INTRODUCTION

Acute Myeloid Leukemias

Acute leukemias are clonal malignant hematopoietic disorders that result from genetic alterations in normal hematopoietic stem cells. These alterations induce differentiation arrest and/or excessive proliferation of abnormal leukemic cells or blasts.[1]

Acute myeloid leukemia (AML; also known as acute nonlymphocytic leukemia) is a heterogeneous group of disease[1] characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis.[2]

1. Epidemiology

Although-acute leukemias are infrequent diseases, they are highly malignant neoplasms responsible for a large number of cancer-related deaths. AML is the most common type of leukemia in adults, yet it continues to have the lowest survival rate of all leukemias. While results of treatment have improved steadily in younger adults over the past 20 years, there have been limited changes in survival among individuals of age >60 years.[3,4]

Acute myeloid accounts for approximetly 20 % of all leukemias in adults in the West and constitutes the most frequent form of leukemia. [5]Worldwide, the incidence of AML is highest in the USA, Australia, and Western Europe. The age-adjusted incidence rate of AML in the USA is approximately 3.7 per 100000 persons. In the USA, 13410 men and women (7060 men and 6350 women) are estimated to be newly diagnosed with AML in 2007.[6]

In the National Cancer Institute (NCI) Cairo University, out of a total of 19405 new cancer cases, 169 patients (1.8 %) were diagnosed as AML.[7]

2. Etiology

The development of AML has been associated with several risk factors. Remarkably though, as of yet defined risk factors account for only a small number of observed cases.[8] These include age, antecedent hematological disease, genetic disorders as well as exposures to. radiation, viruses, chemical or other occupational hazards, and previous chemotherapy. [9,10]

2.1. Age

Acute myeloid leukemia makes up only 15-20% of cases in those aged 15 years or younger.[11] The peak incidence rate occurs in the first year of life and then decreases steadily up to the age of 4 years. The incidence rate remains relatively constant in childhood and early adulthood. [12] AML occurs predominately in adults, and it afflicts the elderly more frequently than the young. Epidemiologic surveillance shows that more than half of patients with AML are older than 60 years. For old-age patients with AML, the complete remission (CR) rate after induction therapy ranges from 40% to 50% and <10% of these patients are expected to be alive at 3 years.[13]

2.2.Genetic factors

Genetic disorders and constitutional genetic defects are important risk factors associated with AML in children.[14] Children with Down syndrome have a 10- to 20- fold increased likelihood-of developing acute leukemia. [15] Other inherited disease associated with AML include Klinefelter's syndrome (presence of extra X chromosome in males), Li-Fraumeni syndrome (high risk of developing breast cancer and sarcomas), [16] Fanconi anemia, and neurofibromatosis. Furthermore, risk factors for developing AML in children were identified and include race/ethnicity, the father's age at time of conception, and time since the mother's last live birth.[9]

2.2.1, Acquired Genetic Factors

Acquired ("somatic") clonal chromosomal abnormalities are found in 50– 80 % of AML [17,18] with rising incidences in patients with secondary leukemia [19] or older age.[20,21] Frequently found abnormalities include loss or deletion of chromosome 5, 7, y, and 9, translocations such as t(8;21)(q22;q22); t(15;17) (q2;qll), trisomy 8 and 21, and other abnormalities involving chromosomes 16, 9, and 11.[21]

2.3. Physical and Chemical factors

A variety of environmental and chemical exposures are assumed to be associated with a variably elevated risk of developing AML in adults. A selection of hazards will be mentioned here.[22]

Exposure to ionizing radiation is linked to AML. [22]Among survivors of the atomic bomb explosions in Japan, an increased incidence of AML was observed with a peak at 5-7 years after exposure. Also, therapeutic radiation has been found to increase the risk of secondary AML. [23] Chemotherapeutic agents, such as alkylating agents and topoisomerase II inhibitors, have been reported to increase the incidence of AML. [24] Chronic exposure to certain chemicals clearly shows an increased risk for the development of AML. Benzene is the best studied and widely used potentially leukemogenic agent.[25] Persons exposed to embalming fluids, ethylene oxides, and herbicides also appear to be at increased risk. [26] Furthermore, smoking has been discussed to be associated with an increased risk of developing AML, especially in those aged 60 – 75.[10] Drugs such as chloramphenicol, phenylbutazone, chloroquine, and methoxypsoralen can induce marrow damage that may later evolve into AML.[1]

2.4. Viruses

Viruses particularly RNA retroviruses have been found to cause many neoplasms in experimental animal models, including leukemia. [27] As of now, a clear retroviral cause for AML in humans has not been identified even though an association between the exposure to certain viruses and the development of AML has been suggested. parvovirus B19 could thus play a role in the pathogenesis of AML. [28] It has so far not been demonstrated, however, that simple infection with either a RNA- or DNA-based virus alone is a cause of AML.[7]

2.5. Secondary AML

"The true secondary AML" has been recommended to be referred to patients who have a clear clinical history of prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents; it is thus a rather broad category. [29] Secondary leukemias are in more than 90% of myeloid origin. Patients have a particularly poor outcome, with a lower incidence of achieving complete remission and shorter duration of survival than for patients with de novo AML. [30]

Treatment-related secondary leukemia was first observed in survivors of successfully treated Hodgkin's disease. [31] Later on, survivors of acute lymphoplastic leukemia (ALL)[32] and other disease entities such as ovarian or breast cancer and multiple Myeloma were included.[33] The development of secondary AML shows a maximum in the 5 – 10 years following therapy. [34] AML arises after previous therapy for other malignancies in a subset of 10 – 20% of patients. The risk of therapy-related AML after intensive chemotherapy may be increased to more than 100 times.[35]

Specific cytogenetic abnormalities currently serve as the most important factor in diminishing differences in AML biology, response to treatment and prognosis. [36] The different abnormalities result in gene rearrangements that may reflects the etiology and pathogenesis of the disease. [2] Treatment-related or secondary leukemias are examples in which genetic aberrations provide information on its specific etiology.

3. Leukemogenesis

Multiple lines of evidence indicate that tumorigenesis in humans is a multistep process. In leukemia, multiple acquired genetic changes must occur in order to convert a normal hematopoietic stem cell (HSC) to leukemic stem cell (LSC). AML is characterized by the accumulation of large numbers of blasts arrested at varying stages of differentiation; thus, a perturbation of the normal differentiation program with maturation arrest is a key event in leukemogenesis.[37]

There are three possible scenarios by which LSC could be formed, and how their genesis might influence therapeutic outcome (figure 1). The first scenario (panel a) depicts LSC that arise directly from normal HSC. The initial mutation occurs in HSC, leading to the formation of a preleukemic stem cell. Secondary mutation(s) in the pre-LSC then gives rise to LSC. Both the initial and secondary mutation(s) in this scenario are at the stem cell level. The second scenario (panel b) shows an initial mutation at the HSC level, followed to a preleukemic myeloid progenitor (MP) stage and subsequently "differentiation secondary mutation(s) leading to the LSC. A third possible scenario (panel c) suggests that HSC first differentiate to normal MP, and then undergo primary and secondary mutation to ultimately generate LSC.[38]

