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ASSIGNMENT

Discuss in details the aspects of medical biotechnology

ANSWER

- Pharmacology
- Gene therapy
- Stem cells
- Tissue engineering
- Xeno -transplantation
- Vaccines
- Antibodies

PHARMACOLOGY

Pharmacology is a branch of medicine and biology concerned with the study of drug action, where a drug can be broadly defined as any man made, natural or endogenous molecule which exerts a biochemical and physiological effect on the cell, tissue, organ or organisms. Study of the interaction that occurs between a living organism and chemical that affect normal or abnormal biochemical function.

1 INSULIN PRODUCTION

Production of genetically engineered human insulin was one of the first breakthroughs of biotechnology in the pharmaceutical company. Insulin was first produced in Escherichia coli through recombinant DNA technology in 1978.

PRINCIPLE: Mass production of human proteins, vaccines etc. by genetically modifying bacteria or viruses.

PROCESS: The human gene for insulin is placed into the bacteria, are cultured and allowed to produce insulin which is collected, purified and sold to diabetics worldwide.

- Grow bacteria that make the insulin protein(fermentation).
- Isolate the protein from all the other stuff that was in the fermentation tank(purification).
- Convert the insulin to its active form(processing).

2 HUMAN GROWTH HORMONE

Production of human growth hormone was first done in 1979 using recombinant DNA technology. Scientists produced human growth hormone by inserting DNA coding for human growth hormone into a plasmid that was implanted in *Escherichia coli*. This gene that was

inserted into the plasmid was created by reverse transcription of the mRNA found in pituitary gland to complementary DNA.Prior to this development, human growth hormone was extracted from the pituitary gland of cadavers, as animal growth hormones have no therapeutic value in humans.

3 HUMAN BLOOD ClOTTING FACTORS

Production of human blood clotting factors was enhanced through recombinant DNA technology. Human clotting factor is was the first to be produced through recombinant DNA technology using transgenic Chinese hamster ovary cells in 1986. Plasmids containing the factor ix gene, along with plasmids with a gene that codes for resistance to methotrexate, were inserted into Chinese hamster ovary cells via transfection.

4 GENE PILL

it is a technique for oral delivery of non-viral DNA. The idea behind the pill is that the gastrointestinal organs will convert the introduced DNA to therapeutic proteins that will be distributed naturally by the body. Gene Pill enables DNA delivery in a non-invasive manner, leading to the secretion of therapeutic proteins into a patient's blood, supplanting the need for injection of therapeutic protein products.

The gene pill also has potential for the development of oral DNA vaccination through expression of protein antigens in the gut lymphoid tissue. This approach limits the bio distribution of the delivered DNA to the gut and retains all of the safety advantages of non-viral gene delivery, including repeat dosing.

- Gene pill delivers DNA to intestine.
- DNA is absorbed by gut cells
- Protein drug is synthesised inside the cells.
- Protein drugs is secreted into the blood.

5 MONOCLONAL ANTIBODIES (MAB)

Monoclonal antibodies (mAb or moAb) are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have monovalent affinity, in that they bind to the same epitope (the part of an antigen that is recognized by the antibody.

They are so called because they are clones of an individual parent cell. Remember,antibodies are specific proteins that target pathogens invading our bodies.

Steps in making them

1 Human antibody genes are put into a mouse.

2 Mouse is infected causing it to make human antibody producing cells.

3 These cells are removed from the mouse and fused with a tumour cell.

4 Now we have a tumour cell this is constantly producing antibodies and more cells like it self.

Applications

- **Diagnostic tests**

Once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence of this substance. Proteins can be detected using the western blot and immuno dot blot tests. In immunohistochemistry monoclonal antibodies can be used to detect antigens in fixed tissue sections, and similarly, immunofluorescence can be used to detect a substance in either frozen tissue section or live cells.

- **Analytic and chemical uses**

Antibodies can also be used to purify their target compounds from mixtures, using the method of immunoprecipitation.

