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Research Article

IMMUNOBIOLOGICALS

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ABSTRACT

Immunobiologicals are the biologically active agents with immunological actions that are useful for the management of immunologically mediated diseases of infectious or non-infectious origin.

Keywords: Immunobiologicals, Epitope, Interferon, Monoclonal antibodies.

INTRODUCTION

Biologicals are molecules that modify the cascade of immunological processes leading to inflammation. Principal immunobiologicals are monoclonal antibodies (Mabs), fusion inhibitors, and interferons (IFNs). Paul Ehrlich first described Mab as "magic bullets" in search of toxins.

An antibody is a protein used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. Each antibody recognizes a specific antigen unique to its target.

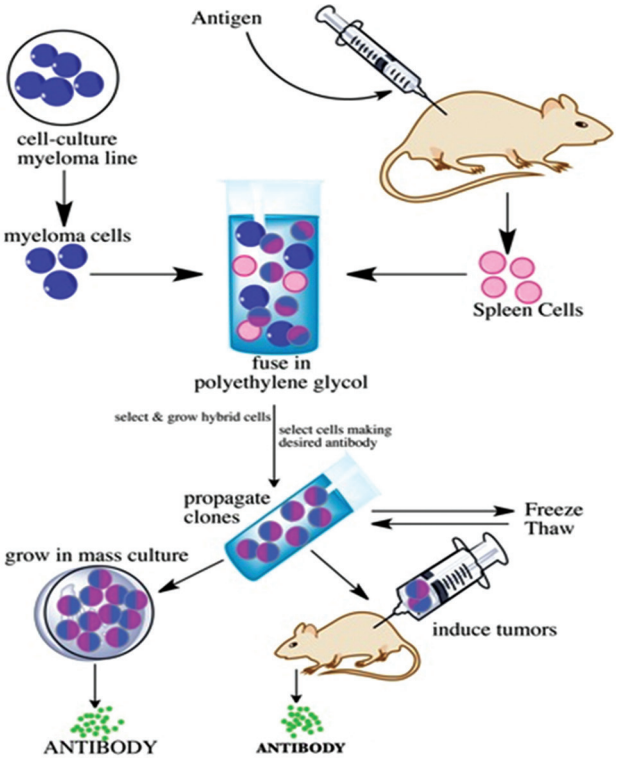
Mabs are antibodies that are identical because they were produced by one type of immune cell, all clones of a single parent cell. Polyclonal antibodies are antibodies that are derived from different cell lines. They differ in amino acid sequence.

The antigen associated with tumor cells are called as the "TUMOR MARKER." Antibodies produced as a result of specific tumor markers monoclonally can be conjugated with drug molecule which, in turn, can be targeted to the specific cells or tumor tissues. Targeting antibodies with drugs involve the following steps: (1) Identification of the new antigen produced by the tumor cells, (2) production of antibody monoclonally against the identified new antigen, and (3) formation of drug antibody conjugate or complexes.

These complexes concentrate at the tumor site and deliver the drug. There are several advantages when drugs are delivered as antibody conjugates. The conjugates can specifically reach the target cells without causing any damage to the normal tissue. The drug antibody conjugate could be expected to be the ideal agents for drug targeting in chemotherapy.

Production of Mab

An antigen is injected into a mouse, and after a few weeks, its spleen is removed and plasma cells are extracted. The mouse's spleen cells are fused with myeloma cells to create hybrid cells called hybridoma cells. Each hybridoma cell indefinitely produces identical antibody, and the hybridoma cells are then screened using an antigen/antibody assay that will reveal which cells produce the desired antibody. The collection of selected hybridoma cells that produce the preferred antibody is rescreened multiple times until a pure line is isolated. These cells are grown in a culture and/or injected into mice to induce tumors. The cells can also be frozen and saved for later use. The hybridoma method for producing Mab is useful because large amounts of specifically tailored identical antibodies can be produced easily [1].



PRODUCTION OF MAB

Mabs are classified according to the decreased order of antigenicity of their components intomurine, chimeric, primatized, and humanized.

