

The process of hematopoiesis and how its controlled biology essay



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In humoral mediated response of the immune system, the clonal proliferation results into antibody – secreting plasma cells and memory B-cells. The primary response has a lag of about 5-7 days during which the B-cells becomes activated by the antigen and T-helper cells. During the lag period, differentiation and proliferation of B-cells takes place into plasma cells. Antibody level begins to increase and reaches its peak at about day 14 and the drop begins once the plasma cells die. In the secondary response, clonal expansion of memory B-cells takes place and the antibody levels are much higher. These memory cells respond more rapidly to the antigen. Moreover, since many memory cells are present for the primary response, the number of plasma cells generated are more in the secondary response and the antibody levels are higher [2].

3. Briefly describe the functions of the following cells of the immune system; dendritic cells; macrophages; neutrophils; T helper cells.

Ans) Dendritic Cell – These cells resemble the dendrites of the nerve cells and have a long membrane extensions. They can be either present on the epidermis (skin) and mucous membranes (Langerhans cell) ; heart , lungs, kidney, GI tract (interstitial dendritic cell) ; T-cell are of secondary lymphoid and thymic medulla (Interdigitating dendritic cell) and in blood and lymph (circulating dendritic cell). They represent high levels of class II MHC molecules. Dendritic cells are APCs. They engulf the antigen by phagocytosis/endocytosis and carry it to the various lymphoid organs where they represent the antigen to T lymphocytes [2].

Macrophages - They arise from monocytes. It functions as a scavenger that ingest debris, damaged and dying cells as well as foreign organism. They either contain class II MHC molecules or the co-stimulatory B7 membrane molecules. Once the foreign organism is inside the macrophage, they are either killed by lysosomal enzymes or by O₂ free radicals which is released by phagosomes[1].

Neutrophils - They are active phagocytic cells and always reach the site of inflammation. The foreign body is killed by the various lytic and bactericidal substances which are present within the primary and secondary granules. They employ both O₂ dependent and O₂ independent pathway to generate antimicrobial substances. It is better than macrophage since they exhibit larger respiratory burst and express higher level of defensins [2].

T-helper cells- T-cells are formed in the bone marrow but mature in the thymus. There are two types of T-cells- TH and TC . TH cells have CD4 whereas TC has CD8. The TH cells gets activated when the cell recognizes and interacts with an antigen. After it is activated, it forms into an effector cell and secretes growth factors known as cytokines. These cytokines play an important role in activating B cells, Tc cells, macrophages and elicits an immune response. Different types of immune response occurs due to different types of cytokines[2].

4) What are the two fundamental approaches to drug discovery?

Ans) The two approaches to drug discovery are rational drug design and molecular diversity.

Rational drug design - The drugs work in the body by interacting with the receptor and they alter the activities in such a way that it brings about a betterment of the body. This method uses the information about structure of the drug receptor or create a candidate drug. The 3-D structure of the protein can be determined using methods such as X-ray crystallography or nuclear magnetic resonance spectroscopy. The researchers in the pharmaceutical industry can use whatever information is available on the databases and find a chemical compound which can react with the receptor and can be tested in the labs. If the interacting compound cannot be found then other programmes can be used to find the compounds with similar properties to known ligands. This method is done to avoid the expenses. The first drug produced by this method is Relenza which is used to treat influenza. The other drugs developed to treat HIV infections are Ritonivir and Indinavir [3].

Molecular diversity - The strategy applied in molecular diversity is the isolation of bioactive molecules molecular libraries such as nucleic acids, amino acids and small organic molecules. The main goal is to isolate molecules from libraries of chemical compounds or proteins and study the structure or shape of their target with the binding with affinity and specificity. The anti-inflammatory mAb Humira is a biologic isolated from molecular diversity.

5. How does the flu virus infect cells? Give a brief overview of how the flu drug relenza was discovered. (Note : Relenza is not as biologic but a small molecule drug).

Ans) Influenza viral particles are surrounded by an outer envelope - a lipid bilayer which they acquire from the plasma membrane of the infected host cell during the process by budding. In the envelope the two glycoproteins which are present are Hemagglutinin (HA) and neuraminidase (NA). HA is responsible for attaching the virus to the host cell. HA is a trimer and it binds to the sialic acid groups on host cell glycoproteins and glycolipids by conserving the amino acid sequence to form a small groove in the HA molecule. Neuraminidase cleaves N-acetylneuraminic (sialic) acid from the viral glycoproteins and the host cell membrane glycoproteins. This facilitates viral budding from the infected host cell. Once the virus is inside the host cell, the HA binds to the walls of the endosome (acidic nature) because of which the viral coating collapses. Within the envelope, matrix protein surrounds the nucleocapsid which consist of 8 different strands of single stranded (ssRNA) and are associated with protein and RNA polymerase. Once inside the cell, the RNA strand encodes one or more different influenza proteins. Many copies of the virus are made in the nucleus and then it moves to the cytoplasm to form viral proteins including HA and NA. The new viruses which are formed move out of the cell by forming buds and moving out against the plasma membrane[2].