- **Therapeutic uses**

Therapeutic monoclonal antibodies act through multiple mechanisms, such as blocking of targeted molecule functions, inducing apoptosis in cells which express the target, or by modulating signalling pathways.[

- **Cancer treatment**

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immune response against the target cancer cell. Such mAbs can be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate or to design bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell. Every intact antibody can bind to cell receptors or other proteins with its Fc region.

GENE THERAPY

Gene therapy is the insertion of genes into an individual's cells and tissues to treat a disease, and hereditary diseases in which a defective mutant allele is replaced with a functional one. Gene therapy (also called human gene transfer) is a medical field which focuses on the utilisation of the therapeutic delivery of nucleic acid into a patient's cells as a drug to treat disease.

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. It derives it’s name from the idea that DNA can be used to supplement or alter genes within an individual cells as a therapy to treat disease. The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene to replace a mutated gene.

Genes are the basic units of heredity. When one is damaged or missing, genetic disorders can result. Gene therapy is a technique for correcting defective genes. This can be done by:

- Inserting a normal gene into a nonspecific location
- Swapping abnormal gene for normal gene
- Repairing abnormal gene
- Turning a gene on or off

Usually, a normal gene is inserted into the genome by a carrier molecule called a vector. A common vector is a virus whose disease-causing genes have been replaced by therapeutic genes.

Gene therapy is of two types : **somatic gene therapy** and **germ line gene therapy.**

- **Somatic gene therapy:** transfer of a section of DNA to any cell of the body that doesn't't produce sperm or eggs. Effects of gene therapy will not be passed onto the patient's children.
- **Germline gene therapy:** transfer of a section of DNA to cells that produce eggs or sperm. Effects of gene therapy will be passed onto the patient's children and subsequent generations.

Gene therapy has made important medical advances in less than two decades. Within the short time span , it has moved from conceptual stage to technology development and laboratory research to clinical translational trials for a variety of deadly diseases. The most notable advancements are the following:

SEVERE COMBINED IMMUNE DEFICIENCY (ADA-SCID)

ADA-SCID is also known as bubble boy disease. Affected children are born without an effective immune system and will succumb to infections outside of the bubble without bone marrow transplantation from matched donors. The therapeutic gene called ADA was introduced into the bone marrow cells of such patients in the laboratory, followed by transplantation of the genetically corrected cells back to the same patients.

The immune system was reconstituted in all six treated patients without noticeable side effects who now live normal lives with their families without the need for further treatment.

CHRONIC GRANULOMATOUS DISORDER (CGD)

CGD is a genetic disease in the immune system that leads to the patients inability to fight off bacterial and fungal infections that can be fatal. Using similar technologies as in the ADA-SCID trial, investigators in Germany treated two patients with this disease, whose reconstituted immune systems have since been able to provide them with full protection against microbial infections for at least two years.

HAEMOPHILIA

Patients born with haemophilia are not able to induce blood clots and suffer from external and internal bleeding that can be life threatening. The therapeutic gene was introduced into the liver of patients, who then acquired the ability to have normal blood clotting time.

Multiple gene therapy strategies have been developed to treat varieties of acquired diseases like

- Cancer
- Parkinson's disease
- Huntington's disease
- influenza
- HIV
- Hepatitis

STEM CELLS

A stem cell is a cell that has the potential to become any cell type in the human body. Everyone has stem cells, but they are very hard to access. The easiest place to get stem cells is from an embryo. Stem cells are introduced into damaged areas of the body where, under the right conditions, will replace the damaged area. A stem cell is a cell with the unique ability to develop into specialised cell types in the body. In the future they may be used to replace cells and tissues that have been damaged or lost due to disease.

Stem cells are currently been tested to treat everything from Crohn's disease to baldness. The main areas where stem cells have proven their worth is in bone marrow transplants, replacing damaged heart tissues after a heart attack and replacing damaged nerve tissue which gives hope to anyone who has had a spinal cord injury.

STEM CELLS(sources)

- Embryonic stem cells
- Infant and adult stem cells

Present in small numbers in

- Bone marrow
- Peripheral blood
- Skin epithelium
- Umbilical cord blood
- Dental pulp of infant teeth

May be obtained by reprogramming somatic cells

Introduction of retroviruses carrying reprogramming genes into fibroblasts.

