ScieniQ Publishers

Advance Medical and Clinical Research

Research Article

New insights into the complex diseases such as aging, degenerative disorders and cancer

Maojin Li

The Beijing Prevention and Treatment Hospital of Occupational Disease / Beijing Institute of Occupational Disease Prevention and Treatment, Beijing 100093, China.(180# Hanheyuan Minzhuanglu Haidian District, Beijing 100093, China.)

***Corresponding author**
Maojin Li . The Beijing Prevention and Treatment Hospital of Occupational Disease / Beijing Institute of Occupational Disease Prevention and Treatment, Beijing 100093, China.(180# Hanheyuan Minzhuanglu Haidian District, Beijing 100093, China.)

Received: 30 January 2026
Accepted: 05 February 2026
Published: 25 February 2026

Abstract
The complex diseases, such as the cancer, aging, hypertension, arteriosclerosis, diabetes, Alzheimer's disease, degenerative diseases, autoimmune diseases and so on, are the main diseases that threaten human life and health. The causes and mechanisms of these chronic and refractory diseases remain unclear, which makes them difficult to cure and often requires lifelong medication. Today, new insights into the mechanisms of these complex diseases have been put forward. These chronic refractory diseases are probably derived from the abnormal nuclear cells existing in human body for a long time, a kind of pathological cells or functional defective cells with nuclear abnormalities. The abnormal nuclear cells with a nuclear dysfunction and disorders of gene expression, usually unable to maintain a stable differentiation state (dedifferentiation). The nuclear abnormalities are derived from the nuclear damage caused mainly by the radiation, virus and various carcinogenic compounds. The cancer cell is probably derived from the reactivation of the dormant genes related to division and proliferation resulting from the nuclear damage. The so-called characteristics of cancer cells (shedding, metastasizing, immune-tolerant, uncontrolled by the body, etc.) are in fact the characteristics of abnormal nuclear cells. The human body produces abnormal nuclear cells all the time, and there are more of them as we age, so the incidence of the chronic refractory diseases increases with age. The so-called stem cells currently used in clinical therapy are probably abnormal nuclear cells resulted from the nuclear damage. The senescence and death is a special life phenomenon of human beings and multi cellular organisms.

Keywords: Abnormal nuclear cell; nuclear abnormality; functional gene; sealed gene; cancer; aging; stem cell; cell differentiation

Introduction
The causes and pathogenesis of the chronic refractory diseases, such as the cancer, hypertension, diabetes, arteriosclerosis, Alzheimer's disease, degenerative diseases, autoimmune diseases and aging are not clear, today. A large number of literatures have discussed the mechanisms of the diseases at molecular level; however no single gene or molecule has been satisfactorily found to explain the causes and mechanisms of the diseases [1-5]. The most studies didn't work out so well probably due to the researchers attempt to elucidate the mechanism of these diseases only by one gene or molecule that had been studied by them. The main reasons may be that such diseases are caused by multiple genes or molecules, and involved many complex molecular networks. The chronic refractory diseases, such as aging, cancer, degenerative diseases, are probably derived from the nuclear damage and/or the nuclear dysfunction [6-8]. The cancer is probably not caused by the gene mutation or chromosomal aberrations, but by the nuclear damage and changes in the state of cell differentiation leading to the reactivation of genes related to mitosis. In this paper, the pathogenesis of the diseases are analyzed and summarized from the whole cell nucleus or molecular networks, and some new viewpoints and hypotheses are put forward which may be making it more understanding.

The nuclear damage and the abnormal nuclear cells
The abnormal nuclear cells as a result of nuclear damage caused mainly by the radiation, virus and various carcinogenic compounds are a kind of pathological cells or functional defective cells existing in human body for a long time [9-11]. The cells usually have abnormal nuclei in morphology, structure and function derived from the damage of molecular adhesion, fracture, chemical modification and so on[6,7]. All molecules in the nucleus can be damaged, including the chromosomal DNA damage (i.e. chromosomal aberration) [12,13]. After nuclear damage, it is often unable to maintain stable differentiation state (dedifferentiation), resulting in nuclear dysfunction, gene expression disorder or abnormality [13,14]. The other organelles or molecules can also be damaged, but can generally be replenished, repaired, or replaced by re-synthesis as long as the nucleus is functioning properly. Therefore, the cell function mainly depends on the functional state of nucleus, and the latter is mainly reflected in whether the differentiation state is stable, whether gene expression and regulation are normal and smooth (Figure.1).

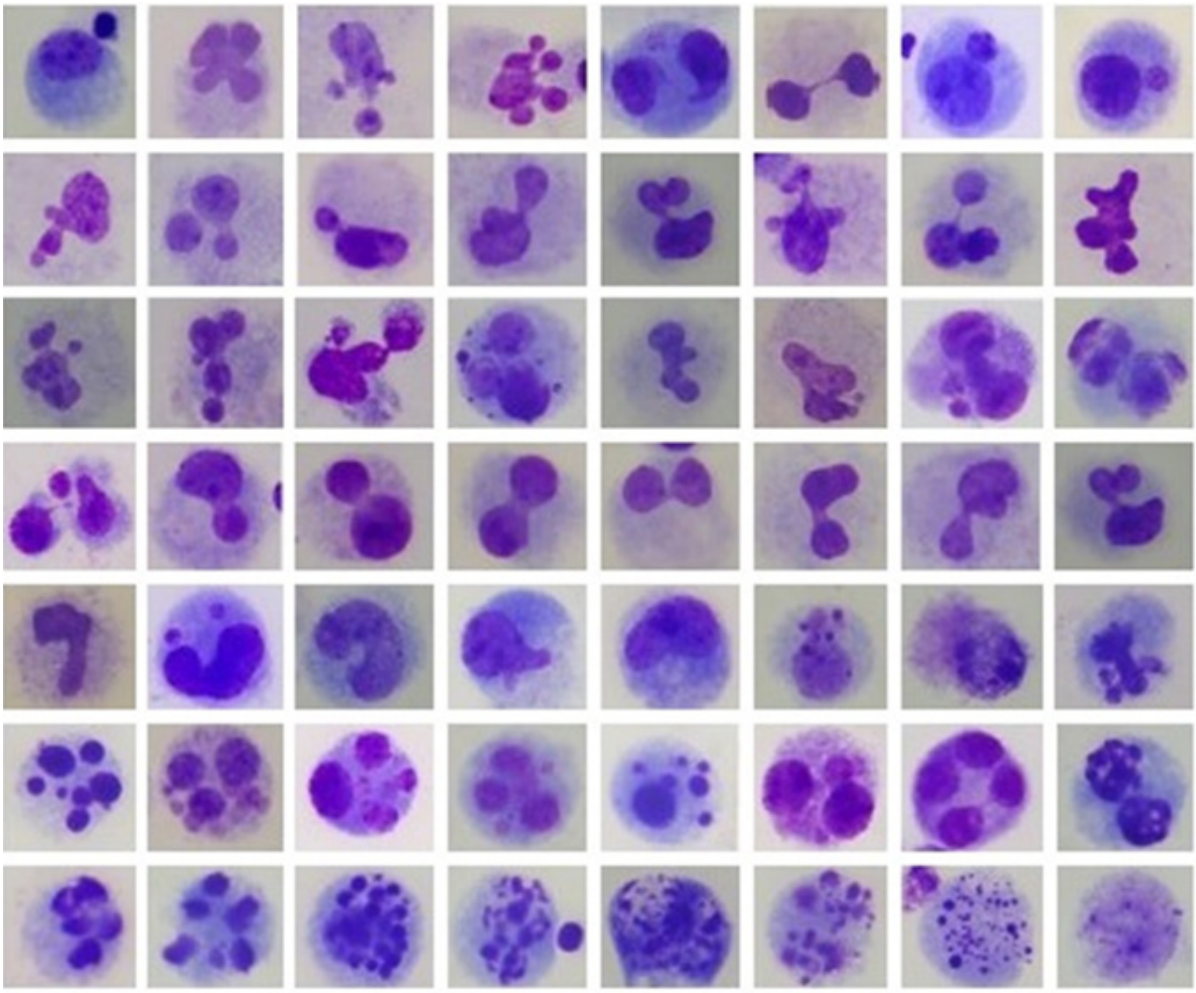

Figure.1 Abnormal nuclear cells resulted from the nuclear damage

The pathophysiological or molecular cellular mechanisms of cell nuclear damage

The cell nuclear damages result in disorders in the regulation of gene expression