TYPES OF MAB

1. Murine Mab: Whole antibody is of murine origin produced by hybridoma technology. Major problems with murine Mabs include reduced stimulation of cytotoxicity, formation of complexes after repeated administration, allergic reactions, and anaphylactic shock, for example, Afelimomab.
2. Chimeric Mab: Chimeric antibodies composed of murine variable regions fused onto human constant regions developed by recombinant DNA technology. Antibodies are approximately 65% human origin. This reduces immunogenicity, thus increases serum half-life, for example, Basiliximab and Cetuximab.
3. Humanized Mab: Humanized antibodies are produced by grafting murine hypervariable domains into human antibodies are

approximately 90–95% human origin this bind weakly to the antigens, for example, Apolizumab and Atlizumab.

4. Human Mab: Human Mabs are produced by transferring human immunoglobulin genes into the murine genome, after which the transgenic mouse is vaccinated against the desired antigen, leading to the production of Mab, for example, Belimumab and Cixutumumab.

Mechanism of action of Mab

Antibody-dependent cell-mediated cytotoxicity (ADCC)

ADCC immunoglobulin's clustered on the surface of the targeted cells and exposes its tail (Fc) region to be recognized by the Fc receptors present on the surface of the macrophages and neutrophils. This causes lysis of tumor cell.

Radioimmunotherapy

It involves the use of radioactively conjugated murine antibodies against cellular antigens. Emitted radiation causes tumor cell lysis. More applicable to lymphomas as they are highly radiosensitive malignancies.

Antibody-mediated enzyme prodrug therapy

An antibody developed against a tumor antigen is linked to a drug-activating enzyme and injected to the blood subsequent systemic administration of non-toxic agent or prodrug results in its conversion to a toxic drug and results in cytotoxic effect.

Immunoliposomes

These are antibody conjugated liposome's can carry drugs or therapeutic nucleotides and when conjugated with Mab, deliver the entrapped drug or toxin, especially to the target cells.

Immunotoxins

Immunotoxins are proteins that contain a toxin along with an antibody that binds specifically to target cells. All protein toxins are work by enzymatically inhibiting protein synthesis. Various plant and biological toxins have been genetically fused/chemically conjugated with the antibodies that bind to cancer cells.

Antibody drug conjugates

Antibody-drug conjugates are Mab attached to biologically active drugs by chemical linkers with liable bonds reduce side effects and show wide therapeutic window doxorubicin, duanomycin, chlorambucil, etc., can be conjugated with Mab.

Fragments of Mabs

Fragments of Mabs Fab and F(ab) 2 are less immunogenic but have greater tumor penetration power than normal antibody and are helpful in detecting smaller lesions (<2 cm) not seen on computed tomography. ScFv is mainly used as delivery vehicles for cancer therapy.

Table 1: Immunobiologicals [2]

