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The Genotoxic Damage and Diseases

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ABSTRACT

The genotoxic damage generally refers to the chromatin or DNA damage, mainly including the gene mutations and chromosomal aberrations. A large number of reports have suggested that the cancer is associated with the gene mutations and chromosomal aberrations, and thus it has been a focus of research. Today new insights are proposed by analyzing relevant literature, suggesting that the cancer is not caused by the gene mutations and chromosomal aberrations, but by the regulatory dysfunction of gene expression resulted from the nuclear damage, among which, the gene mutations and chromosomal aberrations are only an accompany phenomena also resulting from the nuclear damage. The gene mutations generally do not cause diseases, but if they do, they mainly cause the single-gene diseases. The chromosomal aberrations usually refer to the abnormalities in chromosome structure and number, often leading to cell death or inducing various chromosomal diseases. Some chronic refractory diseases, such as the cancer, Alzheimer's disease, degenerative diseases, are probably not caused by the gene mutations and chromosomal abnormalities, but rather by the abnormal regulation of gene expression and the dysfunction of DNA transcription-protein synthesis resulted from the nuclear damage. These diseases are all the diseases of nuclear dysfunction and collapse of differentiation.

Keywords

Gene mutation, Chromosomal aberration, Nuclear dysfunction, Nuclear damage, Regulation of gene expression, Disruption of differentiation state, Functional gene, Sealed gene.

Introduction

he gene mutations originally referred to the changes in protein-coding sequences, but later came to refer to alterations in the entire chromosome DNA sequence. The chromosomal aberrations usually refer to the structural and numerical anomalies of chromosomes. There is no clear boundary as to how many base changes are considered a gene mutation or chromosomal aberration. Sometimes, a change of several or dozens of bases is still regarded as a gene mutation, while some micro-deletions and micro-repeat sequences involving only a few bases are also called chromosomal aberration. Some literature even considers that the broad-sense mutations include both chromosomal aberrations and gene mutations, while the narrow-sense mutations refer only to point mutations [1]. Some literature directly refers to both as genetic changes or reduced genomic stability [2,3]. The gene mutations often lead to hereditary diseases, such as hemophilia, thalassemia [4,5]. The chromosomal aberrations mainly cause the chromosomal diseases and birth defects [6,7]. There are numerous reports have suggested that the gene mutations and chromosomal aberrations are associated with the cancer [8,9]. Now studies show that the gene mutations and chromosomal aberrations are also associated with the chronic and refractory diseases such as the aging [10,11], hypertension [,12,13], diabetes [14], Alzheimer's disease [15,16], degenerative diseases [17-19] and so on. In fact, the gene anomalies only represent the abnormalities in one peptide chain or one protein. Not all gene mutations can cause diseases, and if they do, mainly lead to the single-gene diseases. For instance, p53 is the gene with the highest mutation rate in cancer, but it is only in 50% of tumor patients [20,21]. The nucleophosmin gene mutations occur in only 30% of AML patients and most of them have a normal karyotype [22]. The relationship between the chromosomal aberration and cancer is also unclear, for example, only a portion of acute lymphocytic leukemia cases are Ph+, and a minority of follicular lymphomas are associated with the t(14;18) translocation [23-25]. It is evident that whether the gene mutations

and chromosomal aberrations can cause diseases and what kind of diseases they can cause is also related to the factors such the gene type, gene functional status, type of mutation/aberration, and cell type. The following is an analysis of the differences between the gene mutations and chromosomal aberrations and their pathogenicity.

