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THE INEVITABILITY OF BALANCED LIVES: GENES AND, FOODS IN ACTION AND, INTERACTIONS

Amro Abd–Al–Fattah Amara*

Protein Research Department, Genetic Engineering and, Biotechnology Research Institute, Mubarak City for Scientific Research and, Technology Applications, Alexandria, EGYPT

ABSTRACT

This review is a "Food For Thought" about the role of the DNA repair genes, Food and, our genes in health maintaining. From the different kind of diseases could be happening (including the degenerative diseases) because of the defect or leakage in the DNA repair system; facts will be pointed about its role in protecting us against "the major human killer" the "Cancer". The different types of interaction between our genes and, our Food have been addressed. There is a need for systematic rearrangement of the information in our hand for better understanding for the role of the DNA repair genes and, better use of our Food. I direct this review content to prove the "Inevitability of Balanced lives" for good health and, safe life.

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***Corresponding author:** Email: amroamara@hotmail.com; Tel: +966–599593353; Fax: +966–4676383

[I] INTRODUCTION

We have perfect bodies designed to give each of us a happy life. If not, so why many of us are healthy? Those who start their lives with healthy bodies but gain illness –made by themselves– such as smokers and, alcoholism are exceptions [1, 2]. Others were born with genetic disorder diseases. The genetic disorders were investigated at the molecular level. Scientists aim to find a solution. In many cases, they related such disorders to inherited factors [3–5]. In fact, the public did not receive a clear message about the steps, which could lead to protection. A simple solution will be the avoidance of continual marriage from relatives for several generations. That will save us from most of the genetic disorders [6–8]. Marriage from foreigners will give our offspring; more chances to escape from the existence of alleles carry genes responsible for different genetic disorders. Even our bodies were created perfectly to resist most of our mistakes; some irreversible damages if happened could not be recovered. Particularly those affect important genes. Before damages become built in, signals and, alarms are given. We should not ignore the alarms and, the signals given by our bodies. Such alarms and, signals include; pain, tiredness, inflammation, fever, headache, and, so on. We must never believe or think that our bodies will resist all the side effects and, will pass all our wishes in case of misuse [7]. Diseases, which, we are not responsible for, can be avoided (most of them). At least we can limit their side effects. Science gave us variable knowledge could lead to solutions. It is our turn to react. "*Not all infections are evil*!" There is a general ignoring of scientific facts in our life. Professionals are involved in such misuse. "Physicians are treating the mild bacterial infection with broad spectrum antibiotics" The misuse of antibiotics leads to the elevation of different microbial resistance [8]. Perhaps, and, because nearly all biological creatures following the same laws; our bodies will be affected by the misuse of the antibiotic too. Such effect will be clear with antibiotics and, drugs can effect on DNA, RNA, protein synthesis and especially in the mitochondria [9]. It is wrong to say, "*Antibiotics and, drug effects on protein are safer than those effects on DNA or RNA*". Proteins in the cell have a long life span [10, 11]. If proteins are chemically modified, they can effect on the other cells' macromolecules including the DNA [12–15]. Some other types of different chemical structures could do the same. In a fine single cell such as *E. coli*, an analog to the lactose –the Isopropyl–*β*–D–thiogalactoside (IPTG) could impair the lactose metabolism and, its regulation [16, 17]. How many synthetic chemical compounds were added to our Food could do the same! [18]. We have a big genome [19], (three billion base pair) and, we could not know where the attack has been happening. In pregnancy, the effect of different forms of chemical compounds will be exponential and, clear, while if one cell is affected, it will be divided into many others. Even the effect is clearer in the pregnancy but adults are not safe. What happens to us with all those chemicals enter our bodies through different routes? We should reduce the use of synthetic chemicals. In fact, our bodies are in a daily struggle to escape from their side effect

even after their degradation [20]. However, the chemical compounds are not shamefaced alone. Each of us has a powerful biological system that was created to tolerate a lot [21]. Huge knowledge about our biological system was elevated [22]. We are in need to apply such knowledge to the best of our health and, lives. Important criteria could be a guide. It is "*natural and, non–natural*" [23, 24]. One should trust more in natural compounds [25, 26]. Non–natural or synthetic forms are not harmful in all cases but we should put them under inspection [27]. In contrast, some natural phenomena even apparently seem to be evil but they are not. Those natural phenomena that do not agree with our understanding and, considering odd from the biological system are a Bell alerts for us to avoid them. Opportunistic pathogens are a real example about how nature could be on our side if we understand their actions [31]. Opportunistic pathogens give us a first sign that our health has some leakages, even they are not perceptible. Our biological system works perfectly but even so, it could be affected if misused or extra–used. To understand how could a fine change in the DNA cause illness; Sickle cell anemia will be given as an example [28]. The studying of this disease enables the establishment of many modern biological and, molecular issues. This will open our eyes for a better understand for many natural facts. To get the benefit and the goodness from them rather than stand against them. Knowledge will give us the upper hand. The protection is always better than the treatment or cure. Regular cold (Catch cold) caused by mild virus and, bacterial infection should be re–evaluated. Normal mild infection should be an additional natural source for activating the innate immune system to be ready for the worse [29]. There might also be other mechanisms, which we did not observe yet. "*We should react naturally*". As an example, melatonin is excreted correctly only if we follow a correct day and, night cycle and, sleep in dark [30]. Again, we should stop and, think how we could detect and, repair leakages in our health? Those who are being able to believe in the "*Balanced Life*" will understand that what is existed naturally is on our side. As an example the endogenous source of oxidants and, free radicals in our bodies (if exists in their natural concentration) are helpful. Illness will change the oxidant concentration level, but they are still natural. One should differentiate between diseases could pass and, diseases need an extra aid. If we are able to recover from a disease after a certain period, why should we force the condition to be passed faster? Why should we force our bodies to recover faster? Why not naturally? Unusual life style against the nature could be harmful for us. Antioxidants, which are believed to have an absolute positive action, are harmful if they exceed certain concentration [31]. An extra supply of antioxidants will aggressively interfere with the endogenous oxidant and, antioxidant system. Some foods work as a chelating agent and, can get rid of some types of toxic compounds but if they exceed a certain limit they will trap essential divalent cations such as Fe^{+2} causing anemia [32]. Through all those mechanisms and, other we should navigate correctly, wisely and, naturally. How can we keep our perfect biological system working well? And, how can we implement our knowledge to avoid dangerous diseases such as the degenerative diseases? This will be an aim of this review. Some examples will be selected to highlight the power of the biological system; to prove and, to touch facts about "*Inevitability of Balanced lives*"; particularly how we can protect our DNA and, the genes responsible for their maintenance and, repair. "*For a natural–auto–extra–protection*"

[II] A FLASH. SICK BACTERIA! A LESSON FROM PROKARYOTES

Could unicellular organism is being sick? Could Bacteria is being sick? For me, Yes. When I have run the first experiment with *E. coli* XL1 Red, I start to refresh it from a stock was frozen at –80°C, and, to re–cultivate it in an LB plate. I incubate the plate that contains the *E. coli* at 37°C for overnight. After three days, there was no growth. By referring and, asking about that I have been informed that this strain is sick and, I should wait for other days. In the fourth day a fine growth was appeared. Then the bacteria are starting to grow but slowly. This bacteria was *E. coli* XL1 Red strain (F–end*A1*, gyr*A96* (*nal*^{R}), *thi–1*, *relA1*, *lac glnV44*, *hsdR17*, (r^{-}_{k} m^{+}_{k}), *supE44*, *lac mutD5*, *mutS*, *mutT*, *Tn10* (Tc^{r})) made by Stratagene© (later owned by Agilent Technologies) [33, 35]. This strain grows extremely slow in rich media (such as LB medium), having a doubling time of ~90–120 min [39, 40]. This deficiency enables irreversible DNA mistakes, which cause mutations. Continuous protein production causes stress to its genes. In the absence of efficient repair mechanism, the conditions will encourage the mutation formation. As an example, Amara et al. (2002) established an *in vivo* a random mutagenesis protocol for mutants screening. *phaC*$_{Aeromonas\ punctata}$ synthase was the targeted gene **[Figure –1]** [36]. XL1 red was used by other researchers to study/mutate different genes [37, 38]. Why XL1 Red is a mutator strain? Something makes it difference from other *E. coli* strains. Normal or recombinant *E. coli* has a series of DNA repairing genes. Three DNA genes that were impaired in *E. coli* XL1–Red strain is responsible for primary DNA repair pathways [34–36]. They are *mutS* (error–prone miss–match repair), *mutD* (3' –to 5' – exonuclease of DNA polymerase III) and, *mutT* (hydrolyse 8–oxod GTP). MutS recognize mismatched DNA with an efficiency depending on the mismatch type and, sequence context (G:T and, A:C > G:G and, A:A>T:T, C:T and, G:A>C:C) [39]. The three genes and, others are important for correcting natural mistakes happened during DNA polymerization. Such mistakes happened spontaneously or caused by environmental stresses. DNA polymerase has its own correct system and, does an accurate DNA polymerization. It makes errors about one error in every 10^{7}–nucleotide [40]. It has an error–correcting activity called proofreading [41, 42]. Before the enzyme adds a nucleotide to a growing DNA chain, it checks whether the previous nucleotide added is correctly base–paired to the template strand. DNA polymerases are highly selective when dNTPs bind to the template–primer–enzyme ternary complex [43]. Mispaired nucleotides bind less well than that correctly paired ones [44]. Proofreading is made by a 3' to 5' exonuclease activity intrinsic to the DNA polymerase [45].

Polymerase tests the accuracy of each addition step. It removes mispaired bases by cutting the phosphodiester bond it has just made, releases the nucleotide, and, starts again. The major opening for proofreading occurs at the beginning of the subsequent polymerization cycle. If the energy level is correct, the polymerase adds the next nucleotide, if not the polymerase removes the mispaired nucleotide. MutT is an enzyme, which repair damaged nucleotides before they are inserted into the DNA [46]. MutS starts repair by binding to the mismatch and, activates with other endonucleases, which incises at hemimethylated dam cites and, thereby mediates strand dissemination [47]. Key genes in the DNA repairing system are more important than others. PCR could be used in random mutagenesis if unbalanced amounts of nucleotides were used [48–50]. One should observe that *E. coli* is tiny unicellular prokaryotic. On higher eukaryotic such as human the processes even similar but will be more complicated. Different mechanisms for protection are in use, so the defect in one mechanism could be complement –even partly– by another one(s) [51]. And, each of us has two similar chromosomes in each cell. Each carries one allele of a certain gene. Hopefully, the second allele is correct. The aid of our intelligent DNA repair system will give us an additional chance to pass any abnormal conditions [52]. DNA repair system is able to repair a lot; or it can kill cells having serious defect. However, if one gains an incorrect copy at birth, genetic disorder could be elevated in clear form [53].

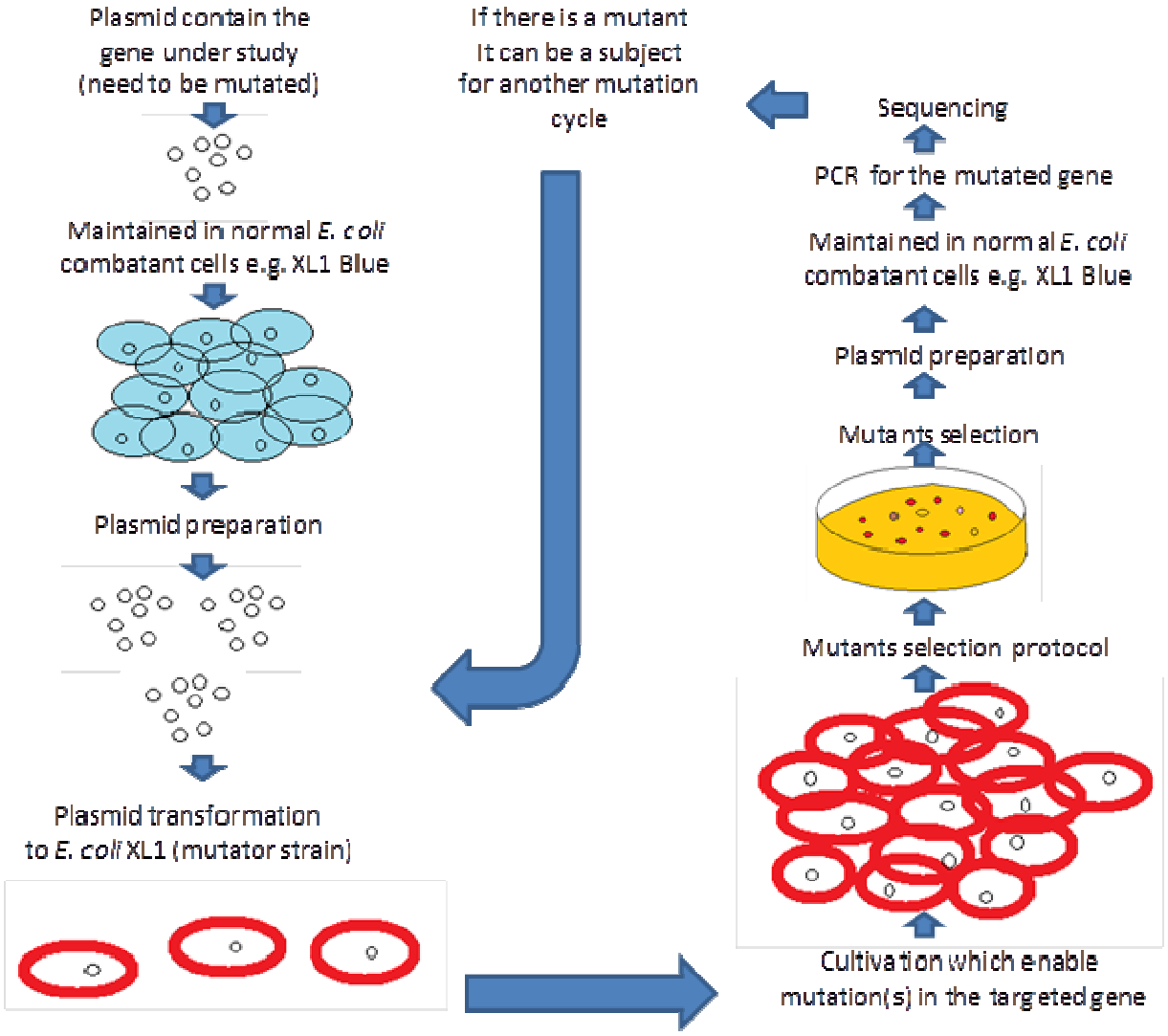

Fig. 1: XL1 Red mutator strain and, the *in vivo* random mutagenesis step lead to mutating a particular cloned gene carried on a suitable plasmid. A process includes plasmid preparation, transformation, *in vivo* mutagenesis, mutants selection and, another cycle for mutation/selection.