The cell nuclear damage leads to dysfunction in gene expression regulation, that is, the genes that should be expressed fail to do so, while the genes that should not be expressed are expressed instead. Some genes in human body are continuously expressed, some are not expressed for a lifetime, and some are intermittently switched on and off [14,15]. Thus, a gene has 3 kinds of state: open/express, close/standby and seal/dormant. The close is only temporarily not expressed and can be opened when needed, whereas the seal is a state of never expressed again a lifetime (inactivated genes, recessive genes, sealed genes or dormant genes). Each cell contains a full set of genes, but only a few genes can be expressed. The genes in the open state are functional genes (FG), which generally play a role and are necessary for the normal physiological functions of the human body [16, 17]. On the contrary the non-expressed genes are generally unrelated to cell survival, function or role playing. The functional genes can be divided into three categories: genes related to cell survival (survival genes, SVG), genes related to cell role playing (role genes, RG), and auxiliary matching or functional support genes (helper genes, HG). The survival genes are related to cell metabolism and energy production, and mainly belong to housekeeping genes [16, 17]. The role genes are associated with undertaking specific functional tasks for a cell. The helper genes include the receptor signaling molecule genes, the adhesion molecule genes, the vector channel protein genes, chaperone protein genes and so on [18]. A role gene in one cell may be a dormant gene in another. For example, the insulin gene is a role gene in islet cells, but a dormant gene in brain and erythrocyte cells. The cell nuclear damage usually leads to the functional genes fail to express, sealed genes (SG) are reactivated, standby genes switch disorderly (Figure.2, 3).

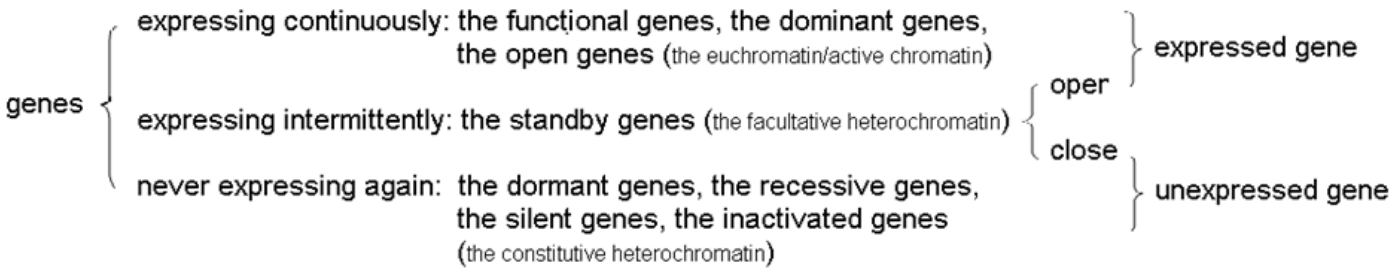

Figure.2 Genes can be classified into three categories based on their expression states.

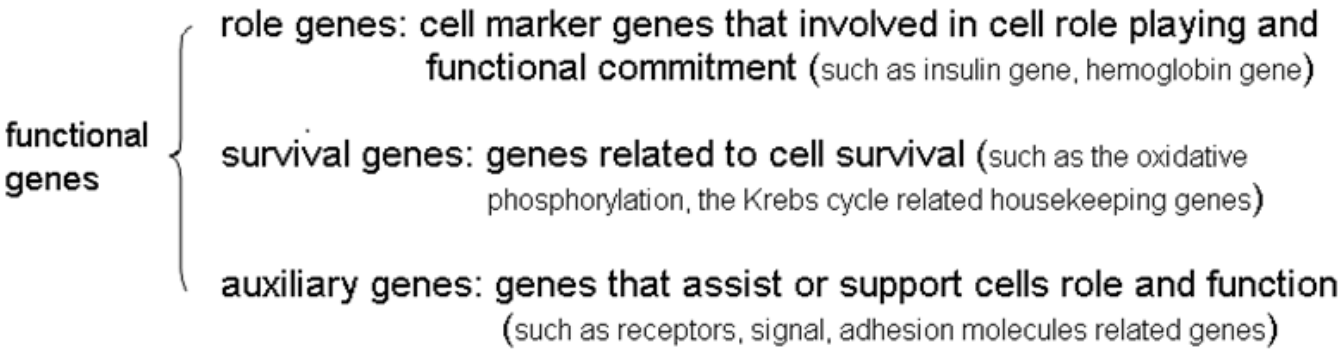

Figure.3 Functional genes can be classified into three types based on their functions

The cell nuclear damage disrupts the differentiation state and alters the gene expression profile

The nuclear damage leads to disorders of cell differentiation and gene expression. All cells in the human body come from a single cell, the zygote, and the process from the zygote to an adult cell is called differentiation. The differentiation is the process of reconfiguring the gene profile of expression in cells, and is reserving the functional genes and inactivating the irrelevant genes. The gene profile and cell type remain unchanged throughout life after cells are transformed into role functional cells, that is the differentiation state remain until the end of life [19,20]. The means of gene allocation or cell differentiation is selective gene expression, namely gene expression regulation. The regulation of gene expression involves numerous genes or molecules and many complex molecular regulatory networks as well as complex cell-cell interactions [21-24]. These molecules and molecular regulatory networks are generally transient, and most of them are disassembled and dissipated after gene configuration or cell transformation. There would be no human and multi cellular organisms without differentiation. Once a cell does differentiation, it is necessary to maintain the differentiation state stably. Only by maintaining the state of differentiation can cells play corresponding roles and undertake corresponding functional missions, and people can live a long and healthy life. The so-called maintenance of differentiation state refers to the timely expression of required genes (functional genes) and timely closure or inactivation of unwanted genes [18]. The cell nuclear damages disrupt the differentiation state and alter the gene expression profile, leading to expressional disorders of the functional genes and reactivation of the sealed genes (Figure.4).

