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参与人员：Involved: Writing Department: Ray Liu, Katherine, Jan Zhiyuan, Leona Xie, Polaris Zhao, Olivia, Arrietty, Edith, Rachel, Icey; Design Department: Wakanda, Vanessa, Rachel, Cylina; General Planner: Cylina Wang

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Environmental pollutants and maternal health

Introduction

Fine particulate matter (PM) and pesticides are two of the most prevalent environmental contaminants that have been shown to be harmful to expectant women's health. The most common sources of fine particulate matter (PM) in modern times, when environmental pollution and climate extremes are on the rise, maybe smog an vehicle exhaust, but PM can also be found in less apparent places, such as road dust and sea salt. As suggested by Rachel's article in Silent Spring, dichlorodiphenyltrichloroethane (DDT) i highly toxic, bioaccumulative, and persistent, with potentially harmful effects, despite claims that it has no adverse effects. Pesticides are indispensable to the evolution of agricultural practices. The presence of fine particulate matter in a pregnant woman's prenatal space, as well as pesticides in potable water and food, can have a significant impact o the pregnant woman's physical health and the development of the fetus.

Fine particulate matter and maternal health

In the sixth update of the World Health Organization's fifth air quality database of more than 6,000 cities, published in 2022, it was discovered that, despite individual countries' efforts to reduce particulate matter levels in the air, the vast majority of cities around the world are well above the WHO's air quality guideline levels. In contrast, only about 17% of the total population of the studied cities resides in urban areas with such air quality. In the meantime, accelerated industrialization and GDP growth may lead to an increase in particulate emissions. According to data from 2000 to 2016, Monaco has the lowest average annual industrial PM2.5 emissions at 3,381 kg, while the United States has the highest at 4,721,297,957 kg. High emissions may pose a global health concern (Sarkodie et al.).

Fine particles (PM), usually characterized as PM2.5, have a mass concentration of less than 2.5 μm, have a relatively small particle size and a large specific surface area, and have a higher capacity to adsorb harmful substances, which makes it easier for heavy metals to enrich. Particulate matter (PM) has long been of interest due to its greater impact on visibility. Recent studies have found a relationship between PM exposure and adverse effects in pregnant women correlation (Zhao et al.; Zhu et al.). The research indicates that PM enters the body through three main routes: inhalation, ingestion, and skin contact (Caggiano et al.). PM enters the body more extensively through the respiratory tract and accumulates in the fine bronchi and alveoli of the respiratory tract or enters the bloodstream, causing a variety of respiratory and lung diseases due to its smaller particle size. In addition, PM may leach through the interstitial areas of the alveoli, and the various heavy metals present in PM can cause inflammation in the body. Exposure of expectant women to PM2.5 in late pregnancy has been linked to a condition that promotes inflammation in both the mother and the fetus. Heavy metals in the particulate matter can cross the placenta, alter its function and gene expression, and be absorbed by the fetus, indicating that particulate matter may be detrimental to fetal nutrition and development. Environmental particulate matter levels are positively correlated with birth weight and preterm birth rates (Zhu et al.). The onset of asthma in neonates and pregnant women has been linked to prenatal and postnatal exposure to PM (Jung et al.). Preterm birth and miscarriage have been linked to premenstrual syndrome (Fried et al.).

Pesticides and maternal health

Pesticides, which include a wide range of herbicides, insecticides, and fungicides, an integral part of modern agriculture and have considerably increased global food production over the past four decades (Carvalho and security). Pesticides are believed to be used in the production of nearly one-third of all commercially available agricultural products (Zhang et al.). Approximately 3.5 billion kilograms of pesticides are sprayed on agriculture annually, according to one study (Shattuck).

Due to the extensive use of pesticides, something negative has occurred.

It has been discovered that 74.8% of the world's agricultural territory (approximately 280 000 km2) is threatened by pesticide contamination (Tang et al.). Pesticide residues were detected in over fifty percent of the examined coastal samples (Riascos-Flores et al.).

Pesticides are commonly used to eliminate pests and control weeds, but their toxicity to plants and insects has prompted further research into their health risks to humans. Due to their high bioaccumulation, toxicity, and persistence, pesticide residues can be found in water, air, soil, and food. Due to their bioaccumulation, pesticides are transmitted along the entire food chain and accumulate, posing a significant health risk.

According to one study, there are approximately 385 million cases of unintentional acute pesticide poisoning (UAPP) annually, with approximately 11,000 fatalities (Boedeker et al.). Pesticides and their metabolites have been detected both inside and outside of expectant women's bodies, according to a number of recent studies. Significant quantities of pesticides and their metabolites have been detected in the hair of pregnant women in France, indicating their exposure to and level of pesticide exposure (Beranger et al.). Multiple pesticides were detected in the plasma of 83% of pregnant women examined, with some correlation to pesticides detected in air samples during pregnancy (Whyatt et al.). In the urine of expectant women, organophosphorus pesticide residues and their metabolites were detected (Ye et al.). The lower birth weight of infants may be the result of pesticides' increased oxidative damage and genotoxicity. Certain pesticides can reduce thyroxine levels, and prenatal pesticide exposure in expectant women can have detrimental effects on neurodevelopment (Chevrier et al.). As a consequence, pregnant women may need to be more cognizant of the prenatal effects and components of the environment.

Conclusion

In the preceding sections, we discovered that despite the implementation of new policies to manage environmental pollutants in a variety of nations, environmental pollutants are on the rise. This is especially true for pesticides, which are introduced each year in vast quantities despite the silence on the issue of whether or not they are detrimental to human health. People may envision haze when they think of fine particulate matter, but PM10, PM2.5, and other forms of environmental particulate matter can enter the body in a variety of ways. During pregnancy, a woman is extraordinarily sensitive to her surroundings, including the air she breathes and the food she feeds. The increase in particulate matter (PM) and pesticide use may have contributed, at least in part, to the increased economic pressure associated with global health hazards for pregnant women.