[III] FOOD AND, GENES INTERACTION: LAC OPERON

For a tiny microbe with a small genome such as *E. coli* **[Table–1]**, it is able to differentiate between similar sugars such as; the lactose and, the glucose. This is mainly happening by the *lac* operon aided by some regulatory genes. The *lac* operon and, its transcription regulatory region are responsible for the transportation and, metabolism of lactose in *E. coli and,* some enteric bacteria. *lac* operon contains three genes. The *lac* transcription regulator region contains one gene, *lac* I (encoded the repressor gene). The three genes of the *lac* operon are *lacZ*, *lacY* and, *lacA* (*lacZYA*). *lacZ* encodes *β*–galactosidase, *lacY* encodes *lac* permease and, *lacA* encodes thiogalactoside trancacetylase **[Figure –2b]** [54]. The lactose permease transports lactose into the cell. *β*–galactosidase, a cytoplasmic enzyme, subsequently cleaves lactose into glucose and, galactose.

The cell did not allow those enzymes to be expressed if there is no lactose **[Figure– 2c]** or if a simpler and, preferred sugar source is available in the medium such as the glucose. This can be done through an efficient regulation–specific– control for the *lac* genes depending on the availability of the substrate lactose to the bacterium. The *lacZYA* are co–transcribed into a single polycistronic mRNA molecule. Transcription of all genes starts with the binding of RNA polymerase to the promoter region (upstream of the genes). The cAMP–bound catabolic activator protein aids binding of the promoter **[Figure– 2d, 2e]**. cAMP levels are low when intracellular glucose levels are high. Adenylate cyclase (the enzyme that catalyzes forming camp) apparently senses the intracellular level of an unidentified intermediate in glucose catabolism. When glucose levels drop, cAMP levels rise and, cAMP interacts with a protein called cAMP–receptor–protein to form a complex **[Figure– 2b]**. The change increases its affinity to the *lac* operon adjacent to the RNA polymerase binding site **[Figure–2b]**. This binding facilitates transcription of *lac* operon by stimulating the binding of RNA polymerase to form a closed promoter complex. Then, the RNA polymerase proceeds to transcribe all the three genes (*lacZYA*) into mRNAs. The *lac I* gene coding for the repressor protein lies nearly upstream to the *lac* operon and, is always expressed (constitutive). If lactose is missing from the growth medium, the repressor binds tightly to a short DNA sequence just downstream of the promoter near the beginning of *lacZ* called *lac* operator **[Figure– 2c]**. The repressor binding to the operator interferes with the binding of the RNA polymerase to the promoter, and there is no transcription (or low level) **[Figure–2c]**. When the cells are grown in the presence of lactose, a lactose metabolite called allolactose binds to the repressor. The repressor 3D configuration after binding to the allolactose will be changed and, becomes unable to bind to the operator and, the RNA polymerase transcribes the *lac* genes leading to higher levels of the encoded proteins **[Figure –3d]**. Another control mechanism caused by the response to glucose, which is transported into the cell by the PEP–dependent phosphotransferase system. Transport of glucose is accompanied by its phosphorylation by EIIBGlc, which binds to the *lac* permease (*lacY*) and, prevents it from transferring lactose into the cell. Thus, if glucose and, lactose are present, the transport of glucose blocks the transport of the inducer of the *lac* operon. This process is called inducer exclusion [54].

