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MOLECULAR EVOLUTION: A MAGIC TO HEALTH CHALLENGES

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Abstract-The change in chromosome is a genetic change. Following the awareness of molecular biology, this has thrown more light to the field of molecular evolution. With the level of studies on cancer evolutionary changes, much has not been done about the evolutionary mechanics that directs the tumor progression at the molecular level, but depends on the mathematical design of the carcinogenesis. These alterations that take effect in the genome of organisms are being engineered by the use of enzymes generated either in vivo or induced in vitro. However, the use of modern diagnostic tools has helped in the diagnosis of some organisms that are very difficult to be isolated in culture. The review focuses on the genomic variations, biomarkers, enzymes, and uses of molecular evolutions in health and diseases which have led to improvement in diagnosis, clinical, therapeutic and prospects for further development.

Keywords- Molecular, evolution, Enzymes, Cancer, Haemophilia.

I. INTRODUCTION

For the past decades, series of works in molecular evolution have established that it involves alteration in genome of organisms from one generation to another (David 2015) The change that happen in the nucleic acids where the DNA and RNA reside is known as mutation. The DNA as we know is the centre where inherited or environmental pressures exert diversity among species or on the organisms or individuals that carry them or the whole of the carrier organism's offspring from generation to next (Loewe2008). Mutation is synonymous with change in the genetic material of an organism and the DNA is centre where the long –term memory retains. However, the DNA is a double helix and the RNA is a single –stranded polynucleotide. The DNA has a deoxyribose with a phosphodiester linking 5' carbon to the 3' carbon and the RNA has ribose as sugar moiety. For the genetic information to be preserved in an organism, the DNA with the action

of the DNA polymerase duplicates and the RNA polymerase transcribes from the DNA that synthesizes a complementary 5'- 3' strands starting with the lower 3' -5' which acts as a template for DNA strands. But as a result of changes either environmental, chemical substances or radiation lead to nucleotide non complementarities. This leads to mutation; that is an abnormality which changes the genomic structure of an organism. When there is alteration of genetic information due to escape in the cellular repair mechanism is known as point mutation. The mutation happens in two forms: - the silent or synonymous and nonsilent or non synonymous. There will be variation following the locations in the amino acid. The mutation that does not involve the amino acid change is silent whereas the one that incorporates change either in vivo or in vitro in the amino acid is nonsilent or non synonymous. The other type of mutation is recombination. This is a situation where the normal DNA strands which supposed to be double are now collapsed to make a single strand. Splicing is a remarkable feature seen in recombination process. The splicing pattern is known for its deleterious effect in gene function and results in mutant that is a new gene function. For instance, HIV has being implicated in the encoding of two additionally regulatory proteins using *env* gene by alternative splicing and overlapping the reading frames (Carroll 1995). Recombination is also involved in the meiosis by exchanging the alleles for next generation. The genome of virus is so flexible to genetic changes and has polymorphic sites in consonance with a single population. This leaves the HIV with no single genome, but has different dimensions called quasispecies (Eigen and Biebricher1998; Damingo *et al* 1997). This study of changes in the deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins sequence which are engineered either by natural or artificial forces has helped in the diagnosis of various diseases. In recent years, the study of cancer

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biology and genomics has ascertained the evolutionary nature of malignancies (Burrell and Swanton 2014, Gerlinger *et al* 2004). With the level of studies on cancer evolutionary changes, (Michor et al 2004, Sotoriva et al 2011) much has not been discovered about the evolutionary mechanics that directs the tumor progression at the molecular level, but depends on the mathematical design of the carcinogenesis (Beerenwinkel et al 2015). In 1998 and 1999, Dietrich and Hagen traced back molecular evolution from 20th century which started with comparative biochemistry and finger printing methods by the use of immune assays, gel electrophoresis and paper chromatography to discover identical protein in 1950s. The awareness of molecular biology has thrown more light to the field of molecular evolution. Eventually, molecular biologist started to design phylogenies immediately the protein sequencing was discovered which was used to monitor the gap between homologous sequences as a molecular clock to determine the last universal common ancestor (King and Jakes 1969).