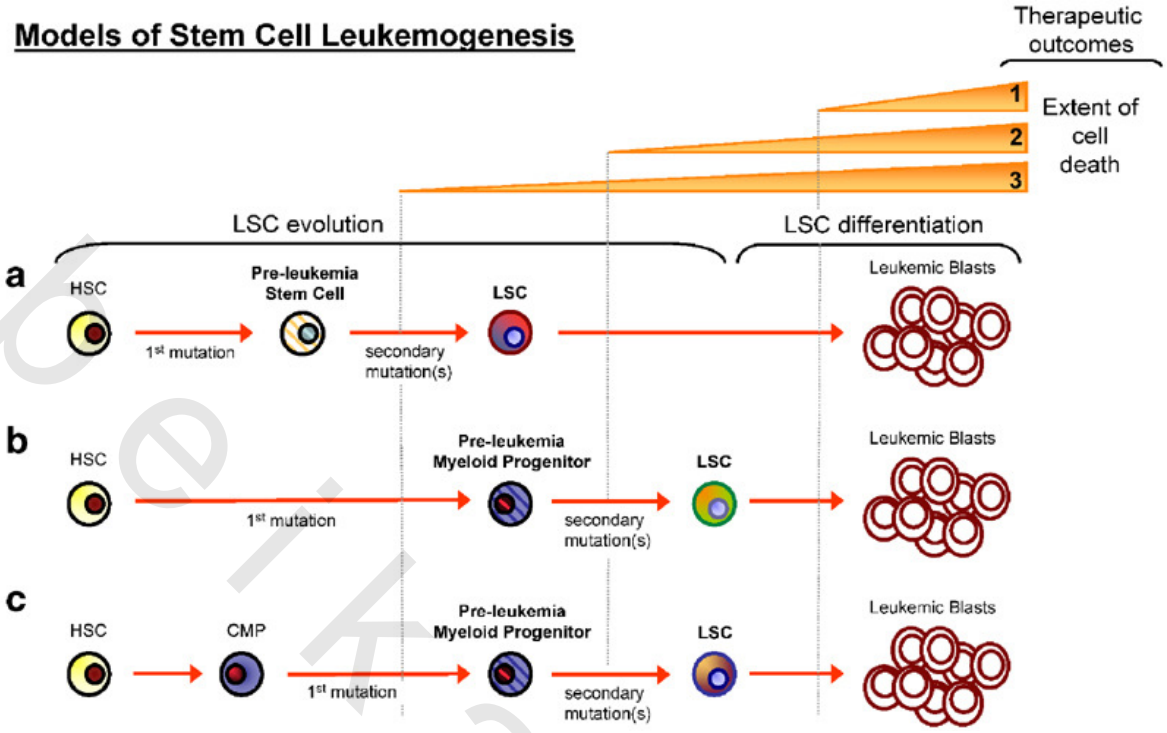

Figure (1): Models of stem cell leukemogenesis. The figure depicts three possible scenarios for the evolution of AML (panels a-c). Hematopoietic stem cells (HSC), myeloid progenitors (MP), or both population are potential targets for primary and-secondary mutations leading to acute disease. Celli bearing a single mutation are termed "preleukemic" and upon undergoing subsequent mutation give rise to leukemic stem cells (LSC). LSC in turn give rise to the majority of malignant cells found in the leukemia population (blasts). Three possible therapeutic outcomes are illustrated by the arrows above the chart. The length of each arrow denotes the degree to which a particular therapeutic regimen might affect the leukemic blasts, stem/progenitors cells, or preleukemic cell types. [38]

In all three scenarios, once LSC are formed, subsequent differentiation generates the leukemia blast population. While the differences in each scenario are subtle and may not be readily evident in the LSC population, the ramifications with regard to therapy are significant. Considering the path by which each type of LSC is generated, the therapeutic outcome of treatment falls into at least three categories. In the first category, the therapeutic agent(s) destroys leukemic blasts but the LSL, regardless of its origin, survives (outcome #1). This might be because the LSC retains certain-properties of the normal HSC or MP that render them resistant to drug therapy. Therefore, a clinical remission is achieved but the disease relapses relatively fast, driven by surviving LSC. In the second category (outcome #2),'the therapeutic agent(s) destroys leukemic blasts and the LSC that originated from preleukemic MP. This gives a relatively stable remission for scenarios b since only the residual preleukemic cells survive. However, the LSC originating from HSC (panel a) are spared and could cause relatively fast relapse of the disease. Of course, the presence of preleukemic MP (b and c) can also lead1o relapse, but remission may be more durable. In the final category (outcome #3), the therapeutic agent(s) destroys Ieukemic

blasts and the LSC, as well as the preleukemic MP in panels b and c. In this situation, leukemia deriving from a myeloid progenitor origin might be completely cured but leukemia with an HSC origin is likely to eventually relapse due to the presence of residual pre-LSC. Relapsed disease arising from preleukemic populations is likely to be caused by new secondary mutations, thereby leading to AML cells that may be biologically distinct from the original disease.(38)

As illustrated in Figure 1, the level of success with therapeutic drugs may depend upon the cell type in which mutation(s) initially occur. HSC populations bearing the initial mutation (panel a) are less likely to be targeted, and these preleukemic cells can cause disease relapse. This might be particularly evident if the preleukemic mutations result in genomic instability and/or increased self-renewal. If the initial mutation is at the MP level (panels b and c), the preleukemic cells might be more sensitive to therapy. Irrespective of whether the initial mutation is at the HSC or MP level, selective pressure from chemotherapy could result in the development of new mutations that render the preleukemic and/or LSC populations increasingly drug resistant. Subsequent relapsed disease would then be expected to respond poorly to further cycles of chemotherapy.(38)

4 . Clinical presentation

The clinical signs and symptoms of AML are diverse and nonspecific, but they are usually directly attributable to the leukemic infiltration of the bone marrow, with resultant cytopenia. Typically, patients present with signs and symptoms of fatigue, hemorrhage, or infections and fever due to decreases in red cells, platelets, or white cells, respectively. Pallor, fatigue, and dyspnea on exertion are common. Leukemic infiltration of various tissues, including the liver (hepatomegaly), spleen (splenomegaly), skin (leukemia cutis), lymph nodes (lymphadenopathy), bone (bone pain), and central nervous system, can produce a variety of other symptoms. An isolated mass of leukemic blasts is usually referred to as a granulocytic sarcoma. Hyperleukocytosis (more than 100,000 white cells per cubic millimeter) can lead to symptoms of leukostasis, such as ocular and cerebrovascular dysfunction or bleeding. There may also be rnetabolic abnorrnalities (e.g., hyperuricemia and hypocalcemia), although these are rarely found at presentation.(2)

5. Diagnosis

The primary diagnosis of AML rests on the rnorphologic identification of leukemic myeloblasts in preparations of peripheral blood and bone marrow stained with Wright-Giemsa. These cells have round to irregular nuclei, distinct nucleoli, and very little cytoplasrn. The cytoplasm frequently contains fine azurophilic granules and a variable number of Auer bodies, or rods. The presence of at least 20 % leukemic blasts in a bone marrow aspirate is required for a definitive diagnosis of acute leukemia; before therapy is initiated.(2)

6. Treatment

The primary objective in treating patients with AML is to induce remission and thereafter prevent relapse. Remission is conventionally defined morphologically by the presence of fewer than 5 percent blasts in bone marrow together with the recovery of peripheral-blood counts.[2]

Induction of Remission

During the past 35 years, a series of studies has established an induction regimen that has become a standard of care for patients not participating on a clinical trial. A widely used combination for induction is the cell cycle-specific agent cytarabine and the non cell cycle-specific anthracycline antibiotic daunorubicin. [39]

With the use of daunorubicin and cytarabine or their analogues, complete remission can be routinely induced in 70 to 8o percent patients who are 60 years of age or younger and in approximately 50 percent of older patients. [40]

Mechanisms of Anti-neoplastic Drug Action

The primary action of anti-neoplastic agents is disruption of various steps required for cell division, with cell targets including the DNA molecule, the mitotic spindle, and nucleotide machinery. Most chemotherapeutic, regimens are combinations of drugs acting on different parts of the cell cycle, especially designed for additive anti-tumour effect and non-additive side effects. Hence, provided the factors necessary for apoptosis are present, the damage caused by chemotherapeutic agents forces the neoplastic cell to either quickly repair the damage or to initiate apoptosis at the G-S checkpoint.[41]