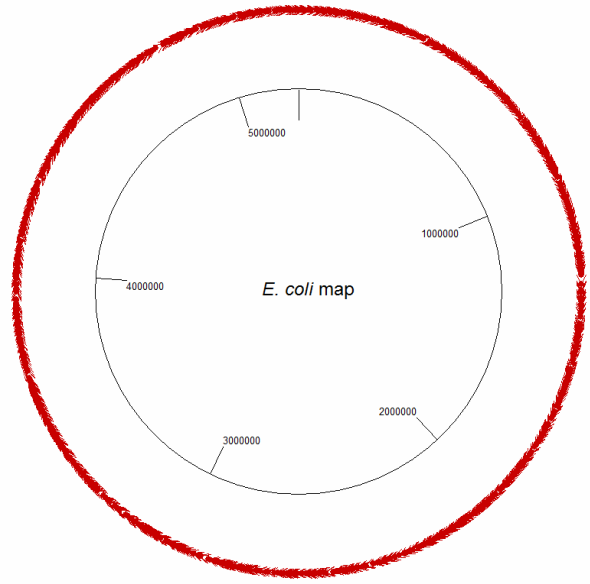

Fig. 2-a

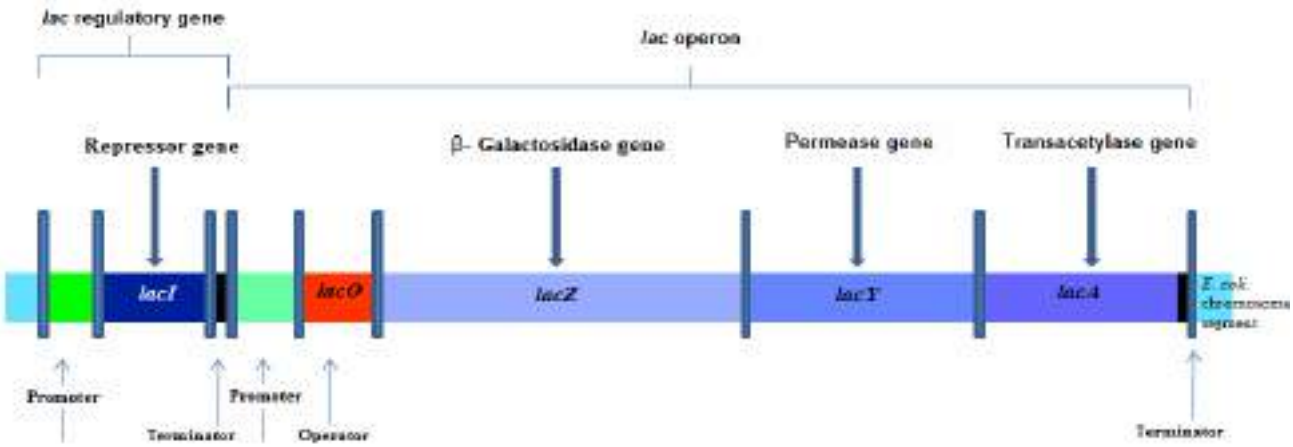

Fig. 2-b

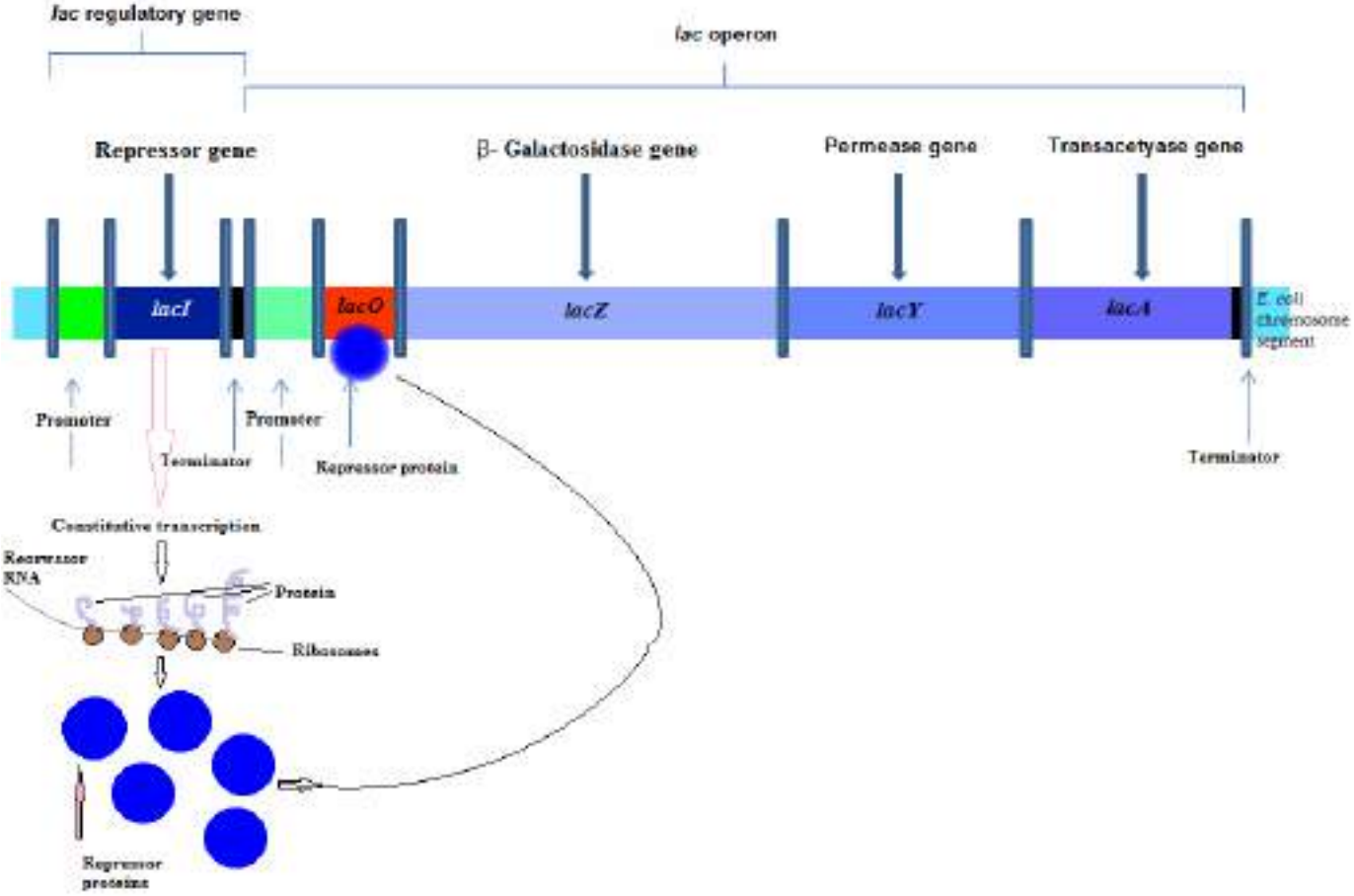

Fig. 2-c

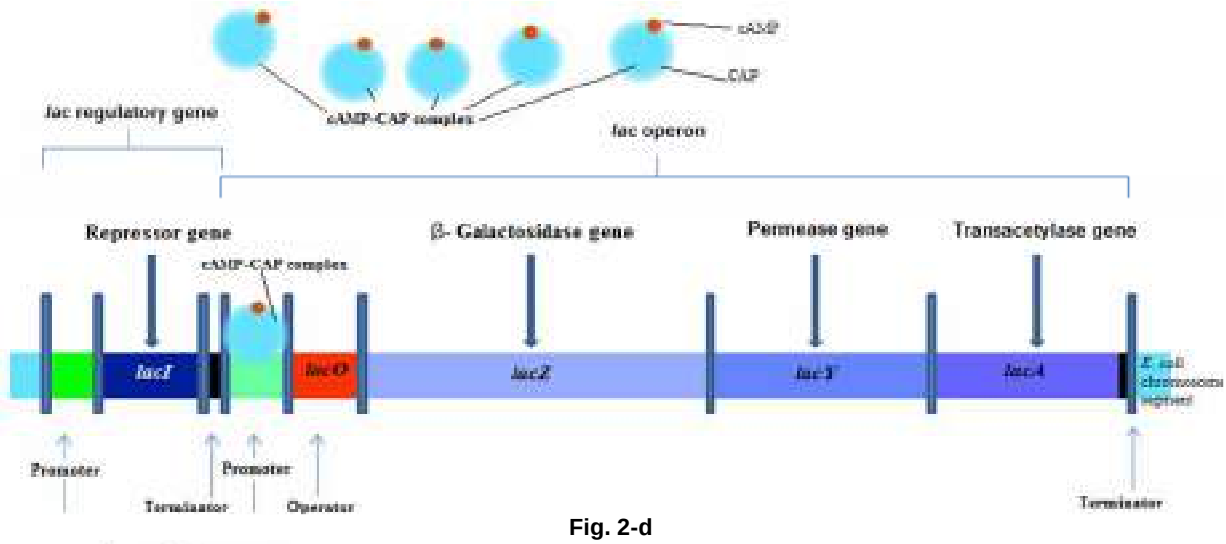

Fig. 2-d

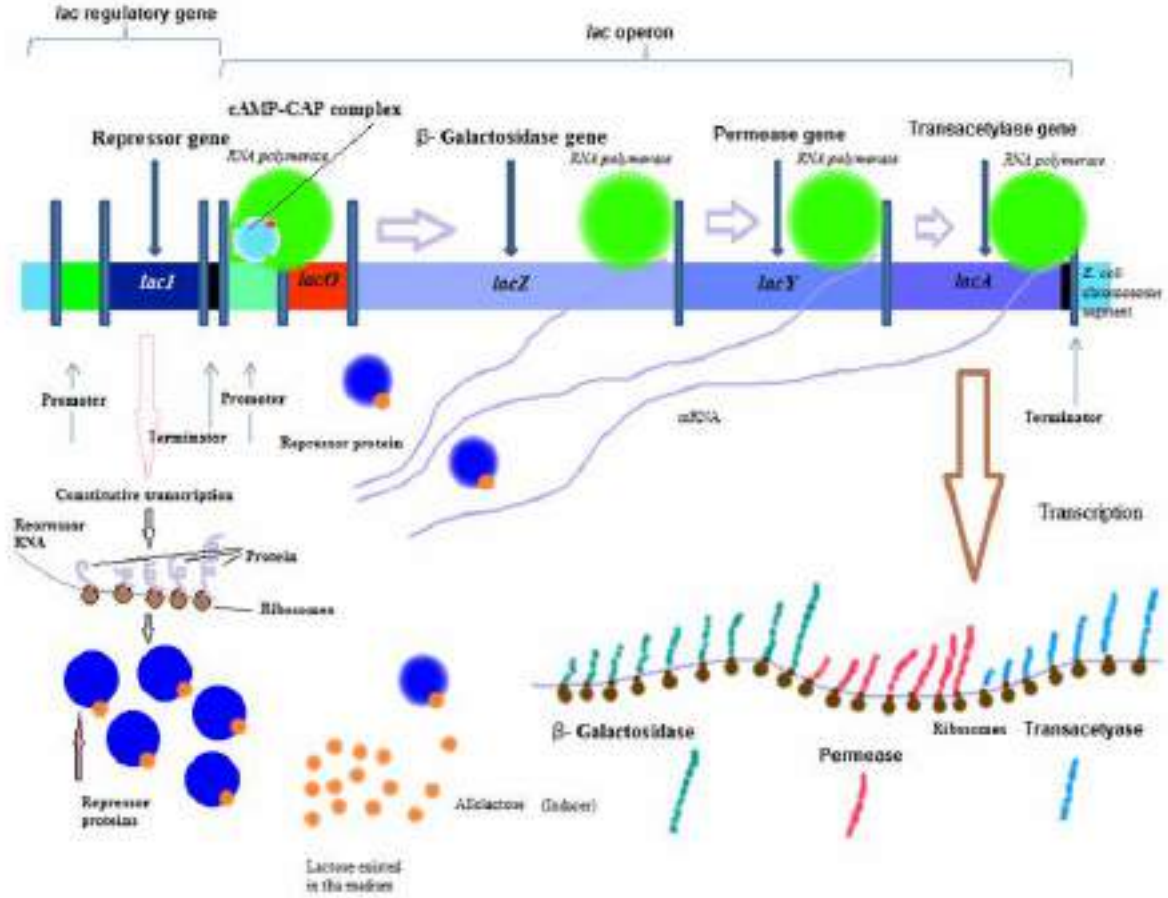

Fig. 2-e

Fig. 2: *E. coli lac* operon; (a) *E. coli* 042 genomic DNA map (5241977 bp) created by GENtle v 1.9.4. Software (This study); (b) *E. coli lac* operon contain: Repressor gene, *β*–Galactosidase gene (*lacZ*), Permease gene (*lacY*), Trancacetylase gene (*lacA*), promoter and, operator region; (c) *lac* operon in absence of lactose; (d) *lac* operon in presence of fewer amount of glucose and, enough lactose amount (e) *lac* operon in the absence of glucose and presence of lactose

3.1. IPTG: A FRAUD

Isopropyle–*β*–D–thio–galactoside (IPTG) is an example about how could analog to a nutrient impairs a highly regulated system such as the lactose metabolism (even in such single cell, the *E. coli*). IPTG binds to the repressor protein and, inactivates it, but it is not a substrate for *β*–galactosidase. Its concentration remains constant [55]. Such Fraud has done for *lac* operon and, its transcription regulator region could happen in our bodies if similar chemical compounds have the ability to find their way to our cells. Those compounds could be due to pollutions, smoking, and so on. Or as a side effect of drugs or even our Food.

3.2. OUR BIOLOGICAL SYSTEM IS PERFECT!

One should ask himself how amazing chemicals arranged in the form of different macromolecules are able doing such work in the different biological system, spontaneously, perfectly and, selectively. Moreover, the above example describes the work done by a few genes [60]. **Table 1** shows what could happen in larger genomes. **Table 1** will give the proper contrast between gene and, genomes.

Table.1: Different genomes from prokaryotic and, eukaryotic system and, one gene (*lacZ*)

Source	Organism/gene	Gene/Genome size	Reference
lacZ	A gene in *lac* operon of *E. coli*	3,075	[54]
Virus	Varicella–Zoster virus	124884	[56]
Bacterium	*E. coli K12*	4,639221	[57]
Insect	*Drosophila melanogaster*	130,000,000	[58]
Mammal	*Homo sapiens*	3,200,000,000	[59]

[IV] THE CELL CYCLE

Cells after completing the differentiation process and, becomes as a part of a tissue and, organ, it will continue in the division by binary division to two identical daughter cells [70]. Completion of the cell cycle requires varying periods from a few hours to several days. The time depends on different factors such as cell type, nutrient, temperature, organism different activities, age, and, others. Different types of cells following (all) nearly the same cell cycle steps [62] with recognized stages **[Figure– 3]**: G1 (gap 1) phase: is a period of intense biochemical reaction. Cells after differentiation into different cell types replicate by dividing each cell into two identical daughter cells [70]. Completion of the cell cycle requires varying periods from a few hours to several days. The time required from one cell to be divided into two daughter cells is different depending on factors such as cell type, nutrient, temperature, organism different activities, age, and, so on. Cells from different tissues and, organs maintain their activities. The cell increases in size, and, its enzymes, ribosomes, mitochondria, and, other cytoplasmic molecules and other structures have also risen in number. These include microtubules, actin filaments, and, ribosomes. Membranous structures, such as the Golgi complexes, lysosomes, vacuoles, and, vesicles, are all apparently derived from the endoplasmic reticulum. The two centrioles start to separate from each other and, to replicate. The cell enlarges and, prepares to replicate the DNA [63]. S–phase (DNA synthesis): DNA makes new identical copies. The first step in DNA replication starts with unzipping process, where the hydrogen bonds between its dsDNA are broken. This results in ssDNA. A new complement produced by the activity of the DNA polymerase enzyme. The new strand is a reverse copy of, or complementary to, the original one. G2 (gap 2): This phase contains few cell activities; the cell synthesizes RNA and, proteins required for mitosis. M–phase (mitosis): The function of mitosis is to finalize the genetic materials in the form of double number of the original chromosomes. Each new cell gets the same number of identical chromosomes. At the end of the cell replication process, the cell is divided into two daughter cells equivalent genetically to its parent cell as well as to its sister cell. Mitosis is divided into: prophase, metaphase, anaphase and, telophase. Mitosis is concluded with telophase, when sister chromatids arrive at the opposite poles of the spindle, decondense and, become enveloped by new nuclear membranes to form the daughter nuclei. After mitosis and, if the genetic materials and, the other components of the cell are identical the process will be followed by *Cytokinesis (C)*, where the two daughter nuclei, cytoplasm, organelles, centrosomes and, cell membrane are divided equally between the two daughter cells. The new cells either may enter G1 again immediately, or alternatively, may undergo a rest period (termed G0) until presented with a stimulus to replicate. G0 is called the restriction point **[Figure–3]**. Cells may undergo up to 30–45 divisions during a lifetime (depending on cell type), after which the cells die (after a period of senescence) [73–75].

4.1. CELL CYCLE REGULATION

Cell cycle's different stages are highly regulated. The nutrient, cell validity and, viability, time, existence of cell damage signals, DNA repair different genes/systems, checkpoints and, other many factors are critical issue in the success of a correct cell division. DNA or genomic damage results in cell cycle delay through activating cell cycle checkpoints. If the damage is repaired then the cycle resumes. If damage is sensible then the cell may undergo apoptosis (programmed cell death). The cyclins, for example Cdc25A and, cyclin D, plus the tumor suppressor protein p^{53}, RB and, PTEN contribute to cell cycle control in mammalian cells [67]. Loss or impairing of genes encoding the proteins involving in the cell division regulation will lead to arrest the cell cycle. The cell is able to detect and, repair many forms of genetic damage. It has various types' of checkpoints to prevent the incorrect cell from exceeding the cell control process during the division process. There are two important cell cycle's regulatory molecules, cyclins and, cyclin–dependent kinases (CDKs). There are two other DNA damage response molecules, which are ATM and, ATR (ATM and, Rad 3–related) protein kinase. ATM mutation was detected in ataxia telangiectasia. ATM and, ATR belong to serine–threonine kinases. They have C–terminal with catalytic motif containing a phosphatidylinositol 3–kinase domain [68, 69]. ATM and, ATR are able to respond to various types of DNA damage.

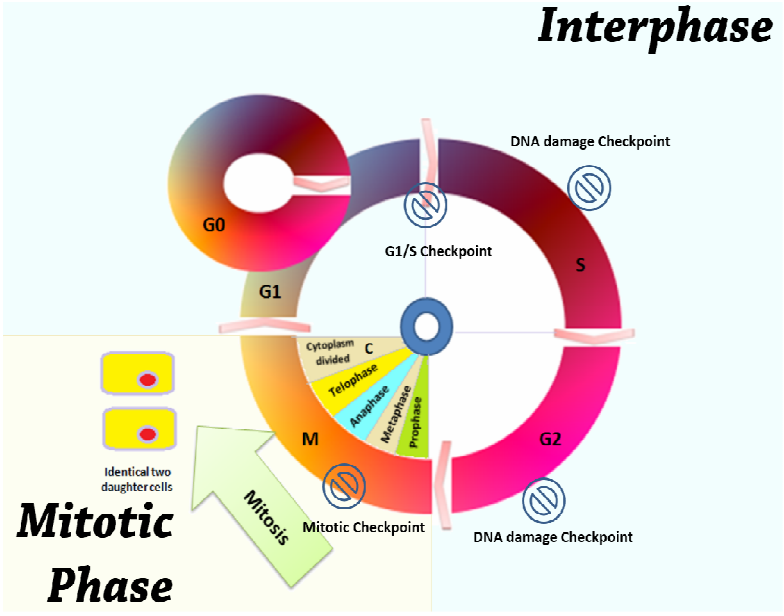

Fig. 3: The cell cycle: G1 Replication of cytoplasmic organelles; S Chromosomal material is replicated: G2 Cell synthesizes RNA and, proteins required for mitosis; M Cell divided into two daughter cells because of the complete division of the cytoplasm, nucleus and, the cell wall.

4.2. Cell Checkpoints

G1 checkpoint: at G1 phase the checkpoint checks for the damaged in the DNA. If there is damage in the DNA, the cell will be prevented from being duplicated [70]. When the cell grows normally in this stage, the p^{53} amount is low because of interaction with MDM2 which targets p^{53} for nuclear export and, proteasome–mediated degradation in the cytoplasm [71]. If there is/are damaged in the DNA, ATM activates Chk2 [72], which turn the phosphonylates residue S20 of p^{53} and, blocks p^{53}/MDM2 interaction and, p^{53} is accumulated in the cell [73]. p^{53} up–regulates some target genes including those involved in the DNA damage response such as MDM2, GADD45 a p^{21}/Cip. By accumulating p^{21}, the cyclin–dependant kinase inhibitor will suppress cycline W/Cdk2 kinase activity resulting in arresting of the cell [70]. S–phase checkpoint: In the S–phase the DNA is synthesized by division and, making a new additional copy. If there is damage in the DNA, the S–phase checkpoint will decrease the rate of the DNA synthesis aiming to give time and, chances for its repair. If there is a break in the genes involved in these checkpoints the cell might pass it and, the digested DNA will duplicate as it is and, the cell either will be unable to live and, will be dead or it will be mutated. For example, ataxia telangiectasia (AT) or Nijmegen breakage syndrome (NBS) fail to decrease the rate of the DNA duplication if exposed to IR [74–76]. However, in normal cell IR will activate the S–phase checkpoint by ATM and, phosphorylating Chk2 kinase (at T68) by ATM [74–76]. It

will be phosphorylate Cdc25A on S123. Dephosphorylated Cdc25A will stop it from removing inhibitory phosphorylation (T14 and, Y15) from Cdk2. Cdk2/cycline A and, E complex become inactive and, DNA synthesis will stop. There are some other mechanisms for DNA synthesis control. Most of them are based on phosphorylation of proteins, which will interfere with the DNA synthesis. Loss of the sites of those proteins where the phosphorylation is happening because of mutation will lead to the interference with S–phase checkpoints validity [74–77]. G2 Checkpoint: Cyclin–dependent kinases Cdc2 control the mitosis step [78]. The validity of the inhibitory phosphorylation on Cdc2 (on T14 and, Y15) is essential for G2 checkpoint activation. ATM and, ATR involved in modulating the phosphorylation status of these sites [77]. If there is a DNA damage, kinases Chk1 and, Chk2 which were activated by ATR and, ATM–dependent phosphorylation will phosphorylate Cda25C on position S215 [79]. The phosphorylated Cdc25C then will bind to the 14–3–3 protein to form 14–3–3/Cdc25c complex and, Cdc25C will unable to activate Cdc2 through removal of the T14 and, Y15 inhibitory phosphorylation. So Cdc2/cyclin B1 complex will not be activated and, the cell wills not mitosis [79].