Gene Mutation

A gene usually refers to a protein-coding sequence, mainly including exons, introns, and regulatory sequences. Among these, only the exons are the coding sequences for polypeptide chains or proteins. The regulatory sequences also include the promoters, enhancers, and silencers [1]. DNA sequences that encode functional RNAs such as tRNAs and rRNAs are sometimes also considered genes. The human genes are discontinuous and can even overlap with each other. The human genes are generally single-copy, but tRNA and rRNA encoding genes are multicopy. The gene mutation refers to changes in the composition or sequence of gene bases, and is divided into base substitution mutations and frame-shift mutations according to the mode mutation. The former, also known as a point mutation, refers to the replacement of one base in a DNA molecule with another; the latter refers to the insertion or deletion of one or more bases in a DNA molecule, resulting in a shift in the coding sequence [1,26]. The gene mutations are classified into synonymous mutations, missense mutations, and nonsense mutations based on the results of the mutations. A synonymous mutation refers to a change in base of DNA that does not alter the encoded amino acid due to the degeneracy of the codon. Since it does not affect the composition and order of amino acids in the peptide chain, the gene products (proteins) before and after mutation are the same, namely, no mutation effect has occurred. The missense mutations refer to the base changes that alter the composition and sequence of amino acids in the polypeptide chain, leading to abnormalities in the structure and function of the protein [27,28]. For example, a base A in the normal human hemoglobin gene mutates to U, causing the sixth glutamic acid in the hemoglobin β to mutate to valine as a result of the sickle cell anemia [29,30]. But if the amino acid that has undergone a change is not in a functional domain, it may not affect the function of the protein; this is referred to as a neutral mutation, and is also one of the missense mutation. A nonsense mutation refers to a codon that originally codes for an amino acid being mutated into a stop codon, causing the synthesis of the peptide chain to terminate prematurely and producing a peptide fragment without biological activity.

Chromosomal Aberration

The chromosomal aberrations include structural and numerical anomalies. The structural abnormalities mainly include deletions, duplications, translocations, inversions, dicentric chromosomes, ring chromosomes, isochromosomes and so on. The numerical abnormalities mainly include euploidy and aneuploidy. The euploidy refers to an increase or decrease in the number of chromosome sets that is a multiple of the normal haploid number, while the anuploidy refers to an increase or decrease in the number of chromosomes that is not a multiple of the normal haploid number, that is, the number of chromosomes has increased or decreased by one or more; such cells or individuals are referred to as aneuploids [27]. The chromosome fragments, micro-bodies, acentric rings and fusions, are all results and manifestations of the chromosomal aberrations. There are more and more reports about the microdeletions and micro-duplications today [28-30]. The aneuploids commonly include the monosomics, nullisomics and trisomics. Most human autosomal monosomies die in the embryonic period, and survivors are mainly Turner syndrome (45, X) [31,32]. Both homologous chromosomes of a pair are missing in a deficiency cell and the individuals of nullisomics are difficult to survive. The trisomic cells have an extra copy of a particular homologous chromosome. The trisomic individuals are often viable, such as the patients with Down who have an extra copy of chromosome 21 [33,34], and the patients with Klinefelter syndrome who have an extra X sex chromosome [35,36]. The number of copies of a particular homologous chromosome in a polyploid cell is more than three.

Distinction Between the Gene Mutation and Chromosomal Aberration

The gene mutation generally refers to a change in one or a few bases in the DNA sequence, and is defined in terms of the linear structure of the DNA. The changes are small in scope, not involving histones and the pentose phosphate backbone, and usually affect only one gene where the base change occurs. The gene mutations generally do not affect the structure and activity of chromatin [22]. The chromosomal aberrations generally refer to the changes in the secondary and tertiary structures of chromosomes, often accompanied by change of the pentose phosphate backbone and histones. The changes are large in scope and involve alterations in large segments or multiple segments of DNA sequences. The chromosomal aberrations often change the overall structure and packaging state of chromosomes, affect the functional activity of chromatin, impact replication, transcription, pairing, and so on. The chromosomes that have not undergone structural variations and chromosome regions without base changes may also be affected, often leading to instability of the genome [18,19].

The gene mutations and chromosomal aberrations often occur and coexist, both being the result of chromosomal damage, with the same or similar causes, of which are caused by the radiation, viruses, and various teratogenic and mutagenic compounds, and are all repaired by the same repair system of DNA damage [37-40]. If the damage is minor, it only involves the linear structure of DNA, changes only a few bases, and affects only one gene, it is a gene mutation. If the damage is severe, being accompanied by changes in the phosphopentose backbone, affects the structural activity of chromatin, and involves large number of genes, it is a chromosomal aberration.