DIFFERENT TYPES OF STEM CELLS

There are three main types of stem cell:

- embryonic stem cells
- adult stem cells
- induced pluripotent stem cells

Embryonic stem cells

Embryonic stem cells supply new cells for an embryo as it grows and develops into a baby. These stem cells are said to be pluripotent, which means they can change into any cell in the body.

Adult stem cells

Adult stem cells supply new cells as an organism grows and to replace cells that get damaged. Adult stem cells are said to be multipotent, which means they can only change into

some cells in the body, not any cell, for example: Blood (or 'haematopoietic') stem cells can only replace the various types of cells in the blood.

Skin (or 'epithelial') stem cells provide the different types of cells that make up our skin and hair.

Induced pluripotent stem cells

Induced pluripotent stem cells, or ‘iPS cells’, are stem cells that scientists make in the laboratory. ‘Induced’ means that they are made in the lab by taking normal adult cells, like skin or blood cells, and reprogramming them to become stem cells. Just like embryonic stem cells, they are pluripotent so they can develop into any cell type.

IMPORTANCE OF STEM CELLS

- **Stem cell research**

Research is looking to better understand the properties of stem cells so that we can:

- ✓ understand how our bodies grow and develop
- ✓ find ways of using stem cells to replace cells or tissues that have been damaged or lost.

We can use stem cells to study how cells become specialised for specific functions in the body, and what happens when this process goes wrong in disease. If we understand stem cell development, we may be able to replicate this process to create new cells, tissues and organs. We can grow tissue and organ structures from stem cells, which can then be studied to find out how they function and how they are affected by different drugs.

- **Stem cell therapy**

Cells, tissues and organs can sometimes be permanently damaged or lost by disease, injury and genetic conditions. Stem cells may be one way of generating new cells that can then be transplanted into the body to replace those that are damaged or lost.

Adult stem cells are currently used to treat some conditions, for example: Blood stem cells are used to provide a source of healthy blood cells for people with some blood conditions, such as thalassaemia, and cancer patients who have lost their own blood stem cells during treatment. Skin stem cells can be used to generate new skin for people with severe burns.

Age-related macular degeneration (AMD) is an example of a disease where stem cells could be used as a new form of treatment in the future. Some people with age-related macular degeneration lose their sight because cells in the retina of the eye called retinal pigment epithelium (RPE) cells stop working. Scientists are using induced pluripotent stem cells to produce new RPE cells in the lab that can then be put into a patient’s eye to replace the damaged cells.

TISSUE ENGINEERING

Tissue engineering is the use of a combination of cells, engineering, and materials methods, and suitable biochemical and physicochemical factors to improve or replace biological tissues.

Tissue engineering involves the use of a tissue scaffold for the formation of new viable tissue for a medical purpose.

A form of regenerative medicine, tissue engineering is the creation of human tissue outsider the body for later replacement. Usually occurs on a tissue scaffold, but can be grown on/in other organisms.

The technique to grow an ear follows the steps:

1)Taking a tiny piece of cartilage tissue

2)Dissolving away the white springy tissue to collect the actual cells inside(the cells are microscopic and trapped inside the white tissue called matrix)

3)Expanding the number of cells by various methods in the lab.

4)placing that increased volume of cells on or in mounds that have a shape of the ear.

5)Implanting the new ear onto the patient.

Tissue engineers have created artificial skin, cartilage and bone marrow.

Current projects being undertaken include creating an artificial liver, pancreas and bladder.

Tissue engineering is a rapidly developing field applying the disciplines of cell biology, developmental biology, molecular biology and biomimetic engineering to regenerate new tissues for replacement therapies in clinical contexts.

Some key research areas include:

Implantation of human liver in mice: The implantation of the engineered human liver into the mice can make the drug interactions similar to that happens in the human system. The test of toxicity, species-specific responses can be easily understood by the researchers.

