

Myeloid Leukemia: A Molecular Focus on Etiology and Risk Within Africa

Muntaser E. Ibrahim and Emad-Aldin I. Osman
*Department of Molecular Biology, Institute of Endemic Diseases,
University of Khartoum, Khartoum,
Sudan*

1. Introduction

The developing world, Africa included, is witnessing an alarming upsurge of cancer incidence. The annual number of new cancer cases is expected to double by 2020 and up to 70% of the 20 million new cases of cancer predicted to occur yearly will be in the developing world (Jones et al., 1999; Ferlay et al., 2003; Yach et al., 2004).

One startling disparity, however, between cancer in the developing and developed worlds is that although the overall incidence of cancer in the developing world is half of that observed in the developed world, survival rates in the developing world are often less than one third of site-specific cancers in the developed world (Sener et al., 2005). This emphasizes the duality of the cancer problem in Africa, for being largely a disease of modern life style, occurring against a background of socio-economic disparities and greater burden of communicable diseases.

The study of genetic epidemiology of cancers in Africa hence entails the study of peculiar features of gene-environment interaction that may be largely private to Africa. In addition to the state of socio-economic underdevelopment that applies almost to the majority of African states, there is the plethora of extreme environments, wide range of climatic conditions and cultures, but most of all the transition state of the African communities from rural subsistent into urban market oriented life style. Furthermore one has to consider the notorious prevalence of infectious and non infectious diseases that may have a bearing both on the initiation of myeloid leukemia, its prognosis and management, e.g. tuberculosis (Omoti et al., 2009), malaria, other chronic infections, sickle cell disease (Ahmed et al., 2008) and common adaptive traits that could modulate the course of the disease, as well as the role of oncogenic viruses discussed below.

One interesting example of a potential trade-off between malignancies and parasitic diseases is CD36 a multiligand receptor associated with a broad array of physiological processes, believed to be under selective pressure from *Plasmodium falciparum*, and deficient or polymorphic in several African populations. The role of CD36 in sickle cell crises and cerebral malaria is debatable. As a receptor for thrombospondin 1, CD36 plays a role in the regulation of angiogenesis, which may be a therapeutic strategy for controlling the dissemination of malignant neoplasm. Moreover, it is commonly expressed on blasts in acute monocytic leukemia, megakaryoblastic leukemia, and erythroleukemia (Ge and

Elghetany, 2005). However, CD36 negative AML cells could be found especially in those populations that usually do not express CD36 (like in several African populations). CD36 negative cells appeared less susceptible to trombospondin-1 induced apoptosis, which make leukemic cells less vulnerable to death through this promising therapeutic strategy (Li et al., 2003).

On the other hand, due to the transition state, a number of risk factors believed to represent etiologic determinants of leukemia like use of pesticides, radiation etc. are not yet commonplace in Africa or at least its rural environment and may explain the differential distribution and the focal nature of hematological malignancies in the continent or/and individual countries. The potential impact of transition to a modern life style with the accompanying risks on the emergence and distribution of these diseases is worth our utmost attention.

Cancers in their complex etiology makes an ideal arena for the classical gene versus environment controversy. Those who favor an upper hand for the environment had their views strengthened by results of studies showing that people who migrate from one country to another generally acquire the cancer rates of the new host country, suggesting that environmental or lifestyle factors rather than genetic factors are the key determinants of the international variation in cancer rates. As far as Africa is concerned, African Americans' disease data, represent a working model to test the role of changing environment and the effect of life style in complex diseases. Interestingly both sides of the argument seem to find support. Chronic myeloid leukemia (CML) patients show worse survival for African American and Hispanics compared to Americans of European origin (Lee et al., 2009). Although the difference in ethnicity data might be argued to reflect socio-economic differences, the current advances in genomics enable the implication of particular genomic regions and genes that explain the ethnic differences in susceptibility to infectious and chronic diseases.

Environmental determinants also falls short of explaining neither the "focality" of cancer types nor the aggressive course of some cancers in Sudan like the breast cancer, a feature that has been claimed to exist across Africa and even among African American women (reviewed by Morris and Mitchell, 2008).

Nutritional factors have also been implicated, adding an extra layer of complexity to the desperately compound picture of cancer etiology. Data on nutrition is greatly deficient in Africa similar to other aspects of genetic epidemiology, although differences in nutritional practices and culture may be key in providing vital clues to the contribution of life style. A study in China (Zhang et al., 2008), for example, suggested that a higher intake of green tea is associated with a reduced risk of adult leukemia. Furthermore, a study by Ross et al. which involved 35,221 older women provided evidence that increased vegetable consumption may decrease the risk of adult leukemia (Ross et al., 2002). Moreover, AML risk was negatively associated with milk intake among women and tea, and positively associated among women with beer, wine and beef (Li et al., 2006). A prospective cohort study by Ma et al. (2009) showed that smoking and total meat intake were risk factors for AML and those who did not drink coffee appeared to have a higher risk of AML.