Diagnosis and treatment of pulmonary tuberculosis

With the improvement of prevalent cognition ,people are more concerned about their physical health , more and more people start to take health examination. Unfortunately, a number of people find that they actually have pulmonary tuberculosis in the physical examination. Facing with this unfamiliar disease, people may be panicked and have no idea about it.In fact, as long as it is properly managed and treated, pulmonary nodules are not terrible. So what is a pulmonary nodule? Lung nodules refer to circular or irregular lesions with a diameter less than or equal to 3 cm in the lungs, which can be manifested as shadows with increased density, and lesions with clear or unclear boundaries. Lung nodules of different densities have different malignancy probabilities. According to the density of nodules, lung nodules are divided into three categories: solid nodules, partial solid nodules and ground glass density nodules. Among them, the malignant probability of some solid nodules is the highest, followed by ground glass density nodules and solid nodules.（CJLC NCBI，2016）

Felt a little uneasy

Wang (Alias),36-years-old, was in his prime time of his life. Becaude of his poor family, there’s no choice but work in a chemical plant in Fujian far away from his home. A month ago, Wang had a cough and no fever. Wang only thought it was good to rest after work, but his girlfriend thought it would be more reassuring to go to the local community hospital for examination. After CT examination, it was found that Xiao Wang had multiple ground glass nodules in his right upper lung, the largest being 0.6cm x 0.5cm. When he heard that something was growing on his lung, Wang immediately thought he had lung cancer and thought he had a terminal illness. In order to further diagnose Wang, the doctor transferred him to a higher hospital.

Luck in misfortune

After referral to a higher-level hospital, the doctor performed an enhanced CT examination and found that Xiao Wang had multiple ground glass nodules and irregular edges. After communicating with the patient and family, the doctor decided to perform thoracoscopic wedge resection of the right upper lung. Intraoperative cryopathology confirmed non-small cell lung adenocarcinoma, carcinoma in situ. The mortality rate of the said lung cancer is extremely high, but if the tumor/nodules can be removed before the IIA stage, the 5-year survival rate is very impressive, reaching more than 60%, and the survival rate increases by 10% for each advanced stage.

Diagnosis and treatment of pulmonary tuberculosis

Felt a little uneasy

Due to the minimal damage of thoracoscopic surgery, Xiao Wang recovered very well and was able to communicate freely in less than two days. He even asked the doctor for advice. There are so many kinds of lung nodules, do all of them need to be operated on? Now only China has a staggering 100 million 20 million known lung nodules. The doctor said: Not all lung nodules require surgery. The doctor will make a comprehensive judgment based on density, size, shape, growth site and growth rate. When lobulation, burrs, and pleural depression appear, it suggests that it may be malignant. Some solid nodules with solid components > 50% often suggest the possibility of malignancy. Most of the persistent ground glass nodules are malignant, and a high CT value indicates a high probability of malignancy. The role of tumor markers is small, but when the PET-CT SUV value is greater than 2.5, the likelihood of malignancy is relatively large. Finally, according to clinical information such as age, occupation, smoking history and family history, a comprehensive decision is made. If the probability of malignancy is small, then 3/6/12 months of follow-up can be made. If the lung nodules develop towards malignancy, immediate surgery is recommended. If the size and shape of the nodules remain unchanged or the nodules shrink after anti-inflammatory treatment, then 12 months of follow-up can be continued. Finally, it is recommended that people over the age of 40 who smoke more than 400 cigarettes per year/who have smoked 400 cigarettes per year but have quit smoking for no more than 15 years, who are exposed to high-risk occupations (such as asbestos, chemical industry), who have COPD, who have a family history of cancer People with long-term exposure to kitchen, and people with secondhand smoke have low-dose CT screening at least once a year

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Intertidal seaweeds —— environmental and ecological distribution
潮间带海藻-环境和生态分布

Abstract:
Intertidal seagrasses are a diverse group of marine organisms that play an important role in coastal ecosystems. This article examines the environmental and ecological distribution of intertidal seagrasses, including their distribution patterns, ecological functions and factors affecting their abundance and diversity. The article also discusses the potential impacts of human activities on intertidal seagrasses and their ecosystems.

潮间带海藻是一个多样化的海洋生物群体，在沿海生态系统中发挥着重要作用。这篇文章研究了潮间带海草的环境和生态分布，包括它们的分布模式、生态功能以及影响其丰度和多样性的因素。文章还讨论了人类活动对潮间带海藻及其生态系统的潜在影响。

introduction:
Intertidal seaweeds are a group of marine algae that live in the intertidal zone, the area between the high and low tide marks. They are important primary producers and form the basis of many coastal ecosystems, providing food and habitat for a wide range of marine organisms. Intertidal seaweeds are also important indicators of environmental change, and their distribution and abundance are influenced by a range of ecological and environmental factors.

潮间带海藻是一组生活在潮间带的海洋藻类，即高潮和低潮标志之间的区域。它们是重要的初级生产者，是许多沿海生态系统的基础，为广泛的海洋生物提供食物和栖息地。潮间带海藻也是环境变化的重要指标，其分布和丰度受到一系列生态和环境因素的影响。

Distribution patterns:
Intertidal seaweeds have a complex distribution pattern that is influenced by a range of physical and biological factors. The response of species distribution to climate is highly complex and manifests itself at different geographic loci. In general, they are more abundant in secluded areas with low wave energy and high nutrient content, such as estuaries, bays and rocky intertidal habitats. However, the habitat distribution patterns of intertidal seagrasses are also influenced by a range of biological factors such as spatial competition, predation and herbivory. Some intertidal seagrass species are more tolerant of desiccation and can survive in the upper intertidal zone, while others are more sensitive to desiccation and are restricted to the lower intertidal zone.

