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RESEARCH ARTICLE

MYELOPROLIFERATIVE CELLS

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ABSTRACT

The physiologic process of formation of blood cells is known as haematopoiesis. It proceeds through different stages starting from early embryonic life- mesoblastic stage (yolk sac), hepatic stage and myeloid (bone marrow) stage. During embryonic and early foetal life, haematopoiesis occurs in the yolk sac (only erythroblasts) and the liver (all blood cells). Some blood cell formation also occurs in the spleen (all blood cells), lymph nodes and thymus (most lymphocytes). Bone marrow starts producing blood cells around 3 to 4 month and by birth becomes the exclusives site of blood cell formation childhood, haematopoiesis becomes restricted to the flat bones such as sternum, ribs, iliac bones and vertebrae and proximal end of long bones. at other skeletal sites haematopoietic areas are replaced by fat cells. However when there is in creased demand for blood cells production, conversion of yellow fatty inactive marrow to red active marrow can occur. In extremely severe cases (severe chronic anaemia) resumption of haematopoitic activity in organs pother than bone marrow such as liver and spleen (extramedullary haematopoiesis) can occur.

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INTRODUCTION

Hierarchy of haematopoiesis: The hierarachy scheme of haematopoiessis, all blood cells are derived from pleuripotenthaematoioietic stem cells, which are present in small numbers in the bone marrow. it has the ability of proliferation, self renewaland differentiation along several lineages. The capacity of self renewal and differentiation along several lineages. the capacity of self renewal permits life long continuation of the process. The myeloid and lymphoid stem cells originate from thepleuripotent stem cells haematopoiesis. arise progressively restricted potential to generate different type of cell are derived. these single lineage progenitors further differentiate to produce morphologically- identifiable blood cells. Red cells granulocytes, monocytes, and platelets are derived from myeloid stem cells while B and T lymphocyted are vformed from lymphoid stem cell through intermediate stages. HGFs are a group of proteins that regulated proliferation, differentiation, and maturation of haematopoietic progenitor cells Influence the commitment of progenitors to specific lineage and Affect the function and survival of mature blood cells. hgfs are produced by different types of cells, which include T lymphocytes, macrophages, fibroblasts, endothelial cells and renal interstitial cells.

HGF's may bind to specific cell receptors on the surface of the cells to directly induce their proliferfation and differentiation or may stimulate the production of other cytokines that then act on the target cells. Two types of HGF's that act on one specific cell line. Examples of multilineage HGF's that act on one specific cell lines. Examples of multilineages HGF's are CSF (granulocyte macrophage colony stimulating factor) and Il-3 (interleukin -3) while lineage – restricted HGF's are erythropoietin. Haematopoietic growth factors (HGFs): HGFs are a group of proteins that regulate proliferation, differentiation, and maturation of haematopoietic progenitor cells, influence the commitment of progenityors to specific lineage and, affect the function and whixsurvival of mature blood cells. HGF's are produced by different types of cells, which include T lymphocytes, macrophages, fibroblasts, endothelial cells, and renal interstitial cells. HGF's may bind to specific cell receptors on the surface of the cells to directly induce their proliferation and differentiation or may stimulate the production of other cytokines that then act on the target cells. Two types of HGF's may be distinguished – multilineage HGF's that have action on more than one cell line and lineage – restricted HGF's that act on one specific cell line. Examples of multilenage HGF's that act on one specific cell line. Examples of multilineage HGF"S are GM-CSF (granulocyte macrophage colony stimulating factor) and IL-3 and a lineage specific cytokines (erythropoietin G- CSF, or MCSF are

required. Many of the HGF's have been produced by the recombinant dna technology and are undergoing clinical trials in various disorders. recently,recombinant GM- Csf and erythropoietin have been approved for clinical use in certain conditions in USA.

GM_ CSF: Gm-CSf stimulates proliferation, differentiation and maturation of lineages and commited to neutrophil and monocyte / macrophage cell lines (CFU-GEMM and CFU – GM) and also enhance the functional activity of mature neutrophils and monocytes. Recombinant GM-CsF is used to enhance the myeloid recovery following autologous bone marrow transplantations in non – myeloid malignancies. It also being used to increase stem cells harvest from peripheral blood in peripheral blood stem cells transplantations, it is being tried in chemotherapy induced myelosuppression and in myelodysplastic syndrome with neutropaenia.

G-CSF: G-CSF stimulate bmyeloid progenitor cells (CFU_G) to form mature neutrophils Recombinant G-CSF is used to reduce duration and severity of neutropaenia in non myeloid malignancies that are being treated with myelosuppressive chemotherapy and in autologous bone marrow transplantation.