Current pharmacologic management of hematologic malignancies is based on four classes of agents: cell cycle-specific agents, cell cycle-nonspecific agents, biological therapies and anti-angiogenic agents.[41]

1. CellCycle-Specific (CCS) Agents

These agents act on cells as they traverse the cell cycle. They include bleomycin peptide antibiotics, podophyllin alkaloids (topoisomerase inhibitors), plant alkaloids (antimicrotubule agents) and antimetabolites (such as Cytarabine).[41]

1.1. Cytarabine

Cytarabine, or cytosine arabinoside, is a chemotherapeutic agent used mainly in the treatment of hematological malignancies such AML and non-Hodgkin lymphoma. [42] It is also known as ara C.[43]

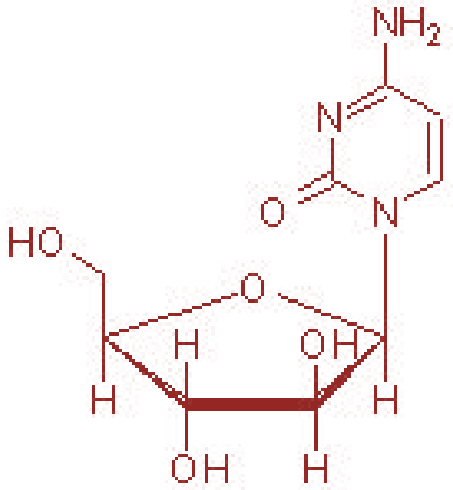

Figure (2): Chemical Structure of Cytarabine [41]

Mechanism of action

Cytosine arabinoside is an antirnetabolic agent with the chemical name of 1β-arabinofuranosylcytosine. Its mode of action is due to its rapid conversion into cytosine arabinoside triphosphate, which damages DNA when the cell cycle holds in the S phase (synthesis of DNA). Rapidly dividing cells, which require DNA replication for mitosis, are therefore most affected. Cytosine arabinoside also inhibits both DNA and RNA polymerases and nucleotide reductase enzymes needed for DNA synthesis. Cytarabine is rapidly deaminated in the body into the inactive uracil derivative and therefore is often given by continuous intravenous infusion. [44]

Pharmacokinetics

Orally, less than 20% of a dose of cytarabine is absorbed from the gastrointestinal tract and is ineffective by this route. Subcutaneously or intramuscularly, tritium-labelled cytarabine produces peak plasma concentrations of radioactivity within 20 to 60 minutes which are considerably lower than those attained after intravenous adrninistration. Continuous intravenous infusion produce relatively constant plasma levels in 8 to 24 hours.

Intravenous doses of cytarabine exhibit biphasic elimination, with an initial distribution half-life of about ten minutes during which time a major portion of the drug is metabolised in the liver to the inactive metabolite uracil arabinoside. The secondary elimination half-life is longer, approximately one to three hours. Metabolism also occurs in the kidneys, gastrointestinal mucosa, granulocytes and other tissues.[44]

Cytarabine is mainly excreted via the kidney with 70 to 80% of a dose administered by any route appearing in the urine within 24 hours; approximately 90% as the metabolite and 10% as unchanged drug.

Clinical uses

Cytarabine is mainly used in the treatment of AML, ALL and in lymphomas, where it is the backbone of induction chemotherapy. Cytarabine also possesses antiviral activity, and it has been used for the treatment of generalised Herpes virus infection. However, cytarabine is not very selective in this setting and causes bone marrow suppression aud other severe side effects, so it is used mainly for the chemotherapy of hematologic cancers.[45]

Side Effects

Possible infection resulting from granulocytopenia and other impaired body defences, and hemorrhage secondary to thrombocytopenia.

Toxicity: Leukopenia, thrombocytopenia, anemia, gastrointestinal disturbances, stomatitis, conjunctivitis, pneumonitis, fever, and dermatitis.[14]

2. CellCycle-Non Specific (CCNS) Agents

These drugs act on cells cycling or resting in the G0 phase. They include anthracycline antibiotics, alkylating agents, and cisplatin.[41]

2.1. Anthracycline antibiotics

(doxorubicin, daunorubicin, idarubicin, mitroxantrone)

This class of antibiotic drugs is regularly used to treat a variety of cancers. Despite their widespread use, their mechanism of action remains unclear. Three postulates exist: 1) anthracyclines intercalate between DNA base pairs leading to unwinding of the super-helix and interfering with DNA and RNA synthesis, 2) they undergo metabolism to form free radicals, and 3) they inhibit topoisomerase II, resulting in DNA strand breakage.

Daunorubicin, which has a narrower spectrum of utility than dox-orubicin, is mainly used in the treatment of acute leukemia. Doxorubicin is used to treat a number of solid tumors as welI as multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma and acute lymphocytic leukemia. Idarubicin is used in the treatment of acute myeloid leukemia. Anthracyclines are metabolized in the liver and excreted in the bile. Dose reduction for patients with decreased liver function is recommended, especially if hyperbilirubinemia is present. Myelosuppression, mucositis and cardiac toxiciiy are common toxicities of these drugs. Irreversible cardiac toxicity is thought to occur via drug induced oxidative damage by free radicals. Use of lower doses and dexrazoxane (an iron chelator that blocks generation of free radicals) have been shown to prevent cardiac toxicity without loss of antitumour activity. [41]

2.1.1, Daunorubicin

Daunorubicin or daunomycin is chemotherapeutic agent of the anthracycline family that is given as a treatment for some types of cancer. It is most commonly used to treat specific types of leukemia (acute myeloid leukemia and acute lymphocytic leukemia). It was initially isolated from Streptomyces peucetius.

Daunorubicin is currently one of the most active chemotherapeutic agents for inducing remissions in acute granulocytic leukemia and in acute lymphocyic leukemia. A metabolic conversion by the reduction of daunorubicin (Dl) to daunorubicinol (D2) by the enzyme daunorubicin reductase was occur (Fig.3). Since this conversion can occur in human blood cells and since blood cells are the site of action of the drug in the leukemias, the concentrations of daunorubicin reductase in these cells, as well as in other tissues,may bear a relationship to the pharmocodynamics of daunorubicin therapy.

Major problems in the study of the biochemical pharmacology of daunorubicin have been the tenacious binding of the drug and metabolites to tissues components, the instability of the glycoside linkage, and the physicochemical similarity of daunorubicin to the metabolite, daunorubicinol, which prevented an easy assay. (46)

Uses

It slows or stops the growth of cancer cells in the body.

Treatment is usually together with other chemotherapy drugs (such as cytarabine), and its administration depends on the type of tumor and the degree of response. In addition to its major use in treating AML, daunorubicin ia also used to treat neiroblastoma. Daunorubicin has been used with other chemotherapy agents to treat the blastic phase of chronic myelogenous leukemia. Daunorubicin is also used as the starting material for semi-synthetic manufacturing of doxorubicin, epirubicin and idarubicin.

Mode of action

On binding to DNA, daunorubicin intercalates, with its daunosamine residue directed toward the minor groove. It has the highest preference for two adjacent G/C base pairs flanked on the 5' side by an NT base pair. Daunorubicin effectively binds to every 3 base pairs and induces a local unwinding angle of 11o, but negligible distortion of helical conformation.