4.3. Other controlling elements

p^{53}: The p^{53} protein is a transcription factor that becomes activated when the cell is subject to various types of DNA damage and/or other cellular stresses. Once activated, p^{53} plays an essential role in inducing cell cycle arrest and, activating DNA repair enzymes. Cells with un–repairable DNA lesions undergo permanent cell cycle arrest or programmed cell death (apoptosis), which may also be initiated by p^{53} [89, 90]. Centrosome: The centrosome is increasingly being recognized as a key player in regulating cell cycle events, such as orchestrating entry into mitosis, anaphase, cytokinesis, G1/S transition, and, monitoring DNA damage. Recently, the centrosome has also been described as a hub where regulatory complexes, such as kinases, phosphatases and, other cell cycle regulators accumulate to coordinate the multiple cell cycle–specific functions [66, 82]. The cell cycle different steps and, checkpoints, DNA replication, and mitosis are highly controlled processed, which are critical to the maintenance of the fidelity of DNA and, genomic stability.

[V] OUR GENETIC MATERIAL

In the previous part issues about single cell, either from prokaryotes or eukaryotes have been highlighted. In the coming part more examples about the existing genetic disorder will be discussed. Each of us has about 3 billion nucleotides for each cell in our body (except haploid cells such as sperm and, ova). Following the cell cycle as above each cell grows, multiplies, dies, and, in between there is an unknown number of biological activities were done daily. In fact, we have different cell types due to the miracle of the differentiation, where a single cell differentiates to different tissues, organs and, biological systems. Different cells are collaborating perfectly and, react wisely. Even differences in their structures they are often being had the same genetic materials. They are doing their work spontaneously and, continuously. But, that is the case of the healthy persons. So what happened to the non–healthy ones? In this review, I will focus on illness got through heredity; those gained due to a hidden problem in the genetic materials or due to a direct and, clear inherited disorder include the cancer (which is not in all of its cases follow the heredity rules). As described above in the cell cycle part, the cell succeeded to arrest its division/self–damage (apoptosis) if there is a clear problem. If the DNA repair system is able to solve the problem(s), the cell will finish the mitotic process, and, will be divided into two daughter cells. However, if an error has been escaped from the mitotic control process it will be a built–in–change in the gene/genes. If it is leathery to the cell, the cell will die. Alternatively, it will not affect the cell survive (directly), but it can affect the tissue or the organ where it existed. And, the health will be affected finally. The changes in a gene could be due to either one nucleotide change or more than one. About diseases caused by a single nucleotide change Sickle cell anemia will be given as an example. More changes that are complicated will be described too. One should highlight that some types of correction could lead to an extra problem such as the excise of mismatched nucleotides in both sides of the DNA (such as in case of xeroderma pigmentosum).

If the excision is happening in both of the DNA sites; this will lead to mutation formation rather than repair [95]. The DNA repair system if not work probably will be a mutation generator. In general, the hereditary diseases are transferred following the Mendelian laws. During meiosis, one member of each of the autosomes and, sex chromosomes pairs are distributed to each haploid egg or sperm. The full set of 46 chromosomes is reconstituted after fertilizing the mother's egg with the father's sperm. If the defected allele is in one chromosome and, another correct one is on the second chromosome (from the second parent) of the autosome, the person will be probably normal or with a mild illness. However if the born child gains two defected alleles, each in one of the parents' chromosomes, the responsible disease because of this deficiency will clearly appear; because in such case there will be no correct copy existed [84]. The genetic problems will be deeper if the disorder was not on one gene but if parts of the chromosome(s) are involved. Such disorder can be detected by a karyotype examination. Change in a chromosome, which contained thousands of genes will be tremendously harmful or fatal. Nonfatal chromosome deterioration will lead to genetic disorder diseases. Nonfatal chromosome abnormalities include trisomy 21 (Down syndrome), trisomy 18 (Cridu Cgat syndrome), Klinefelyer's syndrome and, others [85]. Theoretically, most of the genetic disorder that appears in the children come from parents seems to be normal. For understanding how could a person born

without any apparent illness is a source of genetic disorder to his offspring, an example followed the Mendelian laws will be described. Two apparently normal persons when married could transfer a harmful genetic disorder for their offspring's. Also, such genetic disorder could arise from only one change in one nucleotide from the three billion nucleotides each of us have! When this single nucleotide change becomes a part of the genome, it will not be detected by any of the DNA repair system during the cell cycle steps. Such change will pass from generation to generation until it could find its partner in the second allele, and, then the genetic disorder will appear. Alternatively, it could not be transferred after long time of different generations since the correct allele has given more chances to pass by marriage over the existed wrong one. We should not forget that each of us share his offspring's in 50% of their genes. God wellness when we gained the correct 50% from each parent even one of them has incorrect allele. Nevertheless, the chance for the escaping from the incorrect alleles will be higher if our partner has a completely correct genome. And, better if he/she is not from our relatives

5.1. Sickle Cell Anemia; a nucleotide change!

The hemoglobin 4D structure consists of four polypeptide chains, known as heme. In heme, nitrogen atoms that are part of a structure known as a porphyrin ring hold an iron atom. Sickle cell anemia is a disease in which the 4D of the hemoglobin molecules is defective. It is a disease of genetic disorders caused by Sickle hemoglobin (HgbS or HbS). The mutated allele is recessive, meaning it must be inherited (from each parent) for the individual to have the disease. Even if recessive, it could still affect us if one allele carrying the affected gene is existed. For that, some scientists like to describe Sickle cell alleles as co–dominant rather than recessive [86]. The *β*–globin molecule contains 147 amino acids. Humans carry two *β*–globin alleles. One allele is inherited from each parent **[Figure– 4]**. The existence of one Sickle cell allele in a person will not cause apparent problem, however if two of the Sickle cell alleles exist in one person they will develop, the symptoms of Sickle cell anemia **[Figure 4–7]**. When oxygen is removed from Sickle hemoglobin, those molecules change shape and, combine with one another. The red blood cell structure changes from ring to Sickle shape in absence of oxygen **[Figure– 5]**. This causes blood to clot and, deprives the vital organs from their supply of blood, resulting in pain, intermittent illness, and, in many cases, a shortened life span. The only difference between normal and, Sickle cell hemoglobin is that in each *β*–chain, one glutamic acid is replaced by one valine [87]. Valine, unlike glutamic acid, contains a nonpolar group **[Figure 5–7]**. The result is a hydrophobic "sticky" region that can interact with a hydrophobic region with neighboring molecules, producing the observed clumping **[Figure 5–7]** [100].

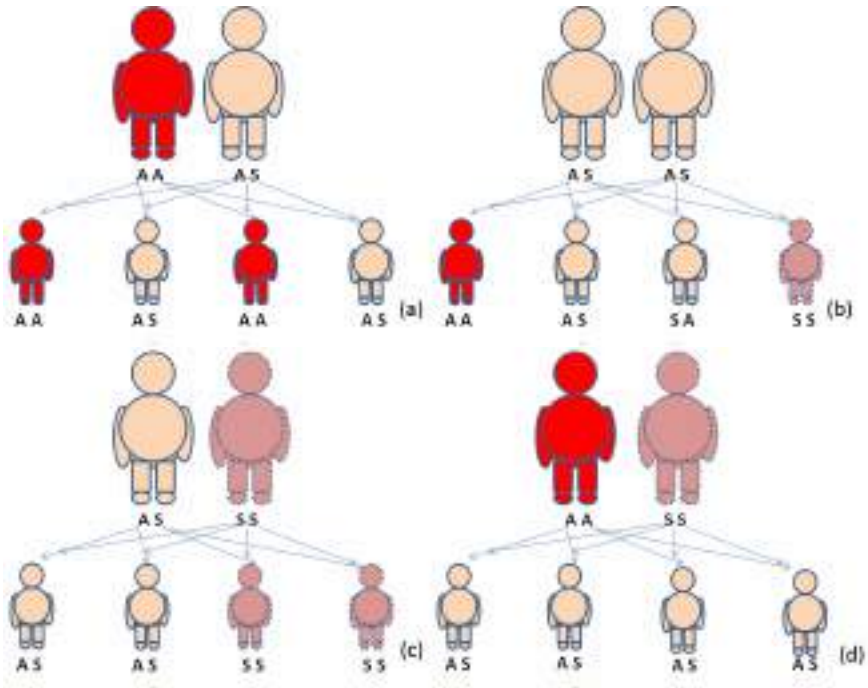

Fig. 4: Different inheritance roots of the normal or the sickle cell alleles of *β*–globin: A normal *β*– globin; S sickle cell *β*–globin ; AA (AA) two normal *β*– globin alleles; SS (SS) two sickle cell *β*– globin alleles; AS (AS) one normal *β*–globin allele and, one sickle cell *β*– globin allele

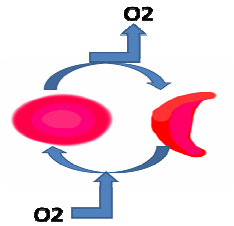

Fig. 5: Exchange oxygen by red blood cell has AS (AS) alleles of *β*– globin

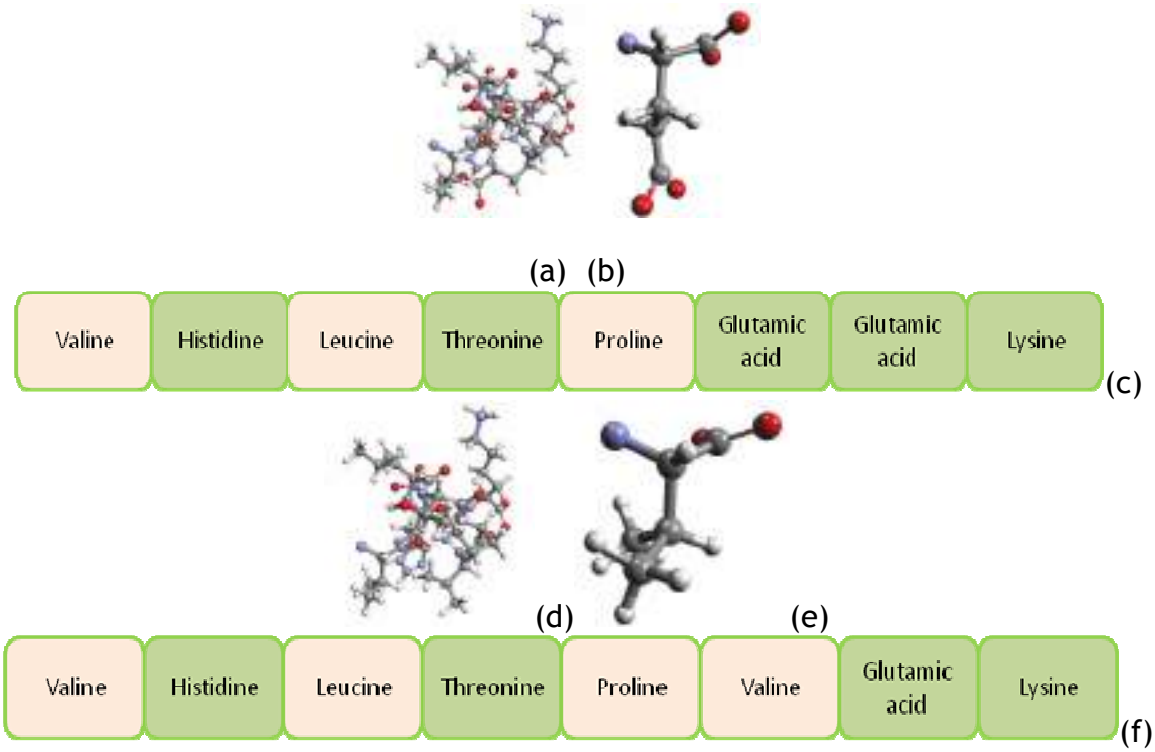

Fig. 6: Fragment of the correct and, the mutant *β*– globin; (a) The 3D of the normal fragment; (b) 3D of Glutamic acid; (d) the amino acids sequence of the normal fragment showing the polar and, the non poler amino acids; (e) The 3D of the mutant fragment; (b) 3D of Valine; (d) the amino acids sequence of the mutant fragment showing the polar and, the non polar amino acids. The fragments and, the amino acids were built using ArgusLab software V 4.0. (in this study) [89].

