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REVIEW ARTICLE

Monoclonal Antiobodies in Cancer Treatment

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Abstract

An antibody is a specialized glycoprotein that is produced from the activated B cells as a result of invasion of any foreign bodies (Antigen) into our body. The Antibodies circulate throughout the body until they find and attach to the antigen. Once attached, they can force other parts of the immune system to destroy the cells containing the antigen.

Keywords: Monoclonal antibodies; Cancer, MAbs.

Introduction

Monoclonal antibodies are identical antibodies that are produced from a single B cell clone.These are immunoglobulins that are identical in its protein sequence, thus same Antigen recognition site, affinity, biologic interactions and downstream biologic effects. Monoclonal antibodies recognise and bind to unique epitopes or binding sites and stimulate the patient's immune system to attack the cells and thus providing protection against disease organisms.

Derivation from a single B cell clones and subsequent targeting of a single epitope is what differentiate monoclonal and polyclonal antibodies. Polyclonal antibodiesare antibodies that are derived from different B-lymphocytes cell lines .Comparing with monoclonal antibody polyclonal antibodies are having different antigen binding sites can bind to multiple epitopes ,have a high potential for cross reactivity and their production is very easy, rapid and less expensive.[1]

Production

Monoclonal antibodies (mAbs) are produced using hybridoma technology. A large number of identical antibodies i.e monoclonal antibodies can be produced using this technique. The first in the production is the immunization of mouse. This is by injecting a mouse or any other mammal with an antigen that induce an immune response that is the B cells start producing antibodies that bind to the injected antigen.[2] The second step involves screening of mice for antibody production by measuring the serum antibodies in the blood samples using ELISA (Enzyme linked immuno sorbant assay) and flow cytometry techniques.Next is the isolation of spleen cells containing antibody producing B cells. After the isolation of spleen cells they are fused with myeloma cells (immortal B cell cancer cells)to produce a hybridoma and this will

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have both the features of spleen cells (antibody producing ability) as well as that of myeloma (longevity & reproductivity). All other unfused B cells are allowed to die by adding a aminopterin to the culture.After the screening of the hybridomas in the hypoxanthine aminopterin thymidine (HAT) medium the desired ones are cloned in the culture and each cell grow into genetically identical hybridomas. Then the supernatant of each clone are screened for presence of desired antibody and the clone of cells containing the desired antibodies are grown in bulk finally the antibody is harvested from the culture.[1]

Advantages[3]

- It is homogeneous.
- Very specific
- They can select a specific epitope and can generate antibodies against a wide range of antigenic determinants.
- Hybridoma serves as an immortal source of monoclonal antibody.
- They can bind to specific diseased or damaged cells and can be used to treat a wide range of conditions.
- Same quality of the antibody is maintained among the different production batches.
- mAbs are highly reproducible and scalable, unlimited production source.
- Better speed, sensitivity and specificity of assays.
- Antigen used for the production need not be pure.
- The side effects can be treated and reduced by using mice human hybrid cells or by using fraction of antibodies.

Disadvantages[3]

- Monoclonal antibodies have a low affinity than polyclonal antibodies.
- Sometimes the desired biology response is note made.
- Small peptide and fragments antigen may not be good antigens monoclonal antibody may not recognise the original antigen.
- The chances for unexpected cross reactions with unrelated antigens is very high.
- This is only well developed for mouse and rat and not for other animals.
- There is possibility of generating immunogenicity.
- In some cases hybridoma culture may subject to contamination.
- During the fusion process more than 99% of the cells do not survive.
- Very large time and effort commitment is needed in its production.

Types of Monoclonal Antibodies[5]

I. Based on Origin

1. Murine Antibodies:

The entire antibody is of murine origin ie, 100% is mouse derived.They can cause reduced stimulation of cytotoxicity ,allergic reactions ,anaphylactic shock in humans.The names of the treatment ends in -omab.

2. Chimeric Antibodies:

CHIMERIC antibodies are approximately 65 percentage human origin.The constant region of the antibody is human origin whereas the variable part is that of murine origin. This decreases immunogenicity and thus increases serum half Life.The names of the treatment ends in -ximab.

3. Humanised Monoclonal Antibodies:

This is mostly derived from human source ie, approximately 95 percentage. The only murine origin is the part of the antibody which binds to the target. The names of the treatment ends in - zumab.

4. Human Monoclonal Antibodies:

Human monoclonal antibodies are 100 percentage derived from a human source. These are produced by transferring human immunoglobulin genes into the murine genomes after which the transgenic mouse is vaccinated against the desired antigen leading to production of monoclonal antibodies. The names of the treatment ends in -umab.