Route of administration

Daunorubicin should only be administered in a rapid intravenous infusion. It should not be administered intramuscularly or subcutaneously, since it may cause extensive tissue necrosis. (47)

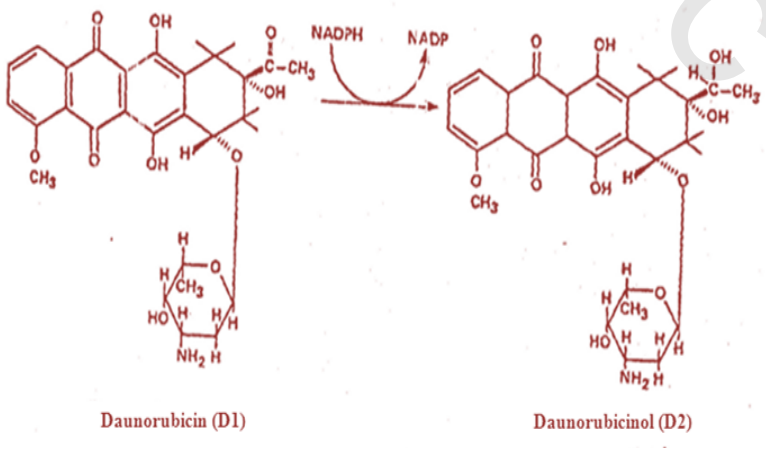

Figure (3): Reaction catalysed by daunorubicin reductase (46)

Acute Lymphoblastic Leukemias

1 -Epidemiology

About 5000 patients with Acute Lymphoblastic Leukemias (ALL) are diagnosed annually in the United States.[48, 49] ALL is the most frequently diagnosed childhood acute leukemia, constituting 25% of childhood malignancies. It represents only 20% of adult acute leukemias. ALL has a bimodal distribution. The incidence is 4–5 per 100,000 population between the ages of 2–4, which decreases during later childhood, adolescence, and young adulthood before a second, smaller peak occurs in patients older than 50 years (incidence 1 per 100,000 population).[50]

Among children, white children are affected more frequently than African-American children. There is little difference in incidence rates by gender among children, but in older age groups, ALL is more predominant in males. The incidence of ALL has remained stable worldwide for decades. An unexplained small increase in the number of cases has been observed recently.[51]

2 -Etiology

Associations with environmental, socioeconomic, infectious, and genetic events are being studied extensively. Few causal links have been established and the etiology of ALL remains obscure in most cases.[52] The strongest associations to date exist with genetic factors and the role of Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) in patients with mature– B-cell ALL.

The role of genetic factors is suggested by several observations. ALL in a monozygotic twin has a 20–25% likelihood of developing in the second twin within 1 year.[53] Among dizygotic siblings, there is a fourfold higher risk of leukemia compared with the general population.[54, 55] Patients with trisomy 21 (Down syndrome) have a 20 fold higher risk of developing ALL compared with the general population.[56, 57] Klinefelter syndrome and inherited diseases with excessive chromosomal fragility (Fanconi anemia, Bloom syndrome, ataxia telangiectasia) also have been associated with the development of ALL.[58, 59]

An increased number of ALL cases have been recorded after the atomic bomb explosions,[60] other nuclearexposures such as the Chernobyl accident,[61] exposure to therapeutic radiotherapy,[62] and in utero exposure.[63] Increased incidence of ALL also has been associated with residence close to industrial sites; exposure to gasoline, diesel and motor exhausts, smoking, and hair dyes[64, 65]; parental use of amphetamines, diet pills, and mind-altering drugs before and during the pregnancy[66]; and exposure to electromagnetic fields.[67]

An increased incidence of ALL has been described with higher socioeconomic status, which may relate to better hygiene, less social contact in early infancy, and thus a differing exposure to infectious agents.[20]

EBV, a DNA virus causing infectious mononucleosis, is associated with Burkitt lymphoma and mature– B-cell ALL including many HIV-related lymphoproliferative disorders.[69] A link between the onset of ALL and seasonality has been described and also may be related to infectious etiologies. [70]

Few cases of ALL after chemotherapy exposure have been described. Translocation t(4;11)(q21;q23) has been demonstrated in ALL up to 2 years after treatment with topoisomerase II inhibitors.[71]

3 - Clinical Presentation

Symptoms arise from expansion of leukemic cells in the bone marrow, peripheral blood, and extramedullary sites. Fatigue, lack of energy, dyspnea, dizziness, bleeding, easy bruising, and infections are common. Extremity and joint pain may be the presenting symptom in children. Physical examination may reveal pallor, ecchymoses, or petechiae. Lymphadenopathy and hepatosplenomegaly are infrequent and rarely symptomatic.[72] Involvement of skin, testicles, kidneys, joints, and bones is uncommon in adults. [73, 74] Central nervous system (CNS) involvement is uncommon at diagnosis, except in patients with mature B cell ALL. These patients may present with cranial nerve deficiencies (especially cranial nerves VI, III, IV, and VII), leading to double vision, abnormal ocular movements, facial dysesthesia, and facial droop. [75] Chin numbness due to mental nerve involvement may be subtle and can be overlooked easily. Patients with T-lineage ALL present with a mediastinal mass on chest X-ray. If the mass is sufficiently large, it results in stridor, wheezing, pericardial effusions, and superior vena cava syndrome.[76, 77] B-cell ALL is a rapidly proliferating tumor. Patients present with signs and symptoms of metabolic hyperactivity, including profound constitutional symptoms, weight loss, and often large abdominal and (especially in children) testicular masses that can lead to obstructive hydronephrosis with renal insufficiency. [78] Involvement of the gastrointestinal tract is frequent and may cause bleeding or rupture.

5 - Diagnosis

I - Morphology and Cytochemistry

In ALL, particularly B-lineage ALL, a characteristic pattern of 'block positivity' is often seen; however, a PAS stain is no longer indicated in suspected ALL, unless there is no access to immunophenotyping. Similarly, an acid phosphatase stain for the recognition of Golgi zone staining in T-lineage ALL is redundant if immunophenotyping is available. [79]

II- Immunophenotyping

Immunophenotyping has contributed to a prognostically relevant view of the leukemic blasts in ALL. Due to the ease of application, accuracy in diagnosis, and quantifiability of results, flow cytometry has become the preferred method for lineage assignment.[80] A distinct lineage determination is possible in greater than 98% of the leukemic blasts. ALL blasts are divided into precursor–B-cell types, mature–B-cell ALL, and T-lineage ALL.[81] Precursor–B-cell ALL includes pre–pre-B ALL (pro-B ALL), common ALL (cALL), and pre-B ALL. [81]

III - Cytogenetic-Molecular Markers

Recurrent cytogenetic-molecular abnormalities occur in about 80% of children and 60–70% of adults.[82] Distinct subsets of ALL can now be identified based on molecular abnormalities with implications on prognosis and on the choice of therapy. [83]

6 - Treatment

The improved rate of cure of ALL can be attributed in large measure to the development of more effective multidrug regimens in well-designed clinical trials. [84]

6.1 - Induction of Remission

The first goal of therapy in patients with leukemia is to induce complete remission with restoration of normal hematopoiesis. The induction regimen invariably includes a glucocorticoid (prednisone or dexamethasone) and vincristine, as well as asparaginase for children or an anthracycline for adults.[85] With improvements in chemotherapy and supportive care, the rate of complete remission now ranges from 97 to 99 percent in children and from 75 to 90 percent in adults. Nonetheless, attempts are being made to intensify induction therapy, especially for patients with standard-risk or high risk disease, on the premise that more rapid and complete reduction of the leukemic-cell burden may forestall drug resistance in leukemic cells, leading to improvements in long-term outcome. Perhaps because of its increased penetration into cerebrospinal fluid and its longer half-life[86], dexamethasone, when used in induction and continuation regimens, provides better protection than prednisone against relapse of central nervous system disease in children with ALL. [87, 88]