分布模式：
潮间带海藻有一个复杂的分布模式，受到一系列物理和生物因素的影响。物种分布对气候的响应是非常复杂的，并且表现在不同的地理位点。一般来说，它们在波浪能量低、营养物质含量高的隐蔽地区更为丰富，如河口、海湾和潮间带岩石生境。然而，潮间带海草的栖息地分布模式也受到一系列生物因素的影响，如空间竞争、捕食和食草。一些潮间带海草物种更耐干燥，可以在潮间带上部生存，而其他物种对干燥更敏感，仅限于潮间带下部。

ECOLOGICAL FUNCTIONS:

Intertidal seagrasses play an important role in coastal ecosystems, providing food and habitat for a variety of marine organisms. They are also important primary producers, contributing to the production of organic matter in coastal waters. In addition, intertidal seaweeds are important indicators of environmental change, and changes in their abundance and diversity can provide early warning signals of environmental degradation.

生态功能：
潮间带海草在沿海生态系统中发挥着重要作用，为各种海洋生物提供食物和栖息地。它们也是重要的初级生产者，为沿海水域的有机物生产作出贡献。此外，潮间带海藻是环境变化的重要指标，其丰度和多样性的变化可以提供环境退化的早期预警信号。

Factors affecting abundance and diversity:
The abundance and diversity of intertidal seaweeds is influenced by a range of factors, including physical factors such as water temperature, light intensity and wave energy, and biological factors such as spatial competition, predation and herbivores. Human activities, such as coastal development, pollution and overfishing, can also have a significant impact on intertidal seaweeds and their ecosystems, leading to declines in abundance and diversity.
影响丰度和多样性的因素：
潮间带海藻的丰度和多样性受到一系列因素的影响，包括物理因素，如水温、光照强度和波浪能量，以及生物因素，如空间竞争、捕食和食草动物。人类活动，如沿海开发、污染和过度捕捞，也会对潮间带海藻及其生态系统产生重大影响，导致丰度和多样性的下降。

Anthropogenic impacts:
Anthropogenic activities can have a significant impact on intertidal seaweeds and their ecosystems. For example, coastal development can lead to habitat destruction and fragmentation, which can reduce the abundance and diversity of intertidal algae. Pollution can also have a significant impact on intertidal seagrasses, as many species are sensitive to changes in water quality. Overfishing can also have a significant impact on intertidal seagrasses, as many herbivorous fish feed on intertidal seagrasses.
人为活动的影响：
人为活动可对潮间带海藻及其生态系统产生重大影响。例如，海岸开发可导致栖息地的破坏和破碎，从而降低潮间带海藻的丰度和多样性。污染也会对潮间带海草产生重大影响，因为许多物种对水质的变化很敏感。过度捕捞也会对潮间带海草产生重大影响，因为许多草食性鱼类以潮间带海草为食。

Conclusion:
In conclusion, intertidal seagrasses are a diverse group of marine organisms that play an important role in coastal ecosystems. Their distribution and abundance are influenced by a range of ecological and environmental factors, and they are important indicators of environmental change. Human activities can have a significant impact on intertidal seaweeds and their ecosystems, highlighting the need for sustainable coastal management measures. Overall, intertidal seaweeds are an important and fascinating group of marine organisms that deserve further research and conservation.
总之，潮间带海藻是一个多样化的海洋生物群体，在沿海生态系统中发挥着重要作用。它们的分布和丰度受到一系列生态和环境因素的影响，它们是环境变化的重要指标。人类活动会对潮间带海藻及其生态系统产生重大影响，突出了可持续沿海管理措施的必要性。总的来说，潮间带海藻是一个重要而迷人的海洋生物群体，值得进一步研究和保护。

The pathogenesis of The Cancer

1. What is cancer?

Cancer is also known as malignant tumor,all organs of human are constitute of cell,when physical cell become cancerous,the tutor,which is consist of cancerous cells,has appeared.Cancer is caused by evolving of cell's ability to adapt to their environment faster than the body's ability to control them.Cancer metastasis is the leading reason of Cancer death.

2. why dose it cause cancer?

There are many carcinogenic factors lurking in everyday life.the carcinogenic factors include physical carcinogenic factor,chemical carcinogenic factor and biological carcinogenic factor.
The physical carcinogenic factors are mostly γ-ray and X-ray,they are also called as ultraviolet rays and radiation.
The chemical carcinogenic factors are common,such as Nicotine and aflatoxin,they are mostly common in bad peanuts and sunflower seeds.
The biological factors,such as some infections caused by virus,bacteria or parasites.

Estimated New Cases

	Males			Females	
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

3. the pathogenesis of cancer

People's understanding of cancer pathogenesis has experience a long way,from the simplex physical carcinogenesis,chemical carcinogenesis,virus carcinogenesis and mutation caicinogenesis theory to the multistep,multifactorial theory of carcinogenesis.the most successful example comes They found that the multi-step process of hyperplasia, benign tumors, carcinoma in situ and invasive carcinoma experienced during colon cancer development runs through a series of molecular event changes. It was found that there were Ras gene mutations and tumor suppressor genes APC and DCC losses in adenomas, and Ras gene mutations and tumor suppressor genes APC, DCC and P53 were lost in cancer. The development of colon tumors appears to begin due to the loss of heterozygosity of the tumor suppressor gene APC. Deletion of APCs can occur in germ cells or somatic cells, resulting in progressively enlarged benign adenomas. In benign adenomas, one of the cells often undergoes a mutation in the Ras oncogene, leading to further clonal development. Subsequent deletion of tumor suppressor genes DCC and P53 promotes benign to malignant progression.from the Vogelstein Lab at Hawkins University in the US,which is studying colon cancer.

4. current status of cancer research

In 20 years,cancer deaths of men and women combined fell by 33%,and the reduction in cancer deaths averted about 3.8 million deaths. For men, prostate cancer is the most, accounting for about 29%. For women, breast cancer is the most, accounting for about 31%. Lung cancer is the first cancer to die. Data show that about 350 people die of lung cancer every day, and of the 127,070 lung cancer deaths in 2023, about 103,000 will be caused by direct smoking and 3,560 cancers will be caused by secondhand smoke.