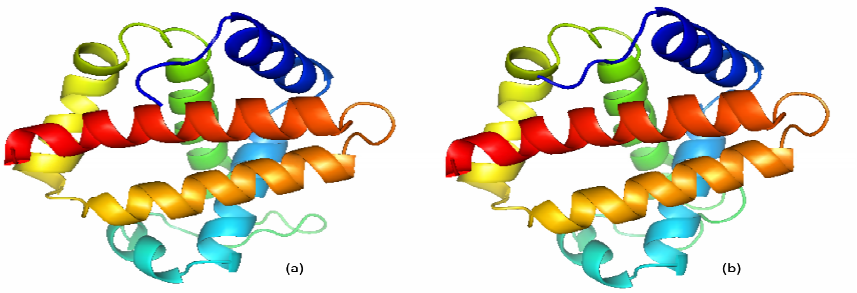

Fig: 7. The 3D structure of *β*–globin: (a) Normal hemoglobin; (b) Sickle cell *β*–globin (Slight differences can be observed). The two protein models were built using Modeller v 9.8 software (in this study).

The HBB gene provides instructions for making *β*–globin. Various versions of *β*–globin result from different mutations in the HBB gene. One particular HBB gene mutation produces an abnormal version of *β*–globin known as hemoglobin S (HbS). Other mutations in the HBB gene lead to additional abnormal versions of *β*–globin such as hemoglobin C (HbC) and, hemoglobin E (HbE). HBB's gene mutants can also result in an unusually low level of *β*–globin; this abnormality is called *β*– thalassemia [90].

[VI] MORE CLEAR GENETIC COMPLICATIONS: THE DEGENERATIVE DISEASE

The degenerative disease is marked by continuous deterioration of cells, tissues, or organs with losses in their function and, the patient's body could not control or recover spontaneously by forming such deterioration. As examples about diseases consider to be related to the degenerative disease group: Amyotrophic lateral Sclerosis (ALS), Alzheimer's disease, Multiple system atrophy, Niemann Pick disease, Atherosclerosis, Progressive superanuclear palsy, Cancer, Essential tremor, Tay–Sachs disease, Diabetes, Heart disease, Keratoconus, Inflammatory Bowel disease (IBD), Prostatis, Osteoarthritis, Ostroporosis, Rheumatoid Arthritis, Huntington's disease, Chronic traumatic encephalopathy, Xeroderma Pigmentosum (XP), Cockayne Syndrome (CS), Trichothiodystrophy (TC) and, Chronic Obstructive Pulmonary disease (COPD). Because of the space of this review, selected diseases will be highlighted during the text. Cancer "*Human Killer*" will take more focus while the concepts of its formation match with the aim of this review. Cancer is a genetic disorder, degenerative disease and, elevated mostly because of genetic change, and, impaired DNA repair mechanism [91–93].

6.1. CANCER

"*Cancer*" is a general term applied to a series of malignant diseases characterized by a rapid and, uncontrolled formation of abnormal cells that may mass together to form a growth or proliferate throughout the body, and, it may progress until it causes the death of the organism [94]. Plants also develop growths that resemble cancer [95, 96]. For more details, refer to 97 and, the references within. Progress on the cancer research was achieved after the discovery of the oncogenic viruses. This enables, *in lab*, tumor induction with clear mechanism. Cancer is modifications happened in the cell genetic material. During the change of the cell from normal to abnormal, the immune system does not recognize the change. In this way, the abnormal cell growth and, multiplies without conflict with the surrounding biosystem. Hanahan and, Weinberg (2000) suggested that six essential alterations in the cell physiology collectively direct malignant growths [96]: (1) *a.* self–sufficiency in growth signals, (2) insensitivity to growth–inhibiting (antigrowth) signals, (3) evasion of programmed cell death (apoptosis), (4) limitless replicative potential, (5) sustained angiogenesis, and, tissue invasion and, (6) metastasis. These criteria are the major and, unique feature of cancer cell. I suggest two other major criteria, that (7) cancer cell still qualitatively similar to normal cell and, (8) cancer cells can escape from the immune system [97]. In general, a certain level of DNA change or damage should be happening to change normal cells to cancer cells. The progress in cancer research will direct us to the real fact that most of the biological functions are caused by a protein that comes from the translation of the RNA. This RNA is a handy copy of the DNA. If this copy is correct, the protein is correct and, the function of the protein is correct too. If not, problems will begin. Thus, cancer is a cell disease and, its start point happened in the DNA. One can simplify the cancer definition in "*Cancer is a sudden (in case of oncogenic viruses or the exposure to a strong mutagen) or accumulative change (mutations) in specific gene(s) or in the cell's genetic materials which causes an irregular uncontrolled growth and, multiplication. This will lead to the death of the host but not the death of cancer cells (whenever there is a nutrient supplement)*" [97]. The change in the cell's DNA which modifies it to a cancer cell can happen in one–step as a direct effect of a strong mutagen, or after a short time but enough for mutations accumulating till forming a true cancer cell. Or, it can start so early in the genome of the ancestors in the same ancestry. The time needed for causing enough mutations in the DNA leading to cancer formation can be so short (such as by some chemical mutagens) or might take some time (like in case of the allele example). In fact, the time can be short, moderate, or longer until the constituents of the cancer formation criteria are satisfied. The different kind of the defense mechanisms can elongate the time for cancer formation or can protect against it. At a certain level of DNA damage, the DNA repair system becomes useless. The damage can attack the DNA repair genes themselves and, become irreversible or hardly corrected, but it can be recovered if there is an extra correct copy as in case of the existence of a second allele. Cancer is mainly an abnormal change in the genetic materials leading to the elevation enough criteria for its formation [97].

6.1.1. The roots of cancer

Perhaps there are three main routes of cancer which by one or another way affect the cell's DNA in level enabling cancer formation: a) through heredity, b) DNA Cracker and, c) mutagens. Any endogenous or exogenous factor(s) that can affect the normal cell and, transform it to a cancer cell is/are a cancer causative agent [97].

6.1.1.1. Through heredity rules

A fit individual can be genetically free from any inherited problem. However, being fit does not mean that your genetic material is accurate. This is because of the presence of two alleles; each can contain one copy of a particular gene. Thus, if one gene was impaired, the other correct one (in the second allele) can probably recover its function. There are many mechanisms and, possibilities transform cancers' causative or initiator genes (oncogenic genes) or causative factors from generation to generation. These possibilities include; each parent has one defect allele while the newborn gains the two defected alleles and, born with cancer **[Figure– 8]**. Only one parent has one defect allele and, the newborn can recover this defect from the other inherited correct allele [97]. This is an important example that clarifies many facts about cancer. After some time, it is possible that a change in the single correct allele can happen. At that stage, the cancer risk probably can be elevated. This simply explained the Knudson's model [97, 98] **[Figure– 9]**. One should consider the amount of such a defect. Defects in many genes could not elevate cancer but can support its formation side by side with other criteria. This proves that our genome and, the genomes of other creatures are subject to a continuous modification as well as continuous repair. "*Observations lead to correct facts*" Those observations start in 1953 when Nording noted that industrialized nations have a higher cancer elevation frequency [99].

Knudson performed a statistical analysis on cases of retinoblastoma, a tumor of the retina that occurs both as an inherited disease and, sporadically. Children with inherited retinoblastoma often developed the tumor in both eyes. Knudson suggested that multiple "*hit*" to DNA were needed to cause cancer. The first hit was inherited in the DNA, and, any second hit would rapidly lead to cancer. In non–inherited retinoblastoma, two "*hit*" lead to take place before a tumor could develop, explaining the age difference [100].

a. DNA CRACKER

The first evidence of tumor viral etiology dates back to 1907 when Ciuffo and, co–workers showed that human warts could be transmitted by cell–free filtrates derived from lesions [101]. Mammalian viral infection and, plant bacterial infection cause cancer. For animals and, human, the oncogenic viruses are the causative agents for cancer. Later the viral infections as a causative agent for malignant tumors was described in chicken sarcoma [102]. In 1911, Peyton Rous at the Rockefeller Institute showed that a Transplantable, spontaneous spindle cell sarcoma derived from a Plymouth Rock chicken could be transmitted to healthy chickens using filtered cell–free tumor extracts [102]. This avian sarcoma induced by Rous Sarcoma Virus (RSV), as it becomes called, was shown a year earlier by Rous to represent a genuine cancer, similar to malignant solid tumors seen in mammals [103]. For plants, *Agrobacterium* is able to introduce cancer [104, 105]. Those causing agents can be called "*the Crackers*", while they are able to crack the genomic DNA and, transform a normal cell into a cancer cell [97, 106].

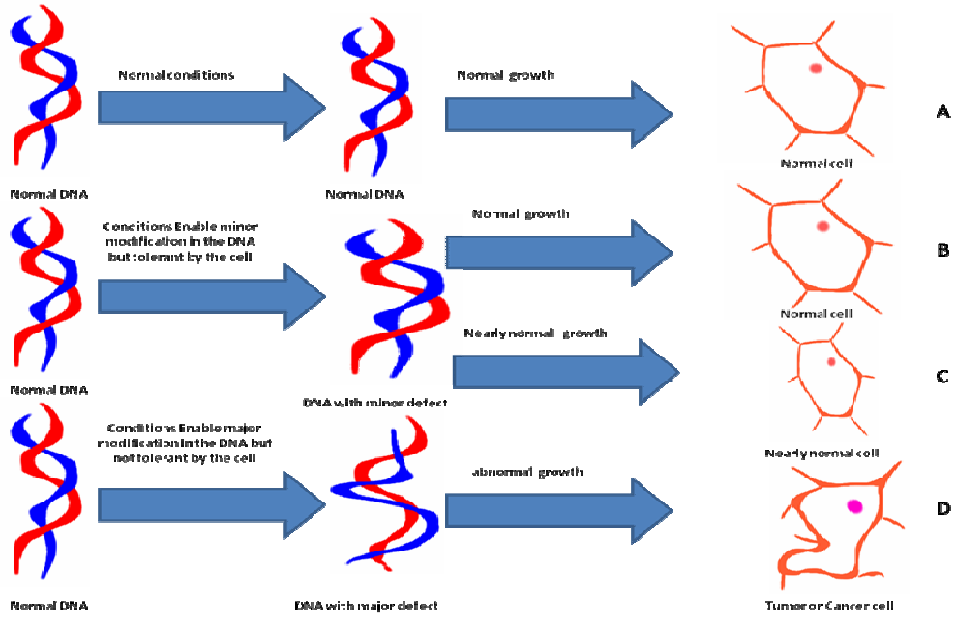

Fig. 8: Normal, nearly normal, and, abnormal cells based on the situation of their DNA; (a) Completely normal DNA lead to a normal cell growth; (b) Minor modification in the DNA with conditions lead to a normal cell growth; (c) Minor modification in the DNA with conditions lead to nearly a normal cell growth and, (d) Major modification in the DNA with conditions lead to an abnormal cell growth (tumor or cancer).

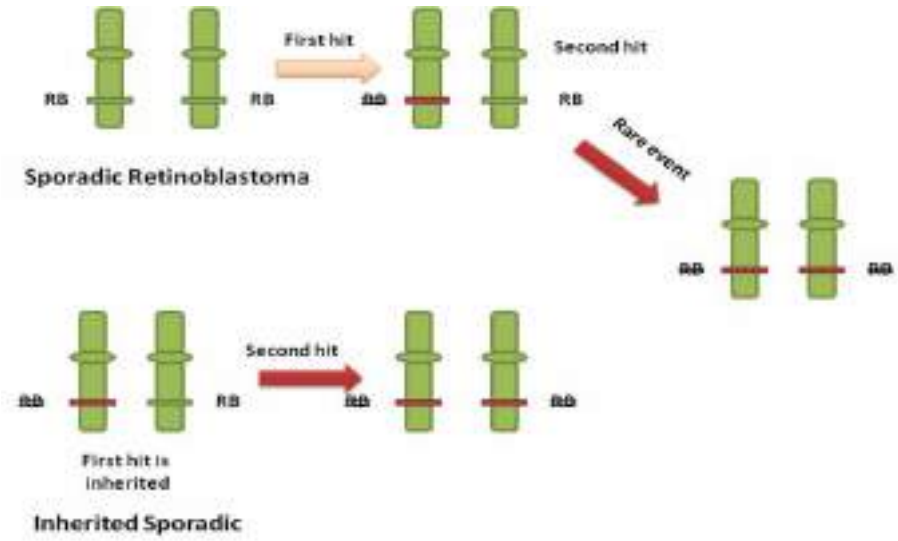

Fig: 9. Retinoblastoma and, two hit hypothesis of Knudson

b. THROUGH MUTAGENS

Mutagen is any causative agent (physical or environmental) that can cause changes to a functional gene affect a function protein. Mutagens cause loss/modification/new trite elevation/tumor/cancer and, death. Ionizing radiations, Ultraviolet light, various chemical smoke from wood, cool and, vegetable leaves, automobile exhaust, cresols and, certain levels of mechanical irritants and, so on., can cause or lead to mutagenesis. These agents, physical and, chemical, are collectively called mutagens. Mutagens are often said to be oncogenic (Gr. *onkos* = mass or swelling). Inefficient or damaged endogenous antioxidant systems cannot be able to protect us from the side effects of the catabolism and, the anabolism or the active endogenous oxidant system. Stress on cell(s)/organ(s), abnormal life style, alcohols, cigarettes, or even an excess of Food will be sources of oxidants and, free radicals, which attack our DNA [107].

