Antibodies for Cancer Therapy

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Abstract

Cancer is one of the biggest killers today. Radiation and chemotherapy are the most commonly used treatments. Efforts are on to discover methods of treatment that are less toxic for the patients. This article reviews the use of antibodies for cancer therapy. Antibodies, on account of their specificity can be used for less toxic and more effective destruction of tumor cells. Antibodies, in conjugation with other agents are being investigated for their superior anti tumor activity.

Keywords: Antibodies, tumor, antigen

1. Introduction

One of the major hurdles in cancer therapy seems to be specificity towards the tumor cells. Immunotherapy helps to achieve substantial therapeutic effect with a high degree of specificity.

Antibodies can be used as probes to find out which components of cells are involved in the particular pathological process.

2. Overview of Antibodies

2.1 Structure of Antibodies[1, 2]

Antibodies are glycoproteins that bind antigens with high specificity and affinity. They are molecules originally identified in the serum and are alternatively termed as immunoglobulins. In humans there are five chemically and physically distinct classes of antibodies: IgG, IgA ,IgM, IgD, IgE.

All antibodies have the same structure i.e. same basic four polypeptide chain units: two light (L) chains and two heavy (H) chains. In this basic unit, one L-chain is bound by two disulphide bridges and two non-covalent interactions, to one H-chain. Similarly, the two H-chains are bound together by covalent disulphide bridges as well as by non-covalent hydrophilic and hydrophobic interactions. There are five different kinds of H-chains (μ, α, γ, δ) which determine the classes of antibody (IgM, IgD, IgA, IgE, IgG). Moreover there are different kinds of L-chains like λ, κ. Each antibody unit can have only λ or κ L-chains, but not both. Both H and L-chains have intra chain disulphide bridges every 90 amino-acid residues, which create polypeptide loops, domains, of 110 amino acids. The domains are referred to as vh, vl, ch1, ch2 etc and have particular functional properties. The n-terminal half of the H-chain and all of the L-chain together make up the Fab fragment and contains the antigen binding site. The antigen binding site of the antibody is composed of the N-terminal quarter of the H-chain combined with the n-terminal half of the L-chain. Since the amino-acids sequence of these regions differ, they are called variable regions and are involved in binding an antigenic determinant. Most of the antibody molecule (the C terminal three-quarters of the H-chain and the C-terminal half of the L-chain) are the constant regions that do not bind antigen, rather determine the fate of antigen bound by the antigen binding site. In particular the C-terminal half of the H-chain (the fc fragment that crystallized) region serves other functions, i.e., combines with complement, is cytophilic (that binds to certain types of cells such as macrophages).

2.2 Monoclonal Antibodies (MAbs)

Monoclonal antibodies are predetermined and monospecific and are prepared by fusion of an immortal cell (a myeloma tumor cell) with a specific predetermined antibody - producing B cell from immunized animals or humans. The resulting hybridoma cell is immortal and synthesizes homogenous, specific, MAb which can be made in large quantities and against every antigen.

2.3 Sources of Various MAbs:[3]

- Murine MAbs:[4]

  They are obtained from murine hybridomas produced by fusion of beta-lymphocytes from immunized mice or rats with murine myeloma cells.

- Chimeric Abs:

  It is formed by combining the antigen binding parts (variable region) of mouse Ab with effector parts (constant regions) of the human Ab.

- Humanized Ab:

  They are those whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans. They produce less immunogenicity than murine and chimeric Abs.

- Fully Human Monoclonal Antibodies[5]:

  The two approaches used are phage display and genetically engineered mice to produce more human like antibodies. They are used to counter side effects of the other types of Abs.

3. Antibodies for Cancer Therapy[6, 7, 21]

3.1 Unconjugated Antibodies from Human or Murine Sources

The immune system attacks foreign invaders in body, but it doesn't always recognize cancer cell as enemies. A MAb can be directed to attach certain parts of a cancer cell thus marking the cancer cell and making it easier for the immune system to find it.

Chemicals called growth factors attach to receptors on the surface of normal cells and cancer cells signaling the cell to grow. Certain cancer cells make extra copies of growth factor receptor making them grow faster than normal cells. MAbs can block to these receptors and prevent growth signal from getting through.