Gene Mutation and Diseases

Effects of Different Types of Mutation in One Gene on Human Health

Whether a gene mutation affects health and the extent of the

impact depends on various factors such as the type of mutation, the mutated gene, the location of the mutation in chromosome, and the type of cells. The same gene can undergo different types of mutations, and the impact of different types of mutations on human health can vary greatly, from no effect to diseases or even death [20-22]. The synonymous mutations do not change amino acids, do not affect the structure and function of proteins, and therefore do not affect human health or cause diseases. Although neutral mutations change amino acids, they do not affect the function of proteins and thus are generally not pathogenic [1]. The gene exon mutations probably cause disease, but the intronic mutations generally do not affect the structure and function of proteins and are not pathogenic [41]. Mutations in gene regulatory sequences can affect gene expression and regulation (affecting gene switches) but the probability is low [42]. The nonsense mutations may reduce the amount of protein, but the homologous cells can increase synthesis to compensate. The missense mutations that may affect protein function can have two consequences, that is, gain or loss of function; the former leading to human evolution, the latter leads to loss of gene function, often causing Mendelian diseases [43,44]. The genes encoding tRNA and rRNA are highly repetitive, and even if individual genes mutate, it will not affect the synthesis of proteins, let alone function of cells and the survival of humans. Protein-coding sequences account for only 1-1.5% of the DNA, while non-gene-coding sequences account for more than 90%. Mutations in this part of the DNA sequence generally do not affect the function of proteins and do not cause diseases [1,27]. It is apparent that different types of mutations can have a wide range of effects on protein function, but most have no effect and are not pathogenic. But any mutation will increase genetic polymorphism, and some mutations may change the immunogenicity of proteins, increasing the susceptibility to disease [45].

Effects of Different Types Genes of Mutation on Human Health

The genes can be distinguished into functional genes and non-functional genes according to their functional status, and non-functional genes are mainly sealed genes. Although each cell in the human body contains a full set of genes, each cell selectively expresses a small number of genes; the expressed genes are the functional genes (dominant genes). The human genes are either continuously expressed, intermittently expressed, or never expressed throughout life. The genes that are never expressed throughout life are called sealed genes (dormant genes, recessive genes). The genes that are intermittently expressed belong to the functional genes when they are open; and are in a standby state when they are closed, namely, standby genes [46]. Thus the human genes have three states: open (expressed), closed (standby), and sealed (dormant). The closure is different from the sealing; the closure is temporary and can be reopened when needed; the sealing is to seal it up, never or lifelong not to express it. The genes in standby can be switched at any time under neuroendocrine regulation. The functional genes are mostly located in the euchromatin and active chromatin regions, the spare genes are mostly located in facultative heterochromatin regions, and the sealed genes are mostly located in constitutive or structural heterochromatin regions. The functional gene mutations may affect cell function, while the sealed gene mutations generally do not affect cell function and are not pathogenic. For example, the mutations in the hemoglobin gene can affect the function of red blood cells, leading to thalassemia and sickle cell an [47,48]. The mutations in the hemoglobin gene of brain cells and skin cells do not affect the function of these two types of cells because the gene is sealed. Therefore, the gene mutations of different types have different effects on cells, and only the functional gene mutations will affect the cell function, while the sealing gene mutations generally will not affect the function of cells.

Not all mutations of the functional genes affect cell function, as mentioned above, it depends on the type of mutation. The synonymous and neutral mutations do not affect the cell function, and only part of the missense mutations (excluding the neutral mutations) affect cell function. From the gene itself, the intron mutations do not affect the cell function, the regulatory sequence mutations mainly affect the function of gene switches, and only the exon mutations may affect the cell function. The sealed genes usually do not affect the cell function or cause disease regardless of the type of mutation that occurs.

Effects of Different Types Cells of Mutation on Human Health

The cell mutations can affect the cell function and state of the organ in which it is located, but generally do not affect the function of other cell and organs, as they can be compensated by other cells. Only a large number of cell mutations can affect the functional state of tissues and organs, and affect human health. The same mutation in different cells can have different consequences; a mutation of the insulin gene that occurs in brain cells and skin cells is not pathogenic, it can trigger diabetes if it occurs in pancreatic islet cells. The gene mutations in somatic cells generally do not affect offspring, and mutations in germ cells also do not affect their own health [1]. The gene mutation and chromosomal aberrations in male sperm can be passed on to the offspring, and may also cause miscarriage, stillbirth, defects or congenital diseases. The egg DNA in female is sealed, generally does not undergo genetic mutations and chromosomal aberrations, and is not easily stamped into a mark, so it is not passed on to the future generations [27]. This also suggests that the information about the human experiences and physical changes in conquering nature may be engraved into the genes of the future generations through male sperm, that is, the human evolution is mainly achieved through men. This is not to say that women are not important, but more important, because the stabilization of the chromosomal genome is mainly done through women.