ERYTHROPOIETIN: Eruthropoietin is a glycoprotein produced in kidneys (90%) and in the liver(10%), it stimulates progenitor cells commited to erytrhroid lineage (CFU_E and BFUE) to proliferate and differedntate. It is indicated in patients with anaemia of chronic remal failure who are on dialysis eho, it also being tried zidovudine – treated HIV positive having anaemia, and in anaemia of cancer. The haematopoietic microenvironment. The existence of hematopoietic microenvironvent is suggested by the fact that formation of bloods cells is restricted specifically to bone marrows. The exact nature of the environment is poorly understood ; however it appears to be composed of endothelial cells, fibroblasts, adipocytes, macrophages and extracellular matrix.Bone marrow environment providers supporting stroma and growth factors for haematopoiesis. stem cells and pro genitors are bound to the stromal cells or to adhesion molecules within the matrix. Release of mature blood cells from the marrow is regulated by the microenvironment.

Red Blood cells:

Stages of erythropoiesis: The earliest morphologicallyt identifiable erythroid cell in the bone marrow, is the proerythroblst (pro normoblast) a large 15 to 20 micrometre cell with a fine uniform chromatin pattern one or more nucleoli and dark blue cytoplasm. The next cell in the maturation process is the basophilic early normnoblast. The cell is smaller in size 12 to 16 micrometre and has a coarser nuclear chromatin with barely visible nucleoli. The cytoplasm is deeply basophilic. The more differentiatederythroid cell is the polychromatic intermediate normoblast sixze 12 to 15 micrometre. The nuclear size is smaller and the chromtin becomes clumped. Polychromas of cytoplasm results from admixture of blue ribonucleic acidand pink haemoglobin. Thus is the last erythroid precursor capable of mitotic division. The orthochromatic late normoblastr is 8 to 12 micro metre in size. The nucleus is small. Dense and pyknotic and commonly eccentrically located. the cytoplasm stains mostly pink due to haemoglobinization. it is called as orthochromatic because cytoplasmic staining is largely similar to that of erythrocyte. The nucleus is ultimately expelled from the orthochromatic normoblast with the formation of a reticulocyte. The nucleus is ultimately expelled from the orthochromatic notrmoblast with the formation reticulum.After 1 to 2 days in the bone marrow asnd 1 to 2 days in the bone marrow and 1 to 2 days in peripheral blood reticulocytes lose rna and becomes mature pin k staining erythrocytes. About four mitotic division and continued differentiation lead to the production of 16 mature erythrocytes from each pro normoblast.

STRUCTURE and function of erythrocytes: Mature erythrocytes is a round biconcave disc about to 7 to 8 micrometre in diameter. Basic structural properties of various red cell components (hemaglobin, enzymes, and membranes) are outlined below.

HAEMOglobin: Haemoglobin is responsible for transport of oxygen from lungs to the tissues and of carbon dioxide fromtissues to the lungs. Hemoglobi n (MW64500 daltons) is composed of haem (consisting of ironand proto porphyrin) andglobin. The globin portion of the molecule consists of four (or two pairsof polypeptide chains. one haem group is bound to each polypeptide chain.

Variants of haemoglobin: haemoglobin is not homogeneous and normally different variants exist such as A. A2, F gower II and Portland. the last three atre present only during embryonic life. Others are present in varying proportions during foetal and adults life. the relative proportiona of different haemoglobin are : adults HBA 97%, Hb A 2.25% and Hb F0.5% ; newborn – Hb F 80% and Hb A 20%. Haemoglobin A Hb A the principle hemoglobin of adults consists of a pair each of alpha and of beta polypeptide chains and its structure is designated as alpha2beta2. FOetalhaemoglobin (HbF), the predominant haemoglob in in foetal life, contains a pair of alpha and a pair of gamma chains. Two types of gamma chains are distinguished, Ggamma, A gamma which have different amino acids either glycine or alanine at position 136. thus HbFis heterogenous and contains alpha 2 gamma 2 136 gly and alpha 2 gamma 2 136 Ala. DURINg embryonic life, there are three haemoglobins: GowerI. GowerII and Portland. with foetal development, synthesis of zeta and epsilon chains is replaced by thet of alpha and gamma chaind respectively. After birth, production of gamma chains switches to that of beta and delta chains. Styructure of globin gene : Normal haemoglobin is atetramer composed of a pair of alpha like and a pair of beta like polypeptide chains. Each chainlinked to one molecule of haem. The alpha like – polypeptide chains zeta and alpha and betya like polypeptide chains.

Zeta and gamma beta and delta are encoded by alpha and beta globin gene clusters on chromosomne 16 and 11 respectively. the order of genes in alpha globin gene cluster gene cluster f.
In humans autosomal chromosomes occur inpair. As each member of chromosomes 16 has two alpha gene loci a locus refers to specific physical position of a gene on chromosomes, there are total four alpha genes. However there is only one beta globin gene locus on chromosomes 11. And therefore beta genes are two in number. Genes are base dequences which are present along the DNA strands and are necessary for the formation of a protein. the different fuction al areas of a globin gene are.