A monoclonal antibody can be used to decrease the number of circulating tumor cells, induce circulating dead cells by forming complexes with circulating antigen.

3.2 Conjugated Antibodies

Monoclonal antibodies conjugated with drugs, toxins, and radioisotopes using the specificity of the monoclonal antibody to carry enhanced killing capacity directly to the tumor cells.

- Radio nuclides – A high dose of irradiation can be achieved by conjugating radioactive elements like As^{211}, Y^{90}, I^{125} with antibodies.
- Chemotherapeutics – The conjugates enter the tumor cells by endocytosis then undergo cleavage to produce the desired cytotoxic effect with high specificity.
- Immunotoxins[8] – Antibodies conjugated with protein toxins based on ricin, gelonin, saporin, diphtheria toxins are used to direct the toxins towards the target tumor cells. They then enter the tumor cells and the toxin moiety leads to interference with protein synthesis eventually leading to cell death.
- Antibody directed enzyme prodrug therapy[11] – Here the antibody is used to direct an enzyme to the tumor site. This enzyme is then used to activate the non toxic prodrug that is administered. Since the drugs are activated external to the cell membranes neighboring cells may also be destroyed.
- Cytokines and inflammatory molecules that include tumor necrosis factor[8, 22] and other messenger molecules of the immune system can cause destruction of tumor cells by producing an inflammatory response.
- Antisense oligonucleotides may be linked to the antibodies or they may be incorporated in viral particles equipped with antibodies on their surface. They can cause disruption in the production of proteins of the tumor cells.

4. Antigen

Antibody therapy is based on the binding of the antibody to the antigen. The requirements of an ideal antigen are: [9]

- The antigen should be expressed only on the tumor cells. It should not be expressed in the host cells. Damage to the cells carrying the antigen should not be toxic to the host.
- Antigen should have some critical biological function and its presence should be essential for survival of tumor cells.
- It should be expressed in all tumor cells so that all of them can be eliminated.
- It should not undergo any form of modulation or mutation i.e. there should be no alternate antigen expression.

All the characteristics may not be absolutely essential for the activity of the antibodies. The absence of some of these characteristics may lead to higher host toxicity and/or reduced anti tumor activity.

5. The Present:

5.1 Problems Faced [10,11]

- Use of antibodies for cancer therapy is limited to its use in solid tumors mainly lymphomas and leukemia. This is mainly due to poor tumor penetration and target specificity. So a small fraction of the antibodies actually reach the tumor. Decreasing tumor size can improve penetration.
- sFvs have better tumor penetration than whole IgG. [12] But the requirement of the attachment of a cytotoxic moiety to the Fc nullifies the benefits attained by size reduction. So there is a need for smaller molecules with improved penetration.
- Antibody reactions are species specific. Clinical studies cannot be conducted like the ones that are conducted for other therapeutic agents.
- Murine proteins are highly immunogenic[7]. Administration of murine antibodies leads to the development of human antimouse antibody.
- Some of the antigens on cancer cell surfaces modulated off the surface and into the circulation when antibody attached. Modulation could also cause internalization of the complex. However this could be exploited to gain a therapeutic advantage by attaching an immunoconjugate, potentially making it more therapeutically active.
- Slow elimination of mab from the blood and poor vascular permeability are problems encountered. Blood concentration however can be reduced by local administration. Retention of antibody conjugate with the tumor can be improved by inhibition of metabolism by using more stable linkage.

5.2 Products in the Market

Rituximab[14] is a chimeric Anti CD20 antibody used in the treatment of relapsed low grade B-cell lymphoma.

Trastuzumab[15] is a humanized antibody that reacts with the second part of the human epidermal growth factor receptor 2. It is used primarily in conjunction with chemotherapy for breast cancer.

Bevacizumab[16] is a humanized monoclonal antibody which targets vascular endothelial growth factor. It acts by reducing blood supply to the tumors thereby slowing down or interrupting growth. It is mainly used in colorectal cancer.

Alemtuzumab[17] is a humanized monoclonal antibody which targets the CD52 antigen found on B lymphocytes. It is used mainly in chronic lymphocytic leukemia.

Cetuximab[18] is a chimeric antibody that acts on epidermal growth factor receptor and has been used along with chemotherapy in the treatment of colorectal cancer.