Three forms of asparaginase, each with a different pharmacokinetic profile, are available. In one randomized trial, the outcome in patients treated with asparaginase derived from *Escherichia coli* was better than that in patients treated with *Erwinia carotovora* asparaginase, which has a shorter half-life in plasma.[89] While, the efficacy of various anthracyclines in adults with ALL has been similar. [90, 91]

6.2 - Maintenance Therapy

With restoration of normal hematopoiesis, patients whose disease is in remission become candidates for intensification (consolidation) therapy. Such treatment, administered shortly after the induction of remission, includes several drugs, most often methotrexate given in high doses with or without 6-mercaptopurine[92]; asparaginase given in high doses for an extended period[93]; an epipodophyllotoxin plus cytarabine[94] ; or a combination of vincristine, dexamethasone, asparaginase, doxorubicin, and thioguanine given with or without cyclophosphamide. [95, 96]

6.3 - Continuation Treatment

With the exception of those with mature B-cell leukemia, children with ALL require prolonged continuation treatment for reasons that are poorly understood. Perhaps long-term drug exposure or the host immune system is needed to kill residual, slowly dividing leukemic cells or to suppress their growth, allowing programmed cell death to occur. [97

6.4 - Therapy Directed toward the Central Nervous System

Realization that the central nervous system can be a sanctuary for leukemic cells has prompted the development of presymptomatic therapy directed toward the central nervous system in patients with ALL. Because of concern that cranial irradiation can involve substantial neurotoxicity and can occasionally cause brain tumors, many therapists instead administer intensive intrathecal or systemic chemotherapy early in the treatment course. The results of chemotherapy are excellent: rates of relapse of central nervous system disease of 2 percent or less have been achieved. [98, 99]

6.5 - Allogeneic Stem-Cell Transplantation

Transplantation of allogeneic stem cells is usually indicated for patients who do not have a response to the initial induction treatment and those who have a second remission after a hematologic relapse.[100] However, for children with late relapses after antimetabolite treatment (more than 36 months after induction), transplantation may be deferred until a subsequent relapse, because these patients have a reasonable chance of cure with retrieval chemotherapy alone. [101, 102]

Renin-Angiotensin System

The rennin-angiotensin system (RAS) is a bioenzymic cascade that plays an integral role in cardiovascular homoeostasis by influencing vascular tone, fluid and electrolyte balance and the sympathetic nervous system (figure 4).The biological actions of the RAS are mediated primarily by the highly active octapeptide angiotensin II (Ang II). Traditionally, the RAS was viewed as a circulating endocrine system, whereby renin released from the juxtaglomerular cells of the kidney cleaves the liver-derived macroglobulin precursor angiotensinogen, to produce the inactive decapeptide angiotensin I, which is then converted to the active octapeptide Ang II by angiotensin converting enzyme (ACE) within the pulmonary circulation. [103, 104]

In addition to the systemic (circulating) RAS, there is evidence to indicate that many tissues, including the vasculature, heart, kidney and brain, are capable of producing Ang II, which may thereby mediate autocrine, paracrine and intracrine effects.[103, 104] Numerous studies have also shown that the requisite components of the RAS, such as angiotensinogen, renin and ACE are present in such tissues.[105] Furthermore, Ang II can be formed via non-ACE and non-renin enzymes (Figure 1) including chymase, cathepsin G, chymostatin-sensitive Ang II generating enzyme (`CAGE'), tissue plasminogen activator and tonin. [106, 107]

In addition to the RAS playing an important role in normal cardiovascular homoeostasis, over activity of the RAS has been implicated in the development of various cardiovascular diseases, such as hypertension, congestive heart failure, coronary ischemia and renal insufficiency.[108] Therefore drugs which interfere with the RAS, such as ACE inhibitors and Ang IIT1R antagonists, have been shown to be of great therapeutic benefit in the treatment of such cardiovascular disorders.[109]

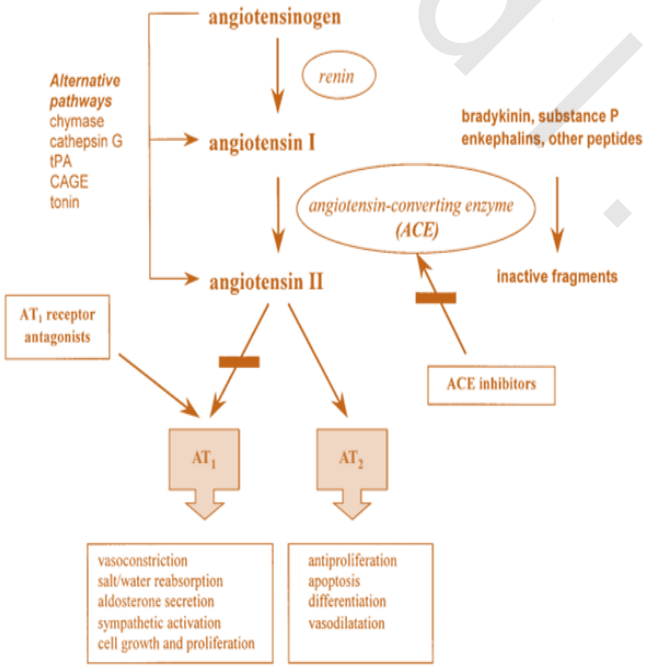

Figure (4): Bioenzymic cascade of the rennin-angiotensin system[106, 107]

Angiotensin Receptors

The actions of Ang II are mediated by specific heterogenous populations of Ang II receptors. Ang II is known to interact with at least two distinct Ang II receptor subtypes, designated Ang IIT1R and Ang IIT2R.[110] The characterization of Ang II receptor subtypes was made possible by the discovery and development of selective nonpeptide Ang II receptor antagonists, namely losartan (Ang IIT1R -selective) and PD123319 (Ang IIT2R -selective).[111] Virtually all the known biological actions of Ang II, including vasoconstriction, release of aldosterone, stimulation of sympathetic transmission and cellular growth, are exclusively mediated by the Ang IIT1R.[111] The functional role of Ang IIT2R receptors is not fully understood, but recent studies have described a possible role of Ang IIT2R in mediating anti proliferation, apoptosis, differentiation and possibly vasodilatation.[112, 113]

ANG IIRT1 Receptors

Properties

Ang IIT1R selectively bind biphenylimidazoles, including losartan, candesartan and irbesartan, with high affinity and are rather insensitive to tetrahydroimidazolpyridines, such as PD123319 and PD123177.[111] Moreover, the affinity of Ang II for the ANG IIR-1 is dramatically decreased in the presence of the reducing agent dithiothreitol and GTP analogues.[114]

The Ang IIT1R gene product consists of 359 amino acids and has a molecular mass of 41 kDa. The human genome contains a unique gene coding for the ANG IIR-1, which is localized on chromosome 3.[115]

The Ang IIT1R belongs to the seven transmembrane class of G-protein-coupled receptors.[116] Four cysteine residues are located in the extracellular domain, which represent sites of disulphide bridge formation and are critical tertiary structure determinants. The transmembrane domain and the extracellular loop play an important role in Ang II binding.[117] The binding site for Ang II is different from the binding site for Ang II T1R antagonists, which interacts only with the transmembrane domain of the receptor.[118] Like most G-protein-coupled receptors, the Ang II T1R is also subject to internalization when stimulated by Ang II, a process dependent on specific residues on the cytoplasmic tail.[119]