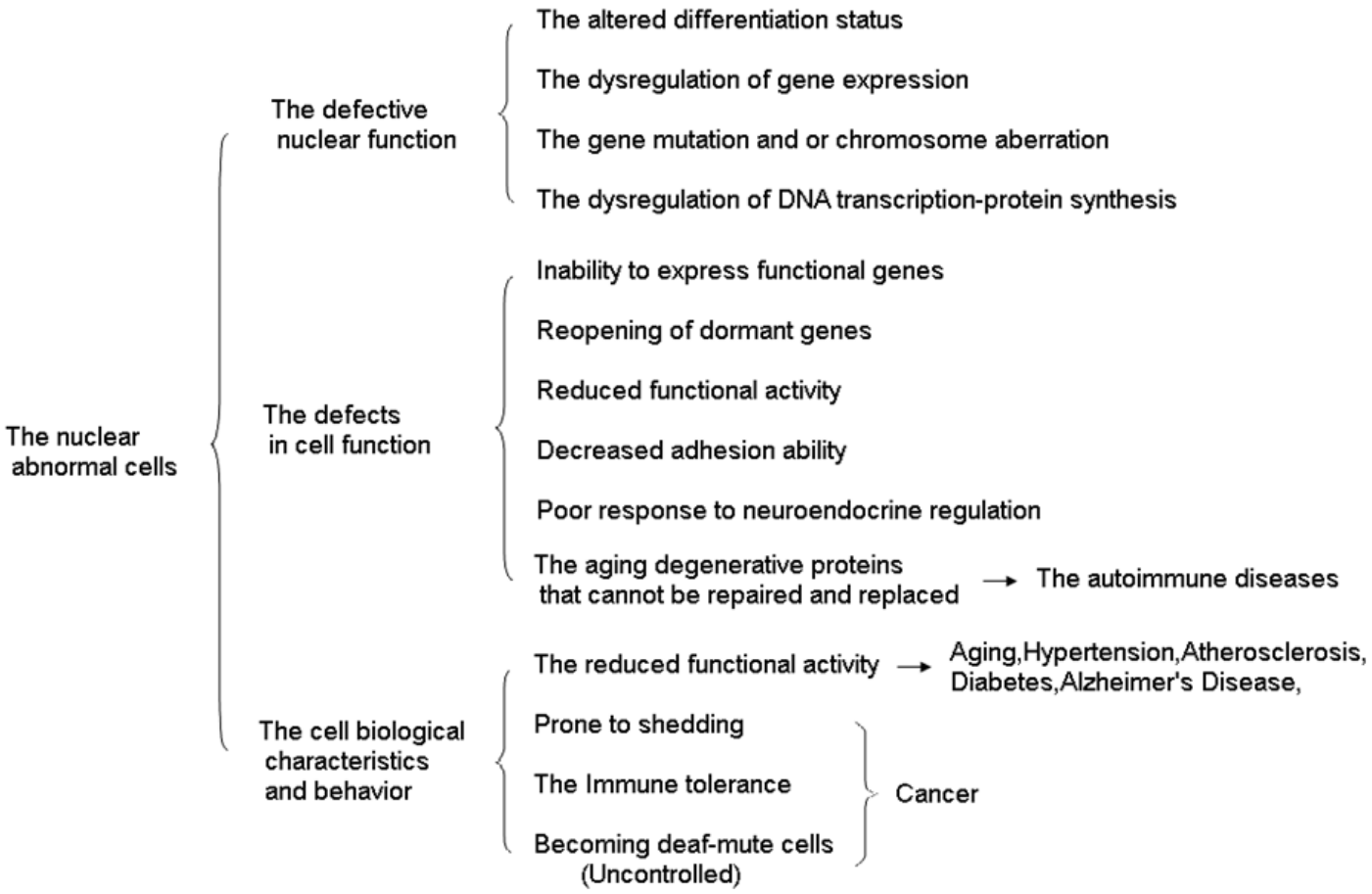

Figure.4 Biological characteristics and behavior of the abnormal nuclear cells.

The cell nuclear damage alters the programmed and regulatory patterns of gene expression

The cells always express as few genes as possible, that is, only a few useful or necessary genes can be expressed. More genes expressing mean that the number of molecules involved in regulation will increase exponentially, and the involved regulation networks of gene expression and its complexity will also greatly increase, and the involved molecular regulation network may also conflict [25]. This can easily lead to molecular malfunctions, resulting in regulatory failures or paralysis and energy depletion. To inactivate unrelated genes is to reduce the number of molecules and molecular networks involved in regulation, simplify the regulation process and steps, and make regulation programmed, patterned and simplified. It can prevent from too much regulation and disorder, avoid molecular network conflict, and reduce energy consumption. Therefore, reducing the number of expressed genes can provide sufficient space for necessary regulation of cells, provide a stable molecular environment for cell survival and role function, and make gene switching smooth, orderly and fast. This is necessary for cells to undertake a certain functional mission or play a good role. The human cells can not differentiate again due to there is no molecular cell environment for differentiation in adult [26-28].This programmed, patterned and streamlined process of gene expression will be disrupted by damage to the cell nucleus.

The cell nuclear damage disrupts the differentiation state but does not cause cell inverse differentiation

The contradiction of replication and transcription is the fundamental reason why human cells cannot reverse differentiate. The human cells are differentiated cells and must first turn on genes related to division and proliferation in order to reverse differentiate into stem cells. As a cell starts division and proliferation, which means DNA must replicate, namely DNA must be opened into a single strand, and replication-related enzymes, regulatory proteins and DNA polymerase must be bound to the DNA strand [29-32]. This inevitably affects the proximity and binding of transcription-related regulatory proteins and RNA polymerases. At the same time, the molecular regulatory network related to replication and transcription is probably conflict. The cell division and proliferation also means that chromatin must be packed, compressed and spiralized to form heterochromatin or chromosomes [33,34], which inevitably affects transcription. During transcription, transcription-related regulatory proteins and RNA polymerases bind to DNA [35,36], which also affect replication and hinder the formation of chromosomes. It can be seen that replication and transcription are contradictory in differentiated cells, that is, DNA cannot serve as a template for transcription during replication, and DNA cannot replicate or form chromosomes during transcription. Therefore, it is impossible for differentiated terminal human cells to reverse differentiate into stem cells.

The paradox of replication and transcription also means that the functional genes must be turned off temporarily when cells proliferated, because they cannot be transcribed during replication. Turning off a role gene means that the cell temporarily loses its role. If the receptor signaling molecule gene is turned off, it means that the cell loses its response to neuroendocrine and becomes deaf and dumb, not under the control of the body. If the gene of adhesion molecule is turned off, it means that the cell detaches from the original tissue and becomes a stray cell, namely shedding, invasion and metastasis [13, 37]. If all cells in an organ or tissue undergo reverse differentiation, all cells will be shed, which means that the organ or tissue disintegrates into a homogenate. If the human differentiated cells

can really become stem cells, it is harmful to human body, either become cancer cells or turn into cell homogenate.

The so-called "stem cells" currently used in clinical treatments are probably abnormal nuclear cells derived from the nuclear damage

Whether cells can differentiate depend on the surrounding molecular and cellular environmental conditions, while cells themselves are difficult to differentiate. The current so-called stem cell therapies attempt to change one type of differentiated cell (such as liver or bone marrow hematopoietic cells) into another type (such as brain cells) by reverse-differentiating into "embryonic stem cells" and then differentiating into target cells [38,39]. Both differentiation and reverse differentiation are impossible because it involves a large number of molecules and complex molecular regulatory networks that no longer exist in adults. The question of stem cell is really a question of regulation of gene expression, and if we can master the regulation of gene expression we can make any cell we want, any cell is a stem cell. For one type of cell to become another, the gene expression profile must be identical, including role-function genes, receptor signaling genes, adhesion molecule genes and so on. However, the so-called "stem cells" in current clinical treatment only express several role proteins of the target cell, far from changing the gene expression profile [40,41]. Injection of such cells into the lesion site not only fails to treat the disease, but also cause inflammatory reactions and even cause cancer [42,43]. And these "stem cells" are unlikely to be redifferentiation into functional cells, let alone to form organs and tissues. These cells are not real stem cells, but are a type of abnormal nuclear cell with nuclear damage induced by drugs or chemicals.