Effect of Mutations from Different Sources on Human Health

The gene mutations can be distinguished between inherited and acquired by source. The mutations inherited is brought about by germ cells, while the mutations acquired is caused by damage to adults or embryos. The mutations inherited often involve all cells in the body, that is, all cells in the body carry the same type of mutation in the same gene [5,49]. The acquired mutations generally

affect only a few cells, and the affected cells can die or survive the disease and become a pathological cell. But the effects on tissues and organs may be modest. The disease caused by the acquired gene mutations often requires multiple types of mutations in many cells and multiple genes. As mentioned above, whether a gene mutation causes a disease depends on the type of cell, whether it is a functional gene, whether it is a missense mutation, and so on. If it is a sealed gene mutation, it does not cause disease regardless of the type of cell or the type of mutation. If it is a functional gene mutation, but the occurrence of synonymous mutations and neutral mutations will not cause disease.

Brief Summary

Because the mutations in non-protein coding sequences, non-functional gene mutations (mainly seal genes), synonymous and neutral mutations in functional genes will not affect the cell function and human health, the gene mutations do not cause disease in most cases, and if they do, single-gene diseases dominate. This also suggests that talking about gene mutations must be clear about the gene of mutation, the type of mutation, the region of mutation in chromosome, whether it is a functional gene or a sealing gene, what kind of cell it occurs in, whether it is somatic cell or germ cell, whether it is inherited or acquired; Otherwise it might not mean much. Unfortunately, most of the existing literature has not clearly defined or explained the above contents, and blindly reporting mutation-causing-disease is not rigorous and may even be wrong. After all, the somatic mutations and germ cell mutations, inherited and acquired mutations, seal gene mutations and functional gene mutations, the consequences and outcomes are different.

Chromosome Aberration and Diseases

The chromosomal aberrations often involve many genes, including both the functional genes and sealed genes, and the expression of genes in regions that have not undergone aberrations can be affected. The chromosomal aberrations often lead to cell death, and a few cells degenerate into functionally defective cells, thus affecting human health [32]. A few cells with chromosomal aberrations probably do not affect the functional state of the organs, because they can be compensated by other cells. The chromosomal abnormalities generally only affect the function of the cell itself and the tissue and organs where it is located, and do not affect the function of other cells and organs. The chromosomal aberrations in somatic cells generally do not affect the offspring, while the chromosome aberrations in germ cells usually affect the offspring [23-25]. Therefore, whether male or female, the mutations and chromosomal aberrations from the somatic cells will not be passed on to the offspring. Since the male sperm are prone to gene mutation and chromosomal aberration, while the female egg DNA is in a sealed state and generally does not undergo gene mutation or chromosomal aberration; therefore, the germ cell mutation and aberration are mainly transmitted to offspring by males. The chromosomal aberrations can also be distinguished by origin as either inherited or acquired, the former being brought about by the germ cells, the latter being caused by the damage of adult and embryo. The aberrations inherited often involve all cells of the body, often give rise to a variety of clinical syndromes or disease complexes [33]. The aberrations acquired after birth generally affect only a few cells, and the affected cells can either die or survive with the disease. The chromosomal aberrations from the somatic cells mainly lead to cell death or become pathological cells, while the chromosomal aberrations from the germ cells mainly lead to miscarriage, defects and chromosomal diseases [34,35].