Relenza

This drug is created by using rational design. The discovery was funded by the Australian biotech company Biota. The structure of neuraminidase was known by X-ray crystallography. A competitive inhibitor which is a sialic acid analogue, is an inhibitor of neuraminidase. The general function of

neuraminidase is that it cleaves sialic acid from the virus and the cell surface
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and prevent clumping and allows the virus to spread to other cells. Relenza induces clumping and reduces viral spreading.

6. What is meant by pharmacogenomics and how might pharmacogenomics be applied to drug development in the future? What is an example of a biologic where patient genetic profiling is used to evaluate the suitability of the patient for therapy?

Ans) Pharmacogenomic is the study of the roles of genetic variation in the response to drugs. It includes information from genomics, proteomics, bioinformatics and other disciplines such as biochemistry and toxicology in order to synthesize newer and safer drugs. As the sequences of all our genes and the protein they encode for are determined, this will reveal many new targets for drug actions. It also reveals polymorphism of enzymes and proteins related to drug metabolism, action and toxicity DNA probes which are capable of detecting them will be synthesized, permitting screening of individuals for potentially harmful polymorphism prior to the start of the therapy. As the structures of relevant proteins and their polymorphism are revealed, model building and other technique will permit the design of drugs that take into account both the normal protein targets and their polymorphism. In simple words, the drugs will be tailor-made for individuals based on their genetic profiles[4]. This is the application of pharmacogenomics in drug development. The example where genetic profiling is used to evaluate the suitability of the patient is ERBB2 is a 185 kDa tyrosine kinase receptor over expressed in approximately 25-30% of human breast cancer .

7. Give an example where over expression of a cytokine results in a disease state. What biologics, if any, have been developed to treat this disease state?

Ans) Rheumatoid arthritis is a an inflammatory disease. The major symptom is chronic inflammation of the joints including shoulders, ankles, elbows and knees. It is characterized by the inflammation of the synovium along with the the destruction of the joint cartilage and bone. The over expression of cytokines such as TNF, IL-1, IL-8, IFN γ have been detected in the synovial fluid. Cytokines such as TNF activate the synovial cells which produce proteolytic enzyme such as collagenase which leads to the destruction of tendons, ligaments and cartilage. The cytokines are produced due to the activity of T cell and macrophage activation. A number of biologics have been approved for treating rheumatoid arthritis[5]. They are cimzia, enbrel, humira, kineret, orenzia, remicade, rituxan and simponi[6].

Rituxan – Rituximab is sold under the trade name Rituxan. Rituxan is a chimeric monoclonal antibody against the protein CD20 which is found on the surface of B cells. Rituxan when given in combination with methotrexate is given to adult patients with minor to acute conditions who had an inadequate response to one or more TNF antagonist therapies. The side effect of rituxan is that patients show hypertension, nausea, upper respiratory tract infection, pyrexia etc.[7] .

8. Interferons are used as biologics to treat viral infections. How does interferon induce the anti-viral state in cells?

Ans) Interferons are antiviral and show their effect in a signaling pathway. There are two types of interferons, type I and type II. IFN-I is produced by cells under appropriate conditions including IFN- α/β . IFN-II are produced by a few number of cells such as NK cells, T-helper cells and dendritic cells. IFN-II includes IFN- γ . IFN-I plays an important role in the innate antiviral response. IFN- α/β is responsible for inducing the anti-viral activity by binding to IFN receptor on the cell surface, which leads to activation of receptor-associated JAKs (Janus Kinase) such as JAK-1 and TYK-2. This activates the STATs (signal transducer and activator of transcription) due to phosphorylation which leads to the formation of ISG factor (ISGF)-3 complex which consists of STAT-1 and -2 and p48. After phosphorylation at Tyr701 and 692 of IFN receptors by IFN-1, STAT-1, and -2, there is formation of a heterodimer which translocates to the nucleus and forms an association with p48(IRF-9). The complex (STAT-1 and -2 and IRF-9) is called as ISGF-3 and it associates with ISREs to activate ISGs. The 3 antiviral proteins involved in IFN-mediated inhibition of virus infection are :

- 1) The Rnase L pathway which degrades viral RNAs and then activates dsRNA.
- 2) PKR inhibits mRNA translation by phosphorylating translation initiation factor
- 3) Mx proteins possessing GTPase activity which restricts virus infection at many stages such as primary transcription, transcription and intracellular trafficking of viral proteins or genomes. Thus, interferons induce the anti-viral state in cells[8].