Discussion on the pathogenic mechanisms of cell nuclear damage

The cell nuclear damages underlie the chronic refractory diseases

The changes in cell differentiation and/or disorders of gene expression resulted from the nuclear damage are the root cause of aging and the chronic intractable diseases such as the cancer, hypertension, Alzheimer's disease and so on. All cells of the human body can be damaged and result in nuclear dysfunction. In the case of the brain cell nuclear damage and dysfunction, the failure of functional gene expression will affect the maintenance of resting potential and synaptic growth. Susceptible to Alzheimer's disease, Parkinson's syndrome and other diseases, manifested by brain atrophy, memory loss, slow reaction [44]. The vascular endothelial nuclear dysfunction will affect the elasticity and contractile function of vascular wall, leading to hypertension and atherosclerosis [45]. At the same time, it will also affect capillary regeneration and the establishment of microcirculation, making organs and tissues in a long-term state of micro-ischemia. In order to increase perfusion pressure, blood pressure has to be increased. The cell nuclear dysfunction related to the gastrointestinal tract will affect digestion and absorption functions, appear in-appetence, dyspepsia, gastrointestinal paralysis and other symptoms. The skin nuclear dysfunction can lead to hair loss, white hair, vitiligo and other diseases. In the case of immune nuclear dysfunction, patients are prone to infection and cold [46]. If it is abnormal protein degradation related enzymes, due to the abnormal structure of the protein cannot be degraded and cleared in time, the immune system will be mistaken for foreign antigens and attack, resulting in autoimmune diseases; such as psoriasis, lupus erythematosus, glomerulonephritis and other diseases [47,48]. The nuclear dysfunction occurs in most cells of the human body, which will lead to senescence and death. The abnormal expression of genes that do not need to be expressed (genes that are inactivation) can induce cancer. Aging is derived from the collapse of cell differentiation caused by the nuclear damage. The nuclear damage is inevitable due to people expose to radiation and various cancer-causing teratogenic compounds all the time. The human body produces abnormal nuclear cells all the time, and there are more of them as we age, so the incidence of chronic and refractory diseases such as cancer, hypertension and Alzheimer's disease increases with age [37]. Most of the cells of the elderly have metamorphosed into abnormal nuclear cells, while the normal cells are less and less, and the function of each organ has declined, resulting in aging and even death (Figure.5).

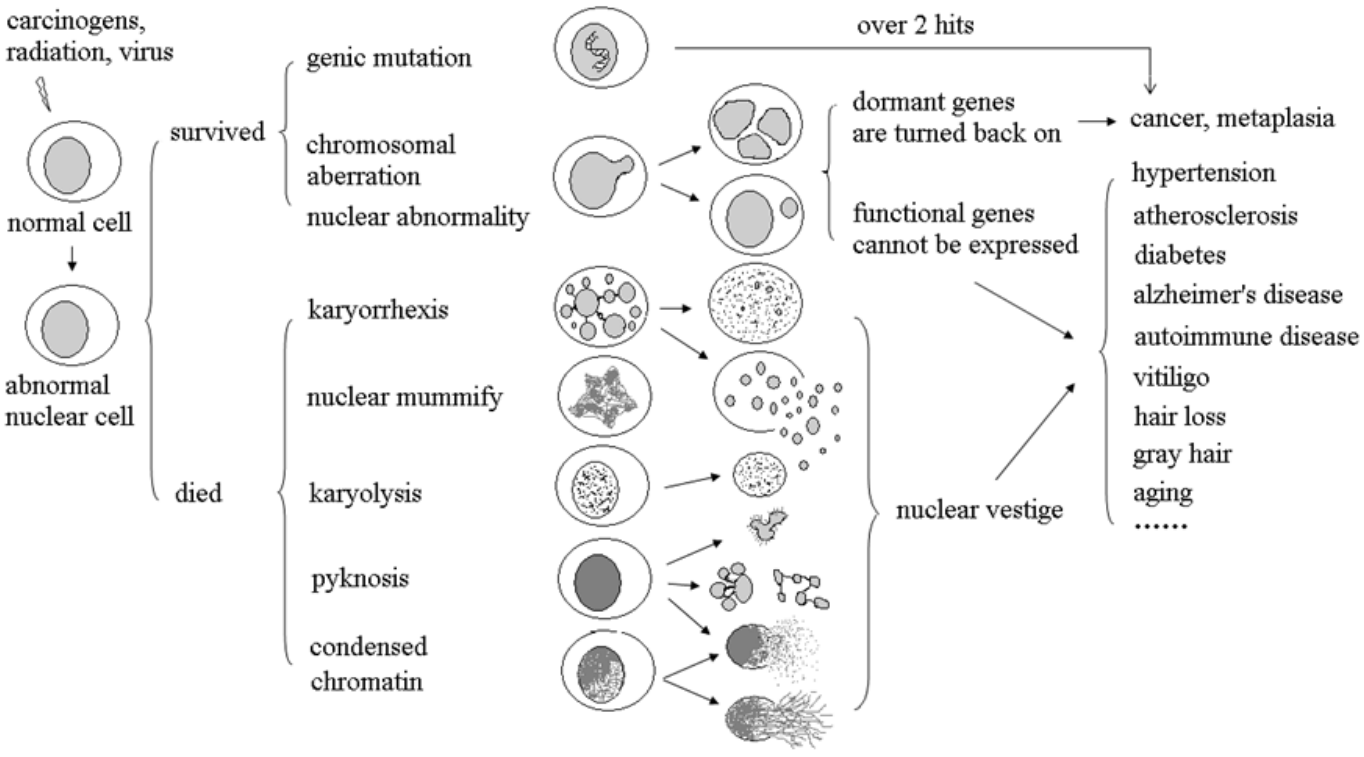

Figure.5 The chronic intractable diseases probably derived from the nuclear damage.

Life cycle

Life is a cycle. For example, the molecular biology: virus - replication - virus; the unicellular organisms: cell - division - cell; the multi cellular organisms such as human: sperm ovum -- fertilized ovum – embryo (differentiation) -- human (aging and death) -- sperm ovum [22, 49,50]. The viruses complete their life cycle by replication; while the unicellular organisms complete their life cycle by division, and the replication is the prerequisite of cell division. The life cycle of multicellular organisms is completed by differentiation and sex differentiation, and the replication and division are the prerequisite of cell differentiation [51,52]. Thus, the cycle body of molecular and unicellular organisms is itself, while the life cycle of multi cellular organisms requires cell differentiation and sex differentiation. The cell of unicellular organisms is itself an organism that will continue to divide as long as it is nourished, and its end point of growth is to divide again, not to die. The cell of multi cellular organism is a differentiated cell or functional cell, generally does not divide, the final result can only be aging and death [53,54].The life cycle originates from the function of replication and transcription of nucleic acid as well as the function of division and differentiation of cells. The nucleic acids build not just individual people, but entire life cycles. The human, as a kind of organism, refers to the whole life cycle, including sperm, egg, zygote, embryo, adult (person). As a biological individual, man is only a link or step in the life cycle. The sex differentiation is necessary and part of the life cycle of multicellular organisms (Figure.6).

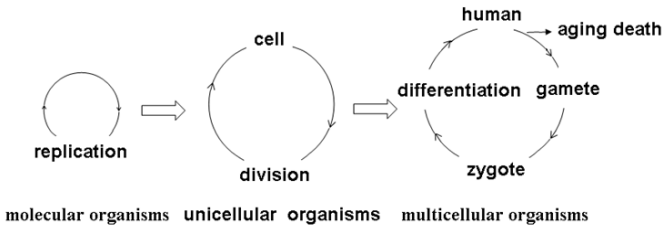

Figure.6 The life cycle

The senescence and death is a special life phenomenon of human beings and multicellular organisms

The birth, aging, illness and death are the inevitable result of differentiated cells and the final destination of human beings and multi cellular organisms [49, 51]. The differentiation creates the cycle of life, and also determines how long we live and how we age and die. The fundamental reason is that the multi cellular organisms still rely on cells to reproduce, so they must throw away a skeleton every cycle and rebuild a new organism through differentiation and sexual differentiation. Man, as an individual creature, is just a skeleton had to build in order to carry out the life cycle. Each cycle, first set aside a part of the cells as fire-seed, namely reproductive cells, other cells into biological individuals, and the formation of male and female, to reproduce offspring to complete the life cycle [22,37]. All living phenomena arise from the replication and transcription which derive from the molecular structure and natural properties of nucleic acids. The human beings are derived from the nucleic acid and subject to nucleic acid. It is nucleic acid that controls human beings rather than genes.