- Exons and introns : the regions oif DNA strand which encode amino acids in the protein product are known as

exons while non – coding regions which interrupt the coding sequencez are known as introns or intertveining sequences. Each globin gene contains three exons and two introns.

- Splice junction sequences : these are sequences at the junction of exons and introns are required for precise splicing or removal of introns during the formation of mRNA.
- Promoter : the promoter regions toward end of the geneand the contains seqwuence to which the RNA polymerase binds ; it is necessary for correct initiation of transcription. Twso promoter sequences are TATA and CCAAT
- Polyadenylation signal: the end of the globin gene contins the sequencwe AATAAA that serves as a signal for the addition of a poly -A track to the mRNA.
- Steps in the synthesis of globin synthesis involves three steps – transcription, processing of mRNA and translation.

Red Cell enzymes: the mature red cell requires energy to preserve the integrity of the cell membrane, for active transport of cations, for nucleotide salvage anf for synthesis of glutathione. This is mostly provided by glycolysis (EMP). IN this metabolic pathway, glucose is converted to pyruvate and lactate through a series of enzymatic reactions while generation of ATP in themiddle of the the net yield of atp from glycolysis is dependent upon the amount of glucose utilized by this shunt. 2,3 -DPG is an important determinant of the oxygen affinity of haemoglobin. A part from atp and 2,3 -DPG another important product of glycolysis is nadh that is required for reduction of methaemoglobintooxyhaemoglobin.

Red cell membrane: The red cell membrane is composed of lipids a complex networks of proteins and a small amounts of carbohydrates. The membrane lipids include phospholipids are arranged in the form of a bilayer. the distribution of phospholipids are arranged in the form of a bilayer. The distribution of phos[holipids o=is asymmetrical with aminophospholipds and phosphatidyl binositols located preferentially in the inner asymmetrical with aminophospholipids in the outer parts. The polar head groups are oriented both internally and externally while the fatty acid achins are oriented toward each other. the red cell membrane proteins are embedded within the lipid bilayer (transmembranous protein) and also form an extensive network beneath the bilayer (suoermembranous proteins). the transmembranous and submembranous proteins constituite the red cell cytoskedleton. Red cell membrane proteins can be seprated according to molecular size by sodium dodecyl sulfate polyacrylamide gedl electrophoresis (SDS_PAGE). Different bands can be visualized when stained with a protein stain such as Coomassie.

The membranous provides mechanical strength anf flexibility atrfength and flexibility to the red cell to withstand the shearing forces in circulation. the red cell membrane lso serves to maintain the red cell volume by the cation pump. The cation pump operated by the cell membrane enzyme ATPase also drives the calcium pump, which keeps the intracellular calcium at a very low level. the red cell exchanges HCO3- formed formedfro the tissue carbondioxide in the lungs with the chlorine through the anion exchanged channel in the membrane.

RED cell destruction: The life span of normal erythrocytes is about 120 days. The senile red cells are recognized by macrophages of reticuloendothelial system and are destroyed mainly in the spleen globin is converted to amino acids which are stored to be recycled again, Degradation of haemliberatesiron and porphyrin. iron is stored as ferritin in macrophages or is released in circulation where it is taken up by transferrin and transported to erythroid precursors in bone marrow. The porphyrin is convereted to bilirubin. A blood cell also called a hematopoietoc cell, hemocyte or hematocyte, is a cell produced through hematopoiesis and found mainly in the blood. Major types of blood cells include red blood cells, white blood cells and platelets. together these three kinds of blood cells and upto a total 45% of the blood tissues by volume, with the remaining 55% of the volume composed of plasma, the liquid component of blood.

Blood dyscrasias: Anaemia is fall in haemoglobin level below normal level for given age and sex. it can result from diverse processes resulting alteration in morphological of RBC's. these form basis of various classification systems.

Morphological classifications

Normochromic normocytic anaemia

- Ananemia of acute blood loss
- Anaemia associated with leukoplakia
- Aplastic anemia.

Hypochromic, microcytic anemia

- Iron deficiency anemia
- Thallassemia

Normochomic, macrocytic anemia

- Pernicious anemia
- Anemia due to folate and b12 deficiency

Normochromic, microcytic anemia

- Anemia due to chronic infections.

Iron deficiency anemia: Iron is essential for synthesis of hem portion of hemoglobin. I ron deficiency anemia is caused by imbalance e between iron intake and loss or intake inadequate utilization.

Cause: It causes but inadequate intake of iron. Malabsorption of iron due to hypochlorideanddiarrhoea. Increased requirement of in a growing child and I pregnancy. Increased loss of iron due to injury, recurrent epistaxis and peptic ulcer. Chronic blood loss such as menstrual and menopausal bleeding. Parturition. subtotal or complete gastrotomy.

Clinical features: It occurs chiefly in women in the 4 and 5 decades of life. The patient experiences tiredness headache. Nails become brittle, flattened and open shape koilonychia there may be tingling pins, and needle sensation in the extremities. Some patients develop pharyngeal mucosal thichenings and mucosal web formation giving rise to dysphagia.