II. MOLECULAR EVOLUTION BIOMARKERS

The mutation that occurs in the particular region of the chromosome is able to be traced within the DNA sequence by the use of genetic or molecular markers. This genetic marker is a gene associated with a specific gene or trait. The alteration is easily noticed in the genomic loci. The marker may be short or long DNA sequence. The short one is the single base –pair change (single nucleotide polymorphism, SNP) while the long one include the mini and micro satellites (Van and Rodgers 1996, Gizaw et al 2007). The molecular markers are classified according to the specific sites and principle of actions. They are morphological, cytological, biological, molecular markers. The morphological marker indicates the shape, skin structure and color of an organism that are more of external features. The cytological marker measures the chromosome karyotypes, bandings, translocations, repeats, deletions and inversions used to check the genetic resources of animals (Yang *et al* 2013). According to Bitgood 1990 a change in chromosome is a genetic variation. The biological marker comprises the blood type and isozymes that can be detected and analyzed by protein electrophoresis to investigate the amino acid composition (Buvanendran and Finney 1967). The molecular marker is regarded as the most reliable that is used in nucleotide sequence mutation to check the individual genome (Yang et *a*l2013). This molecular marker has many techniques. One of the techniques is the allozyme marker for detection of allelic differences using enzyme variants by the protein electrophoresis. It is used to quantify the genetic and geographic variation in wildlife populations (Avise 1994). The change in the amino acid following alteration in the genome is identified through the use of electrophoretic gels (Deyoung and Honeycull 2005). The allozyme analysis is fast and less cost but is underscored to an extent due to its robustness, biased genomic sampling and low number of markers (Hamrick et al1992; Ledig 1998). Restriction Fragment Length Polymorphism (RFLP) was a technique used for DNA analysis in forensic science. This is a molecular technique where nucleotide base substitution or insertion is created or removed from new restriction sites within the whole genome RFLP is used for human genome mapping and to provide data on genetic disease (Yang *et al* 2013). It pinpoints the actual site where disease resides in the chromosome. Also it is used for genetic fingerprinting, profiling and testing. There is still another type called random amplification of polymorphic DNA (RAPD) that is of use from the last decade. This makes use of polymerase chain reaction as a molecular maker for DNA (Kamar and Gurusubramanian 2011). The method screens for DNA sequence based polymorphism at a very large number. The principle uses a single, short oligonucleotide primer, to amplify random sequences from a complex DNA template. The length and size of both the primer and target genome helps in amplified fragment generated (Nandani and Thakur 2014).

III. MOLECULAR EVOLUTION ENZYMES

We have actually seen the impact of molecular evolution both in positive or negative ways. However, mutations in an organism have brought to the limelight the genome editing technologies for the correction of changes through the use of enzymes such as Rad 5 protein, zinc finger nucleases (Z FNs), transcription-activator like effectors nucleases, (TALENS) and clustered regularly interspaced palindromic repeats-association nuclease 9(CRISPR-Cas9)(Ho2018).The alterations that effects in the genome of organism are being enhanced by the enzymes either produced in vivo or induced in vitro by certain factors. The Type 11 restriction end nucleases have contributed a lot in molecular biology (Smith andWilcox1970), the enzyme is so capable to target the DNA sequences into 4-6 base pairs (bp) in length and divide them in a recognized pattern. The Rad 5 protein contributes to the stimulating of homologous recombination that binds to the single strand of the foreign DNA at the 3'end when the complimentary strand of the host DNA is displaced to create single strand cross-over called the Holliday factor (Sung and Klein

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2006).The newly discovered enzymes that have come into play in the distorting and rearrangement of genome are targeted nucleases such as ZFNs, TALENs, mega nucleases, and the CRISPR - Cas 9(Carroll 2014; Armould *et al* 2011). Moreover, the enzymes Cas 9 and chimeric antigen receptors (CART cells are of immense benefits in engineering therapeutic cells for cancer treatment and not only for genome modification of somatic tissue (Couzin-Frankel 2013).`To examine the change in the nucleic acids, it is required that the DNA is isolated and purified. This happens by careful technique which reduces distortion of DNA from mechanical shearing (Rapley 2015) But to achieve high degree of purity, the DNA is put further into density gradient ultracentrifugation with the help of cesium chloride with help for plasmid DNA (Wilson and Walker 2005). With help of agarose gel electrophoresis, the DNA component is discovered by using the fact that I absorbance unit equates $50ugml^{1}$ of DNA and so, 50x A_260 concentration of DNA sample ($Ugml^{-1}$) while for RNA which uses guanadinium thiocynate for extraction is I absorbance unit equates to $40ugml^{-1}$ of RNA. This RNA is often tightly associated with proteins (Farrell 2015).

