

medical milestones

Immunology: making magic bullets

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Continuing developments in our understanding of antibodies are taking us into a future of limitless and highly specific treatments

The discovery of vaccination at the end of the 18th century undoubtedly had a great impact on human survival. Since then, our understanding of the immune system has advanced in leaps and bounds, and we now know how vaccination endows us with the capacity to fight invading pathogens. We appreciate too that our immune system has been shaped by the challenges of dealing with diverse infectious organisms and that similar immune mechanisms underlie conditions such as autoimmunity, allergy, transplant rejection, and tumour immunity, even though these may not involve invading pathogens.

Understanding of how the immune system distinguishes host cells from "foreign" cells leapt in 1958, when the French medical researcher Jean Dausset described the first of many human histocompatibility antigens (HLA antigens). Our immune system uses the pattern of HLA antigens on the surface of cells as a biological signature—one that is almost unique to each of us. Whenever the immune system does not recognise the pattern of HLA antigens on a cell it creates antibodies and other substances to attack and destroy it. This is the main mechanism for immune recognition of infectious organisms. It also explains why our immune system attacks transplanted tissues and organs.

From transplantation to monoclonal antibodies

In the 1950s a Boston based team of doctors led by Joseph Murray transplanted a kidney from a 23 year old man into his seriously ill identical twin. In the following years Murray (who won the 1990 Nobel prize for medicine) and international colleagues were able to show that by matching as many HLA antigens as possible between organ donors and recipients, and by adding therapies to reduce the immune response, organ transplantation was feasible. Since then bone marrow, kidney, liver, skin, heart, and lung transplants have saved more than 400 000 lives.

Greater understanding of the biological weapons that make up our immune system has resulted in antisera and monoclonal antibody technology. This has had a major effect on disease diagnosis and is emerging as an important area for therapeutics. Two early pioneers of antibodies were Emil von Behring (Nobel prize for medicine, 1901) and Paul Ehrlich (who won the prize in 1908), who described the development and standardisation of antisera treatment against diphtheria toxin. Karl Landsteiner (Nobel prize for medicine, 1930) used von Behring and Ehrlich's theories on antisera in 1909 to develop the A, B, AB, and O blood group antigen system, thus leading to the widespread use of blood transfusion.

In 1978 two scientists based in the Laboratory for Molecular Biology in Cambridge, Césaire Milstein and Georges Köhler, showed that single clones of cells that produce antibodies could be formed by fusing individual plasma cells with immortalised B cell myelomas, thus producing millions of identical progeny secreting a single type of antibody. These monoclonal antibodies have revolutionised the

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diagnosis of disease through their application in immunoassays. Harnessing the sensitivity of radioisotopes (radioimmunoassay and immunoradiometric assay) and enzymes (enzyme immunoassay and enzyme linked immunosorbent assay), monoclonal antibodies are used to diagnose and monitor human disease, to ensure the quality of food and other biological materials, and to test for trace amounts of drugs and toxins. They have enabled scientists to visualise the outside and inside of cells, stimulating new imaging technologies such as flow cytometry (used to analyse fluorescently tagged blood and tissue cells) and confocal microscopy (for investigating the interior of our cells).

Initial use of monoclonal antibodies to treat disease in humans was limited, because the molecules were produced in mice and induced an anti-mouse response in the human host. Later, Gregory Winter and Michael Neuberger at the Laboratory for Molecular Biology discovered how to engineer the combining site of the mouse monoclonal antibody into the human immunoglobulin gene. The resulting chimeric antibodies, called humanised antibodies, could now be given to patients with little or no anti-mouse response.

The benefits of humanised monoclonal antibodies in the treatment of otherwise intractable diseases have been dramatic. Monoclonal antibodies to an inflammatory protein, tumour necrosis factor α (TNF- α), have been administered to over a million people with rheumatoid arthritis, with a spectacular reduction of symptoms. Patients treated with anti-TNF- α had fewer symptomatic joints, fewer joint erosions and less joint space narrowing, and better physical function for up to two years than patients who were given traditional anti-rheumatic drugs.

An antibody that depletes B cells shows remarkable efficacy in treating autoimmune diseases such as systemic lupus erythematosus: when compared with traditional treatments it results in significantly less lupus nephritis, arthritis, serositis, cutaneous vasculitis, mucositis, rashes, fatigue, and neurological symptoms. Monoclonal antibodies have helped reduce organ transplant rejection by inactivating the T cells that drive the host's response to the transplant. Passive vaccination with monoclonal antibodies may be used to fight new infections such as bird flu. The applications appear endless and include use in cancer, where monoclonal antibodies can target radioactive and other cytotoxic agents precisely to the tumour, in the so called magic bullet approach.

Limitless possibilities

Where will all this end? It is not really clear yet. Because monoclonal antibodies are so incredibly diverse, new and remarkable properties of antibodies continue to emerge. Some antibodies can mimic the action of specific ligands such as hormones; others can block or inactivate receptors on cell surfaces. For example, a monoclonal antibody has been generated that binds to the human IgE receptor and displaces the patient's own IgE without triggering the hypersensitive response of mast cells and basophils and thus blocks the allergic attack. The number of antibodies produced by mice is as many as 10^9 , and a complete recombination of variable genes performed ex vivo (when there is no elimination of self reactive clones) yields as many as 10^{12} different combinations. Thus the properties and specificities of antibodies that can be selected are effectively limitless. Indeed, it is estimated that more than a third of all drugs currently being developed by drug companies are monoclonal antibodies, and hence antibody technology will enable many more medical milestones to be reached in the foreseeable future.

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