Africa is still contains one of the last and few enclaves on the planet to harbor communities with distinctive patterns of traditional life styles that once used to characterize human existence. Farmers, pastoralists and hunter-gatherers- like societies do preserve their life style and culture and often coexist in shared terrains. These communities adopt

fundamentally contrasting life styles and their food cultures are different. The significance of such disparity to all aspects of health and disease is of interest and the study of potential preponderance of these community members to chronic diseases including hematological malignancies should be investigated.

2. Incidence and epidemiology

The lowest rates of leukemia reported in sub-Saharan Africa probably represent failure of diagnosis or reporting to some extent (Davies, 1973; Fleming, 1993 and Parkin et al., 2005). We should therefore use caution, when drawing conclusions based on the varying prevalence and incidence, as an indication of clustering of cases or an environmental or genetic effect, as this may simply be due to the deficiency of statistics in Africa. The disparity could also be a reflection of the research milieu and capacity of individual countries or research groups, which indeed seem to be the case as most of the current reports on leukemia emerges from countries with well established science capacities.

Even with the scattered and available data, however, the difference from European and global trends could be observed as well as the evolution of the problem of leukemia. An early report from Uganda found that African children in Uganda showed a great and genuine deficiency of leukemia and an excess of solid lympho-reticular tumors (Davies et al., 1965).

In subsequence, the situation seems to change, a study of pediatric leukemia in Cameroon, showed that Acute Lymphoblastic Leukemia (ALL) comprised 78.6%, while AML 21.4% of all pediatric acute leukemia (Obama et al., 1995). In Egypt, the lymphatic and haemopoietic cancer incidence in 2001 have increased approximately 11-fold compared with the incidence in 1972. Moreover, the incidence of leukemia among infant less than 5 years increased exponentially with a higher incidence among boys (Hosny et al., 2002). In Kenya, leukemia in children below the age of 15 years comprised 37% of leukemia in all ages. Childhood acute leukemia formed 52.3% of all the acute leukemia. AML and ALL occurred, in almost equal proportions 42 % and 46 % respectively (Kasili, 1990). In Ethiopia, a report by Shamebo (1990) showed that the commonest type of leukemia was CML 57.8%, acute leukemia and chronic lymphatic leukemia (CLL) accounted for 21.1% each. Of the acute leukemia, 53.3% were ALL while 46.7% were AML (Shamebo, 1990). A recent study in south Nigeria showed that AML comprises 12.3% and CML 23.9% of all leukemia, with a mean age at diagnosis of 25.6 years and 35.2 years respectively (Nwannadi et al., 2011). In the last 25 years in Sudan CML became the predominant cancer in men, while lymphomas remained the second most common cancer. In women, breast, cervical and ovarian cancer remained the three most common cancers over both time periods, but there was also an increase in the incidence of CML among women (Hamad, 2006), the causes of this high incidence of CML are not known.

In Europe AML presents as mainly an adult's disease with a median age at presentation of 64 years, accounting for around 30% of all leukemia in adults, and ~18 000 new patients are diagnosed in Europe each year, representing ~0.6% of all cancers. The annual incidence rate in Europe ranges from two per 100 000/year to four per 100 000/year. In the past decade, the trend in overall incidence of AML has generally been stable or slowly increasing in most European countries, while most cases of CML occur in adults with a median age at presentation around age 60. CML comprises only around 2%-3% of all the leukemia diagnosed in patients <20 years of age but the incidence increases with age slowly until the

mid-40s, then more rapidly from about one per 1000 000/year in children <10 years to two per 100 000 in people in the fifth decade to one per 10 000 at age 80. The disease is more common in males. There is no clear evidence of to geographic or ethnic background that predisposes to CML; however, in the United States the incidence is slightly higher in Caucasians than in Blacks or Hispanics (Lee et al., 2009), and it exhibits a male preponderance, in South African Coloured and Black people, and African Americans in comparison to whites but the reason for this is unexplained. (Jacobs et al., 1983). Furthermore, several reports showed an increased incidence of CML during the first 2 decades of life in African subjects (Haddock, 1967; Lowe et al., 1971; Lowenthal et al., 1975), but other reports by Leibowitz et al., (1976) and Jacobs et al., (1983) disagree with this. Jacobs et al. reported that in comparison with Whites and Coloureds, however, the peak incidence for Blacks was lower, lying between the 3rd and 4th decades. The peak incidence for Coloureds was in the 4th and 5th decades, and that for Whites in the 5th and 6th (Jacobs et al., 1983.)

An interesting study in United Arab Emirate (UAE) found that the rate of AML among UAE female nationals was higher than in nationals male and expatriates. The study proposed that chemicals in henna dye, which is used to decorate the body, as well as a lack of sunlight could be behind the increased incidence (Hassan et al., 2009). Henna is applied in many African countries especially Sudan where it is used by vast majority of Sudanese married women.

3. Molecular etiology

Leukemia in common with other cancers arises from mutations in a single cell, which enable the cell to reproduce excessively, emerging as a dominant clone. A large number of different mutant genes contribute to leukaemogenesis singly or, more often, in combination and many are leukemia sub-type specific (Greaves, 1986). The number of genetic abnormalities is believed to reflect the number of genes that control distinct developmental stages of blood formation and the multiple routes to clonal dominance. These include changes not only in proliferative activity, but in ability to differentiate, in resistance to cell death, in DNA repair activity and in general stability of the genes. Whether any particular mutant genes, or 'hot spots' for mutations within a gene, are linked to particular DNA damaging agents is a topic of considerable relevance to the molecular epidemiology of cancer in general. For these changes to happen some culprit agents has to come into action namely ionizing radiation, chemicals such as polycyclic hydrocarbons and certain drugs, and viruses.