Different living things with different patterns of death

To talk about life, we must first define death. There are 4 ways for death of a cell from the multicellular organisms: ill death, sudden death (acute death), apoptosis and aging death; but only 2 ways for that from the unicellular organisms. The ill death is caused by the disease or hunger, malnutrition or vitamin deficiency. The sudden death is a violent death or sudden disappearance under the action of strong physical and chemical factors. The apoptosis is programmed cell death, generally caused by weak injury factors [55,56]. The aging death is a natural death that occurs without obvious injury or causative factors. There is no death of disease or aging in molecular organisms. The unicellular organisms can die of disease or violent death, but there is no death by senescence. In addition to disease and violent death, the multi cellular organisms can also have senescence and death. Thus, there are 3 ways for death of human beings: ill death, sudden death (acute death) and aging death (Figure.7).

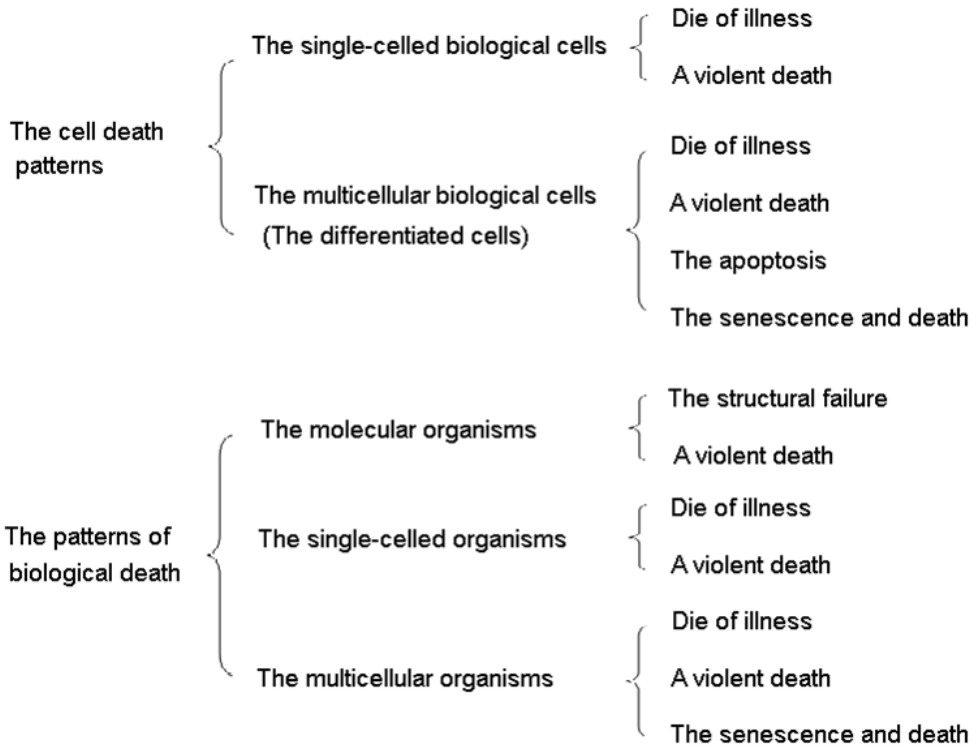

Figure.7 There are 4 death patterns for the living things

The deficiencies of the current theories on aging

There are dozens of theories about aging, the most popular ones are the limit of cell division theory and telomerase theory [57,58]. These theories can be roughly divided into three categories. The first category holds that the reduction or cessation of cell division and proliferation ability is the fundamental cause of human aging, such as cell division limit theory, telomere theory, aging genetics theory and DNA synthesis inhibitor theory [59,60]. This confuses human differentiated cells with unicellular organisms, since division and proliferation are characteristic of unicellular organisms, whereas the human cells are differentiated or functional cells. For example, it is normal for terminally differentiated cells such as brain cells and heart cells not to divide. If brain cells continue to divide, they will not prolong human life, but accelerate human death. There are 200 types of cells in the human body, and the constant division of one type of cell does not necessarily prolong the human lifespan. The red blood cells have a life span of 120 days, and if they don't die, it will accelerate human death. Thus, non-division does not mean that the cell life is short, let alone that the cell is dead. The second kind of senescence theory believes that human aging is caused by cell damage. For example, somatic mutation theory [61,62], collagen cross-linking theory, carbonyl poisoning theory, neuroendocrine theory [63], mitochondrial aging theory, immune function degradation theory. These are the results or manifestations of nuclear damage and senescence. The third type is free radical accumulation theory, the body has a strong free radical scavenging system, generally will not accumulate (Figure.5, 6, 7).

The human lifespan depends on the function of tissues and organs, depends on the collection of various cells, the longevity of a cell does not necessarily prolong human lifespan. Different cells in the human body have different differentiation states, different functional roles and different life spans. Some cell continue to divide, some no longer divide all their lives, some live for a few days, and some can live for dozens or hundreds of years [37]. In a word, the human body cells should split splits, shouldn't split don't split, the longevity is longevity, the short life is short, that be damned to die, the live lives; only in this way can man live a long and healthy life. Therefore, the abnormal cell differentiation state and failure of expression of required genes (the functional genes) caused by nuclear damage is the root cause (Figure.5, 6, 7).

Cancers are probably derived from the cell nuclear damage

The cancer cells are caused by changes in cell differentiation state (de-differentiation) caused by the nuclear damage, and reactivation of genes related to division and proliferation [64,65]. Due to the contradiction of replication and transcription, the functional genes cannot be transcribed once differentiated cells resume division and proliferation. The cells will temporarily lose its role function if the role gene is not expressed; If the receptor signal molecule gene cannot be expressed, the cell will be poor or slow response to the neuroendocrine regulatory signal, become deaf and dumb cells, that is, not controlled by the body; If the adhesion molecule gene is closed, it means that the cell separates from the original tissue and becomes stray cells, namely shedding, migration and metastasis [66, 67]. If all cells in an organ or tissue undergo reverse differentiation, all cells will be shed, which means that the organ or tissue disintegrates into a homogenate. In vitro the cultured cells will also temporarily shrink into a ball when dividing, and then stick to the wall of bottle after dividing. The abnormal nuclear cells derived from the normal human cells are immune tolerant and cannot be removed because they do not express allogenic proteins. The alpha-fetoglobulin, carcinoembryonic antigen, gastric mucosa and intestinal metaplasia are results of abnormal opening of the dormant genes, resulting from the nuclear damage.

The cancer is generally believed to be associated with gene mutations and/or chromosomal aberrations [68,69]. In fact, nuclear skeleton, spindle, histone, related enzymes, abnormal methylation of histone, abnormal methylation of DNA and abnormal transcription factors can also cause cancer [70,71]. Any damage to biological macromolecules in the nucleus may cause cancer, that is, cancer is caused by damage to the entire nucleus. The gene mutations and/or chromosomal aberrations are generally not caused by direct action of rays and carcinogenic compounds on chromosomes, but by first acting on other molecules, mainly water molecules producing free radicals, and then indirectly damaging chromosomes. The nucleus has a strong system of free radical scavenging and DNA repair, as well as a strong repair and maintenance system of chromosome structure [72,73]. Therefore, genetic mutations and/or chromosomal aberrations generally do not occur when the nucleus is functioning properly. The gene mutation and chromosomal aberration are actually the result and expression of nuclear damage(Figure.4, 5).

In a word, the cancer cell is derived from the reactivation of the dormant genes related to division and proliferation resulting from the nuclear damage. The so-called characteristics of cancer cells (shedding, metastasizing, immune-tolerant, uncontrolled by the body, etc.) are in fact the characteristics of abnormal nuclear cells.To re-block the several genes in abnormal nuclear cells that initiate mitotic proliferation is the most ideal measure for cancer prevention and control.

Acknowledgments and Funding

I thank my director, the professor Rouli Zhou, for providing my lots of meaningful thoughts. There was no Funding.