[VII] DNA REPAIR

The existence of a correct copy of each allele has a particular function in the cell and each existed in one chromosome is important for the transcription and, translation process, which will finally lead to the synthesis of an accurate protein folded and, does its function correctly. Any of our genes (in any cell) is under regular attacks by different agents that could mutate it. These agents can arise from endogenous/exogenous physical, chemical, and, biological sources. DNA damage could be lethal for the cells and tissues if we do not have a mechanism for DNA damage sensing, repairing, or even killing. However, cells with problems if killed are better than survive with errors could lead to cancer. We and, the other creature have different kinds of protection against mutagens. Such protective agents include skin, melanin to protect against UV, cytochrome P450s (to degrade nonpolar chemicals), immune system, and, so on. Even our excretion system and, intestinal microflora are involved in protecting us. However, what could happen if certain damage affects our DNA? DNA damage can induce permanent changes in the DNA sequence, contributing to oncogenesis, premature ageing and, severe genetic disorders **[Figure– 10]** [108]. Cells could sense damage for certain limit. Cells have complex signal transduction, cell cycle checkpoints, DNA repair, and pathways to sense most of the types of the DNA damage and, running a system for maintaining genes to promote genomic stability. Respective genes numbers associated with DNA repair were identified in humans to date. Wood et al. (2005) describe about 150 DNA repair genes and, the number is to increase [109]. Exposure of mammalian cells to genotoxic agents activates an intricate network of mechanisms collectively known as the "*DNA damage response*". This response includes DNA repair and, DNA damage signaling pathways that alert the cell to the presence of DNA damage and, coordinate the appropriate response [110, 111]. The DNA damage response leads to slowing or arrest of cell cycle progression at defined checkpoints, and, to activate the DNA repair [112, 113]. The existence of different efficient DNA repair pathways is essential for cells to correct any expected DNA damage. Some of the DNA repair pathways will be described to show the different levels of repairing mechanisms which start from DNA cross linkage, incorrect nucleotide insertion until complete chromosome deterioration. These pathways include the direct reversal pathway, the mismatch repair (MMR) pathway, the nucleotide excision repair (NER)

pathway, the Base Excision Repair (BER) pathway, the homologous recombination (HR) pathway, and, the nonhomologous end joining (NHEJ) pathway.

(a) Direct reversal pathway (figure 11)

There is some direct reversal correction and, repair mechanisms for different types of lesions including: (1) simple nicks can be directly relegated; (2) certain UV photoproduct can be repaired by photoreaction; (3) certain alkylated bases can be repaired by removing of the adduct. A direct reversal of the DNA damage is not possible in most cases because of thermodynamic or kinetic reasons. In some cases, however, the DNA damage can be reversed directly. These repair reactions are direct, and, do not require many proteins like the repair pathways. They are specific to the type of damage and, do not involve breakage of the phosphodiester backbone. UV light induces forming abnormal covalently linked dimmers of cytosine and, thymine bases, which are adjacent to each other on the same strand of DNA [115]. The reverse reaction can occur when the photolyase enzyme is activated by energy absorption of blue or UV light (300–500 nm) [116]. Photolyases are flavoproteins, which are able to cleave the pyrimidine dimmer [66, 115]. Photolyase activation is dependent on energy absorbed from blue/UV light. Alkylating agents can transfer methyl or ethyl groups to various O or N sites in guanine (such as O^6–alkylguanine), thereby modifying the base, and, interfering with its pairing with cytosine during DNA replication. The O^6 site in the guanine (O^6–mG) has the highest mutagenic potential and, besides the N2 position, highly selectively alkylated by substances that react via an SN1 mechanism [117]. The most abundant environmental alkylating substance is dimethylnitrosamine, which is formed during Food preparation and, during chemotherapeutics treatment of cancer. O^6mG adduct can also be generated as a side effect of the reaction of the cellular catabolites with guanine. The methyl group at the O^6 site of guanine is removed by the DNA repair enzyme O^6–methylguanine–DNA methyltransferase (MGMT) via a one–step methyl transfer reaction [118]. During this reaction, the methyl group is transferred from the alkylated base onto an internal cysteine residue within the active center of the alkyl–transferase. This results in the restoration of the guanine within the genomic DNA. The alkyl group transfer leads to irreversible inactivation of the transferase and, targets it for ubiquitylation and, proteasome–mediated degradation. This so–called 'suicide reaction' implies that the cells' capacity for repairing O^6–guanine lesions depends on the pre–existing MGMT levels in the cell, or the rate at which cells can resynthesize MGMT. DNA alkyltransferases are ubiquitously found in prokaryotic and, eukaryotic organisms [109]. The human MGMT acts in a similar way to the Ogt protein of *E. coli*, which is constitutively expressed in this microorganism. O^6–meG lesions, which are not repaired by MGMT, may mispair with thymine during the DNA replication. In the following DNA replication cycle, thymine will pair with adenine. By this mechanism, the O^6–meG lesions cause distinctive G–C to A–T point mutations, which are believed to be the driving force of the carcinogenic effects of alkylating agents. In the event of failure of direct reversal repair, these mispair lesions can potentially be repaired by the MMR pathway [66]. For more detailed about the direct reversal DNA alkylation damage refer to Mishina et al. (2006) [119].

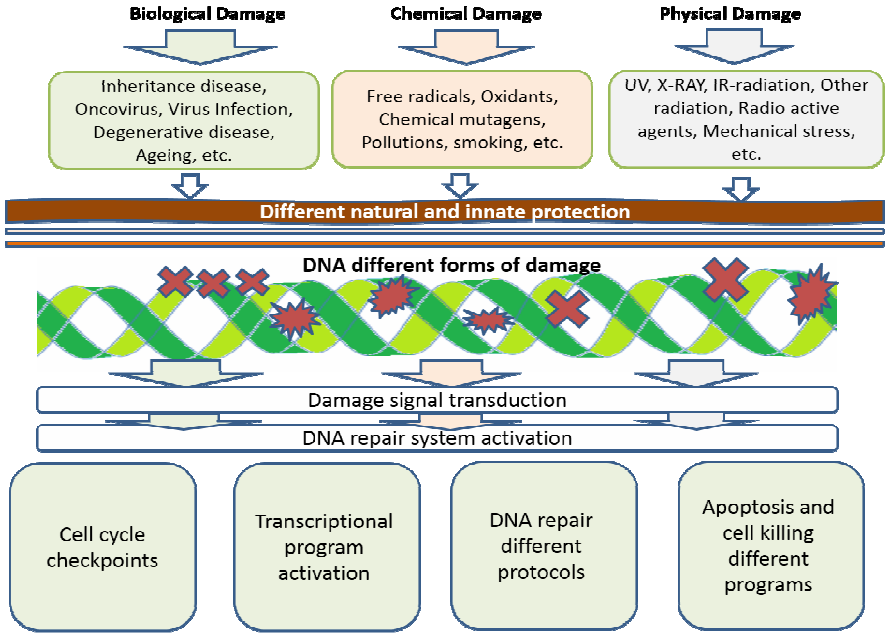

Fig: 10. Different roots of DNA damage (Biological, chemical and, physical) and, the different roots of DNA repair mechanisms.

REPAIR OF SINGLE STRAND NICKS

In this case, the damage is the presence of single strand nicks having free 5-phosphates and, 3–hydroxyls. Nicks with other configurations or nicks accompanied by additional backbone or base damage require more complex processing prior to repair. DNA ligase repairs single strand nicks by catalyzing phosphodiester bond formation using ATP or NAD^+ as energy donor [120]. Okazaki fragment is short, newly synthesized DNA fragment that is formed on the lagging template strand during DNA replication. Completion of lagging strand DNA synthesis requires processing of up to 50 million Okazaki fragments per cell cycle in mammalian cells [121]. Ataxia Oculomotor (AOA1) Apraxia 1 is an example about the problem of unrepaired single strand break and, the accumulations of adenylated DNA nicks [122].

(II) MISMATCH REPAIR (MMR) PATHWAY (FIGURE 12)

Mismatch of bases (e.g. G–T or A–C) is a common DNA lesion due to a failure in proofreading during DNA replication. As in the direct reversal DNA part, mismatch of the base could be due to the filer of direct reversal repair, where in the second cycle of DNA replication the strand that have the incorrect base will be a template for a new strand, which will contain new incorrect but stable base and, finally will lead to a stable mutation. In this case, the new mutation will be homogenous and, built–in within the DNA [123]. If it becomes a fixed change, it could not be detected or repaired by any mechanism anymore. The only cover for such mutation is that, the cell could be dead due to any reason or there is another correct copy in another allele in the cell that could complement the deficiency caused by the new mutant. DNA MMR is a highly conserved process from prokaryotes to eukaryotes. In *E. coli* a number of genes were discovered, which when mutated lead to hypermutation. Thus, the gene products of these genes are called *mutS*, *mutL* and, *mutH*. Their proteins interact with each other as homodimmers or heterodimmers/trimmers and, are the key players in detecting a DNA mismatch and, its preparation for repair. They determine the exact position of the mismatch on the daughter strand; induce the strand separation and, the recruiting of an exonuclease, which excises the mismatched base after the separated daughter strand, was nicked. There are human homologues of *mutS* (*msh2*, *msh3* and, *msh6*) and, *mutL* (*mlh1* and, *pms1*), but not *mutH*. The endonuclease function of MutH in prokaryotes leads to the above–mentioned DNA nicking prior to strand separation. In humans, this function is accomplished by *mutL* homologues [85]. MMR factors also seem to be involved in the physiological function of immunoglobulin (Ig) diversification, an essential process for immunity. Another common lesion in the DNA is incorporated uracil rather than thymine [124].

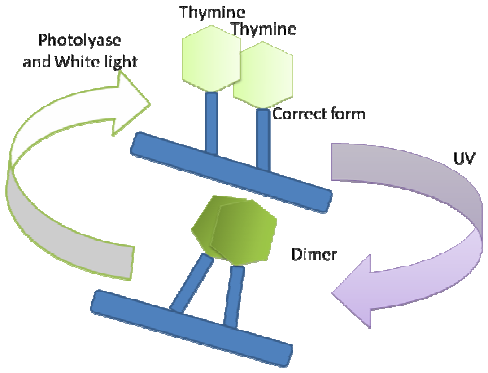

Fig: 11. Direct reversal of DNA damage; UV induce dimmer formation between two thymine while Photolyase and, white light cause reverse repair.

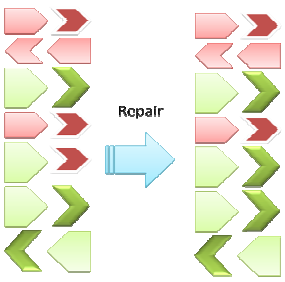

Fig: 12. Mismatch repair (MMR); C , G , T , C

(III) NUCLEOTIDE EXCISION REPAIR (NER) PATHWAY (FIGURE 13)

The NER pathway plays an important role in the repair of different kinds of DNA damage caused by UV radiation and, mutagenic chemicals, and, its impairment in humans is associated with growth defects, excessive UV sensitivity, and, in certain cases, increased skin cancer. In NER, an enzyme system hydrolyses two phosphodiester bonds, one on either side of the lesion, to generate an oligonucleotide carrying the damage. The excised oligonucleotide is released from the duplex, and, the resulting gap is then filled in and, ligated to finish the repair reaction. This nuclease activity, unique of DNA repair, is called excision nuclease (exinuclease). The enzyme activity of exinuclease results from sequential and, partly overlapping activities of several polypeptides that bind to DNA and, utilize the energy released by ATP hydrolysis to deform (kink and, unwind) the DNA and, eventually excise the lesion by dual incisions [125]. A side effect of this wide substrate range is that exinuclease even 'excises' mismatched nucleotides; however, in contrast to the MMR process, the exinuclease will excise a mismatched base from either strand. If two mismatches were removed opposite to each other in each strand of the dsDNA nucleotides excision will induce mutation when both mismatches treated at the same time. This can actually cause mutation fixation rather than mutation avoidance. Only three proteins (UvrA, UvrB and, UvrC) are required by NER in the prokaryotes, whilst more than 30 proteins are involved in the mammalian NER [126].

During the multistep process of the NER pathway, the DNA lesion is recognized and, the oligonucleotide containing the lesion is removed. The gap is then filled with ligating a new oligonucleotide, is complementary to the opposite DNA strand [66].

NER is involved in three human genetic syndromes: Xeroderma pigmentosum (XP), Cockayne Syndrome (CS) and, Trichothiodystrophy (TC). These syndromes are characterized by neurodegeneration, increased cancer frequency and, ageing. XP patients are sensitive to short sun exposures and, have a greater than 1000–fold increased skin cancer risk that usually develops at an average age of 10 years old. XP individuals may also develop neurological abnormalities. CS is an autosomal recessive genetic disease and, it is rare in humans [127]. CS patients are also sensitive to sunlight but they do not have predisposition for skin cancer. This disease is characterized by growth retardation, cognitive impairment and, ophthalmologic disorders. CS individuals have a short lifespan and, usually die in the first or second decade of life. The causes of CS are mutations within two proteins that are essential for DNA damage recognition in NER. TTD is also rare and, inherited as an autosomal recessive disorder. The clinical features of TTD are brittle hair and, nails, dwarfism and, ataxia [127].