5.mRNA tumor vaccine

mRNA tumor vaccines are nucleic acid vaccines that work by looking for genes that can encode the amino acid sequence of antigen proteins in tumor cells. RNA tumor vaccines generally translate proteins, and on this basis to complete the preparation and injection into the body, through the protein synthesis system of human cells to synthesize specific antigen proteins, as a "target", induce the human body to produce immunity to the "target", and finally attack tumor cells.

Advantage:
Short development cycles: mRNA vaccines have shorter development cycles because once the required mRNA sequence information is determined, rapid and large-scale production can be achieved through in vitro transcription.
Dual immunity: mRNA vaccines have a dual immune mechanism. In addition to the antigen-encoding mRNA that stimulates the immune response, mRNA itself has inherent immunostimulating properties. It can improve the immune effect of the vaccine.

Safety: mRNA vaccines do not enter the nucleus and therefore do not pose a potential risk of genome insertion mutations

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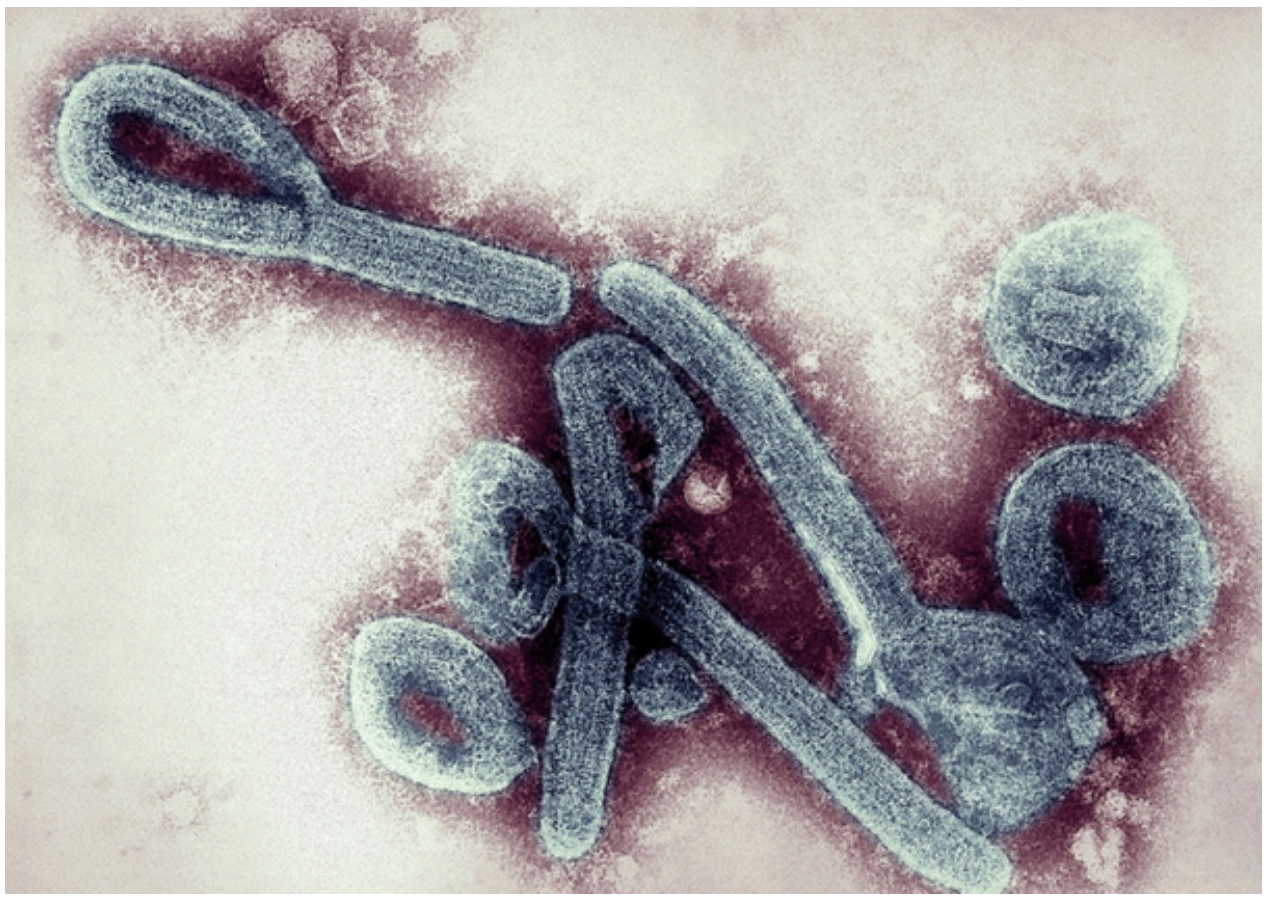
Virus Introduction-Marburg

I. Preface

In 1967, there was a sudden outbreak of a virus in a laboratory in Marburg, Germany, and the infected people had a high fever, diarrhea, and bleeding symptoms. The monkeys were originally used to study the polio vaccine, but the epidemic broke out unexpectedly.

When it comes to the Marburg virus, we have to mention the Ebola virus, both are filoviruses, their origin is unknown, zoonotic, and can cause hemorrhagic fever, patients mainly appear in the early stages of high fever, muscle aches, headaches, 3-5 days after the body rash, accompanied by vomiting, diarrhea, drowsiness, severe bleeding due to Marburg hemorrhagic fever he period he infectious disease, the cause of death of patients usually shock and excessive blood loss, the virus is mainly through The virus is transmitted mainly through body fluids (blood and saliva), and in the 1967 outbreak in Germany, two doctors were infected by accidental contact with the patient's blood while drawing blood. The World Health Organization says that the mortality rate of the Marburg virus in developing countries is 88% to 100%. The main treatment is to balance the electrolytes of the patient, replenish blood loss, and treat complications.