Conflict of Interest Statement

The author declare no conflicts of interest.

Data Availability Statement

The data that support the opinions of this review are openly available.

Institution and Ethics Approval

There were no human subjects in the study, the data were from the literature, and were publicly available.

Transparency Statement

I confirm that the manuscript is honest, accurate, and transparent, no aspects of the study have plagiarized.

Reference

1. Siegel RL, Giaquinto AN, Jemal A. (2024) Cancer statistics, 2024[J]. CA Cancer J Clin. 2024, 74(1):12-49. DOI: 10.3322/caac.21820. Erratum in: CA Cancer J Clin. 74: 203. PMID: 38230766. https://pubmed.ncbi.nlm.nih.gov/38230766/.
2. Falk JM, Froentjes L, Kirkwood JE, Heran BS, Kolber MR, Allan GM, Korownyk CS, Garrison SR. (2024) Higher blood pressure targets for hypertension in older adults [J]. Cochrane Database Syst Rev. 12: CD011575. doi: 10.1002/14651858.CD011575.pub3. https://pubmed.ncbi.nlm.nih.gov/39688187/.
3. Tegegne BA, Adugna A, Yenet A, Yihunie Belay W, Yibeltal Y, et al. (2024) A critical review on diabetes mellitus type 1 and type 2 management approaches: from lifestyle modification to current and novel targets and therapeutic agents [J]. Front Endocrinol (Lausanne). 15: 1440456. doi: 10.3389/fendo.2024.1440456. https://pubmed.ncbi.nlm.nih.gov/39493778/.
4. Beata BK, Wojciech J, Johannes K, Piotr L, Barbara M. (2023) Alzheimer's Disease-Biochemical and Psychological Background for Diagnosis and Treatment [J]. Int J Mol Sci. 24: 1059. doi: 10.3390/ijms24021059. https://pubmed.ncbi.nlm.nih.gov/36674580/.
5. Sąsiadek M, Jacków-Nowicka J. (2024) Degenerative disease of the spine: How to relate clinical symptoms to radiological findings [J]. Adv Clin Exp Med. 33: 91-98. doi: 10.17219/acem/163357. https://pubmed.ncbi.nlm.nih.gov/37549011/.

6. Chiolo I, Altmeyer M, Legube G, Mekhail K. (2025) Nuclear and genome dynamics underlying DNA double-strand break repair [J]. Nat Rev Mol Cell Biol. 26: 538-557. doi: 10.1038/s41580-025-00828-1. https://pubmed.ncbi.nlm.nih.gov/40097581/.
7. Kadali VN, Shoshani O. (2025) Aberrant nuclei with amplified DNA in cancer [J]. Trends Cancer. 11: 9-11. doi: 10.1016/j.trecan.2024.09.005. https://pubmed.ncbi.nlm.nih.gov/39370335/
8. Sánchez-Alarcón J, Bonassi S, Milić M, Ramírez-Durán N, Isaac-Olivé K, et al. Micronuclei and Nuclear Abnormalities in Oral Mucosa as Indicators of Genotoxicity in Healthcare Professionals [J]. Toxics. 2026; 14(1):61. https://doi.org/10.3390/toxics14010061
9. Gómez-Meda BC, Zamora-Perez AL, Muñoz-Magallanes T, Sánchez-Parada MG, García Bañuelos JJ, et al. (2016) Nuclear abnormalities in buccal mucosa cells of patients with type I and IIdiabetes treated with folic acid [J].Mutat Res Genet Toxicol Environ Mutagen [J]. 797: 1-8. doi: 10.1016/j.mrgentox.2015.12.003.
10. Kashyap B, Reddy PS. (2012) Micronuclei assay of exfoliated oral buccal cells: means to assess the nuclear abnormalities in different diseases [J]. J Cancer Res Ther. 8: 184-191. doi: 10.4103/0973-1482.98968. https://pubmed.ncbi.nlm.nih.gov/22842359/.
11. Torres-Bugarín O, Zavala-Cerna MG, Nava A, Flores-García A, Ramos-Ibarra ML. (2014) Potential uses, limitations, and basic procedures of micronuclei and nuclear abnormalities in buccal cells [J]. Dis Markers. 2014: 956835. doi: 10.1155/2014/956835. https://pubmed.ncbi.nlm.nih.gov/24778463/.
12. Yang D, Lai A, Davies A, Janssen AF, Ellis MO, et al. (2024) A novel role for CSA in the regulation of nuclear envelope integrity: uncovering a non-canonical function [J]. Life Sci Alliance. 7: e202402745. doi: 10.26508/lsa.202402745.
13. Selvi S, Real CM, Gentiluomo M, Balounova K, Vokacova K, et al. (2025) Genomic instability, DNA damage response and telomere homeostasis in pancreatic cancer [J]. Semin Cancer Biol. 113: 59-73. doi: 10.1016/j.semcancer.2025.05.005. https://pubmed.ncbi.nlm.nih.gov/40378535/.
14. Lai H, Levitt BB. (2025) Radiofrequency radiation-induced gene expression. Rev Environ Health [J]. 40: 695-719. doi: 10.1515/reveh-2025-0104. https://pubmed.ncbi.nlm.nih.gov/41145349/.
15. Bruns IB, Li Y, Stevens JL, van de Water B, Callegaro G. (2025) Cell type heterogeneity in gene co-expression networks: implications for toxicological research [J]. Brief Bioinform. 26: bbaf421. doi: 10.1093/bib/bbaf421. https://pubmed.ncbi.nlm.nih.gov/40856524/.
16. Hwang KW, Yun JW, Shin YJ, Lee HJ, Kim HS. (2025) Refining housekeeping genes and demonstrating their potential for clinical and experimental applications [J]. Comput Biol Med. 194: 110546. doi: 10.1016/j.compbiomed.2025.110546. https://pubmed.ncbi.nlm.nih.gov/40489916/.
17. Jóźwik M, Sidorkiewicz I, Wojtkiewicz J, Sulkowski S, Semczuk A, et al. (2025) Selecting Optimal Housekeeping Genes for RT-qPCR in Endometrial Cancer Studies: A Narrative Review [J]. Int J Mol Sci. 26: 8610. doi: 10.3390/ijms26178610. https://pubmed.ncbi.nlm.nih.gov/40943534/.
18. Maojin Li, Rugang W, Anyi H. (2019) Analysis of nuclear abnormal lymphocytes in peripheral blood of cancer patients[J]. Public health and preventive medicine. 30: 27-31.http://www.cnki.com.cn/Article/CJFDTOTAL- FBYF201901007.htm.
19. Wu Z, Guan KL. (2021) Hippo Signaling in Embryogenesis and Development [J]. Trends Biochem Sci. 46: 51-63. doi:10.1016/j.tibs.2020.08.008. https://pubmed.ncbi.nlm.nih. gov/32928629/.
20. Harrison SE, Sozen B, Christodoulou N, Kyprianou C, Zernicka-Goetz M. (2017) Assembly of embryonic and extraembryonic stem cells to mimic embryogenesis in vitro [J]. Science. 356: eaal1810. doi: 10.1126/science.aal1810. https://pubmed.ncbi.nlm.nih.gov/28254784/.
21. Sigvardsson M. (2018) Molecular Regulation of Differentiation in Early B-Lymphocyte Development [J]. Int J Mol Sci. 19: 1928. doi:10.3390/ijms19071928. https://pubmed.ncbi.nlm.nih.gov/29966360/.
22. Casey MJ, Stumpf PS, MacArthur BD. (2020) Theory of cell fate [J]. Wiley Interdiscip Rev Syst Biol Med. 12: e1471. doi: 10.1002/wsbm.1471. https://pubmed.ncbi.nlm.nih.gov/31828979/.
23. Leu S. (2021) The role and regulation of Pnn in proliferative and non-dividing cells: Form embryogenesis to pathogenesis [J]. Biochem Pharmacol. 192: 114672. doi:10.1016/j.bcp.2021.114672. https://pubmed.ncbi.nlm.nih.gov/ 34237338/.
24. Ng HL, Quail E, Cruickshank MN, Ulgiati D. (2021) To Be, or Notch to Be: Mediating Cell Fate from Embryogenesis to Lymphopoiesis [J]. Biomolecules. 11: 849. doi:10.3390/biom11060849. https://pubmed.ncbi.nlm.nih.gov/ 34200313/.
25. Sloutskin A, Shir-Shapira H, Freiman RN, Juven-Gershon T. (2021) The Core Promoter Is a Regulatory Hub for Developmental Gene Expression [J]. Front Cell Dev Biol. 9: 666508. doi:10.3389/fcell.2021.666508. https://pubmed.ncbi. nlm.nih.gov/34568311/.
26. Schier AC, Taatjes DJ. (2020) Structure and mechanism of the RNA polymerase II transcription machinery [J]. Genes Dev. 34: 465-488. doi:10.1101/gad.335679.119. https://pubmed.ncbi.nlm.nih.gov/32238450/.
27. Angeloni A, Bogdanovic O. (2019) Enhancer DNA methylation: implications for gene regulation [J]. Essays Biochem. 63: 707-715. doi:10.1042/EBC20190030. https://pubmed.ncbi.nlm.nih.gov/31551326/.
28. Cao Z, Filatova T, Oyarzún DA, Grima R. (2020) A Stochastic Model of Gene Expression with Polymerase Recruitment and Pause Release [J]. Biophys J. 119: 1002-1014. doi: 10.1016/j.bpj.2020.07.020. https://pubmed.ncbi.nlm.nih.gov/32814062/.
29. Batty P, Gerlich DW. (2019) Mitotic Chromosome Mechanics: How Cells Segregate Their Genome [J]. Trends Cell Biol. 29: 717-726. doi:10.1016/j.tcb.2019.05.007. https://pubmed.ncbi.nlm.nih.gov/31230958/.
30. Kang S, Kang MS, Ryu E, Myung K. (2018) Eukaryotic DNA replication: Orchestrated action of multi-subunit protein complexes [J]. Mutat Res. 809: 58-69. doi:10.1016/j.mrfmmm.2017.04.002. https://pubmed.ncbi.nlm.nih.gov/ 28501329/.
31. Bertero A, Rosa-Garrido M. (2021) Three-dimensional chromatin organization in cardiac development and disease [J]. J Mol Cell Cardiol. 151: 89-105. doi: 10.1016/j.yjmcc.2020.11.008. https://pubmed.ncbi.nlm. nih.gov/33242466/.
32. Wiggins KJ, Scharer CD. (2021) Roadmap to a plasma cell: Epigenetic and transcriptional cues that guide B cell differentiation [J]. Immunol Rev. 300: 54-64. doi: 10.1111/imr.12934. https://pubmed.ncbi.nlm.nih.gov/ 33278036/.
33. Pelham-Webb B, Murphy D, Apostolou E. (2020) Dynamic 3D Chromatin Reorganization during Establishment and Maintenance of Pluripotency [J]. Stem Cell Reports. 15: 1176-1195. doi: 10.1016/j.stemcr.2020.10.012. https://pubmed.ncbi.nlm.nih.gov/33242398/.
34. Fiszbein A, Kornblihtt AR. (2017) Alternative splicing switches: Important players in cell differentiation [J]. Bioessays. 39: 6. doi:10.1002/bies.201600157. https://pubmed.ncbi.nlm.nih.gov/ 28452057/.
35. Noe Gonzalez M, Blears D, Svejstrup JQ. (2021) Causes and consequences of RNA polymerase II stalling during transcript elongation [J]. Nat Rev Mol Cell Biol. 1: 3-21. doi: 10.1038/s41580-020-00308-8. https://pubmed.ncbi.nlm. nih.gov/33208928/.
36. Ochs F, Karemore G, Miron E, Brown J, Sedlackova H, et al. (2019) Stabilization of chromatin topology safeguards genome integrity [J]. Nature. 574: 571-574. doi: 10.1038/s41586-019-1659-4. https://pubmed.ncbi.nlm.nih.gov/31645724/.
37. Maojin Li. (2021) The Dynamic Medicine -The Cell Nuclear Dysfunction and Diseases[M]. Second Edition. Hong Kong:China Science Literature Publishing House, 07: P30-35, P36-65, P131-158.