Gastrointestinal symptoms: Liver, spleen may be palpable. There may be gastrointestinal bleeding and menorrhagia there by setting a vicious circle. There is redness, soreness or burning of tongue. the filiform papillae over the anterior two thirds of tongue are the first to undergo atrophy. in severe cases fungiform papillae are also affected leaving the tongue completely smoothand waxy or glistening in appearance.

HIstolpathollogical findings: There is marked thinning of epithelium, absence of papillae in the lamina propria and absence of keratohyaline granules.

Plummer vinson syndrome

Brown Kelly syndrome. It is characterized by dysphagia, iron deficiency anemia, dystrophy of nails and glossitis.
Clinical features:

Vermilion borders of the lip are very thin and there is often angular cheliosis. Patients complaint of spasm in throat or food sticking in throat. There is also complaining of sore mouth and inability to retain dentures. A smooth, red occasionally enlarged and often sore tongue with fissuring is occurs.

Histopathological features: There is atrophic epithelium and atrophy of lamina propria and muscles.

Pernicious anemia: It is also called as primary anemia, addisons anemia, or biemer's anemia. The term pernicious anemia should be reserved for patients who have B12 deficiency secondary to intrinsic factor deficiency.

Causes: It occurs due to atrophy of gastric mucosa resulting in failure to secrete the still unidentified intrinsic factor. it is suggest that is autoimmune disorder because, because autoantibodies to gastric parietal cells are often found in patients.

Clinical features: There is gradual atrophy of the papillae of tongue that eventuslates in a smooth and bald tongue which is often referred as Hunter; s glossitis or moeller's glossitis and is similar to be bald tongue of sandwich seen in pellagra.

Histopathological features: Histologically, oral epithelium cells in pernicious anemia reveal enlarged, hyperchromic nuclei with prominent nucleoli ans serrated nuclear membranes. there is atrophy of epithelium with intra or subepithelial chronic inflammatory cell infiltration. cellular atypia can be seen.

SiCkle cell anaemia: It is an autosomal dominant. It was described by Herrick in1910. This is the most common type by hemoglobinopathy in which there is a substitute of amino acid glutamine on position 6 presentg in the chain of the hbA, that is hemoglobin S. In homozygous individuals, whole of HbA is replaced by HbS and this is known as sickle cell trait. It is chronic hemolytic blood disorders characterized buy abnormal hemoglobin.(deoxygenated hemoglobin0 which under low oxygeb tension results ivn sickling of cell. When HbS is deoxygenated it forms structures known as tactoids which distorts the RBC membrane and produce characterize sickle shaped cell which are destroyed by RE cells. Sickle cells increase blood viscosity and tend to reduce blood flow leading to thrombosis and tissue infarction.

CLINICAl Features: It is common in females and mostly the clinical symptoms become evident before the age of 30 years. Clinical manifestations begin only after several months as fetal Hb protects against sickling phenomenon. It include dehydration chills and infection. there is fatigue, weakness and shortness of breath. Severe abdominal pain and muscke and joint pain. At high temperature which may result in circulatory collapse also occued there is painless hematuria.
There is enlargement of heart and murmur I found in most of the patients. there is in crease susceptibility to infection. most of the persons may expire at the age of 40 years. There is also present of leg ulcer and gall stream and gall stones. Hyperplasia of marrow in first year of life expands the marrow cavituy producing bossing of the skulls, prominent malar bone and proturebant teeth. Sickle cell crisis – there is a long quit spell of hemolytic latency occasionally punctuated by exacerbations called as sickle cell crisis

Oral manifestation; The oral mucosa will show pallor.

Erythroblastois fetalis: I occurs due to isoimmune antibodies, it is also called as hereditary disease of newborn (HDN), congenital hemolytic anaemia due to Rh incompatibility, results from destruction of fetal blood brought about by a reaction between maternal and fetal blood factors, The Rh factor named rhesus monkey was covered by land steiner, and weiner in 1940 as a factor in human RBC, which reacts rabbit antiserum produced by administration of red blood cells, from rhesus monkey.

Pathogenesis: It occurs due to inheritance by the fetus of a blood factor from the father that acts as a foreign antigen to mother, The transplacental leak of red cells from fetus to mother results in immunization of mother and formation of antibodies stimulate the production of maternal antibodies against the fetal antigens.

WHITE BLOOD cElLs

Neutrophils

Stages of granulopoiesis: The maturation sequence in granulopoiesis – myeloblast, promyelocyte, myelocyte, metamyelocyte band cell and segmented granulocyte. this process occurs within the marrow.