The way how these extrinsic factors affect the cell genetically and epigenetically is the core of the functional research in cancer. Although multiple risk factors have been linked to the development of leukemia, however these known risk factors account for only a small number of observed cases. Few epidemiological studies have explored the relation between lifestyle, dietary factors and the incidence of adult Leukemia, and almost none has addressed the molecular and genetic aspects of these interactions.

3.1 Role of viruses

For several reasons pertaining to ecology and the human history in Africa, several pathogens have gained access into human genomes through the African gate. This includes major parasites, viral and bacterial diseases. It is not coincidence that the first well proven

case of viral oncogenesis that of Epstein Barr Virus (EBV) was established in Africa. EBV is a highly prevalent infection in the adult population in Africa and has been associated with a heterogeneous group of lymphomas, including Burkitt's lymphoma (especially the endemic form in Africa), Hodgkin's disease, NK, and T malignancies with cytotoxic phenotypes, and lymphomas in the immune-compromised patient (congenital immunodeficiency, organ transplantation, AIDS). (Rodriguez-Abreu et al., 2007) but not unequivocally with leukemia. Of the oncogenic retroviruses, the Human T-cell leukemia virus (HTLV) type-1 and type-2 have been identified as being related to the development of rare types of leukemia and lymphoma. HTLV-1 is endemic in certain areas including central Africa, and is associated with the development of adult T-cell leukemia or lymphoma (ATLL), which accounts for about half of the lymphoid malignancies in the endemic areas. The virus is transmitted mainly from mother to child, especially by breastfeeding. Sexual transmission and blood transfusion are minor routes of infection and cell-free blood products are not infectious (Rodriguez-Abreu et al., 2007).

The importance of oncogenic viruses stems not only from their transforming oncogenic properties but also from the potential methylating properties of selfish DNA.

Environmental determinant including infection with high-risk viruses are necessary but not sufficient alone in the development of cancer, as most infections regress without intervention. Thus, genetic host factors and cellular immune responses could be potential modifiers for the risk of developing cancer. In particular, p53 and Rb are considered as the most critical tumor suppressor genes involved in regulating cell division. The polymorphism on p53, which encodes either a Proline or an Arginin amino acid residue at codon 72, has been reported as a possible risk factor for several cancers including breast and cervical cancer in Sudan (Eltahir et al, submitted.).

3.2 Population and ethnic diversity

In the last decade the importance of ethnicity, socio-economic and gender differences in relation to disease incidence, diagnosis, and prognosis has been realised. Gender and ethnic differences in these areas should have a focus in health policy in Africa. A study by Lee et al. examined the demographic and clinical features of CML in an ethnically diverse population and found that Hispanic patients present with lower risk profile CML and achieve better treatment responses compared to non-Hispanic patients. The vast majority of their non-Hispanic patients were African American or Asian. This study proposed that biological/genetic factor can contribute to this observed ethnic differences in disease presentation and behavior. Hispanic ethnic group is thought to be the least diverse ethnic group, at the opposite site the African descent is the most diverse ethnic group. African populations are characterized by greater levels of genetic diversity, extensive population substructure, and less linkage disequilibrium (LD) among loci compared to non-African populations (Reich et al., 2001; Campbell and Tishkoff, 2008). Due to the long evolutionary history in Africa there is more genetic diversity within and between populations in the African continent, than between Africans and other peoples in the world (Cavalli-Sforza, 1997). African populations thus vary considerably in their genes. Moreover Africa shows a wide range of environments, climatic, vegetative and zoological. Thus human cancer patterns are expected to show a similar degree of diversity, the study of which would contribute to our understanding of their causes.

The majority of cancers as genetic disease of complex nature involve a multiplicity of genetic loci that cooperates to make the disease happen (the multiple -hit theory). It is expected that such genetic component will be influenced by the genetic background of the population at risk. In one of the few studies on a cancer susceptibility genes background mutational profile in different populations, Africans were found to harbor more mutations in their BRCA2 than populations from the rest of the world (Wagner et al., 1999.) which is expected given their larger effective population size.

Africans also possess a number of genetic adaptations that have evolved in response to diverse climates and diets, as well as exposure to infectious disease (Campbell & Tishkoff, 2008), that diversity may carry great challenge in leukemia presentation and behavior/prognosis and treatment. Moreover, experimental studies using synthetic peptides identical to the BCR-ABL fusion region in CML patients region have revealed the capability of specific peptides to bind to human leukocyte antigen (HLA) class I molecules (HLA-A2, A3, A11, B8) and class II molecules (HLA-DR1, DR2, DR3, DR4 and DR11). Individuals expressing HLA-A3, B8 or DR4 have a diminished risk for the development of CML in Caucasian populations. A statistically significant increase in the frequency of Cw3 and Cw4 antigens in Caucasians and European CML patients has been reported. Another report in Indian population showed that expression of HLA-Cw6 may result in a protective effect on CML acquisition (Chhaya, 2006). A study in Chinese population indicated that the expression of HLA-A*30, DRB1*07 might imply a protective effect on CML acquisition, while B*81 might be associated with CML susceptibility factors in that population (Miao et al., 2007). These results suggest that the development of CML is apparently associated with HLA phenotypes specific to each population. These data is missed in Africa and we intend to investigate this in Sudanese population.