38. Kethiri AR, Grönroos P, Nagaraj ASC, Skottman H. (2025) Co-differentiation and enrichment of corneal endothelial cells and keratocytes from human pluripotent stem cells [J]. Sci Rep. 15: 18750. doi: 10.1038/s41598-025-03509-3. https://pubmed.ncbi.nlm.nih.gov/40437144/.
39. Götz M, Torres-Padilla ME. (2025) Stem cells as role models for reprogramming and repair [J]. Science. 388: eadp2959. doi: 10.1126/science.adp2959. https://pubmed.ncbi.nlm.nih.gov/40310926/.
40. Alessandrini M, Preynat-Seauve O, De Bruin K, Pepper MS. (2019) Stem cell therapy for neurological disorders [J]. S Afr Med J. 109: 70-77. doi:10.7196/SAMJ.2019.v109i8b.14009. https://pubmed.ncbi.nlm.nih.gov/31662153/.
41. Müller P, Lemcke H, David R. (2018) Stem Cell Therapy in Heart Diseases - Cell Types, Mechanisms and Improvement Strategies [J]. Cell Physiol Biochem. 48: 2607-2655. doi:10.1159/000492704. https://pubmed.ncbi.nlm.nih. gov/30121644/.
42. Liu XY, Yang LP, Zhao L. (2020) Stem cell therapy for Alzheimer's disease [J]. World J Stem Cells. 12: 787-802. doi: 10.4252/wjsc.v12.i8.787. https://pubmed.ncbi.nlm.nih.gov/32952859/.
43. Kawabori M, Shichinohe H, Kuroda S, Houkin K. (2020) Clinical Trials of Stem Cell Therapy for Cerebral Ischemic Stroke [J]. Int J Mol Sci. 21: 7380. doi:10.3390/ijms21197380. https://pubmed.ncbi.nlm.nih.gov/33036265/.
44. Kritsilis M, V Rizou S, Koutsoudaki PN, Evangelou K, Gorgoulis VG, et al. (2018) Ageing, Cellular Senescence and Neurodegenerative Disease [J]. Int J Mol Sci. 19: 2937. doi: 10.3390/ijms19102937. https://pubmed.ncbi.nlm.nih.gov/30261683/.
45. Foo MXR, Ong PF, Dreesen O. Premature aging syndromes: From patients to mechanism [J]. J Dermatol Sci. 2019 Nov;96(2):58-65. doi:10.1016/j.jdermsci.2019.10.003. https://pubmed.ncbi.nlm.nih.gov/31727429/.
46. Chapman NM, Shrestha S, Chi H. (2017) Metabolism in Immune Cell Differentiation and Function [J]. Adv Exp Med Biol. 1011: 1-85. doi:10.1007/978-94-024-1170-6_1. https://pubmed.ncbi.nlm.nih.gov/ 28875486/.
47. Borgoni S, Kudryashova KS, Burka K, de Magalhães JP. (2021) Targeting immune dysfunction in aging [J]. Ageing Res Rev. 70: 101410. doi: 10.1016/j.arr.2021.101410. https://pubmed.ncbi.nlm.nih.gov/34280555/.
48. Makkoukdji N, Satnarine T, de Almeida AX, Wyke M, Kim IH, et al. (2025) Inborn Errors of Immunity in Apoptosis [J]. Front Biosci (Landmark Ed). 30: 27231. doi: 10.31083/FBL27231. https://pubmed.ncbi.nlm.nih.gov/40464495/.
49. Palková Z, Váchová L. (2025) Cell differentiation, aging, and death in spatially organized yeast communities: mechanisms and consequences [J]. Cell Death Differ. 9: 1557-1569. doi: 10.1038/s41418-025-01485-9. https://pubmed.ncbi.nlm.nih.gov/40158069/.
50. de Magalhães JP. (2025) An overview of contemporary theories of ageing [J]. Nat Cell Biol. 7: 1074-1082. doi: 10.1038/s41556-025-01698-7. https://pubmed.ncbi.nlm.nih.gov/40595368/.
51. Lee Y, Boschian C, Ko K. (2025) MicroRNA-mediated regulation of proliferation, lineage differentiation, and apoptosis in neural stem cells [J]. RNA Biol. 1: 1-17. doi: 10.1080/15476286.2025.2558631. https://pubmed.ncbi.nlm.nih.gov/40924462/.
52. Danti L, Lundin K, Nedeczey-Ruzsák P, Tuuri T, Tapanainen JS. (2025) FOXL2 drives the differentiation of supporting gonadal cells in early ovarian development [J]. Reprod Biol Endocrinol. 23: 44. doi: 10.1186/s12958-025-01377-0. https://pubmed.ncbi.nlm.nih.gov/40102860/.
53. Duval CJ, Bottone S, Schaffner-Reckinger E, Abankwa DK. (2025) The impact of RAS on cell differentiation in health and disease [J]. Biochem J. 482: 1737–56. doi: 10.1042/BCJ20253364. https://pubmed.ncbi.nlm.nih.gov/41248180/.
54. Rando TA, Brunet A, Goodell MA. (2025) Hallmarks of stem cell aging [J]. Cell Stem Cell. 32: 1038-1054. doi: 10.1016/j.stem.2025.06.004. https://pubmed.ncbi.nlm.nih.gov/40562035/.
55. Xu X, Lai Y, Hua ZC. (2019) Apoptosis and apoptotic body: disease message and therapeutic target potentials [J]. Biosci Rep. 39: BSR20180992. doi:10.1042/BSR20180992. https://pubmed.ncbi.nlm.nih.gov/ 30530866/.
56. Nguyen TNA, Lai HT, Fernandes R, Dall'Olio FG, Blériot C, et al. (2025) Apoptosis-inducing factor (AIF) at the crossroad of cell survival and cell death: implications for cancer and mitochondrial diseases [J]. Cell Commun Signal. 23: 264. doi: 10.1186/s12964-025-02272-2. https://pubmed.ncbi.nlm.nih.gov/40468311/.
57. Engin AB, Engin A. (2021) The Connection Between Cell Fate and Telomere [J]. Adv Exp Med Biol. 1275: 71-100. doi: 10.1007/978-3-030-49844-3_3. https://pubmed.ncbi. nlm.nih.gov/33539012/.
58. Aguado J, d'Adda di Fagagna F, Wolvetang E. (2020) Telomere transcription in ageing [J]. Ageing Res Rev. 62: 101115. doi: 10.1016/j.arr.2020.101115. https://pubmed.ncbi.nlm.nih.gov/32565330/.
59. Tabibzadeh S. (2021) Cell-centric hypotheses of aging [J]. Front Biosci (Landmark Ed). 26: 1-49. doi: 10.2741/4888. https://pubmed.ncbi.nlm.nih.gov/33049664/.
60. Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, et al. (2019) Cellular Senescence: Aging, Cancer, and Injury [J]. Physiol Rev. 2: 1047-1078. doi: 10.1152/physrev.00020.2018. https://pubmed.ncbi.nlm.nih.gov/ 30648461/.
61. Melzer D, Pilling LC, Ferrucci L. (2020) The genetics of human ageing. Nat Rev Genet [J]. 2: 88-101. doi: 10.1038/s41576-019-0183-6. Epub 2019 Nov 5. PMID: 31690828. https://pubmed.ncbi.nlm.nih.gov/31690828/.
62. Ou HL, Schumacher B. DNA damage responses and p53 in the aging process [J]. Blood. 2018 Feb 1;131(5):488-495. doi: 10.1182/blood-2017-07-746396. https://pubmed.ncbi. nlm.nih.gov/29141944/.
63. van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, et al. (2018) The physiology of endocrine systems with ageing [J]. Lancet Diabetes Endocrinol. 8: 647-658. doi: 10.1016/S2213-8587(18)30026-3. https://pubmed.ncbi.nlm.nih.gov/30017799/.
64. Alsatari ES, Smith KR, Galappaththi SPL, Turbat-Herrera EA, Dasgupta S. (2025) The Current Roadmap of Lung Cancer Biology, Genomics and Racial Disparity [J]. Int J Mol Sci. 26: 3818. doi: 10.3390/ijms26083818. https://pubmed.ncbi.nlm.nih.gov/40332491/.
65. Bolin JD.(2025) Tumor Differentiation and the Role of Nuclear Medicine Scintigraphy and Therapy [J]. J Nucl Med Technol. 53: 132S-140S. doi: 10.2967/jnmt.125.271082. https://pubmed.ncbi.nlm.nih.gov/41344836/.
66. Saadh MJ, Allela OQB, Kareem RA, Baldaniya L, Ballal S, et al. (2025) Prognostic gene expression profile of colorectal cancer [J]. Gene. 955: 149433. doi: 10.1016/j.gene.2025.149433. https://pubmed.ncbi.nlm.nih.gov/40122415/.
67. Vij M, Calderaro J. (2021) Pathologic and molecular features of hepatocellular carcinoma: An update [J]. World J Hepatol. 13: 393-