Both the Gene Mutation and Chromosomal Aberration Are Derived from the Nuclear Damage

Since the opportunity for rays and various carcinogenic compounds to directly interact with the chromosomes is limited, they usually first interact with water molecules to produce reactive oxygen and free radicals which then interact with the chromosomal DNA to induce gene mutations and or chromosomal aberrations [50,51]. Since the cell nucleus has a powerful free radical scavenging system, DNA damage repair system, and a system of maintaining the chromatin structure and activity, the gene mutations and chromosomal aberrations generally do not occur as long as the cell nuclear functions keeping normally. Therefore, the gene mutations and chromosomal aberrations are both results and manifestations of the nuclear damage and dysfunction. The cell nuclear dysfunction is also manifested in the destruction of cell differentiation status, changes in gene expression profiles, regulatory dysfunction of gene expression and obstacles in DNA transcription-protein synthesis. It can also affect the DNA replication in proliferating cells.

The function of the nucleus is mainly DNA replication, transcription, and ribosome synthesis. For non-proliferating cells such as the brain cells and heart muscle cells, since they do not replicate, the main functions of their cell nuclei are transcription and ribosome synthesis, both of which aim to synthesize proteins. Therefore, the damage to the cell nucleus of such cells mainly affects the function of DNA transcription-protein synthesis. Moreover, the conversion of chromatin structure activity in such cells mainly serves transcription. In many cases, the gene itself (gene structure) is normal, it's just that it can't be turned on (abnormality of gene switches) [52-54]. Therefore, there are two types of gene abnormalities, namely, the abnormal structure of gene (abnormal DNA sequence of gene) and abnormal switching of gene. The former is caused by the gene mutation and chromosomal aberration, while the latter is the abnormality of gene expression and regulation, mainly caused by the nuclear damage. The gene expression and regulation involve the chromatin structure activity, nuclear skeleton, histone, transcription factors and RNA polymerase, as well as the methylation and phosphorylation of DNA and histone, all of which depend on an intact nucleus. Therefore, the nuclear damage can affect the transcription, gene expression and regulation [55-57]. The profile of gene expression is created by the differentiation and cannot be changed. The nuclear damage can destroy the differentiation state, change the state and profile of gene expression, affect gene expression and regulation, and lead to the dysfunction of DNA transcription-protein synthesis; which also means that the genes that need to be expressed cannot be expressed, and genes that do not need to be expressed are expressed. That is, the functional genes cannot

be expressed and the sealed genes are restarted [58]. All kinds of functional activities of cells are carried out and completed on the basis of the differentiation, and the destruction of differentiation state will inevitably affect the function and biological behavior of cells. The proteins will continue to denature and aging while playing their functional roles, and the human body needs to constantly synthesize new proteins to supplement or replace them. Therefore, the protein synthesis and degradation are always in a dynamic balance [59]. The inability of functional gene expression and the dysfunction of DNA transcription-protein synthesis mean that the proteins needed by the human body cannot be synthesized, resulting in the degenerative proteins cannot be replaced. Therefore, the functional state of cells will be affected, and eventually the function of tissues and organs will decline, thus inducing various chronic and refractory diseases, such as the hypertension, atherosclerosis, diabetes, Alzheimer's disease, premature aging, degenerative diseases, autoimmune diseases, and so on [60-62]. If the dormant gene unseals and restarts on this basis, it will lead to cancer. These diseases are probably not caused by the gene mutations and chromosomal aberrations, but by the nuclear damage, disruption of differentiation, dysfunction of gene expression and regulation, and dysfunction of DNA transcription-protein synthesis. The nuclear damage is the link between genetic and environmental interaction, the so-called polygenic disease is not really caused by multiple genes, but caused by the dysfunction of gene expression and regulation.

Conclusions

In summary, a gene mutation generally does not cause diseases, if it does, mainly causes monogenic diseases. The chromosomal aberrations often lead to cell death, so they may not cause disease, if they do, mainly induce chromosomal diseases. The chronic and refractory diseases such as cancer, hypertension, atherosclerosis, diabetes, Alzheimer's disease, degenerative diseases, autoimmune diseases and premature aging are all caused by the nuclear damage, dysfunction of DNA transcription-protein synthesis, and belong to the diseases of nuclear dysfunction, that is, the diseases of differentiated collapse and decay. In the above chronic refractory diseases, the gene mutation and chromosomal aberration are only a concomitant phenomenon, both are the result and manifestation of the nuclear damage and nuclear dysfunction. The mechanism of these chronic refractory diseases should be discussed by analyzing the expression and regulation of gene, functional state and biological behavior of the cells with nuclear abnormalities resulting from the nuclear damage.

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