Signal transduction

There are five classical signal transduction mechanisms for the ANG IIR-1; activation of phospholipase A2, phospholipase C, phospholipase D and L-type Ca2+ channels and inhibition of adenylate cyclase (Figure 5). Stimulation of phospholipase C-β which is coupled to Gq/11 protein, is the most well described intracellular signalling pathway, in which two secondary messengers Ins (1,4,5) P_3 and diacylglycerol, are formed by hydrolysis of PtdIns (4,5) P_2. Ins (1,4,5) P_3 stimulates the release of Ca2+ from intracellular stores, and diacylglycerol induces protein kinase C activity, both of which lead to vasoconstriction.[120, 121] Activation of phospholipasesA2 and D stimulates the release of arachidonic acid, the precursor molecule for the generation of prostaglandins.[120, 121] Ang II-mediated stimulation of the ANG IIR-1coupled to G i/o protein can also inhibit adenylate cyclase in several

target tissues, including liver, kidney and adrenal glomerulosa, thereby attenuating the production of the second messenger cAMP.[122] cAMP is a vasodilator and when its production is decreased due to Ang II T1R activation, vasoconstriction ensues. Moreover, the Ang II T1R is also involved in the opening of Ca 2+ channels and influx of extracellular Ca 2+ into cells. This mechanism has been linked to Ang II-mediated stimulation of aldosterone production and secretion, as well as vasoconstriction.[123]

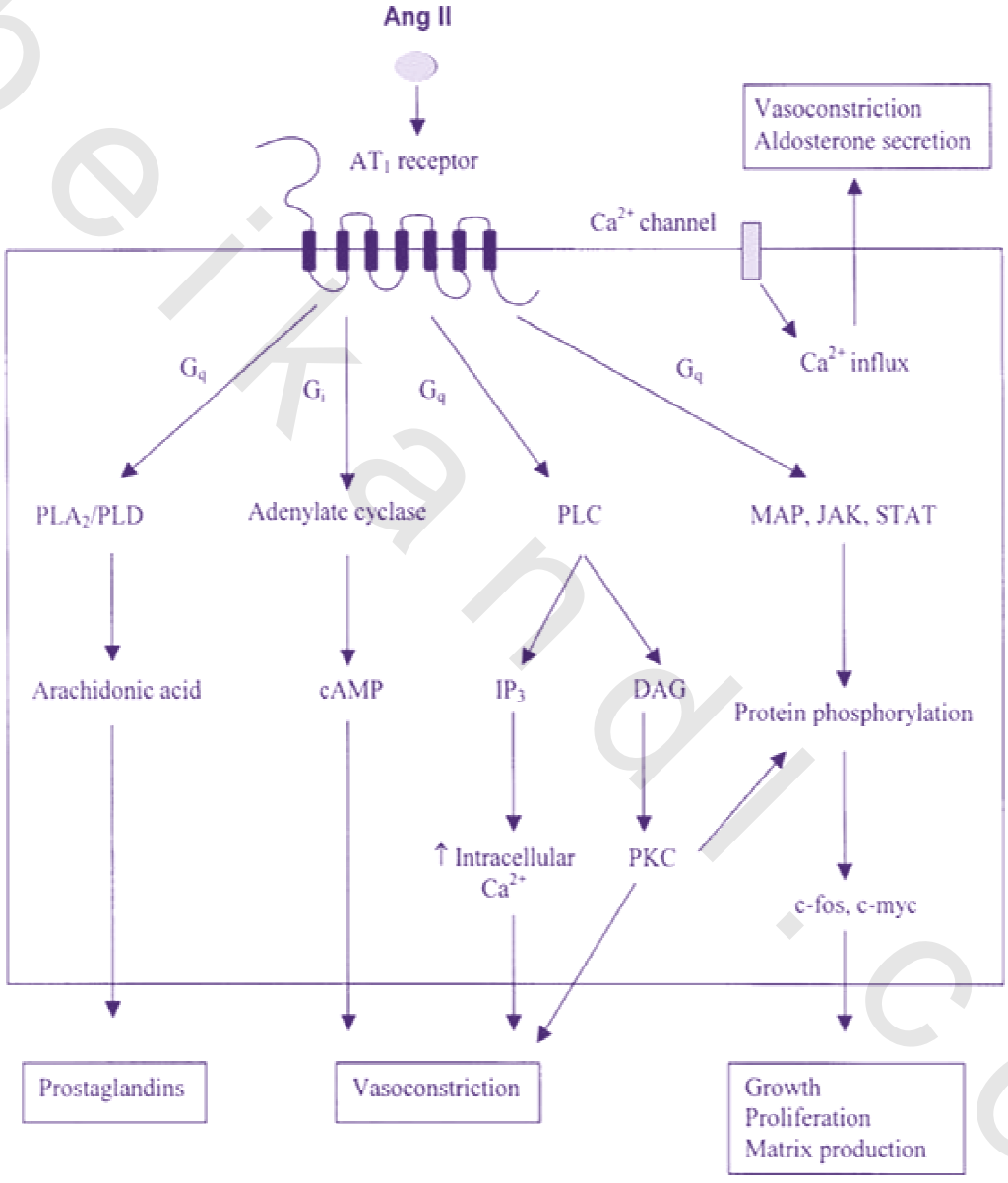

Figure (5): Signal transduction mechanisms and physiological effects mediated by the Ang IIT1R[120, 121]

It has been reported that activation of the Ang IIT1R stimulates growth factor pathways, such as tyrosine phosphorylation and phospholipase C-γ, leading to activation of downstream proteins, including mitogenactivated protein (MAP) kinases, Janus kinases (`JAK'), and the signal transducers and activators of transcription (`STAT') proteins.[124, 125] Ang IIstimulating cellular proliferation and growth has been defined in adrenal medulla and vascular smooth muscle cells (VSMC). These growth-like effects are associated with increased tyrosine phosphorylation and activation of MAP kinase and related pathways, which results in increased expression of early response genes, such as c-fos, c-jun and c-myc, which control thymidine incorporation, cellular proliferation and growth.[126] Such actions have been linked to cardiovascular diseases, including hypertension, cardiac failure and atherosclerosis.

Distribution and location

Ang IIT1R are primarily found in the brain, adrenals, heart, vasculature and kidney, and serve to regulate blood pressure and fluid and electrolyte balance. Ang II T1bR have been demonstrated in the central nervous system of the rat[127], rabbit[128] and human[129, 130], using in vitro autoradiography and more recently with in situ hybridization histochemistry.[131] Ang II T1R are localized to areas of the brain that are exposed to blood borne Ang II. Furthermore, other regions of the hypothalamus, nucleus of the solitary tract and ventrolateral medulla in the hindbrain also contain a high density of Ang IIT1R.[127]

Ang IIT1R have also been identified in the adrenal gland of rodents, primates and humans.[132, 133] Ang IIT1R receptors are localized mainly in the zona glomerulosa of the adrenal cortex and chromaffin cells of the adrenal medulla. In the heart, the highest density of Ang II T1R is found in the conducting system.[134, 135] The anatomical distribution of the Ang IIT1R in the kidney has been mapped in various species.[136, 137] High levels of Ang IIT1R binding occur in glomerular mesangial cells and renal interstitial cells located between the tubules and vasa recta bundles within the inner stripe of the outer medulla. Moreover, moderate binding is located in proximal convoluted tubular epithelia.

More recently, the presence of Ang II T1R has been shown in the human prostate, being concentrated around the peri-urethral region and localized to stromal smooth muscle.[138] This finding suggests that Ang II may play a role in this region by modulating cellular growth and sympathetic activity in the prostate, in relation to urinary flow.