Regeneration of a new kidney: The kidney scaffolds seeded with epithelial and endothelial cells developed in organ tissue. The tissue produced urine both in-vitro and in-vivo in rats. The ability to regenerate a new kidney is a leap forward in overcoming the problems of donor organ shortages.

Regeneration of Damaged Tissues

The applications of Tissue Engineering have been helpful in overcoming problems of any damaged tissues.

Bone Tissue Engineering

Bones are composed of collagen and have the property to regenerate, repair in response to an injury. The requirement of bone graft takes place during large bone defects occurring after trauma, infection, tumour resection or skeletal abnormalities.

Producing the features of bones in-vitro is very challenging. So to obtain an ideal scaffold for bone tissue regeneration is also difficult. Scientists have been able to develop 3D porous scaffolds with similar composition to the bone and, for better compatibility, Bioceramic scaffolds are used. The osteo-inducive scaffolds make use of bimolecular signalling and progenitor cells for new bone formation. In the bone defect models, the nanoparticles

designed for the release of osteogenic factors showed increased in-vitro and in-vivo osteogenic differentiation.

Cartilage tissue engineering

Cartilage is a connective tissue found in elbows, knees, and ankles. Like bone tissue engineering, challenges also lies with cartilage tissue engineering. Several scaffolds have been used for cartilage repair but, the most relevant are the synthetic scaffolds like polyurethane, Poly (Ethylene Glycol) (PEG), elastin-based polymers.

Cartilage is composed of chondrocytes so, an ideal donor cell type for cartilage repair is autologous chondrocytes. However, they are difficult to obtain and require invasive techniques. Therefore, Mesenchymal Precursor Cells (MSCs) collected from different sources, such as adipose tissue or bone marrow have been used as an alternative source. They can be easily cultured in-vitro and have the ability to proliferate and differentiate towards osteogenic, adipogenic, chondrogenic and myogenic lineages.

Apart from bone and cartilage tissue engineering, certain other TE like cardiac tissue engineering, pancreas tissue engineering, vascular tissue engineering has also been done.

XENO-TRANSPLANTATION

Xeno-transplantation is the use of live cells, tissues or organs from non-human animal species, for transplantation into a human patient. Xenotransplantation is any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs.

Interest has grown in this area of biotechnology because up to 50% of people waiting to receive vital organ transplants such as kidney, liver and heart, die while waiting for a donor organ.

Disadvantages of Xeno-transplantation

A) Potential health risk

- Allergies
- Toxicity
- Nutrients imbalance
- Decrease of food diversity

B)Environmental effects

C)Cost

VACCINES

Vaccines are chemicals that stimulate the body's immune system to better fight pathogens when they attack the body. They achieve this by inserting attenuated (weakened) versions of the disease into the body's bloodstream. This causes the body to react as if it was under attack from the non-attenuated version of the disease. The body combats the weakened pathogens and through the process takes note of the cell structure of the pathogens and has some cell 'remember' the disease and store away the information within the body.

Vaccines contain the same germs that cause disease. (For example, measles vaccine contains measles virus, and Hib vaccine contains Hib bacteria.) But they have been either killed or weakened to the point that they don't make you sick. Some vaccines contain only a part of the disease germ.

A vaccine stimulates your immune system to produce antibodies, exactly like it would if you were exposed to the disease. After getting vaccinated, you develop immunity to that disease, without having to get the disease first. This is what makes vaccines such powerful medicine. Unlike most medicines, which treat or cure diseases, vaccines prevent them.

- **Reverse vaccinology**

The basic idea of reverse vaccinology is that an entire pathogenic genome can be sequenced and screened by employing bioinformatics methods to explore genes. Functional genomics approaches, such as DNA microarrays, proteomics, and comparative genome analysis, are used for the identification of virulence factors and novel vaccine candidates. This new computational approach allows prediction of all antigens, independent of their abundance and immunogenicity during infection. The first attempt at reverse vaccinology began with Meningococcus B (MenB) vaccine. Moreover, it has been used on several other bacterial vaccines such as antibiotic- resistant Staphylococcus aureus and Streptococcus pneumoniae.