Cytokine blocking agents	Target	Type	Indication
Afelimomab	Anti-TNF-α	Protein	Sepsis
Infliximab (Remicade)	Anti-TNF-α	Chimeric	Behcet's disease Toxic epidermal necrolysis
Etanercept (Enbrel)	Anti-TNF-α and TNF-ß	Fusion protein	Pemphigus
Agents targeting cell surface epitopes			
Alefacept (Amevive)	CD-2-LFA-3	Fusion protein	Psoriasis
Alemtuzumab (Campath)	CD-52	Humanized	Chronic lymphocytic leukemia
Apolizumab	HLA-DR beta	Humanized	Non-Hodgkin's lymphoma
Belimumab (Benlysta)	B-cell-activating factor (BAFF)	Humanized	Sjogren's syndrome Systemic lupus erythematosus (SLE)
Bevacizumab (Avastin)	Vascular endothelial growth factor (VEGF)	Humanized	Colorectal cancer
Basiliximab (Simulect)	CD-25	Humanized Mab	Transplant rejection
Cetuximab (Erbitux)	Epidermal growth factor receptor (EGFR)	Chimeric	Head and neck cancer
Certolizumab (Cimzia)	Inhibition of TNF-α signaling	Humanized	Crohn's disease
Cixutumumab	IGF-1 receptor	Human	Metastatic Rhabdomyosarcoma Hepatocellular carcinoma
Daclizumab (Zenapax)	CD-25	Humanized Mab	Transplant rejection
Denileukin Diftitox (Ontak)	CD25/Ib 2	Fusion toxin	Cutaneous T-cell lymphoma
Efalizumab (Raptiva)	CD-11 a/CD18	Humanized Mab	Psoriasis
Eculizumab (Soliris)	Complement system protein C5	Humanized	Paroxysmal nocturnal hemoglobinuria
Gemtuzumab (Mylotarg)	CD-33	Humanized	Acute myelogenous leukemia
Ibritumomab (Zevalin)	CD-20	Murine	Non-Hodgkin's lymphoma (with Yttrium-90 or Indium-111)
Mepolizumab (Nucala)	IL-5 α of Eosinophil	Humanized	Asthma
Siplizumab	CD-2	Humanized Mab	Graft versus host disease psoriasis
Tocilizumab (Actemra)	IL-6	Humanized	Rheumatoid arthritis
Visilizumab (Nuvion)	CD-3	Humanized	Cohn's disease ulcerative colitis

Mabs: Monoclonal antibodies, IL: Interleukin, TNF: Tumor necrosis factor

Table 2: Dosages of some Mab

Mab	Dosages
Infliximab (REMICADE)	5 mg/kg/dose i.v alone or in combination with other agents 100 mg injection
Etanercept (ENBREL)	25 mg subcutaneously. Twice weekly for minimum 12 weeks
Alefacept (AMEVIVE)	10–15 mg intramuscular injection once weekly for 12 weeks
Efalizumab (RAPTIVA)	0.7 mg/kg subcutaneous injection (conditioning dose) followed by weekly subcutaneous doses of 1 mg/kg (maximum single dose not to exceed a total of 200 mg). A single vial delivers 125 mg
Denileukin Diftitox (ONTAK)	9–18 mcg/kg/d intravenous infusion daily for 5 days every 3 weeks, six courses are required to show partial or complete response. A single vial delivers 150 mcg/ml per vial

Mabs: Monoclonal antibodies

Table 3: Indications and doses of intravenous immunoglobulins

Indication	Doses and duration
Pemphigus vulgaris	2 g/kg i.v. single dose monthly or 1 g/kg/day×3 days every month or 0.5 g/kg/day×5 days every month
Toxic epidermal necrolysis	0.8–5.8 g/kg for 1–5 days
Dermatomyositis	2 g/kg i.v single dose monthly for 2–4 months
Graft versus host disease (GVHD)	250–500 mg/kg weekly from day 8 to day 111 after bone marrow transplantation
Autoimmune urticaria	0.4/kg/day for 5 days
Kawasaki disease	2 g/kg i.v as single dose
Congenital/acquired agammaglobulinemia or hypogammaglobulinemia	0.25 g/kg every 3 weeks in childhood
Scleromyxedema	2 g/kg i.v. monthly for 3 months
Pyoderma gangrenosum	1–2 g/kg i.v. monthly for 2–4 months

Problems of drug delivery by Mab[12]

1. Slow elimination of Mab from the blood.
2. Poor vascular permeability.
3. Cross-reactivity with normal tissues, metabolism of Mab conjugates.
4. May bind with the targeted epitopes present on other tissues, which may lead to the damage of normal cells.
5. Tumor uptake may be increased through administering high doses.

Disadvantages of Mab

1. Mab production, a time-consuming process because entire process requires 3–4 months for one fusion experiment.
2. Average affinity of Mab is generally lower.
3. Any physical/chemical treatment will affect all Mabs in that production.

IFN

IFNs are a family of glycoproteins which are synthesized by leukocytes (IFN-α), fibroblasts (IFN-β), and immune cells (IFN-ɤ) against viral infections and other non-viral challenges that in addition to having antiviral properties, also modulate various cellular functions. IFN-α is mainly used for therapeutic purposes.