Myeloblast: Myeloblast is the earliest recognizable cell in the granulocyutic maturation process. it is about 15 to 20 micrometre in diameter with a large round to oval nucleus and small amount of basophilic cytoplasm. the nucleus contains 2to 5 nucleoli and nuclear chromatin is fine and reticular. Promyelocyte: the next stage in the maturation is promyelocyte which is slightly larger in size than myeloblast. primary or azurophil granules appear at the promyelocyte stage. The nucleus contains nucleoli as in myeloblast stage, but nuclear chromatin shows slight condensation.

Myelocyte: Myelocyte stage is characterized by the appearance of secondaryor specific granules neutrophilic eosinophilic or basophilic. myelocyte is a smaller cell with round to oval eccentrically placed nucleus, more condensation of chromatin than in prfomyelocyte stage, and contain both primary and secondary granules.
Band stage (stab form) this is characterized by band like shape of the nucl;eus with constant diameter throughout and

condensed nuclear chromatin. Segmented neutrophil: polymorphonuclear neutrophil with leishman's stain, nucleus appears deep purple with 2 to 5 lobes which are joined by thin filamentous strands. Nuclear chromatin pattern is coarse. the cytoplasm stains light pink and has small, specific granules.

Primary and secondary granules: the neutrophil granules are of two types primary or azurophilic granules and secondary orspecific granules, azurophil granules contain myeloperoxidase lysozyme acid pohosphatase, elastse, collagenase and acid hydroloses. Specific granules contain lysozyme, lactoferrin, alkaline phosphatsses, vitamin b12-binding protein and other substances. Function of neutrophils: after their formation neutrophils remain in marrow for 5 more days asa reserve pool. Neutrophils have a life span of only 1 to 2 days in circulation. In response to infection and inflammation neutrophils come to lie closer to endothelium (margination) and adherent to endothelial surface (sticking0. This is followed by escape of neutrophils from blood vessels to extravascular tissue (emigration). The escape of neutrophils is guided by chemotactic factors present in the inflammatory zone. Chemotactic factors for neutrophils include bacterial factors, complement components such as c3a and c5a, breakdown products of neutrophils, fibrin fragments and leukotriene b4. phagocytosis follows which involves three steps – antigen, recognition, engulfment and killing of organism. neutrophils have receptors for fc portion of immunoglobulin and for components. many organisms are identified by neutrophils after they are immunoglobulins and for complement. many organisms are identified by neutrophils after they are coated with opsonins (igG1, IgG3, c3b). Cytoplasm of the neutrophil extend in the form of pseudopods around the microorganisms, and the organism is eventually completely enclosed within the membrane bound vacuole.

Eosinophils: eosinophils forms via same stages as the neutrophil and the specific granules first become evident at the myelocyte stage. The size of the eosinophil is slightly greater than that of neutrophil. The nucleus is often bilobed and the cytoplasm contains numerous large bright orange red granules. The granules contain major basic protein, cationic protein peroxidase (which is distinct from myeloperoxidase). Eosinophilic peroxidase along with iodide and hydrogen peroxide may be responsible for some defense against helminthic parasites.

Basophils: basophils are small round to oval cellas which contain very large, coarse deep purple granules. The nucleus has condensed chromatin and is covered by granules. Mast cells in connective tissue or bone marrow differ morphologically from basophils in following respects : mast cedlls 10 to 15 micrometre are larger than basophils 5-7 micrometre ; mast cells have a single round to oval eccentrically placed nucleus while nucleus of the basophils is multilobed and the cytoplasmic granules in mast cells are more uniform. Tissue mast cells are of mesenchymal origin.

Monocytes: the initial cells in development is monoblast, which is indistinguishable from myeloblast. The next cell is promonocyte which has an oval or clefted nucleus with fine chromatin pattern and 2 to 5 nucleoli, the monocyte is a arge cell 15 to 20 micrometre with irregular shape oval or cleft nucleus and fine, delicate chromatin.monocytes circulate in blood for about 1 day and then enter and sttle in tissues where they are called AS MACROPHAGESOR HISTIOCYTES, IN SOME ORGANS Macrophages have distginctive morphologic and functional characteristics.

Macrophages phagocytosis is slower as compared to neutrophils. macrophages have receptors for fc portion of igG and C3b and cause phagocytosis some target substances macrophages also recognize and phagoctoses some target substances by their surface characteristics. Macrophages may be activated by certain stimuli such as lymphokines interferon gamma secreted by t- lymphopcytes direct contact with microorganisms, phagocytized material and complement components. activated macrophages are larger and have enhanced metabolic and phagocytic activity.

Activated macrophages secrete a variety of biologically active substances

- Cytokines – interleukin 1, tumour necrosis factor alpha, interferons alpha and beta
- Growth factors fibroblast growth factors, haematopoietic growth factors b(GM- CSFand G_ CSF), angiogenesis factor, transforming growth factor beta;
- Complement proteins
- Coagulation factors example thromboplastin
- Oxygen – derived free radicals – hydrogen peroxide, supetroxide
- Prostaglandins and lekotrieneswhich are chemical mediators in inflammation
- Enzymes elastases, collagenase, lysozyme, plasminogenactivator, lipases
- Fibronectin
- Transferrin, transcobalaminII.