(IV) BASE EXCISION REPAIR (BER) PATHWAY

Base damage is the most common insult to cellular DNA. Base damages are repaired by the Base Excision Repair pathway (BER) [66]. BER includes a short–patch BER sub–pathway that replaces a single nucleotide, and, a long–patch sub–pathway during which 2–13 nucleotides are incorporated. Initially the damaged base is removed by glycosylases such as Ogg1 and, MUTYH. The base is removed by hydrolysis if the N–glycoside bond which attaches it to the sugar ring in the DNA backbone. After excision of the base by the DNA glycosylase, an AP (apurinic/ apyrimidinic) site is generated [128]. The endonuclease APE1 then digests the DNA strand at the apurinic or apyrimidinic site. DNA polymerase β (Pol β), in the case of the short–patch BER sub–pathway, or Pol β and/or Pol e or d, in the case of the long–patch BER sub–pathway, fills the gap by incorporating nucleotides in the DNA strand. The complex XRCC1/ligase III then carries out the strand ligation during the short–patch sub–pathway. Other proteins are involved in the long–patch sub–pathway for the DNA synthesis step, and, ligase I carries out the strand ligation [129].

Examples of BER include removal of uracil, hypoxanthine and, methyladenine from DNA; however, BER has a limited substrate range because the DNA glycosylases that initiate the repair process are in intimate contact with the lesion during catalysis. BER is involved in human disorders or in cancer [66, 130]. The main function of the glycosylase MUTYH in the BER is the excision of adenines misincorporated opposite 8–oxoG when oxidative DNA damage occurs. When this damage is not repaired properly, G:C > T:A mutations are induced. These mutations are typically found in the adenomatous polyposis coli (APC) gene in MAP tumors [131].

(V) HOMOLOGOUS RECOMBINATION (HR) and, NONHOMOLOGOUS END JOINING (NHEJ) (FIGURE 14)

DNA double strand breaks (DSBs) are considered the most dangerous form of DNA damage [66]. They are generated when the two complementary strands of the DNA double helix are broken simultaneously at sites that are sufficiently close to one another that base pairing and, chromatin structure are insufficient to keep the two ends juxtaposed. DSBs can be generated due to many factors such as: IR, X and, γ rays which is probably the most significant exogenous agent inducing DSBs; radiomimetic or chemotherapeutic drugs, such as bleomycin, neocarzinostatin, etoposide and, other topoisomerase inhibitors [132]. DSBs are generated also by endogenous agents such as reactive oxygen species (ROS) produced during cellular metabolism [66]. HR is involved in copying the missing information from undamaged homologous chromosomes. It is an error free process. In

contrast, NHEJ is an error–prone process. It joins the broken DNA ends using little or no sequence homology. For more detailed refer to Lynch (2009) [66].

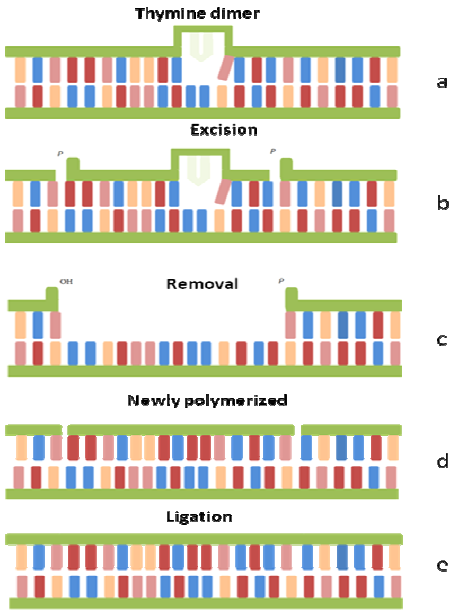

Fig. 13: Nucleotide Excision Repair (NER); (a) Thymine dimmer formation; (b) Excision; (c) removal; (d) newly polymerized; (e) ligation and, (f) back to the normal DNA.

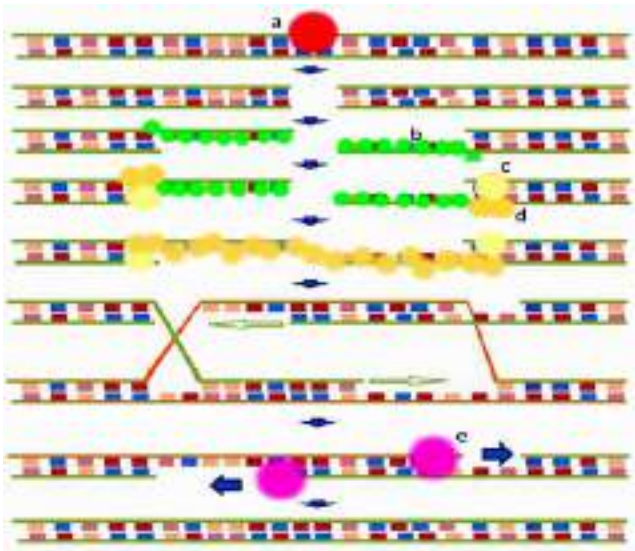

Fig: 14. Homologous recombination repair (HR); (a) Oxidant, free radicals and, radiation cause DNA double strand break; (b) Coating of ssDNA with Replication protein A; (c) Loading of BRCA2; (d) loading of RAD51; (e) after homologues recombination polymerization using DNA polymerase and, dsDNA is formed [133].

[VIII] THE THIRD EYE

The pineal gland, which secretes the hormone melatonin, is a small lobe in the forebrain, lying near the center of the brain in human. Melatonin production rises sharply at night and, falls rapidly in the daytime. Exposure to light during the dark cycle interrupts producing melatonin. Melatonin decreased production during long–day period is believed to be associated with the increase in the sexual hormone [66]. Missing a correct day/night cycle will cause illness due to melatonin deficiency. Melatonin deficiencies are believed to be associated with some

disorders includes: Schizophrenia (Only in a subpopulation) [134]; Multiple sclerosis [135], Primary obsessive–compulsive disorder [136], Menière's disease [137], Fibromyalgia, Pain [138, 139], Migraine [140], Cancer [141] Critical illness [142] and, other forms. There are a respective number of diseases associated with the melatonin disorder. As a part of our hormone system, and, is mainly excreted in the correct day/night time, it could explain the importance of the correct lifestyle for our health.

[IX] NITRIC OXID AND, THE RELAXATION OF ARTERIOLES

Endothelial cells are able to release substance named, endothelial–derived relaxing factor (EDRF). EDRF released from all arteries, microvessels, veins, and, even lymphatic endothelial cells. Apparently, Nitric Oxide (NO) or a related compound was formed by the action of nitric oxide synthase on arginine. NO causes relaxation of vascular smooth muscle by inducing an increase suppresses platelet activation and, reduces adhesion of leukocytes to endothelial cells. Almost any type of endothelial damage decreases formation of EDRE. Neutrophils and, macrophages use arginine specifically for the production of nitric oxide and, stimulation of both cell types increase nitric oxide synthesis [151]. NO is a labile bio–regulatory molecule that is synthesized by many cell types from L–arginine with L–citrulline as the major co–product. It is highly lipophilic and, therefore rapidly traverses cell membranes making it an effective intra– and, inter–cellular messenger. It has a short half–life (3–9 seconds) and, must be produced in large quantities or over a long period to have prolonged biological effect. When produced by cell such as macrophages it can rapidly enter microorganisms and, tumor cells and, exert cytotoxic and, the cytostatic effect of rising cyclic–GMP synthesis and, inhibiting host mitochondrial electron transport and, DNA replication [152].

NO BECOME A PARADOX

Is NO a tumor suppressor or inducer? Apparently its amount and, from which cell type it was produced are crucial points. However, as a part of our endogenous oxidant system [107] it has many vital roles. Crowell et al (2003) reports its presence in high amount in much type of cancer cells [153]. Abnormal amounts of NO does not mean that it is harmful. The cancer cell is a cell out of control, and, the amount of NO on it does not mean that NO is a cancer promoter. However, NO produced in our body by a healthy person is a clear cut proving that it involved in vital mechanisms [154].

[X] NUTRIGENOMIC

Food has a direct effect on the gene expression. The *E. coli* lactose metabolism has been well studied by scientists. From the eukaryotic system, the glucose level and, the insulin expression are an example. The relationship between nutrients and, gene expression lead to elevating the science of "*Nutritional genomics*" which also called "*Nutrigenomics*". Mistakes in a gene will be result in a modified protein with altered activity or dysfunction, which could elevate disease. Such diseases are specified as a genetically bases disease. The environment and, the type of the sublimated nutrients could cure disease side effect. Why not? If a disease is responsible for a certain product deficiency; which is essential for the cells and, their biological activities, exo–source could cover such deficiencies. Meanwhile nutrients could have bad side effect when they influence some diseases rather than recover. For that, the type of the used nutrient will be linked to the type of the missed metabolites and, will fill in the leakage caused by the partially defected gene or recover it in case of complete defect. In simpler words, if gene 'A' responsible for producing proteins 'A' which produce a product 'A' used by protein 'B'. If the gene 'A' is defected, product 'A' will not be produced and, the gene's 'B' protein will be useless. However, if we gained the product 'A' from an exo–source gene B and, its protein will work and, the deficiency will be recovered. Exo–source of nutrient such as the type of Food could also help in increasing the expression of certain metabolic pathways, which is in need for stabilizing certain illness. If the defect was in gene 'B', the product of gene 'A' will be accumulated and, could be harmful to the cells and, the body. Accumulating metabolites intermediate, which did not satisfy the cellular demand or might interact wrongly could cause an extra illness. So, nutrient is important as a therapeutic tool for improving health and, minimizing the risk of disease in susceptible individuals. Drug metabolism is different from person to person regarding to a genetic basis. Food will have the same effect. Different persons metabolize Food differently. For this reason, Food should be personalized. Genetic and, nutritional science is identifying the influence of the Food constituents on the gene expression. A science, which named "*Nutrigenomic*". The Food decreases the load on cell macromolecules by supplying it with similar gradients (it produced). This will lead to safe the cell time and, energy. and, will allow the cell to do more argent biological activities [107] and, to reduce the total number of DNA/RNA/Protein cycles, which could induce spontaneous mutation [155]. Food science has shown an increasing interest perhaps for the following reasons: Food is safe (in most cases), if used wisely, Human has experienced different types of Food and, has a good background about their different positive and, negative effects, Food is cheaper than the other medical forms, Food has fewer side effects, Food is in continuous demand by our bodies. So it can be accepted as a key for treatment by anyone, Many Food forms are rich in some special vitamins, elements, sugars etc, and, can used in different kind of illness. They are recently called "*Nutraceutical Food*", Using incorrect Food for a short time will not give the same side effect as in using the incorrect drug.

[XI] OUR GENES AND, ITS RESPONSIVENESS TO NUTRITION THERAPY

Epigenetics, genetic polymorphism, genome and, proteome

Epigenetics is characterized by alterations to the DNA molecule that affect gene expression but do not change the nucleotide sequence [85]. There are at least three known mechanisms: DNA methylation, Histone modification, and, genomic imprinting. Genetic differences could affect the interaction between the genes and, the nutrients or active compounds in Food. Such differences including mutations, impaired genes, methylated genes, single nucleotide polymorphism (SNP) and, damaged genes. Differences across entire regions of an individual's genome result from various nutrient imbalances and, deficiencies. Genetic variation between individuals is the rule not the exception [107, 156]. As an example about the role of genetic variation which could interact with our Food there are three isoforms of super oxide dismutase SOD (SOD1, SOD2 and, SOD3), SOD2 polymorphisms have largely been implicated with cancer risk. The most commonly studied polymorphism of Mn–SOD is Val 16 Ala on mitochondrial target sequence. Other examples like Pro 197 Leu SNP of the Glutathione peroxidase GPx1 (GPx) gene have been associated with FRs–O related diseases [157]. CAT SNP is responsible for Japanese acatalasemia [158]. The CAT C–262T SNP is the most widely studied to date; it has been associated with a decrease in Catalase CAT activity and the risk of developing FRs–Os [149]. Other SNPs located within this region include G–844A, which was associated with hypertension [107]. These SNP regions can influence either nutritional status or the re–nutrition process because re–nutrition becomes progressively more difficult with age [159]. The success in using the new molecular biology tools such as genomics, proteomics, and, metabolomics [150] will map the interactions between genes, nutrients, and, environment and, in this way will highlight their downstream effects on human health [124]. Adequate supplement of antioxidants could recover such illness is critical for the above genetic disorder to avoid health deterioration.

[XII] EXTERNAL HELP!