ELECTRON MICROGRAPH OF THE MARBURG VIRUS SOURCE: BSIP/UNIVERSAL IMAGES GROUP/GETTY IMAGES

II. TEXT

(I) Introduction of the virus
Marburg virus is classified as a single-stranded retrovirus, family Filoviridae, and genus Marburg virus. It is shaped like a filament, with a length of 800-14000 (nm), and is most infectious at 790 (nm). Since it is difficult to distinguish Marburg hemorrhagic fever from other infectious diseases, the main methods of diagnosis are TR-PCR, ELISA, and antigen detection tests.

(ii) Vaccines and related drugs
According to the World Health Organization, monoclonal antibodies are being developed, and antiviral drugs such as Remdesivir and Favipiravir used in clinical studies of the Ebola virus can be used as compassionate drugs.

Zabdeno (Ad26.ZEBOV): This vaccine is an anti-Ebola vaccine that was approved by the European Medicines Agency in May 2020 as a vaccine against the Marburg virus.

Mvabea (MVA-BN-Filo): Originally an anti-Ebola vaccine, this nRNA vaccine contains the MVA virus (Vaccinia Ankara Bavarian Nordic) modified to produce the four proteins of the filovirus and was approved by the European Medicines Agency in May 2020, along with Zabdeno, as a vaccine against Marburg virus. The vaccine was approved by the European Medicines Agency in May 2020, together with Zabdeno, as a vaccine against the Marburg virus.

Neither of these vaccines has been proven in clinical trials

III. CONCLUSION

(a) How to prevent

1. Avoid contact with the remains of patients
Many outbreaks in Africa have been associated with local burial customs. The remains of patients should be buried and cremated within 24 hours.

2. Avoid contact with wild animals
Fruit bats are considered natural hosts and the Marburg virus in fruit bats can be transmitted directly to humans. Therefore, avoid prolonged exposure to veins and caves inhabited by fruit bats and wear gloves and appropriate clothing if you must enter caves (e.g., for work, or sightseeing).

3. Keep your hands clean
Hands are part of the body most likely to come into contact with the eyes, mouth, and nose, so hand washing is an important concept for disease prevention.

4. Avoid contact with body fluids
Therefore, avoid contact with the contaminated environment and body fluids of patients, wear protective equipment when caring for patients, and avoid sexual intercourse with patients until you are sure that body fluids are virus-free.

(2) Conclusion
Although this virus sounds scary, as long as you take precautions, it is very difficult to be infected, and if you are unfortunately infected, the possibility of being cured is still very high. Nowadays, with advanced technology, we believe that vaccines and drugs will be developed as soon as possible.

the treatment of obesity

TIRZEPATIDE

author: Leona

Vocabulary

Morbidity: the morbidity of a disease is how many people have it in a particular population
Glucose-dependent insulinotropic polypeptide: a 42 amino acid hormone that is produced by enteroendocrine K-cells and released into the circulation in response to nutrient stimulation.
placebo: a substance given to someone who is told that it is a particular medicine, either to make that person feel as if they are getting better or to compare the effect of the particular medicine when given to others

New diabetes drug that requires only one injection per week

Situation

Diabetes is a metabolic disease characterized by hyperglycemia. Hyperglycemia is caused by a defect in insulin secretion or an impairment of its biological action, or both. Long-term hyperglycemia leads to chronic damage and dysfunction of various tissues, especially eyes, kidneys, heart, blood vessels and nerves. Eli Lilly recently announced that the U.S. Food and Drug Administration (FDA) has approved Mounjaro (tirzepatide) injection, a new, once-weekly GIP and GLP-1 receptor agonist, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes (T2D). Mounjaro has not been studied in patients with a history of pancreatitis and is not indicated for patients with type 1 diabetes (T1D). It is worth mentioning that Mounjaro is the first and only GIP/GLP-1 receptor agonist approved by FDA in the United States, which also represents the first new class of hypoglycemic drugs approved for marketing in the past decade. According to the third-quarter results released in October last year, Lilly submitted a priority review certificate (PRV) to the FDA to speed up the tirzepatide review, which can shorten the review cycle by four months. Currently, tirzepatide is also under regulatory review in the European Union, Japan, and several other markets.

Figure 1 Symptoms of diabetes

What is diabetes?

Diabetes is a chronic metabolic disease characterized by hyperglycemia. Under normal circumstances, when humans eat, the carbohydrates absorbed by the body will be broken down into glucose, glucose into the blood will cause blood sugar to rise, provide energy for cells, while glucose can also stimulate insulin secretion, and insulin is the only hormone in the body to reduce blood sugar, if insulin can not be secreted or cells are not sensitive to insulin. Blood sugar will not come down, which will lead to diabetes. High blood sugar can cause "three more and one less" symptoms, including polydipsia, polyphagia, frequent urination and weight loss. When high blood sugar exists in the body for a long time, it will cause complications, leading to cardiovascular and cerebrovascular diseases, amputation, blindness, renal failure and other problems. Diabetes can be roughly divided into four types, namely type 1 diabetes, type 2 diabetes, special type diabetes and gestational diabetes, but mainly type 1 and type 2 diabetes. Type 1 diabetes is mostly seen in children and young adults, who are due to congenital immune problems resulting in the lack of insulin secretion, and the pathogenesis is unknown. Type 2 diabetes is the most common form in adults and may be caused by genetic problems, lifestyle and environmental factors. At present, there is no cure for diabetes, but we can improve the quality of life and prolong the life span of patients through reasonable methods. Uch as medication and blood glucose monitoring. Drug therapy can be divided into oral drugs and injectable drugs, of which the first known injectable drug therapy is insulin.

SUMMARY

The benefit of Mounjaro (tirzepatide) injection is its convenience, because patients only need to inject once a week to control blood sugar levels, while the hidden needle of the pre-installed injection pen also provides a safe and convenient way for patients to inject drugs, so that users can increase compliance and reduce fear of injecting drugs. Tirzepatide is not only a hypoglycemic drug, but also a very powerful weight-loss drug, but because tirzepatide is a receptor dual stimulator, it may have greater side effects than single-target GLP-1, for patients with severe obesity or poor blood sugar control after GLP-1 use. Consider tirzepatide.