Panitumumab[19] is a totally human antibody acting on epidermal growth factor receptor and is used in the treatment of colorectal cancer.

In addition there is one drug immunoconjugate and two radioisotope immunoconjugates.

Gemtuzumab ozogamicin (Mylotarg)[20] contains the antibiotic calicheamicin conjugated with the humanized antibody that acts on the CD33 antigen is used for leukemia treatement.

Tositumomab containing I^{131} conjugate[13] (Bexxar) and Ibritumomab containing Y^{90} conjugate (Zevalin)[17] are anti CD20 antibodies used for lymphoma treatment.

6. Conclusion

Since 1983, antibodies have been investigated for their use in cancer therapy. Initially immunogenicity due to murine antibodies was one of the major hurdles. But today with the availability of modern recombinant technologies, production of chimeric, humanized and completely humanized antibodies has become possible. Also immunoconjugates are proving to be highly useful for producing required therapeutic effect with acceptable levels of toxicity. Immunotherapy can thus help make cancer treatment more specific, effective and less traumatic to patients by reducing toxicity levels.

7. References

Book References

1. Lydyard P. M., Whelan A., Fanger M. W., Instant notes in immunology, Bios Scientific publishers, UK 2003, 63-66.
2. Voet Donald, Voet Judith, Biochemistry, J Wiley and sons, USA, 2004, 1207- 1214.
3. Harlow Ed, Lane David, Antibodies- A Lab Manual, Cold spring harbor lab, USA, 1988, 141-276.
4. Monoclonal antibodies: Methods and Protocols, Humana Press, USA 2007, 1-30.
5. Maher Albitar, Subramanian G., Antibodies Volume 2, Novel technologies and therapeutic use, Kluver Academic/ Plenum publishers, USA, 2004 1-49.
6. Waldmann H., Gilliard L., Cobbold S., Hale G., Fundamental immunology 4th edition, Paul W., Lippincott Raven publishers, 1511-1530.
7. Foon Kenneth, Monoclonal antibody therapy of human cancer, Martinus Nijhoff publishing, USA, 1985, 1-135.
8. Maloney. J. David, Monoclonal antibody based therapy of cancer, Grossbard M, Marcel Dekker Inc, USA, 1998, 53-80
9. Harris. W, Adair J , Antibody therapeutics, CRC press, USA, 1997, 277-341.
10. Vyas S.P., Khar Roopkrishan, Targeted and controlled drug delivery, CBS publishers, 521- 538.
11. Michael Page, Tumor targeting in cancer therapy, Humana Press, USA 2002, 1- 235.
12. Welschof M, Krauss J, Recombinant antibodies for cancer therapy, Humana press, USA 2003, 235-250.
13. Goldenberg David, Cancer therapy with radiolabelled antibodies, CRC Press, USA, 1995,217-228.

Journal References

14. Coiffier B., Lepage E., Briere J., et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. New England Journal of Medicine Jan 2002, 346, 235-242.
15. Bostrom J. et al,, Variants of the antibody Herceptin that interacts with HER2 and VEGF at antigen binding site, Science, March 2009, 323, Issue no 5921, 1610-1614.
16. Hurwitz H., Fehrenbacher L., Novotny W., et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. New England Journal of Medicine, June 2004, 350, 2335-2342.
17. Cheson B.D., Leonard J. P., Monoclonal antibodies for B cell Non Hodgkin's lymphoma, New England Journal of Medicine, Oct 2008, 359, 613-626.
18. Cunningham D., Humblet Y., Siena S., et al, Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer, New England Journal of Medicine, July 2004, 351, 337-345.
19. Cierdiello F., Tortora G., EGFR antagonists in cancer treatment, New England Journal of Medicine, March 2008, 58, 1160-1164.
20. Edward A. Stadtmauer, Gemtuzumab ozogamicin in the treatment of acute myeloid leukaemia, Current oncology reports, Oct 2002, 4, Issue No 5, 375-380.

Magazine References

21. Rao Rama, Prasanthi N. I., Manikaran S., Pratyusha J., Drug targeting to cancer cell: role of MAbs in cancer therapy, Pharmabuzz, Nov 08, 30-35.
22. Frances Balkwill, Tumor necrosis factor and cancer, Nature reviews cancer, May 2009, Vol 9 no 5, 361-368.

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