Common polymorphism like the codon 72 in p53 has been argued to unlikely have major genetic effect since polymorphism in loci with major deleterious nature will not be selected for to reach such frequencies unless it is a balanced polymorphism. (i.e. selected for under the influence of the other allele possessing an favorable adaptive trait). Interestingly It has been proposed that the p53 polymorphism at times when the risk of tumors was not a Human concern, gave a reproductive leverage by increasing reproductive success (Kang et al., 2008). The cost of such trade off will not be visible as long as the conditions that predispose for tumors are absent. In fact the derived allele (arginine), almost reached fixation in some populations.

The p53 codon 72 was studied both in normal Sudanese (Bereir et al., 2002) and in the distribution of the polymorphism in different cancers in Sudan, (not including leukemia). The results show that the different alleles pose different risk ratios in different cancer. The Arg allele which is known to be more resistant to cell death was overrepresented breast carcinoma patients from different linguistic groups as compared to controls with an Odd ratio of 19.44 CI 6.6 - 78.3 $P < 0.0001$. In cervical cancer the homozygous Arg genotype was detected in 42.3% (33/78) in cervical cancer patients while the heterozygous arg/pro in 38.5% (30/78) and only 19.2% (15/78) had the pro/pro genotype, with an allele effect of 2.4 (CI 1.12 - 5.33, $P = 0.015$). In Burkitt's lymphoma the opposite seems to be true with a major effect from the Pro allele, where the homozygous Arg accounted for only 6.9%, (OR 0.18 CI 0.02 - 0.89, $P = 0.018$) while the Arg/Pro was 51.7% and pro/pro 41.4% (OR: 0.57, CI 0.23-1.42, $P = 0.1$). Possibly indicating the different biological pathways of tumorigenesis (Eltahir et al., submitted).

3.3 Gene and chromosomal rearrangements

Cancers as a group of diseases display the entire range of inheritance modes from the single gene like disorder to the complex inheritance pattern seen in chronic diseases. The paucity of genetic investigation in Africa of cancer susceptibility genes and chromosomal aberrations linked to cancer, makes the picture even more opaque. The few examples discussed above and below demonstrate the great relevance of studying the genetic population structure of African populations and establishing the frequencies of the individual SNPs, Ins/dels and chromosomal abnormalities associated with diseases that may be necessary to define the molecular etiological basis of each cancer. In fact both molecular and genetic abnormalities became an important factor for characterising, treating and risk stratifying of myeloid leukemia. In 2002 the WHO classification of Myeloid Neoplasms showed that AML classification includes specific genetic subcategories; thus, determination of genetic features of the neoplastic cells must be performed if possible. Many recurring genetic abnormalities in the myeloid neoplasms can be identified by advanced molecular and cytogenetic techniques. In the WHO classification, the blast threshold for the diagnosis of AML is reduced from 30% to 20% blasts in the blood or marrow. In addition, patients with the clonal, recurring cytogenetic abnormalities $t(8;21)(q22;q22)$, $inv(16)(p13q22)$ or $t(16;16)(p13;q22)$, and $t(15;17)(q22;q12)$ should be considered to have AML regardless of the blast percentage. On the other hand, according to the WHO classification, CML is defined specifically as a myeloproliferative disease that is characterized by the invariable presence of the Philadelphia (Ph) chromosome or the BCR-ABL fusion gene. Although in most cases the diagnosis is easily made from morphologic evaluation of the blood smear, confirmation by genetic studies is essential, particularly in view of the advent of therapy that targets the BCR-ABL fusion protein (Vardiman et al., 2002)

Despite their diagnostic and prognostic values, studies on gene and chromosomal rearrangements associated malignancies is greatly lacking on the African continent, and in spite of the mandatory genotyping of the BCR-ABL as a prerequisite of administering the drug imatinib, in several African countries, there are very few reports on its frequencies. Among the few reports on its association with other leukemias, a multi-country study comprising 181 children with newly diagnosed ALL were tested in laboratories in India, Pakistan, Myanmar, and Sudan, following a common protocol. Across the four countries, the ETV6-RUNX1 (TEL-AML1) fusion gene was present in only 5% of cases. All the positive samples were from children aged 1 to 10 years, in whom the prevalence of this fusion gene, which is associated with good prognosis, was 7.4% (9 out of 121 samples), a much lower rate than reported from Western populations. In the 18 ALL cases tested in Sudan, a notable excess of MLL-AF4 (17%) and BCR-ABL1 (22%) fusion genes was found (Siddiqui et al., 2010).