What is Mounjaro (tirzepatide)?

Mounjaro (tirzepatide) injection, developed by Eli Lilly, was approved by the US Food and Drug Administration (FDA) in May 2022 to treat patients with type 2 diabetes. The drug is the first and only glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1) receptor dual agonist approved for marketing in the past decade. Both GIP and GLP-1 are natural polypeptides secreted by human gastrointestinal mucosa, which can regulate the secretion of insulin and glucagon, increase satiety, reduce weight, and achieve the dual effects of hypoglycemic and weight loss. Patients only need to inject once a week to keep blood sugar stable. Tirzepatide has launched six doses (2.5mg, 5mg, 7.5mg, 10mg, 12.5mg, 15mg), and Lilly has launched its own patent for patients'fear of needles, an automatic injector device with a pre-installed injection pen to hide the needle, which will be "hidden". A patient can not visually see that existence of the needle when in use, and the needle is discard after use, thereby provide a convenient and safe injection process for the patient.

Figure 2 Mounjaro (tirzepatide) Injection In terms of safety and efficacy, Lilly has launched a series of global clinical trials on tirzepatide, including a 40-week global Phase 3 SURPASSO-2 clinical trial. In this trial, tirzepatide was the most effective at lowering blood sugar in patients with type 2 diabetes compared with semaglutide. Subjects who received 15 mg of tirzepatide experienced a 2.46% decrease in average A1C (glycosylated hemoglobin) and also lost 12.4 kg of body weight, nearly twice as much as those who received semaglutixe. If 5 mg of tirzepatide was injected, A1C decreased by 2.19% and body weight decreased by 7.8 kg. Compared with other control groups, such as dulaglutide, Insulin Glargine, Insulin Degludec, Insulin Lispro, etc. The tirzepatide is also effective in lowering blood sugar and losing weight, especially in weight loss. It should be noted that tirzepatide has not been studied in patients with a history of pancreatitis and is not indicated for use in patients with type 1 diabetes. Common side effects with tirzepatide include nausea, diarrhea, vomiting, and constipation.

Figure 2 Mounjaro (tirzepatide) injection

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introduction

It has been possible to control the diverse differentiation of animal cells in germline and embryonic and induced pluripotent stem cells, but no naturally occurring adult pluripotent stem cells have been identified in Ascaris, flies, fish or rodent model systems. In these animal species, true vermiform flatworms and cavernous animals possess specific populations of adult stem cells, collectively referred to as neoblasts, which include a pluripotent subpopulation of clonal neoblasts with the ability to enable systemic regeneration and apparently unlimited tissue homeostasis. Although pluripotency regulators have been identified in neonatal cells and studied using RNA interference, the lack of reliable culture methods and transgenic approaches limits the possibility of developing adult stem cell pluripotency.

Current situation:

Currently, genetic transformation strategies are mainly used: asexual propagation by neoplastic cell proliferation and differentiation, followed by transplantation of these cells into a host lacking neoplastic cells (e.g., after lethal radiation) to repopulate stem cells and rescue the host within one month after radiation. Thus, the transformation of DNA or RNA into neonatal cells prior to transplantation could produce transgenic vortexes and subsequently lead to a major breakthrough in understanding the control of animal pluripotency. However, there are no reports describing the further development and genetic modification of nascent cells. What is missing is a robust culture method for establishing pluripotent neoblasts that also requires the ability to efficiently screen for successful delivery and transgene expression of exogenous DNA or RNA.

Establishing standardized neoblast culture conditions

The researchers first screened 23 different types of media, both the reported formulation and the diluted versions, to better mat the osmolarity suitable for planarian cells.
For the cells' viability, it's shown that in all mediums except CMFB (with or without 5% CO2 conditions), there's high viability and low percentage of dead cells. Among these viable cells, the proportion that are neoblasts is also assessed by quantifying the number of smedwi-1+ X1(FS) cells. In diluted (d) Grace's, IPM, KnockOut DMEM, dL15, dKnockOut DMEM, dSchneider's, and dDMEM media, there is a greater number of smedwi-1+ neoblasts than all other conditions, and the neoblasts are all confirmed to be viable. These neoblasts are also able to last at least three days. These seven medium are determined to be the focus in the remainder of the study.

Next, the ability of the cultured neoblasts to divide in vitro is assessed. Time-lapse microscopy imaging show that divisions do occur in the neoblasts. However, only in IPM, KnockOut DMEM, and dL15 medium are symmetric and asymmetric cell divisions observed, and they also have a greater number of proliferating cells than the other four mediums. Following the in vitro assessment, the ability to divide in vivo is also assessed. That capability exists in those cultured in IPM, KnockOut DMEM, dL15, dKnockOut DMEM, dSchneider's, and dDMEM mediums, though for all of those, the ability diminish significantly after three days. Finally, the pluripotency of the cells are assessed as the ability to rescue the lethally irradiated sexual S. mediterranea hosts. For that, cells grown in KnockOut DMEM exhibited the highest and most robust host rescue.

Establishing an alternative source of transplantable neoblasts

The researchers then aimed to enrich the neoblasts for culture. The found that the SiR-DNA/CT co-staining method showed comparable performance to Hoechst 33342 sorting method for enriching smedwi-1+ neoblasts. Cells obtained by this co-staining method is designated SiRNeoblasts. Also, these SiR-DNA stained cells can still divide in vivo after staining, which is not possible in Hoechst 33342 sorted cells. Observing the chromosomal separation dynamics of dividing SiRNeoblasts in vitro showed that confirmed the occurence of cell division in test conditions. In conclusion, the SiR-DNA/CT dual label-based cell sorting could be used to isolate neoblasts, and these isolated SiRNeoblasts can be maintained and serve as future donor cells.