Function

Ang II stimulation of Ang II T1R in blood vessels causes vasoconstriction leading to an increase in peripheral vascular tone and systemic blood pressure. [139] Ang II T1R in the heart are known to mediate the positive ionotropic and chronotropic effects of Ang II on cardiomyocytes.[140] Ang IIis also known to mediate cell growth and proliferation in cardiac myocytes and fibroblasts, as well as in vascular smooth muscle cells, and can induce the expression and release of various endogenous growth factors, including fibroblast growth factor, transforming growth factor-β and platelet-derived growth factor.[141, 142] It is now clear that these long-term trophic effects of Ang II are implicated in the development of cardiac hypertrophy and remodelling, and in the pathophysiology of hypertension.[143, 144] Recently, it was shown that transgenic mice over-expressing the Ang II T1R in cardiac myocytes developed cardiac hypertrophy and remodelling, with no change in blood pressure, and died prematurely of heart failure.[145] This suggests that Ang

II, via activation of Ang IIT1R, is directly involved in the development of cardiac hypertrophy and heart failure, independently of blood pressure.

It is well documented that Ang II facilitates sympathetic transmission by enhancing the release of noradrenaline from peripheral sympathetic nerve terminals, as well as from the central nervous system. [146] Moreover, Ang II stimulates the release of catecholamines from the adrenal medulla and aldosterone from the adrenal cortex.[147] Ang II also exerts diverse actions on the brain by modulating drinking behaviour and salt appetite, central control of blood pressure, stimulation of pituitary hormone release and has effects on learning and memory.[148] Renal Ang II is involved in regulating sodium and water reabsorption from the proximal tubules and inhibition of renin secretion from the macula densa cells[149], the latter action preventing further activation of the RAS.

Angiotensin-receptor signaling pathways related to cancer

Signaling pathways associated with activation of Ang II T1R and Ang II T2R in various cell types have been the subject of extensive studies. The major intracellular pathways that might be involved in the potential effects of these receptors in cancer cell proliferation, angiogenesis and inflammation are summarized in Figure 6.[150]

Cell proliferation

It is now well established that Ang IIT1R induces cell proliferation in a variety of cellular models, including human cancer cells[151, 152], by activating various intracellular cascades of protein kinases usually associated with growth factor stimulation. Most notably, Ang IIT1R transactivates the EGFR in prostate[153] and breast[154] cancer cells, leading to extracellular-regulated kinase (ERK) activation, phosphorylation of signal transducer and activator of transcription 3 (STAT3) and activation of protein kinase C (PKC) (Figure 7a). Ang IIT1R mediated transactivation of EGFR is particularly relevant, to cancer because EGFR amplification is frequently associated with tumor progression, efficient anticancer strategies are nowbeing developed using monoclonal antibodies to the EGFR.

In line with its antiproliferative effects, the Ang IIT2R trans-inactivates the EGFR by inhibiting its autophosphorylation.[155] In some cell types, this effect involves the activation of the tyrosine phosphatase SHP-1 (the Src homology region 2 domain, containing tyrosine phosphatase 1)[156]; the role of SHP-I in cancer has recently been reviewed[157], Ang IIT2R also directly interacts with ErbB3 a member of the EGFR family[158], although the functional consequence of this interaction has not yet been established. Also, recent studies have identified a novel family of Ang IIT2R -interacting proteins (ATIP) that inhibit EGF-induced cell proliferation[159] and participate in Ang IIT2R transportation to the plasma membrane[160], Of note, ATIP (also designated MTUS1 and MTSG1) has been reported to be a putative tumor suppressor gene whose expression is reduced in pancreatic cancer.[161]

Angiogenesis

The diverse actions of Ang II on the endothelium have been recently reviewed,[162] Proangiogenic effects of the Ang IIT1R mostly result from the upregulation of VEGF acting on endothelial cells in a paracrine-autocrine manner. In endothelial cells, Ang II T1R also increases the expression of VEGF2 receptor (VEGFR2)[163, 164] and angiopoietin-2, a major determinant of angiogenesis acting through binding to the Tie-2 receptor tyrosine kinase, but not that of angiopoietin-1[165], In microvascular endothelial cells, Ang IIT1R upregulates VEGF and angiopoietin-2 levels by the transactivation of the EGFR, and the Ang IIT2R subtype counteracts these effects by inhibiting EGFR autophosphorylation.[165] The Ang IIT1R subtype also displays antiapoptotic effects in microvascular endothelial cells by up-regulating survivin and suppressing caspase-3 activity, via activation of the phosphoinositide-3 kinase (PI-3K)-Akt pathway. [166] By contrast, the Ang II T2R inhibits VEGFR2-induced phosphorylation of Akt and endothelial NO Synthase (e-NOS), leading to reduced human endothelial cell migration and tube formation. [167] These data suggest a dual effect of Ang IIT1R and Ang IIT2R on the VEGFR2 pathway, acting by regulating the expression levels of VEGF and its receptor VEGFR2, and by interfering with VEGFR2-activated intracellular mediators (figure 7b).

Inflammation

Activation of the Ang IIT1R promotes the transcriptional upregulation of several inflammatory cytokines and chemokines [e.g. interleukins (ID-6/12 and IL-8, and monocyte chemoattractant protein-1 (MCP-1)] via signaling pathways involving nuclear factor kappa B (NFkB), activator protein-1 (AP-1) and ROS[168] (Figure 7c). In vascular smooth muscle cells, Ang IIT2R has been reported to contribute to Ang ll-induced activation of NFκB[168] or to inhibit MCP-1 production by stabilizing inhibitory proteinκB (IκBα) through a SHP-1- dependent pathway.[169] In human monocytes, the Ang II T1R induces migration by activating Src, ERK1/2 and p38, and phosphorylating the cytoskeleton-associated proteins", Pyk2 and paxillin.[170] Ang IIT1R also activates human neutrophils via multiple signaling pathways involving mitogen-activated protein kinases (ERK1/2, p38 and' c-Jun N-terminal kinase 2), ROS and NFκB activity.[171] In endothelial cells, Ang IIT1R induces VCAM-1 synthesis by inducing H_2O_2 production and NFκB activity[172] and in fibroblasts, the major stromal cellular components involved in tumor-related angiogenesis and inflammation, Ang IIT1R Receptor upregulates VEGF by activating NFκB, AP-1 and PKC.[173]