The significance of studying the frequency of these rearrangements and their relation to pathology, is to establish the level of culpability of the molecular events. A study on Nigerian breast cancer patients suggest that while BRCA1 genomic rearrangement exists, it does not contribute significantly to BRCA1-associated risk in the Nigerian population (Zhang et al., 2011).

Chromosomal translocations in myeloid leukemia yield hybrid RNAs capable of encoding fusion chimeric proteins. The unique amino acid sequences found in these oncogenic fusion proteins represent true tumor-specific antigens that are potentially immunogenic. Although

these leukemia-specific fusion proteins have an intracellular location, they might be recognized immunologically by T lymphocytes if peptides derived from the unique sequences are capable of presentation by the major histocompatibility complex (MHC) molecules on Leukemic cells (Bocchia *et al.*, 1995). The ability of a series of synthetic peptides corresponding to the junctional sequences of CML-derived BCR-ABL fusion proteins spanning the b3a2 and b2a2 breakpoints to bind to purified class I molecules was studied by Bocchia *et al.* Four peptides derived from b3a2 CML breakpoint bound with high or intermediate affinity to HLA A3, A11, and B8. None of the CML b2a2 junctional peptides showed affinity of this magnitude for the HLA class I molecules tested. Which draw another important conclusion on the significance of the types of BCR-ABL fusion transcripts among populations in relation to vaccine development? The frequencies of the types of the fusion transcript in Ecuadorian population for example consist of 95% b2a2 (Paz-y-Mino *et al.*, 2002) indicating that they may not benefit much from such vaccine.

Several studies estimated the types of BCR-ABL fusion transcript in CML in different populations. The distribution of transcript type has been studied in European and some other populations (Eisenberg *et al.*, 1988; Lee *et al.*, 1989) with frequencies for b2a2 and b3a2 transcripts being roughly of the order of 40% and 55%, and that for co-expression of b3a2 and b2a2 representing 5% of the cases. A study on an Ecuadorian population, however, registered very different frequencies: 5% for b3a2 and 95% for b2a2 (Paz-y-Mino *et al.*, 2002). In our report in Sudanese patients (Osman *et al.*, 2010), a frequency of 53.5% and 41.9% for b2a2 and b3a2, respectively, was reported, values that are relatively closer to those from a Mexican population (Arana-Trejo *et al.*, 2002). This difference in frequencies may be due to the genetic differences of the populations. Many Controversial reports about the clinical significance of the transcript type in CML were published; however it has a considerable importance in the diagnosis and follow up.

Recently, a polymorphic base in exon 13 of the BCR gene (exon b2 of the major breakpoint cluster region) has been identified in the eighth position before the junctional region of BCR-ABL cDNA. Cytosine replaces thymidine; the corresponding triplets are AAT (T allele) and AAC (C allele), respectively, both coding for asparagine. Therefore, this polymorphism has no implication in the primary structure of BCR and BCR-ABL proteins.

Co-expression of b2a2 and b3a2 transcripts has been linked to two polymorphisms, T to C at exon 13 and A to G at intron 13 (Meissner *et al.*, 1998; Branford *et al.*, 2002). However, in our study by Osman *et al.* (2010) six PCR products from four patients were sequenced to confirm the products of four b2a2 and two b3a2 and one was found to harbor T to C at exon 13 and expressed only b2a2 transcript which might indicate that this exonic polymorphism is not obligatory for co-expression, as reported by Mondal *et al.* (2006). Moreover, this polymorphism has no implication on the primary structure of BCR and BCR-ABL proteins. However, since the alteration is located close to the fusion region, it may have a significant influence on the annealing of PCR primers, probes for real time PCR, and antisense oligonucleotides. This polymorphism could be also a useful marker for the differentiation of normal and rearranged BCR alleles in heterozygotes patients and during follow up of minimal residual disease. The allele frequency for this SNP varied markedly between different world populations, with European attaining intermediate values between African and Asians (Table 1)

The molecular basis of CML is well defined and highly consistent, yet prognosis varies considerably. This could reflect the biological diversity occurring in normal populations.

Population	T allele	C allele
African American	0.55	0.45
Sub-Saharan African	0.425	0.575
Asians	0.922	0.078
Chinese	0.91	0.09
Japanese	0.98	0.02
European	0.70	0.30

Data from NCBI/dbSNP/Short Genetic Variations

Table 1. The frequencies of T and C alleles of BCR exon 13 SNP in different populations and ethnic groups

The study by Gordon et al 2003 suggest that variation among normal individuals may contribute to inter patient heterogeneity in CML. Differences in behaviour of haemopoietic progenitor cells from different normal individuals may be attributable to genetic diversity or other variables. de Haan et al. (2002) concluded that the expression levels of a large number of genes might be responsible for controlling stem cell behaviour. These collections of genes may be analogous to those responsible for the inter-individual diversity in progenitor cell behavior

In CML, the occurrence of additional specific cytogenetic and molecular changes subsequent to the initiation of t(9;22) translocation herald disease progression prior to haematologic and clinical manifestation. These events occur in 50 to 80 percent of patients during the transition from the chronic phase of the disease to the accelerated and blast phases. Minor cytogenetic changes include monosomies of chromosomes 7, 17, and Y; trisomies of chromosomes 17 and 21; and translocation t(3;21)(q26;q22) (Mitelman, 1993). Major changes include trisomy 8, isochromosome i(17q), trisomy 19, and an extra Ph chromosome (double Ph). Trisomy 8 is most common, and isochromosome i(17q) occurs almost exclusively in the myeloid type blast phase (Kantarjian et al., 1987; Derderian et al., 1993; Mitelman, 1993).