Exogenous mRNA delivery by electroporation

Following the optimization of in vitro culture conditions, the different conditions for the delivery of exogenous molecules into neoblasts for genetic transformation of the planarians are assessed. The most optimal delivery condition for the dextran-FITC into X1 cells is at 100–120V. However, the application of voltage is harmful to the cells, with no cells subjected to more than 100V forming colonies after transplantation into a lethally irradiated host. Using SiRNeoblasts in place of the X1 cells show that they are more viable after the application of voltage, lasting for more than a day afterwards. Then, the researchers assessed whether exogenous mRNA could be delivered into SiRNeoblasts by electroporation. The most optimal way of introducing the tdTomato mRNA is at 110V, with pluripotency and viability well maintained. Also, the sucess does not depend on presence or absence of RNase A.

Expression of nanoluciferase mRNA in differentiating SiRNeoblasts

In order to detect the expression of tdTomato mRNA, the researchers references previous research wherein reported expression of nanoluciferase mRNA in planarian cells. Thus, they suspect that the NanoLuc reporter could provide tracking of transgene expression in the neoblasts. NanoLuc expression was observed, and at higher levels in SiRNeoblasts cultured in modified KnockOut DMEM with 5% CO2 atmosphere than in cells grown under the same conditions without supplements. As for the method of delivering NanoLuc mRNA into neoblasts, NanoLuc signal was only detectable following TransIT transfection, and not in electroporation. Electroporation consistently falls short of the efficiency and success rate of delivery than TransIT transfection. Surprisingly, none of the other mRNA (NanoLuc, smed-histone3.3-2xflag, mCherry, or NanoLuc-mCherry) are able to be sucessfully transfered and expressed in the neoblasts at detectable levels by Western plot. Also, the NanoLuc signal was almost exclusively transferred into the somatic cells, suggesting that planarian neoblasts prevents exogenous nucleic acids before differentiation.

Discussion

The inability to genetically modify true vortex worms has posed a long-term obstacle to studying this highly versatile model of pluripotency and systemic regeneration, with major technical limitations including determining the optimal culture conditions for maintaining pluripotent neoplastic cells and identifying effective methods for delivering exogenous nucleic acids to these cells. The cell culture system developed by the experimentalists in this work addresses the former problem and enables further testing of strategies for exogenous delivery, such as fluorescent conjugated dextran and mRNA. first, the use of SiRNeoblasts ensures the purity and viability of nascent cells, thus making it relatively easy to screen for transgene delivery strategies. Second, the low efficiency of transfection and translation may also be due to the relatively reduced metabolic activity of cultured cells. The enhanced translation of NanoLuc mRNA observed after addition of the supplement suggests that mRNA uptake and translation depend on meeting the metabolic requirements of cultured nascent cells. Third, given that neonatal cells are in fact the selective units of vorticillium and that the viability of these animals depends heavily on their normal function and survival, it is logical that these cells have evolved robust molecular mechanisms to protect their genomes from foreign nucleic acid damage. In summary, the researchers describe FACS isolation strategies used to maintain clone formation in vitro, pluripotent nascent cells and primary cell culture conditions for transplantation, repopulation, etc. with hosts exposed to lethal radiation in the short term.

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Author：Icey

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INTRODUCTION

On the evening of October 7, 2020, the Nobel Committee announced that Emmanuelle Charpentier and Jennifer A. Doudna had won the 2020 Nobel Prize in Chemistry in recognition of their CRISPR-Cas9 genome editing method. This landmark scientific and technological innovation is known as an important breakthrough in the field of genome editing. With this technology, the DNA of animals, plants and microorganisms can be precisely changed. More importantly, it can provide new treatments for cancer and other diseases. The powerful power of genome editing has made breakthroughs in all aspects of research.

FIGHTING AGAINST BACTERIA

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeat) is a repetitive DNA sequence discovered in the genomes of prokaryotes such as bacteria and archaea by Jansen Laboratory through bioinformatics in 2002. These sequences come from DNA fragments of viruses previously infected with prokaryotes. The operational mechanism of the CRISPR-Cas system was fully revealed in 2011. When viruses invade bacteria, they can capture foreign DNA fragments and integrate them into the CRISPR sequence of their own genome. When the virus invades again, CRISPR transcribes to produce precursor crRNA (pre crRNA), which then forms cr-RNA. Cr-RNA recognizes the homologous sequence of the virus genome and mediates the binding and cleavage of Cas protein with it. This is an adaptive immune defense formed during the long biological evolution of bacteria and archaea, and therefore an immune weapon for prokaryotes to fight against viruses. This is the origin of CRISPR-Cas9 genome editing technology.

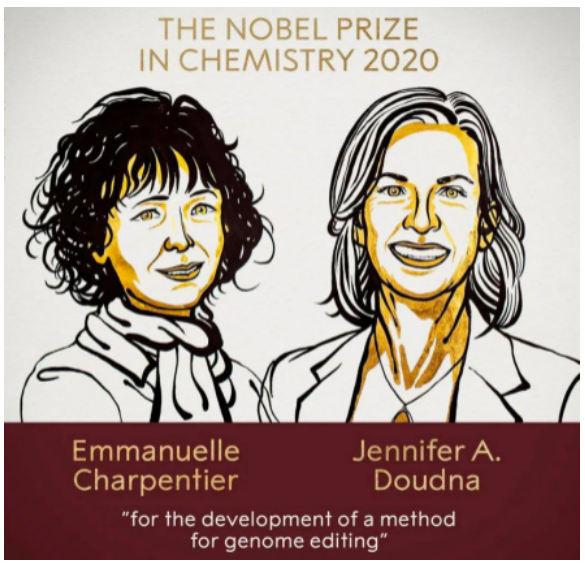

Figure 1: Nobel laureates in chemistry Emmanuelle Charpentier and Jennifer A. Doudna

TO REWRITE THE LIFE CODE

Editing genes is an important factor in exploring the internal systems of organisms, which was initially considered impossible by researchers. It is the "Gene Scissors" CRISPR-Cas9 technology that has broken this bottleneck. It works like scissors, cutting DNA and then rearranging the genetic code.