Reverse vaccinology have changed the concepts and approaches for vaccine candidate selection and design. Genome investigation and selection of antigens provide a new way to study the pathogenesis mechanisms. The resulting lists of novel candidates which reveal new aspects of pathogenesis will promote the rational design of optimal vaccine antigens. Applying genomic approaches to study both hosts and pathogens will ultimately drive and guide next- generation vaccine design.

- **Recombinant subunit vaccination**

The gene cloning is a powerful tool to synthesize protein materials to subunit vaccine by recombinant DNA techniques. Recombinant subunit vaccines are made from a fragment of protein (antigen) expressed in the laboratory using the viral DNA, for example, hepatitis B (HB) vaccine. The hepatitis B virus (HBV) gene that codes for the antigen is inserted into baker's yeast genome and then expresses the antigen protein. The antigen protein is harvested and purified to be used for the vaccine. This technique is also being used to explore a vaccine against hepatitis C.

Recombinant- DNA techniques can facilitate the development of new principles to design and produce subunit vaccines. The recombinant subunit vaccine can furthermore be adapted by gene- fusion technology, to be efficiently incorporated into immunopotentiating adjuvant

systems. The recombinant strategies have become increasingly important to the passive vaccination strategy and use antibodies or antibody fragments to prevent infectious diseases.

- **Recombinant protein vaccination**

Upon infection, a pathogen produces proteins to elicit an immune response from the infected body. The gene encoding such a protein is isolated from the causative organism and used to develop a recombinant DNA which is expressed in a heterologous expression system (e.g., bacterium, yeast, or insect). Recombinant protein vaccines, such as cholera vaccine, diphtheria toxoid, and tetanus toxoid, are composed of protein/toxin antigens that have either been produced in another host organism or purified from large amount of pathogens. The vaccinated persons produce antibodies to the protein/toxin antigen to protect themselves from diseases.

The baculovirus- insect cell expression system is also a recombinant protein manufacturing platform for the production of complex proteins. The technology is used for the mass production of various recombinant protein vaccines. The major advantage is that a universal "plug and play" process may be used to produce a variety of protein- based prophylactic and therapeutic vaccines for human uses

- **Deoxyribonucleic acid (DNA) vaccination**

DNA vaccination is a technique for protecting against diseases through the direct injection of genetically engineered DNA. The gene responsible for the immunogenic protein is cloned with a corresponding expression vector. This DNA will trigger an immune response and the individual is successfully vaccinated. DNA vaccines may have the ability to induce a wider range of immune response types over conventional vaccines.

Despite several DNA vaccines are available for veterinary uses, none of them is commercial for human uses. Research is being investigated using the approach for controlling infectious diseases and several cancers in humans. For instance, a synthetic consensus anti-spike protein DNA vaccine induces protective immunity against Middle East respiratory syndrome (MERS) coronavirus in nonhuman primates. The improved formulations and delivery methods can increase the uptake of vaccine plasmids by cells. The optimization of vaccine vectors and encoded antigens, and the adding of novel adjuvants potentially increase and direct the host immune responses. Therefore, current DNA vaccines may induce more potent, cellular, and humoral immune responses to be tested for both preventative and therapeutic uses.

- **Messenger ribonucleic acid (mRNA) vaccination**

mRNA vaccines consist of mRNA, which is encoded by antigen genes of an infectious agent. When the mRNA is administered into host cells, it will translate protein antigens that elicit protective immunity against the infectious agent. Vaccines based on mRNA may offer a solution as sequence- matched, clinical- grade material could allow quick responses to the emergence of pandemic microbe strains.

mRNA vaccines have an outstanding safety profile and the unmet genetic flexibility. mRNA vaccines can induce a balanced immune response comprising both cellular and humoral immunity. Compared with DNA vaccines, mRNA offers stronger safety advantages

in which it harbours only the elements directly required for expression of the encoded protein and hardly interacts with the genome. Because any protein can be encoded and expressed by mRNA without the need to adjust the production process, mRNA vaccines offer maximum flexibility with respect to vaccine production, and principally enable the development of prophylactic and therapeutic vaccines fighting against infections and cancers.