The major function of macrophages are processing and presentation of antigens to T lymphocytes during immune respons, killing of intracellular pathogens, tumoricidal activity and phagocytosis of organism and of injured and senescent cells.

Lymphocytes: These are of two types small and large. Most of the lymphocytes in peripheral blood are small. The nucleus is round or slightly clefted with coarse chromatin and occupies most of the cell, the cytoplasm is basophiolic, slight and is visible as a thin border, around the nucleus. Around 10 to 15% of lymphocytes in peripheral blood are large. their nucleus is similar to that of small lymphocytes but their cytoplasm is relatively more and contains few azurophilic (dark red) granules. On immunophenotyping there are two major types of lymphocytes in peripheral blood Blymphocytes and Tlymphocytes, difference between B and T lymphocytes are presented, about 10 to 15% of lymphocytes are of natural killer cell type.

BLymphocytes: B lymphocytes arise from the lymphoid stem cells in the bone marrow from where further differentiation occurs on antigenic stimulation.On activation by antigen B cell undergo differentiation and proliferation to form plasma cells and memory cells plasma cells secrete immunoglobulins while memory cells have a life span of many years and upon restimulation with the same antigen undergo proliferation and differentiation. Plasma cell is a round to oval cell with eccentrically placed nucleus and deeply basophilic cytoplasm nucler chromatin is dense arranged ina radiating or cartwheel pattern. the function of Blymphocytes is production of antibodies after differentiation to plasma cells, antibodies can cause destruction of target cells / organisms either directly or by opsonization.

B cell ontogeny: During Bcell; development sequential genotypic and phenotypic changes occur which can be detected by immunological markers and gene rearrangement studies, important features in B cell ontogeny are outlines below: There are two stages of B cell development antigen – independent antigen independent development occurs in bone marrow while antigen dependent development occurs in peripheral lymphoid tissues.

- Rearrangement of immunoglobulin genes and immunoglobulins expressions : initially there is rearrangement of heavy chains genes which is followed by rearrangement of light chains, in pre beta cell rearrangement of heavy chains genes which is followed by reaarengement of light chains genes.
- Cell surface antigens : the earliest antigens expressed during B cell development are dT within the nucleus HLA DR on cell surface these are however not specific for Bcells there is a sequential appearance of antigedns on developing B cells, CD19 < CD10 andCD20 with development and maturation new antigens ARE expressed while some of the previous ones re lost, plasma cells express specific antigens such as CD38.
- According to the fundamental theory of lymphoid neoplasms, the neoplastic cells represents cells arrested at various stages of normal llymphocyte development.

Tlymophocytes: Tymphocytes originate from the progenitor cells in the bone marrow and undergo maturation in thymus, after their release from thymus, Tcells circulates in peripheral blood and are transported to secondary lymphoid organs (ie paracortex of lymph nodes and periarteriolar lymphoid sheaths in spleen). There are two major subsets of mature T cells : Thelper – inducer cells and Tcytotoxic cells. helper – inducer T cells regulate the functions of Bcells and cytotoxic T cells > thelper – inducer cells recognize antigen

Tlymphocytes: T lymphocytes originate from the progenitor cells in bone marrow and undergo maturation in thymus. after their relese from thymus, T cells circulate in peripheral blood and are transported to secondary lymphoid organs (ie paracortex of lymph nodes and periarteriolar lymphoid sheaths in spleen). There are two major subsets of mature T cells : T helper inducer cells and T cells regulate the functions of bcellss and cytotoxic T cells, T helper – inducer cells recognize antigen presented by antigen presenting cells in association with MHC class I molecules and play a n important role in cell – mediated immunity. Tlymphocytes secrete cytokines such as interferon gamma GM- CSF, tumour necrosis factor and certain interleukins.

Tcell ontogeny: progenitor T cells from the bone marrow are transported to thymus where they undergo maturation. DURing maturation there is rearrangement of TCR genes, expression of some surface proteins and acquisition, ability to distinguish self antigen from foreign antigens. Initially immature cortical thymocytes express CD7, TdT and cytoplasmic CD3, those T followed by TCRalpha gene. expression of alpha beta TCR occurs in association with expression of CD3 on surface of cells. initially both CD4 and CD8 antigens are required with further maturation cell retains either CD4 or CD8 antigen. CD4+ and CD8 antigen are acquired with further maturation cell retains either CD4 or CD8 antigen. CD4+ cells are called as helper – inducer T cells where as CD8+ cells are called cytotoxic T cells.

The mature T cells are released from thymus, circulate in peripheral blood, and are transported to peripheral lymphoid organs.