410. doi:10.4254/wjh.v13.i4.393. https://pubmed.ncbi.nlm.nih.gov/33959223/.
68. Hartner S, Abolfathi H, Rezanejad M, Liu B, Karimi E, et al. (2025) Oncogenic driver mutations underlie the spatial tumour immune landscape of non-small cell lung cancer [J]. Nat Commun. 16: 8402. doi: 10.1038/s41467-025-63465-4. https://pubmed.ncbi.nlm.nih.gov/40998804/.
69. Vatrano S, Pepe P, Pepe L, Vella N, Alario C, et al. (2025) BRCA mutations and prostate cancer: should urologist improve daily clinical practice? [J] Arch Ital Urol Androl. 97: 13635. doi: 10.4081/aiua.2025.13635. https://pubmed.ncbi.nlm.nih.gov/40247739/.
70. Hussain MS, Khan Y, Maqbool M, Khan G, Mawkili W, et al. (2025) Epigenetic alterations in prostate cancer: the role of chromatin remodeling [J]. Epigenomics. 14: 967-991. doi: 10.1080/17501911.2025.2535938. https://pubmed.ncbi.nlm.nih.gov/40694614/.
71. Zappe K, Cichna-Markl M. Aberrant DNA Methylation of ABC Transporters in Cancer [J]. Cells. 9: 2281. doi:10.3390/cells9102281. https://pubmed.ncbi.nlm.nih.gov/ 33066132/.
72. Kozłowska M, Mik M, Nowicki M, Śliwińska A. (2025) DNA Damage and Repair in Pancreatic Cancer-The Latest Findings [J]. Int J Mol Sci. 26: 10106. doi: 10.3390/ijms262010106. https://pubmed.ncbi.nlm.nih.gov/41155399/.
73. Roddan R, Henderson LR, Ratnaweera M, McHugh PJ. (2025) Transcription-coupled repair of crosslinking DNA damage [J]. DNA Repair (Amst). 152: 103869. doi: 10.1016/j.dnarep.2025.103869. https://pubmed.ncbi.nlm.nih.gov/40706399/.

Cite this article: Maojin Li. (2026) New insights into the complex diseases such as aging, degenerative disorders and cancer. Advance Medical & Clinical Research. 7 (1): 268-278.