Type IV drug allergy
  - 발현 시간; 24-72 hrs.
    - Delayed(지연형)
  - T-cells
  - 종류
    - Topical application of drugs
      - contact dermatitis