IV. MOLECULAR EVOLUTION AND CANCER

Molecular evolution, especially in case of malignancy follows change in single cell genome (Wang and Navin 2015) but was found out that the change is as a result of molecular discoveries rather than a single event (Yarus 2017). Incidentally, the development in the formation of main biomolecules that includes the nucleotides has been obtained through the analysis that made of HCN and H_2s which occurs at one place (Sutherland 2016). Current reactions that do not need catalysis had led to the covering of RNA – like multiplier that led to generation of proto cells (Prywes 2016). However, to find out how biological expression and inheritance, it is done through the ribonucleotides of established performance and of small RNA rather than large RNA (Yarus 2015). The changes in the development cancer growth on or before have been monitored by the use of relaxed molecular clocks (Zhao *et al* 2014). This has helped in the monitoring of molecular evolution. The germ line evolution is quite different from somatic cancer evolution (Sidow and Spies 2015) and convergent evolution helps to find our driver genes with some methods for non-coding regions the intron (David 2015).The evolution in cancer biology has come out with certain biomarkers which has helped in monitoring of treatment and prevent drug resistance (Jawel-Hanjani *et al* 2015, Mc Granahan and Swanton 2015).

V. MOLECULAR EVOLUTION AND SICKLE CELL TREATMENT

Sickle cell diseases is single point disorder caused by mutation in the β- globin gene which changes A – to T (β 6 Glu- Val) that produces abnormal haemoglobin (Hbs)(Betty et al 2012). People with genotype of homozygous mutation have sickle cell disease (Megan et al 2016). According to Ingram and colleagues described mutant sickle haemoglobin (HbS) has been different from haemoglobin A following a single change in amino acid. Currently, allogenic haemopoietic stem cell (HSC) transplantation has played a major role in treatment of sickle cell disease (Locatelli et al 2013).

VI. MOLECULAR EVOLUTION AND COAGULATION DISORDERS

The use of single factor replacement therapies through the infusion of protein concentrates pooled from either plasma or recombinant DNA have helped in the treatment of some inherited bleeding disorder such as hemophilia A (Factor viii), B (Fix) factor Xi deficiencies and Von willebrand diseases (Key and Negrier 2007).

Understanding the dynamics in the DNA, RNA and protein composition has paved way in the treatment of diseases. Many strategic approaches have come into place in the treatment of bleeding and thrombotic disorders by which targeted single factor is either removed or put in or both the multiple components of the haemostatic response Laura and David 2016). However, Rodgers 2012 and Nascimento 2014 found out that infusion of either multifactor concentrates (prothrombin complex, Von Willebrand factor VII, IX and X) and cryoprecipitate Von Willebrand, factor VIII, XIII and fibrinogen or plasma are manageable tools for haemophilia, liver disease and consumptive coagulapathies.

VII. MOLECULAR EVOLUTION AND MODERN DIAGNOSIS.

Polymerase chain reaction (PCR) (Heim et al2003), recombination antigens and monoclonal antibodies have been used effectively as a major diagnostic tool in the field of molecular biology. The molecular advances have led to the use of erythropoietin and alpha interferon for anaemia and viral disease respectively (Rehman *et al* 2015, Seago et al 2007) and insulin against type 1 Diabetes Mellitus (Johnson 1983). Some organisms which are so problematic to be isolated in culture medium such as HIV, Mycobacterium and Plasmodium are identified through the use of molecular diagnosis (Louie et al 2000). Many diseases of broad diversities are now made know with easy both less resources and fast time by the

use of multiplex polymerase chain reaction (Harris *et al* 1998).

VIII. CONCLUSION

Molecular evolution has come with good impact in the modern medicine because of its tremendous advantages. This has helped in crime detection following the discovery of finger printing technology. Also it has contributed a lot in the diagnosis, treatment and management of coagulation disorders and gene therapy. However, some organisms that cannot be discovered through culture are now uncovered through the molecular changes such as Tb, HIV and malaria by the techniques of PCR and more are on the way.

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