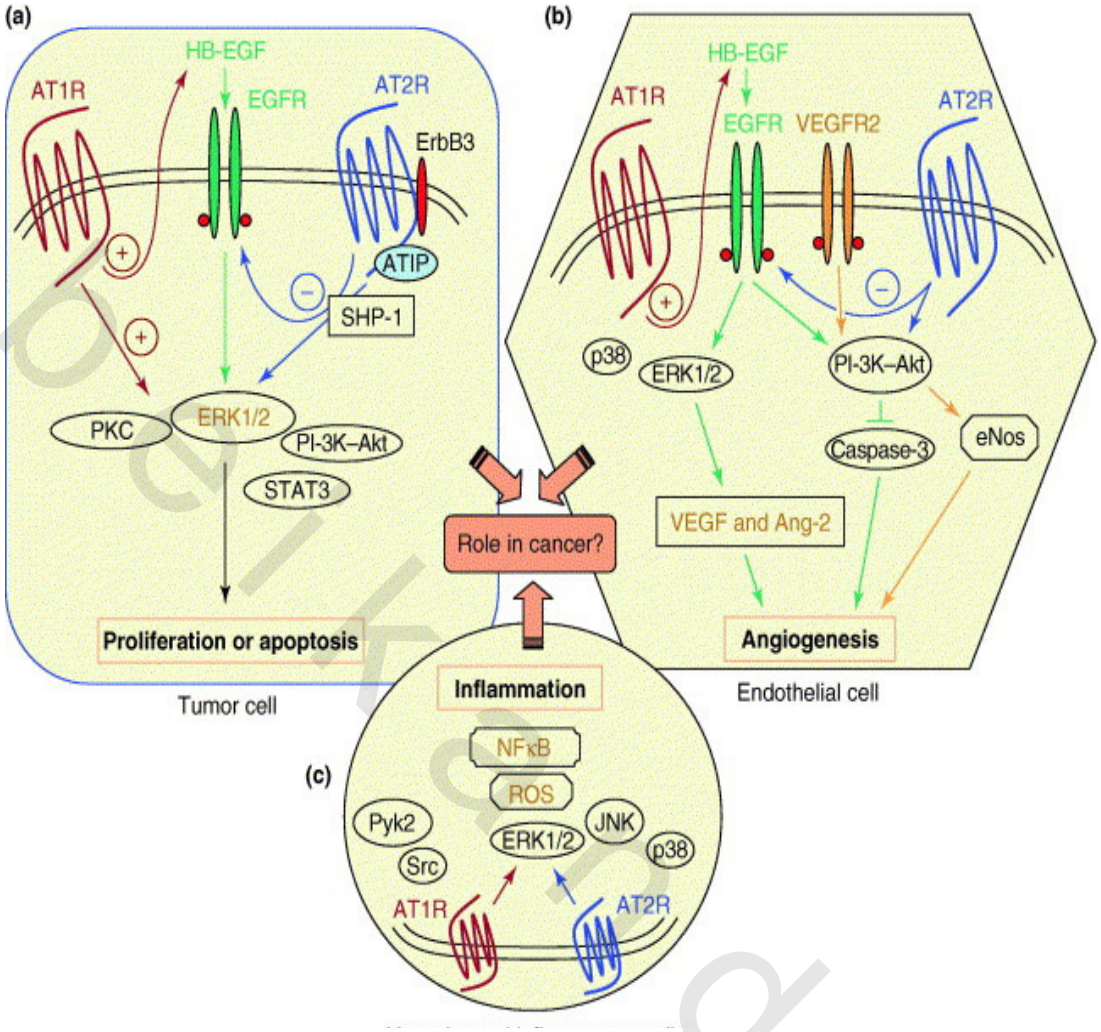

Figure (6): Major ANG IIT1 R and ANG IIT2 R signaling pathways related to cancer cell proliferation, angiogenesis and inflammation. Diverse signaling pathways activated by ANG IIT1 R and ANG IIT2 R in (a) tumor, (b) endothelial and (c) inflammatory cells might contribute to cancer development. Ang II T1R signaling pathways implicate EGFR transactivation by metalloprotease cleavage of heparin-binding EGF (HB-EGF), whereas Ang II T2R inhibits EGFRautophosphorylation. (a)EGFR-activated extracellular-regulated kinases (ERK 1/2) and protein kinase C (PKC) are major mediators of cell proliferation in cancer cells, (b) Increased levels of VEGF and angiopoeitin.2 (Ang-2) account for ANG IIT1 R-medlated angiogenesis in endothelial cells. (c) The inflammatory process mainly implicates production of reactive oxygen species (ROS) and NF-B activation in vascular (smoothmuscle and endothelial cells) and inflammatory (noutrophils and monocytes) cells. Being developed using monoclonal antibodies to the EGFR.[150]

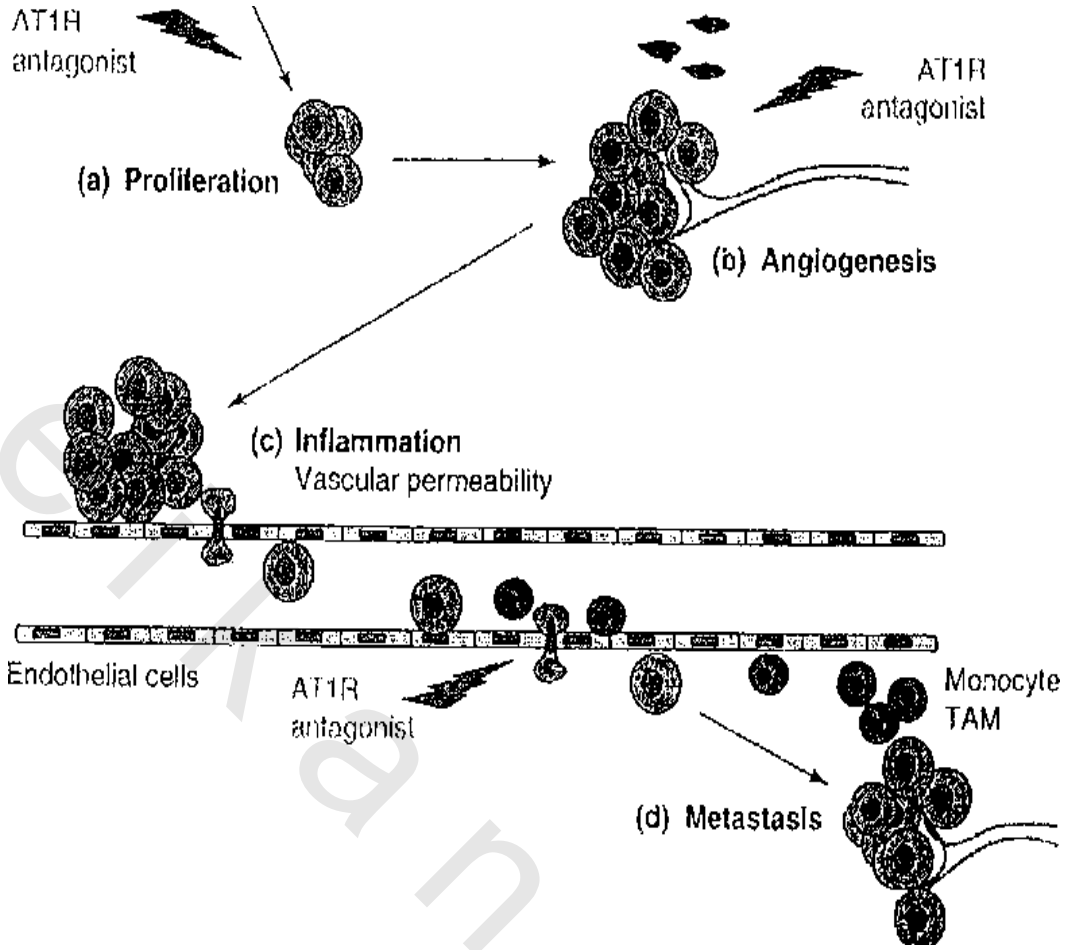

Figure (7): Schematic representation of various steps of cancer progression potentially Involving Angll. Tumor development is a multistep process Including a) cancer cell proliferation and (b) angiogenesis, the formation of a vascular network that provides the growing tumor with oxygen and essential nutrients. (c) Production of VEGF and inflammatory cytokines leads to increased vascular permeability and leukocytc infiltration, a process known to facilitate the extravasation of tumor cells and thus,d) the formation of metastases. The use of ANG IIT1 R antagonists (shown In red) might have a protective effect on each step of tumor formation.[151, 162, 168]

Angiotensin Converting Enzyme

ACE, angiotensin I and angiotensin II are part of the renin-angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body. ACE is secreted in the lungs and kidneys by cells in the endothelium (inner layer) of blood vessels.[174, 175]

It has two primary functions:

- ACE catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor in a substrate concentration-dependent manner.
- ACE degrades bradykinin, a potent vasodilator, and other vasoactive peptides.

These two actions make ACE inhibition a goal in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy, and type 2 diabetes mellitus. Inhibition of ACE (by ACE inhibitors) results in the decreased formation of angiotensin II and decreased metabolism of bradykinin, leading to systematic dilation of the arteries and veins and a decrease in arterial blood pressure. In addition, inhibiting angiotensin II formation diminishes angiotensin II-mediated aldosterone secretion from the adrenal cortex, leading to a decrease in water and sodium reabsorption and a reduction in extracellular volume. [176, 177, 178]