Natural killer (NK cells): About 10 to 15% of peripheral blood lymphocytes are natural killer cells. these cells do not require previous exposure or sensitization for their cytotoxic action. they play a significant role in host defense against tumour cells and virally – infected cells. Morphologically these cells are large granular lymphocytes.

wHITE CELL ANTIGENs: the HLA system or human leucocyte antigens are encoded by a cluster of genes on short arm of chromosomes 6 called as major histocompatibility complex (MHC), there are numerous allelic genes at each locus which makes the HLA system extremely polymorphic. The antigens are called HLA because they were are first detected on white blood cells, although they are present on several other cells also.Types of HLA antigens : there are three types of HLA antigens on several other cells also. TYPES of HLA antigens: there are three types of HLA antigens CLass, CLassII and class III

Class I antigens: genes at HLA, HLA – B and HLA-C positions specific class I antigens. class I antigens are glycoproteins chains which are associated non covalently with beta2 microglobulin. almost all nucleated cells possess classI antigens. CLass II antigens Hla – D region HLA – DR, HLA – DQ and HLA -DP) encodes class II antigens. These consists of two glycoproteins chains alpha and beta which are bound noncovalently. CLassII antigens are present on monocytes, macrophages, B- lymphocytes and and stimulated T lymphocytes.

CLASSIII antigens: genes specifying class III antigens are situated between genes which specify CLASSI and class II antigens. CLASS III genes encodes certain complement components and cytokines (TUMOUR necrosis factor). The HLA genes are closely linked and are inherited by an individual as Haplotype from each parent. IN a given population, certain HLA haplotypes occur much more frequently than expected by necrosis factor). The HLA gene are closely linked and are inherited by an individual as a haplotype from each parent. In a given population certain HLA haplotypes occur much more frequently than expected by chance alone (linkage disequilibrium)

Significance of HLA antigens

- Thay are important as histocompatibility antigens in organ transplantation,
- HLA antigens play a major role in recognition of foreign antigens and in immunity
- In transfusion medicine HLA antigens are responsible for alloimmunization against platelet antigens and refactoriness to platelet transfusions, febrile transfusions reactions, and graft versus host disesease
- A reflactionship exist between presence of some HLA antigen s and susceptibility to certain diseases
- HLA antigen typing can be used for paternity testing.
- IMMUNE system: as white cells play a major role in immunity, it is appropriate to consider antibodies and complement here.

ANTIBODIES: antibodies are immunoglobulins that react with antigens. thay are produced by plasma cells which in turn are derived from b lymphocytes.

STUCTURE OF immunoglobulins: the immunoglobulin molecule consist of two identical heavy H chains and two identical chains. the H and L chains are linked together by disulfide (s-s) bonds. Five classes of immunoglobulins are recognized based on the type Of H chain : The IgA alpha or alpha H chain, IgD delta <IgE or epsilon IgG and IgM. light chains are of two varieties – kappa and lamda. A molecule of immunoglobulin consist of the samr type (either kappa or lamda ; both types of light chains are never present together. Kappa and lamda chains are present in 2:1 propoirtion in immunoglobulins.

Each chain has a constant and a variable region. Amino acid composition in the carboxyterminal region of heavy chain and light chain is the constant region ; in the heavy chain it determines the class of the immunoglobulin molecules. the CH1 domain in IgG binds complement while CH2 domain is flexible and is called hinge region; due to this two antigen – binding sites can move in relation to each other spanning variables distances. EACh immunoglobulin molecule can be digested by a proteolytoic enzyme papin just above the disulfide bond joining the two heavy chains into three parts: one of Fc anf FAB fragments. the fragment, which contains the carboxyterminal and constant parts of heavy ahains is called the Fc fragment crystallizable fragment > each Fab fragment. the fragment crystallizable fragment, each Fab fragmant antigen binding fragment contain aminoterminal portion of H chains and complete light chain an d has the antigen – combining site.

Classes of immunoglobulins: IgG this is the major immunoglobulin in plasma comprising about 75% of all circulating immunoglobulins. IgG is the monomer of the basic comprising about 75% of all circulating immunoglobulins. IgG is the monomer of the basic immunoglobulin structure. there are four subclasses of IgG: IgG1, igG2, igG3 and igG4. relative concentration in serum is usually produced during secondary immune response. It is the only immunoglobulin, which is trfansferredtranspalcentally to the foetus from the mother. The foetus cannot synthesize IgG and thderfore IgG antibodies in the newborn represent those passively gained from the mother. IgG is capable of fixing complement with order of efficacy being IgG3, IgG1 and IgG2 IgG4 cannot bind compleent in the classical pathway. only iGG3 and IgG1 can bind to Fc receptors on macrophages.

IgM: This has high nmolecular weight and is also called as macroglobulin due to its large size. IgM moleculea have a pentameric structure, five units are joined together and also have an additional short polypeptide chain (jor joining chain)O. it comprises 5 to 10% of circulating immunoglobulin. IgM is the first antibody produced in response to the antigen (primary response). in contrast to IgG, IgM cannot cross the placenta. the foetus is able to produce IgM after maturation of its immune system. IgM is thehighly efficiently in binding complement. A single molecule of IgM can bind complement while two molecules of IgG are necessary for complement – binding. the order of efficiency of complement binding of immunoglobulin is IgM, IgG3, IgG1 and IgG2. There are no receptors on macrophages for IgM.