Molecular abnormalities may correspond to cytogenetic changes. These include abnormalities in p53 (on chromosome 17p13); RB1 (13q14); c-MYC (8q24); p16INK4A (9p21); RAS; and AML-EVI-1, a fusion protein resulting from translocation t(3;21) (q26;q22). Alterations of p53 (deletions, rearrangements, and mutations) occur in 20 to 30 percent of patients with CML in the blast phase (Ahuja et al., 1989) and are associated exclusively with myeloid transformation (Stuppia et al., 1997), whereas abnormalities of RB1 are associated more with lymphoid transformation, although the association is weaker than it was between p53 and myeloid transformation. Mutations of p53 in the progression of CML are associated with an aberrant methylation status of CML cells (Guinn et al., 1997). The introduction of a methyl group causing transcriptional silencing of the calcitonin gene has been found in the transition of chronic-phase CML to blast-phase CML (Malinen et al., 1991). Altered methylation was also described within the M-bcr of cells from patients with chronic-phase CML (Litz et al., 1996). Up to 50 percent of patients with lymphoid transformation have homozygous deletion of p16INK4A (Sill et al., 1995). Alterations of RB1, amplifications of c-MYC, and mutations of RAS are less frequent (Faderl et al., 1999).

The genetic variation in Africa is poised to constitute major challenge for diagnosis and management. In a world where the diagnosis and prognosis of diseases and particularly cancer is increasingly dependent on molecular approaches such diversity might constitute a

hurdle for future intervention against cancer in general. The anticancer drug imatinib has shown remarkable success in treatment of CML. Though a variety of resistance mechanisms can arise, in the majority of patients resistance coincides with reactivation of the tyrosine kinase activity of the BCR-ABL fusion oncoprotein. This can result from gene amplification and, more importantly, point mutations that disrupt the bind of imatinib to BCR-ABL itself (Nardi et al., 2004). Although there are no indication of resistance so far in Sudan (Alkhatib, 2011), perhaps due to the limited use of the drug, the risk of resistance is proportional to the number of mutations that exist within the kinase domain and even outside the domain which are expected to be higher in Africa given the increased genetic diversity of African populations. The risk of resistance increases with the identification of Novel potential signaling pathways associated with drug resistance (Duy et al., 2011).

The significance of population genetic background extends to diagnostic and prognostic markers that may be applied to populations and to individuals. This is expected to form a trend in the management of diseases of complex inheritance as we learn more of the biological networks in function during diseases and the role of each individual molecule. In a study by Elamin et al., (submitted), aimed at developing biomarkers for breast cancer, Peroxyredoxin V turned to be a potentially useful marker both as a prognostic and treatment marker in Sudanese breast cancer but not among Chinese.

3.4 Drug metabolizing enzymes

The drug metabolizing enzymes system has been shown to influence the susceptibility, sequel and outcome of cancer treatment. These systems include the Glutathione transferases a family member of genes encoding enzymes involved in the metabolism of many chemicals and shown to be polymorphic with *GSTM1* and *GSTT1* being deleted in proportion of individuals where in the homozygous state results in a phenotypic absence of the corresponding enzyme. These enzymes are considerably important in the detoxification of many environmental compounds and reactive oxygen species, and hence may constitute important cancer predisposition genes.

It includes also the cytochrome P450 enzymes one of the best studied for risk association with cancer (Aqundez, 2004). The P450 shows conflicting and variable degree of association with cancer, possibly reflecting, variation in the role played by these enzymes in carcinogenesis and the genetic background of the population.

In some populations like those of the Indian subcontinent, the frequencies of homozygous 3/3 genotype and CYP3A5*3 allele were elevated significantly in the CML group compared to controls ($\chi^2=93.15$, $df=2$, $p=0.0001$) (Sailaja et al., 2010).

In India also, a statistically significant difference between an AML group and normal control was observed in the case of glutathione-S-transferase M1 null (odds ratio 3.25, 95% confidence interval 1.9-5.58, $P<0.001$) and N-acetyl transferase 2*6B (odds ratio 3.04, 95% confidence interval 1.79-5.16, $P<0.001$) genotypes. Combined deficiency of N-acetyl transferase 2 and glutathione-S-transferase M1 genes produced an odds ratio of 11.91 (95% confidence interval 4.06-34.96, $P<0.001$). Those with glutathione-S-transferase M1 null genotype and N-acetyl transferase 2*6B allele are at increased risk of developing AML, and the risk is considerably enhanced in persons with both glutathione-S-transferase M1 and N-acetyl transferase 2 deficiency (Majumdar et al., 2008).

Increased risk of AML has also been reported for combined polymorphisms in detoxification and DNA repair enzymes (Voso et al., 2007), and patients that achieved

complete molecular response following administration of imatinib showed significantly ($p=0.013$) higher in vivo CYP3A activity than patients achieving partial molecular response (Green et al., 2010).