Our bodies could not survive out of nutrient. However, certain nutrients could satisfy our request but it should include some types of constituents, which our bodies could not be able to synthesis from other intermediates. Certain amino acids, fatty acids, vitamins, and, minerals cannot be synthesized by the body and, must be provided through the diet to prevent dysfunction and, disease. For example, human being lacks the enzyme gulonolactone oxidase and, cannot synthesize vitamin C, human being are unable to synthesize the essential amino acid and, fatty acids. Antioxidants as an example protect us from different types of oxidants (Os) and, Free Radicals (FRs). Antioxidants are essential for our survive and, could be produced either by endogenous or exogenous sources. Harman (1956) was the first to describe the damage (cell organisms and, tissues) caused by FRs and, oxidants OS. FRs include $OH^{\bullet}$, $O2^{\bullet -}$, $NO^{\bullet}$, $NO^{2\bullet}$, $ROO^{\bullet}$ and, $LOO^{\bullet}$ [151]. Os such as H_2O_2, O_3, $1O_2$, HOCl, HNO_2, $ONOO^{-}$, N_2O_3, and, LOOH. FRs–Os as a part of the biological system, they are involved in many essential and, vital processes [for more detailed refer to [107] and, the references within]. FRs–Os are generated either from endogenous or exogenous sources. Examples about the endogenous sources are included: mitochondria, respiratory chain, immune system activity, inflammation, mental stress, excessive exercise, ischemia, infections, cancer, change in the intestine microflora, ageing, genetic susceptibility, phagocytosis, and, cytochrome enzymes P450 (CYP450) [152]. Examples about the exogenous sources are included: air and, water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs such as ciclosporine, tacrolimus, gentamycin and, bleomycin, industrial solvents, cooking (smoked meat, used oil, fat) and, radiation [91]. Diet, lifestyle, and, the exposure levels are important factors in determining the capacity of an organism to mount a protective response [107]. Different diseases were associated with the high level of FRs–Os such as cancer, artherosclerosis, pulmonary disease, cardiovascular diseases, neurodegenerative diseases, allergies, metabolic diseases, ageing, insulin resistance, Down's syndrome, familial ALS, transplantation complications, and, many other [107]. We have a complete endogenous antioxidant system, which can protect us from the FRs–Os. An extra exo–source (exo) of antiOs could be supplemented through diet. The mitochondrion is a built–in and, a continuous source of FRs–Os. Activating the endo–antiO system is a process consumes energy. The mutant generation rate in the presence of high levels of FRs–Os is greater than that produced in normal cases [107]. AntiOs are doing their functions by slowing down or preventing the oxidation process. We have different types of endo–antiO enzymes such as superoxide dismutase (SOD), which was the first antiO enzyme to be discovered [153]. Catalase (CAT), glutathione peroxidase (GPx) (both of which reduce peroxides to water), glutathione S–transferases, hemeoxygenase–1 (HO–1), thiol–specific antiO enzyme and, macrophage stress protein all play a central role in protecting against FRs–Os [154]. They are in most cases working as a network. As an example, glutathione and, vitamin C can act in concert to alleviate a variety of O stresses. Vitamin C is able to regenerate tocopherol in the lipid phase [155]. β–Carotene and, tocopherol act synergistically against lipid peroxidation. Polyphenols, such as flavonoids, provide antiO protection, which is enhanced by vitamin C. AntiO vitamins play major roles in the protection against FOs–Os and, different related diseases [107, 156]. The endogenous antioxidant system could not stand alone but diet dependent [157]. AntiO responds differently in different tissues, which should have some link to the tissue gene specificity. A study shows that an oversupply

of antiOs could inhibit the endogenous antiO system. AntiOs cause a reduction in the intracellular environment, which keeps more Keap1 molecules in the reduced configuration. With less oxidized Keap1 molecules present, ubiquitination and, degradation of Nrf2 increases. A decline in Nrf2 would lead to impairing the endo–antiOs [158]. Calculated antioxidant amounts in the Food diet should be used for each age/situation. The need will be more argent in some cases such in case of the existing of inherited diseases [159].

[XIII] OVERVIEW

This review is aimed to highlight that a correct healthy life is based on maintaining certain balance between many factors. It focuses on the role of the genes and, the Food in our health as well as the interaction between both of them. It contains some examples from the prokaryotic and, eukaryotes to support its aim. Those examples highlight the importance of understanding the role of the genetic materials in performing correct different biological activities and, in maintaining our health. Prokaryotes and eukaryotes biological system are following nearly the same roles. They react with similar biological macromolecules proteins' activities which responsible for specific functions. Those proteins should be in certain 3D folding configuration to do such functions correctly and, efficiently. Any modification in such 3D configuration could lead to incomplete, inaccurate, and, nonspecific function(s). Alternatively, could impair completely protein function. The source of each of those proteins is a gene. Different genes located in the organism genome. If this gene copy is correct, it will be transcribed to a full RNA, which will be translated into a correct protein. This is not always the case. Some changes could be happening in the genes leading to a mutation. Sickle cell anemia was given as an example. Strong evidence reclaimed that Sickle cell anemia was coming as a natural selection for people having such change. Such selection was done by malaria. Sickle cell anemia patient is able to survive if infected by malaria. Was it due to mutation or did it exist in our first father genome? Science was not able to prove such issue yet, even the source of the mutation in prokaryotic due to environmental factors is clear, but in case of eukaryotic system, the case is different. In eukaryotic system, transforming genetic materials from generation to generation is different. Both parents give 50% to their newborn. But, why brothers are different? This is mainly happening during the meiosis stage to form sperm or ova. Moreover, to be inherited, mutation should reach either the sperm or ova. For that, the genetic disorders are not common among different human populations; however, it becomes clear in populations where marriage between relatives is more common. Such marriage should be avoided. One person having a genetic disorder disease will not be able to cure from this disease by all the technologies we have. However, he might be able to recover its side effect with the aid of the foods or drugs able to supply the body with missing nutrients. Food science will play a crucial role in future due to that. Food is the most clinically studied compounds over thousands of years. "*Lemon could protect us from Catching cold or from Scurvy*" Nearly all populations on the earth know that. Keeping our bodies safe is much better than taking herbaceous and, synthetic drugs. Why taking herbs containing vitamin C if we can buy some fresh lemon from the market? It seems that the quality and, quantity of our daily consumption of Food will be the final winner over the synthetic medicines, drugs, and, herbaceous plants. The most promising Food materials for treating particular disease will be that which are edible but contain high amount of active constituents. Those compounds are now known as "*Nutraceutical Food*". The role of the various effects of the different types of foods in our genome and, the genomes of other creature was illustrated. Lactose metabolism in *E. coli* was given as an example. This single cell microbe can utilize lactose through its *lac* operon. The process could differentiate between lactose and, the other sugars. If a sugar is preferable for the cell, *E. coli* will stop the metabolism of lactose as well as its transport. In contrast, one analog to allolactose, the IPTG, is able to activate the metabolism of lactose in the absence of lactose itself. Moreover, and, because IPTG was not degraded in the presence of the *β*–galactosidase, the activation/production process will not be stopped. I wonder how many similar compounds (similar to IPTG) are we consuming daily among the huge amount of synthetic compounds in our Food? In this review I aim to clarify the role of genetic materials in degenerative disease, an example from prokaryotes was discussed. It was about the role of *E. coli* XL1 Red in mutating genes. As above, this strain was impaired in three of their DNA repairing genes. This will take us directly to the mutation and, the DNA repair issues. DNA repairing genes is essential for any of the biological forms. *E. coli* XL1 Red has deficiencies in three of its DNA repairing genes, lead to mutations formation during its normal growth. This microbe becoming a well known mutator strain and, used to induce a different kind of mutation. Particularly it used as *in vivo* random mutagenesis package. This clarifies that; if mutations have been happening in the DNA repairing genes they will be unable to correct the spontaneous mutations happened or even they will be a source for the mutation promotion. In the eukaryotic system, as we are part of it, we have a bigger genome. One or more mutants can be happened in a useless or function less DNA part, which will not affect on us. Additionally we are a multicellular creature, and, if one or even a few cells have been affected, we still have a big chance of survive. Or it is a correct mutation in an important gene lead to an important protein. This mutant could lead to a disease. However and, due to that we have another copy in the second allele we have, the defect due to this mutant will be recovered. Why *E. coli* XL1 Red is able to introduce stable mutants? This is because it was impaired in three keys of its DNA repair genes. It will be unable to correct changes happened in its genome. In this review, I described that if one mispaired nucleotide has escaped from the DNA repair system and, pathways; it will become a fixed mutant in the second cell

division and, will not be detected anymore during the further DNA replication. As a single cell, the rate of mutation will be high in *E. coli*. In a single cell organisms, the rate will be either one mutant/cell (in case of single mutant) or many mutant/cells (in case of multiple mutant). However, in a eukaryotic organism such as human, the mutation rate will be one mutant/ 100 trillion cells or many mutant/ 100 trillion cells. Which might be considered as nothing particularly if such mutant/mutants happened after complete cell differentiation. This proves that we are naturally protected. For an extra natural safety, we gain only 50% of our genome from one of our parents. Therefore genetic disorder probability is rare to happen. It is happening mainly due to a rare chance. However, the genetic disorder chance will be higher with those who are married from relatives. Relatives should have similar alleles. At the molecular level, proteins are the macromolecules in our bodies, which are responsible for doing nearly all functions. Few seldom structures out of this role could do some activities similar as the protein could do. So, if the protein is correct due to a correct start point (correct DNA) it will do its function perfectly and, correctly. From diseases such as Sickle cell anemia, we can learn a lot. A single base pair change has led to a new amino acid. This single base change will change one of the *β*–globin amino acids. This amino acid, even one out of 147 amino acids which draw the 3D structure of the *β*–globin; it causes enough interaction to deform the correct structure. It interacts wrongly with its neighboring molecules and, gives the Sickle shape structure. A single amino acid converts the Red Blood Cells from its normal shape to the Sickle shape causing a disease, which is painful and, harmful to us. What makes such example unique is that it happened at the start point during fertilization, so existed in the genome of our cells. For that, it could not be repaired only if a mechanism for modifying the whole genome is discovered or invented by the molecular biologists. The inheritance role is clear in our case of Sickle cell anemia. Such disease as shown in **Figure 5** could not be appeared if one of the parents has completely healthy genes. Marriage from foreigner will give more chances for healthy children. The bigger the genetic distance between parents the better the results. If a single genetic disorder appears within a family, then members of this family should directly avoid marriage from their relatives. Traditionally, in Middle East and, in Far East in countries such as Kazakhstan there is a believe that marriage of relatives should not be repeated but after seven generations. What about those, which are already, have a genetic disorder? Is there any solution. Being having a defect gene; one of the solution is to us the similar product produced by another creature have the similar correct genes. "*Gene lead to a product*" But if one has not had such a gene (as well as such a product); why not to get a benefit from the existence of correct genes in other creatures? In another world, we can recover such deficiency through different routes, and, our Food is the easiest one. Our foods were subjected to the longest known clinical trials and, prove over decades to be safe as well as their different effects were well known. A particular type of Food could supplement use with certain products in higher amounts. Fortunately, we all have a defect gene for vitamin C production. We should not neglect or misevaluate the experiences gained from long human observation. At least we should evaluate them and, take what is beneficial for us. There are many examples, and scientist should give clear and, simple advices to people to help them to escape from such diseases, like the most forms of the degenerative and, inheritance disorder. It is our role and, it is an ethical need to advise those who do not have such knowledge. It will be easier to give students at schools clear information about such issues when they are still young. Such issues should not be shamed or judged as non–scientific or professional materials. The molecular biology tools were widely involved in clarifying different types of biological mechanisms in our bodies such as: the cell cycle, DNA repair genes, the role of the inheritance factors in our health, the importance of the protein 3D structure, the effect of FRs and, oxidants in our macromolecules, the roots of cancer and, the different mechanisms associated with it, and, many others. Some of them were described in more detailed than the others in this review. However, a hidden line connecting all those things together was touched through this long article. It is the "*Inevitability of Balanced Lives*". Aiming that this review will be read by specialized and, non–specialists, I had simplified my scientific words in many parts to make this review readable. Back to the "*Inevitability of Balanced Lives*" we could sense it in every example that was described in this review. Might be the only example given from prokaryotes look apparently to be odd. In fact not. *E. coli* XL1 Red is a sick bacteria have three impaired DNA repair genes. It is sick bacteria. If we give it Food and, allow it to do continuous replication, any gene –it could be carrying– will be a subject to mutation. If such gene is carried in extra–chromosomal mobile elements such as a plasmid, the condition will be worse. Why? This is because during each cell division the strain will duplicate its content for two copies. However, the extra–chromosomal element will be multiplied until about 100 copies (in some plasmids). This will put such mobile genetic material under more chances to give us more mutation. If one of the genes carried by such plasmid is a subject of expression, mutation rate is expected to be even higher. In our case, we will be the XL1 Red if we are sick, and, the gene on a certain plasmid will be the tissue or the organ, which is under stress due to the missus. It is clear that this part (of our bodies) will be a subject for an extra–deterioration. When we are sick or old we should be wiser. Youths should prepare themselves for the time they will be old. They should avoid their bodies from extra use or misuse. We should react naturally, avoiding stress, anger, excessive work, control our Food amounts etc. In other simple words, we should not exhaust ourselves with many things. Food could eliminate most of the deficiencies in our bodies by supplying them with nutrient are missing or could not synthesize. "*One should control his own desires and, the desires for others; spreading clear knowledge and, advices since protection is more useful than living long painful lives*

even in the presence of the many intelligent drugs that were discovered". *The author*

CONFLICT OF INTERESTS

The author confirms that there is no conflict of interest

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ABOUT AUTHOR

Associate Prof. AMRO ABD-AL-FATTAH AMARA *is working in the field of molecular microbiology and, biotechnology. He works in the protein research department in Mubarak City for scientific research and, technological applications. He is interested in linking science to the real life to find simple solutions for problems.*