II. Other Types-

1. Naked:

In this antibodies, no drug or radioactive material are attached to them.They work by themselves. It is the most common mAbs used in the cancer treatment.

2. Conjugated:

Monoclonal antibodies joined to a chemotherapy drug or radioactive particle.These mAbs are used as a homing device to take one of these substances directly to the cancer cells.

3. Radiolabelled

Antibodies have small radioactive particles attached to them.The antibody delivers radioactivity directly to cancer cells.Treatment with these types of mAbs is also called radio-immuno therapy.

4. Chemolabelled

Powerful chemotherapy or other drug are attached to them. They are also known as antibody-drug conjugates.

4. Bispecific:

These are made up of two different monoclonal antibodies so that they can attach to different proteins at the same time.

Application[4]

1. Diagnostic Application

Monoclonal antibodies are used for the diagnosis of various infectious diseases, for detecting pregnancy, monitoring drug levels, matching histocompatibility antigen etc. It is widely used in the detection of various infections like hepatitis, influencer streptococcal, Chlamydia.

A monoclonal antibody can also be used for detection of pregnancy (only after 14 days of conception). Because of the selective binding property of monoclonal antibodies it helps in the detection of low level human chorionic gonadotropin (HCG). This test improves the accuracy of serum beta HCG radio immunoassay for confirmation of normal pregnancy or evaluation of possible abnormal pregnancy.

mAbs is also used to detect presence and quantity of substances for instance in a Western blot test or immunofluorescence test and also used to purify a substance with techniques called immunoprecipitation and affinity chromatography. Another ability is to detects protein of interest either by blotting or by immunofluorescence. Diagnostic test of Cancer like radio immunodetection (RID) and radio immunotherapy (RIT) uses monoclonal antibodies to specifically target antigen cells that are associated with tumors and then blast this with a lethal dose of radiation also minimising the level of radiation absorbed by normal cells.

2. Therapeutic Applications

Monoclonal antibodies plays an important role in the treatment of various diseases like cancer, asthma, cardiovascular diseases, autoimmune disorders like rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, Psoriasis, ulcerative colitis, multiple sclerosis, septicemia, poisoning, substance abuse, viral infections etc.

Monoclonal antibodies (mAbs) have a potential therapeutic application in Cancer. The monoclonal antibodies when enters the body attaches to the cancer-specific antigen. This induce various immunological responses to cancer cells like apoptosis, inhibiting growth by blocking the growth signals or stopping formation of new blood vessels. Conjugated monoclonal antibody therapy is the another therapy used in the treatment of cancer.Toxins or radioactive isotopes are bound to the constant region of mabs. when the monoclonal antibodies bind to the surface cell of a tumor the toxin or radioactivity will kill the cancer cells and all cells within a certain radius. In this way cancer cells within the tumor will be killed.Mabs are also used in radioimmunotherapy , antibody directed enzyme prodrug therapy, immuno liposomes etc. Bispecific monoclonal antibodies with their Fab regions can bind to both target antigen and to a conjugate or effective cells. Mabs can also be modified for delivery of a toxin radioisotopes cytokines or other active conjugates.

The first monoclonal antibody to be licensed for human use was the orthochrome OKT3 (developed as an antibody to the T3 antigen). This is very useful for the treatment of organ transplant rejection as well as in the management of immune-related graft rejection events.

The murine intact IgG antibody directed against CD3 antigen on t-lymphocyte is used unconjugated to effectively a reverse acute rejection episodes with renal, hepatic, cardiac or combined kidney pancreas transplants. A ricin toxin immuno conjugate directed against CD5 antigen of T lymphocytes is effective both in the treatment and prevention of graft versus host diseases.

Various mabs like infliximab, adalimumab is used for the treatment of many autoimmune disorders like rheumatoid arthritis kaunse disease ulcerative colitis by inhibiting TNF a. Omalizumab is useful in moderate to severe allergic asthma and this is by inhibiting IgE. Likewise Basiliximab, Daclizumab inhibit IL-2 on activated t cells and their by help to prevent acute rejection of kidney transplant.

Sideeffects of Monoclonal Antibodies

Monoclonal antibodies are actually safe and they tend to have a fewer serious side effects when compared to that of chemotherapy drugs or any other drugs, but still it can cause problems like various allergic reactions, fever, headache, chills, fatigue, low blood pressure, nausea, vomiting, diarrhoea etc.

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