In Sudan impact of the distribution of the *GSTM1* and *GSTT1* genotype leukemic patients was studied in 77 leukemic patients and 107 controls by Tagelsir et al., (Submitted). The results suggest that these genotypes could play a role in the development of leukemia particularly AML. Statistical analysis showed a significant preponderance of null genotype of both genes among pooled cases [*GSTM1* OR 3.45 (95% CI, 1.65 - 7.19); $P = 0.001$] for; *GSTT1* OR 8.57 (95% CI, 3.68 -19.93); $P < 0.0001$]. Double null was also higher in patients compared to controls ($P = 0.01$). When the cases were stratified according to the disease type, AML showed the highest positive predictive value for both loci (*GSTM1* $P < 0.0001$, *GSTT1* $P < 0.0001$), ALL and CLL showed similar patterns for *GSTT1* ($P = 0.001$) while the P -values for *GSTM1* were (0.01) and (0.007) respectively. CML displayed the least positive predictive value for *GSTM1* (0.02), while for *GSTT1* the result was as same as AML ($P < 0.0001$). Double null, however, showed only association with AML ($P < 0.0001$).

When the distribution of the *GSTM1* and *GSTT1* null genotypes were compared between linguistic groups of the control subjects, different percentages were obtained and *GSTT1* null genotypes was statistically different between the Afro-Asiatic and the Nilo-Saharan groups ($P = 0.01$). Difference in frequencies between Africans population is reported; Egyptians 15-29% (Abdel-Rahman, 1996; Hamdy et al., 2003), Tunisians 29% (Hanene et al., 2007) and Zimbabweans 26% (Masimirembwa, et al., 1998). generally speaking the *GSTM1* frequency (10.3%) is close to sub-Saharan Africa range; Nigerians 22% (Zhao et al., 1994) and Zimbabweans 24% (Masimirembwa, et al., 1998). while the previously reported frequency from Sudan is 39% (Tiemersma et al., 2001) . Other African populations frequencies are; Egyptians 44-55% [Abdel-Rahman, 1996 Hamdy et al., 2003), Tunisians 50% (Hanene et al., 2007).

The Tagelsir study suggests an increased risk for leukemia associated with *GSTM1* and *GSTT1* null genotypes and highlights a potential role of genetic make up in leukaemogenesis. The most statistically significant association for *GSTT1* observed for both AML and CML may highlight a possible role of *GSTT1* enzyme in protection of the myeloid series. Allelic variation in the gene encoding the GST isoform theta (*GSTT1*) enzymes was found to modulate the rate of benzene metabolism and excretion (Rossi et al., 1999) as well as benzene-induced myelotoxicity (Wan et al., 2002; Chen et al., 2007). AML - which showed the strongest association with both genes- comprises a distinct type of leukemia with different subtypes and is shown to be to somewhat associated with environmental exposure. Epidemiological studies have shown association between AML (M2, M4, and M5) and maternal exposure to marijuana and alcohol, and maternal and paternal exposures to pesticides, (Buckley et al., 1989; Robison et al., 1989; Severson et al., 1993; Shu et al., 1996). In addition to that AML is shown to be associated with exposure to benzene and may arise as therapy related complication after treatment of other cancers (Hoffbrand & Pettit, 2001).

Paradoxically, the presence of these genes could not be excluded as a possible risk factor for leukemia as some times these enzymes are involved in bioactivation of some chemicals producing more reactive metabolites that could confer threat to the cell. An example of such risk in other cancer was found in a study on Chinese population which showed that the genotype combination of *GSTM1* and *GSTT1* double positive confers a 4.2-fold higher risk for developing esophageal cancer and a 2.6-fold for esophageal hyperplasia (Lin et al., 1998).