IFN synthesized by recombinant techniques have therapeutic value in the treatment of viral infections of the skin and cutaneous malignancies. They are the products of bacterial fermentation of particular strain of *Escherichia coli* consisting genetically engineered plasmid containing a specific IFN gene from human leukocytes.

Mechanism of action of IFN

Antiviral

It induces enzyme 2′-5′ a synthetase, polymerizes ATP, activates cellular endonuclease, and degrade both viral and cellular RNA.

Antiproliferative effect

It inhibits mitosis of the cells and downregulates their growth factors.

Immunoregulatory effect

It induces expression of Classes I and II MHC complexes antigens on immune cells, enhances number of natural killer cells.

Principle indications of IFN

IFN-α2A

Recurrent aphthous stomatitis
IFN-α2A administered orally once daily in a low concentration (1200 IU/day) for 1 week [3].

Hemangioma

IFN-α2A 3 million units/m^2 per day should be used only in life-threatening hemangiomas act by inhibiting angiogenesis in whom high-dose corticosteroid therapy failed [4].

Chronic hepatitis B infection

About 10 MU/L pegylated IFN-alpha is used in the treatment of chronic hepatitis B infection [5].

Malignant melanoma

About 20 MU/m^2 i.v over 20 min for 5 consecutive days/week for 4 weeks (induction phase) followed by 10 MU/m^2 s.c injection 3 times/week for 48 weeks (maintenance phase). IFN-α2b has a dual effect of TAP1 (antigen-presenting cells of MHC complex) upregulation in antigen-presenting cells and in silent metastatic melanoma cells [6].

AIDS-related Kaposi's sarcoma

30 MU/^{m}2/dose subcutaneously or intramuscularly 3 times a week for 16 weeks of treatment till maximum response.

Condyloma acuminata

1 MU per lesion (maximum of 5 lesions in a single course). Intralesional injections should be 3 times weekly on alternate days for 3 weeks directed toward the center of the base of the lesion, which produce a small wheal if done correctly. An additional course may be administered at 12–16 weeks [7].

IFN ɤ

Used for the treatment of recalcitrant moderate-to-severe atopic dermatitis acts by inhibiting IgE synthesis by promoting proliferation of Th1 cells administered by weekly subcutaneous injections [8].

Intravenous immunoglobulins

Intravenous immunoglobulins are heterogeneous human gamma globulins consisting IgG with trace of IgA and IgM prepared by cold ethanol fractionalization of pooled human sera harvested from thousands of donors. Intravenous immunoglobulins are an important safe, effective therapeutic option as an immunomodulatory agent in the management of skin disorders where corticosteroids and immunosuppressive agents cannot be used.

Mechanism of action of intravenous immunoglobulins

1. Neutralization of microbe or toxin.
2. Inhibition of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α.
3. Superantigen neutralization.
4. Modulation of complement activation.
5. Acceleration of IgG catabolism.
6. Saturation of Fc receptors on macrophages (Fc receptors play a role in cytotoxic cell-mediated immunity and opsonization).
7. Suppression of antibody production and idiotypic (the variable part of an antibody including the unique antigen-binding site is known as idiotype) antibodies.
8. Helps to clear immune complexes from the body in patients affected with systemic lupus erythematosus.

5% lyophilized powder dissolved in 5% dextrose. Available as immuglob 2.5 g/100 ml or 5 g/200 ml Vial. Since it is not compatible with normal saline, it has to be diluted with 5% dextrose in water.

Disadvantages of intravenous immunoglobulins

1. All intravenous immunoglobulins must be screened to minimize the risk of transmission of HIV, hepatitis B virus, and hepatitis C virus infection.
2. Can interact with live virus vaccines. Such vaccines should not be given 14 days before or 3 months after intravenous immunoglobulin administration.
3. Have risk of autoimmunity owing to infusion of antibodies.
4. Rebound flare-up can occur after discontinuation of intravenous immunoglobulins.
5. Anaphylactic reactions can occur.

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