IgA: there are two subclasses of igA: iga1 IgA2. IgA is present mostly in body secretions such as gastrointestinal and respiratory mucosal secretions, saliva tears, et.. secretory Iga is mostly IgA2 and exists as a dimer. Serum IgA which is mostly IgA1 is a monomer.

IgD and IgE both are present in trace amounts in serum and are monomeric. Most IgD and IgE is bound to basophils or mast cells through heavy chains. when a specific antigen combines with Ig E is the bound to basophils or mast cells through heavy chains. When a specific antigen combines with IgE, vasoactive substnces are released from these cells and lead to anaphylaxis. Allo antibodies versus autoantibodies, alloantibodies are those which are produced by an individual against antigens present in anothers individual of the same species, autoantibodies are those which are produced by an individual

IMMUNE SYSTEM: As white cells play a major role in immunity, it is appropriate to consioder antibodies and complement here.

ANTIBODIES: Antibodies are immunoglobulin that react with antigens. they are produced by plasma cells, which in turn are derived from B lymphocytes. The activated C1 clea

COMPLEMENT: Complement are serum proteins which when activated react in an orderly manner with each other to cause immunologic destruction of target cells (lysis or phagocytosis) there are two pathways of complement activation : classical and alternate.

Classical pathway: Classical pathway is usually initiated by reaction of antibody (IgG or IgM) with antigen example red cells. binding of only a single IgM pentameric molecule or of IgG doublet to an antigen are necessary for complement activation. The complements are activated in the following order : Ag – Ab complex –C1C4C2C3C5C6C7C8C9. This process occurs on the surface of target cells example red cells. Binding of antibody to antigen causes exposure of complement – binding site on immunoglobulin. The activated C1 cleaves C4 to form C 4a and C4b, C4a is released into the body fluid while C4b attaches to the red cell membrane. ACtivatedC! Also cleaves C2 to form C2a. the C4b2a complex (C3 convertases) is formed. the C$B2a complexattached to cell membrane has enzymatic activity and can cleavage several hundred C3 molecules. THE C3a is released into plasma while C3B attaches to the cell membrane. C3 b attaches to the cell membrane. C3b however is rapidly degradable into C3dg. C3b is not enzymatically active by itself, but presence of C3b is not enzymatically active by itself but presence of c3b on the cell surface is recognized by specific receptors on the surface of macrophages and this causes phagocytosis of C3b on the cell surface is recognized by specific receptors on the surface of macrophages and this causes phagocytosis of C3dg cannot adhere to macrophages and this causes phagocytosis of C3b – bearing cells.

Alternate pathway: In alternate pathway C3 is activated directly with no role of earlier complement components, it does not require antigen- antibody reaction. C3 can be activated pathway by endotoxins, complex carbohydrates such are present on some microorganisms and aggregates of IgA. A serumproteins called properdin, factors B and abdmagnesiums ions are needed for activation of alternate pathway.

Normally C3 is being continuously cleaved at low level, probably by factor B resulting C3b is rapidly cleared from the plasma, however when C3b B o0ccurs on the surface of microrganisms then association ofC3bB occurs on the surface of microorganisms in the presence of magnesium. Factor B is cleaves by factor D to form C3bB properdin may stabilize C3bBB. C3bBbsplits C3 to generate more C3b thus forming an amplification loop, alternate pathway plays an important role in initial defense against infection in nonimmune persons.

THrombocytopoiesis: The various morphologically identifiable satges are megakaryoblast, promegakaryocyte, megakaryocyte and platelate. A unique feature of thrombocytopoiesis is endomitosis. This refers to nuclear division with cytoplasmic maturation but without cell division, as the cell matures from megakaryoblast to the megakaryocyte, there is gradual increase in cell size, number of nuclear lobes and red pink granules, and gradual decrease in cytoplasmic basophilia, a humoral factor, thrombopoietin controls the maturation of megakaryocytes.

Normal haemostasis: Haemostasis is the mechanism by which loss of blood from the vascular system from thed vascular system is controlled by a complex interaction vessel wall, platelets and plasma proeteins, following vessel injury, haemostasis can be considered as occurring in two stages: primary and secondary primary haemostasis is the initial stage during which vascular wall and platelets interact to limit the blood loss from damaged vessel.

During secondary haemostasis a stable fibrin clot is formed from coagulation factors by enzymatic reactions, although formation of blood clot is necessary to arrest blood loss, ultimately blood clot needs to be dissolved to resume the normal blood flow. The process of dissolution of blood clot is called as fibrinolysis, the role of vascular wall, platelets and plasma proteins in normal haemostasis are briefly outlined below.

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