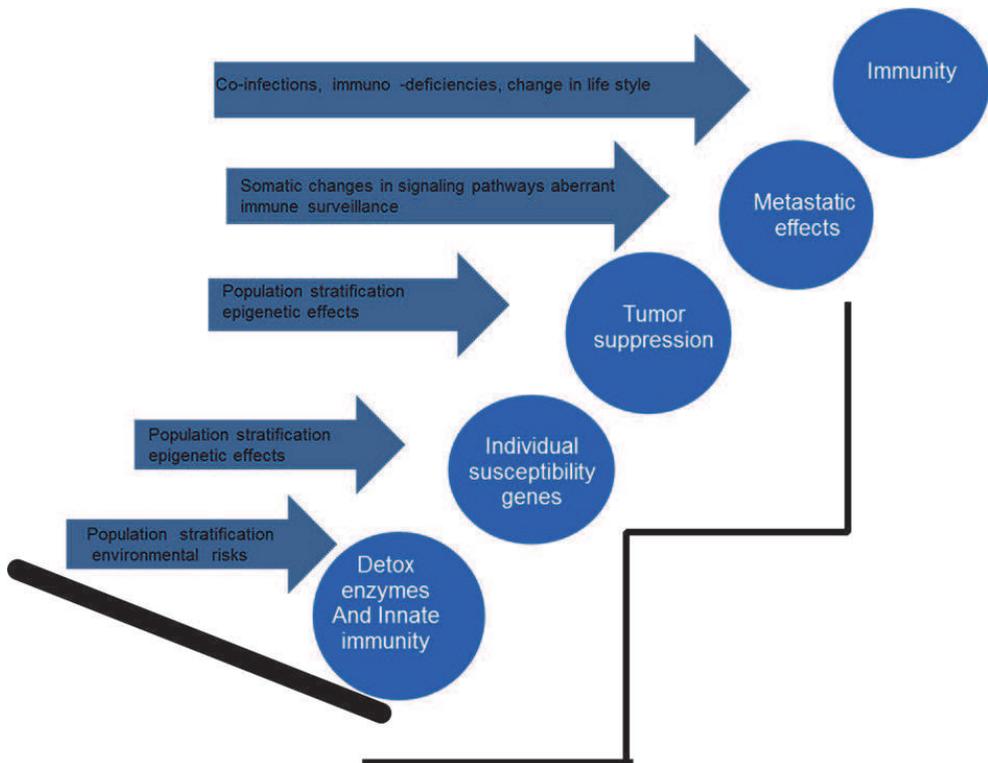


Fig. 1. The ladder and lever mechanism towards carcinogenesis. As the cancer cell struggles through multiple accumulative genetic events leading to cancer (the ladder), the cell will gain the upper hand in its surrounding tissue environment and eventually metastasize, it encounters various modifications and modulating effects that vary between individuals and communities. The variety of effects and the modifier action is expected to be greater in Africa. The up scaling of the ladder requires a lifting effect from the Environment (lever).

3.5 Epigenetics

DNA promoter methylation and histone modification are increasingly recognized as of primary importance in carcinogenesis. The two forms of aberrant methylation, hypomethylation and hypermethylation, are both well documented features of tumor cells (Hanahan and Weinberg, 2000; Jones and Baylin, 2002). The transcriptional silencing of tumor suppressor genes via promoter CpG island hypermethylation constitutes a key tumorigenic process contributing to all the typical hallmarks of a cancer cell that can result from tumor suppressor inactivation. Profiles of tumor suppressor methylation vary according to tumor type (Esteller et al., 2001) and each tumor apparently displays a distinct 'DNA hypermethylation pattern.

Recent studies revealed that specific patterns of DNA methylation characterize AML and help to distinguish AML subtypes. The contribution of this epigenetic dysregulation to leukemogenesis in AML is currently unclear. However, interactions between mutated transcription factors and epigenetic networks have already been shown to be partially responsible for leukemic transformation, for e.g. in acute promyelocytic leukemia (APL). Also, direct mutations in the epigenetic master regulators EZH2 and DNMT3A were recently identified in AML and in diseases leading to secondary leukemia (Schoofs and Muller-Tidow, 2011).

New studies reveal that 20% of individuals with AML harbor somatic mutations in DNMT3A (encoding DNA methyltransferase 3A). Although these leukemia have some gene expression and DNA methylation changes, a direct link between mutant DNMT3A, epigenetic changes and pathogenesis remains to be established.

The disruption of key protective genes through methylation is not confined to tumor suppression, it extends to other vital genes in protection /susceptibility to cancer like drug metabolizing enzymes, as been reported for the glutathione-S-transferase P1 gene silencing (Karius et al., 2011)

4. Future directions

The burden of myeloid leukemia is expected to rise as part of a global trend of increase in cancer incidence. In Africa the cost of this rise given the compound problems of health systems will be devastating. One pressing need is to challenge the preconception of cancer being a disease of the developed societies and show how this image is changing under the rapid sweep of "globalization. Even now the limited data available on leukemia indicate that the incidence of CML in some African countries may exceed those of the industrialized world. The understanding of cancer complex etiology is a prerequisite for successful management and control efforts.

Myeloid leukemia including the chronic subset that behave like a single gene disorder with the predominance of the Ph chromosome, posses complex etiology that includes multiple steps from environmental switches to inactivation of tumor suppression and other guardians of genome integrity and stability and ending with the impact of immune competence. Such complexity renders the handling of each of these potential culprits a daunting task especially in Africa. Without research into the etiology and genetic epidemiology of myeloid leukemia with all possible risk factors considered, including the genetic structure of population at risk, individual genetic effects, role of chronic and concomitant infections, and the possible trade off between infections and malignancies. For

diagnosis and management an integrated genomic approach is the way forward. The vision for this approach entails an integrated and automated approach to these analyses, bringing the possibility of formulating an individualized treatment plan within days of a patient's initial presentation. With these expectations comes the hope that such an approach will lead to decreased toxicities and prolonged survival for patients (Godley et al., 2011). Such integrated approaches are expected to meet challenges pertinent to the peculiarity of African genetics.

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6. References

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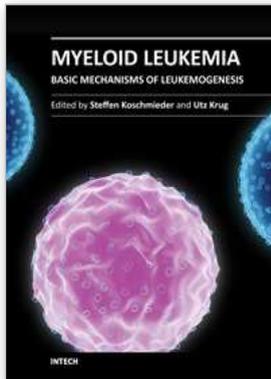
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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