In 2012, two scientists, namely the Nobel Prize winner in 2020, applied CRISPR CAS system to genome editing technology for the first time. Pre crRNA can form double stranded RNA with tracrRNA through base complementary pairing. tracrRNA is transcribed from repetitive sequence regions and has a hairpin structure, while pre crRNA is a large RNA molecule transcribed from the entire CRISPR sequence. Subsequently, pre crRNA, tracrRNA, and Cas9 encoded proteins will be combined to select the corresponding spacer sequence RNA, and ultimately obtain mature crRNA. From this, the complex of crRNA, tracrRNA, and Cas9 was obtained. This combination can accurately strike DNA by scanning the DNA sequence to identify complementary sequences with crRNA, and locate them in the PAM (protospacer advertisement motif) region of DNA. At this point, the double stranded DNA will unravel and complement the crRNA, and Cas9 will launch an attack at this time, cutting the DNA strand to form double strand breaks (DSBs). This is the working principle of CRISPR-Cas9. Its genome editing technology is to identify the target genome sequence and guide the cutting of Cas9 through the artificially designed sgRNA, also known as guideRNA. Damage can cause gene knockout or gene insertion, thereby editing DNA.

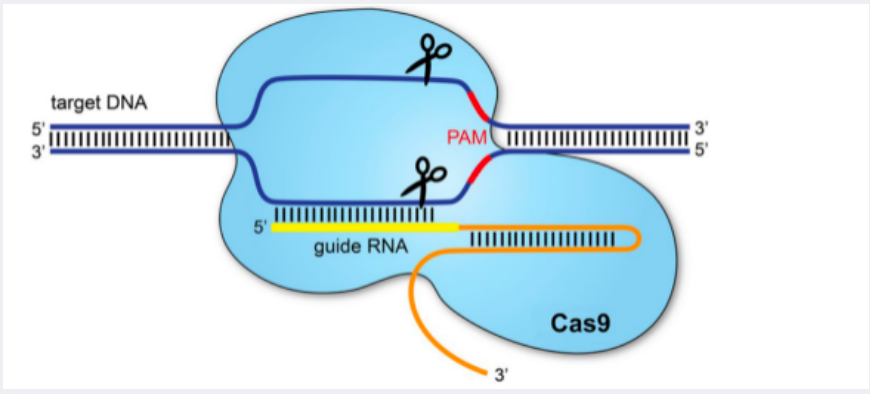

FIGURE 2: GENOME EDITING

FUTURE OUTLOOK

CRISPR/Cas9 technology has broad application prospects in the future. First, in the treatment of gene diseases, CRISPR/Cas9 can accurately edit the human genome and correct the defects of human genes, thus opening up a new way for the treatment of gene diseases. CRISPR/Cas9 can also be used in the field of biological agriculture to improve the productivity and quality of crops and livestock by editing plant and animal genomes. In addition, CRISPR/Cas9 can also be used for environmental remediation, and genome editing technology can be used to improve the ability of environmental pollutant degrading bacteria to accelerate the treatment of environmental pollution. The future application prospects of CRISPR/Cas9 technology are very broad, which will deeply affect the development of human health, food security, environmental protection and other fields.

damage and repair DNA

author: Katherine

KEYWORDS: MOLECULAR BIOLOGY, DNA DAMAGE, DNA REPAIR

I. INTRODUCTION

DNA is the foundation of life and is responsible for maintaining the normal life cycle and function of cells. However, DNA is easily damaged by various internal and external factors. Therefore, understanding DNA damage and repair is critical to maintaining health.

DNA damage refers to any alteration of the DNA molecule, including breaks, base damage, and cross-links. These injuries can lead to genetic mutations, cell death, and abnormal proliferation, leading to disease. Therefore, the importance of understanding DNA damage is self-evident.

DNA repair refers to the restoration of the integrity and function of damaged DNA through a series of mechanisms. These repair mechanisms can be roughly divided into three types: direct repair, base excision repair, and recombination repair. Direct repair refers to the repair of some simple DNA damage, such as alkylation and photodamage. Base excision repair repairs some common DNA damage, such as oxidative damage, isomerization, and single-strand breaks. Recombination repair is the repair of complex DNA damage, such as double-strand breaks. These repair mechanisms will be further explained in the following paragraphs, and understanding these repair mechanisms can help us prevent DNA damage and disease.

More than 4,000 human genetic diseases have been discovered so far, many of which are related to DNA repair defects. Xeroderma Pigmentosum (XP) was first described by dermatologist Moriz Kaposi in 1874. He found that the patient's skin was dry, with dark spots, and extremely sensitive to sunlight. About 100 years later, James Cleaver discovered that the occurrence of Xeroderma Pigmentosum was related to defects in DNA repair. It is also the first genetic disorder of DNA repair deficiency found.

II. CAUSES OF DNA DAMAGE

Although DNA is protected layer by layer by the human body, DNA is still easily damaged by interference from various internal and external factors, which in turn affects the integrity and function of DNA. The causes of DNA damage can be roughly divided into three types: chemical damage, physical damage, and biological damage.

(1) Chemical damage

Chemical damage refers to DNA damage caused by chemicals. Common chemical damages include oxidative damage and alkylation. Oxidative damage is usually caused by free radicals and other oxidizing species that cause the oxidation of the bases in the DNA molecule. Alkylation is caused by chemicals containing alkyl groups, which introduce isomerization and base deletions in the DNA molecule. These chemical injuries can lead to unwanted consequences such as genetic mutations and cell death.

(2) Physical damage

Physical damage refers to DNA damage caused by physical factors, such as ultraviolet (200-300 nm wavelength) radiation and ionizing radiation (X-rays) are the most common physical damage factors. UV radiation induces the bonding of adjacent pyrimidines in the DNA strand, forming pyrimidine dimers. Ionizing radiation induces DNA mutations in cells by generating free radicals that generate reactive oxygen species (ROS) and causes single- and double-strand breaks in the double helix.

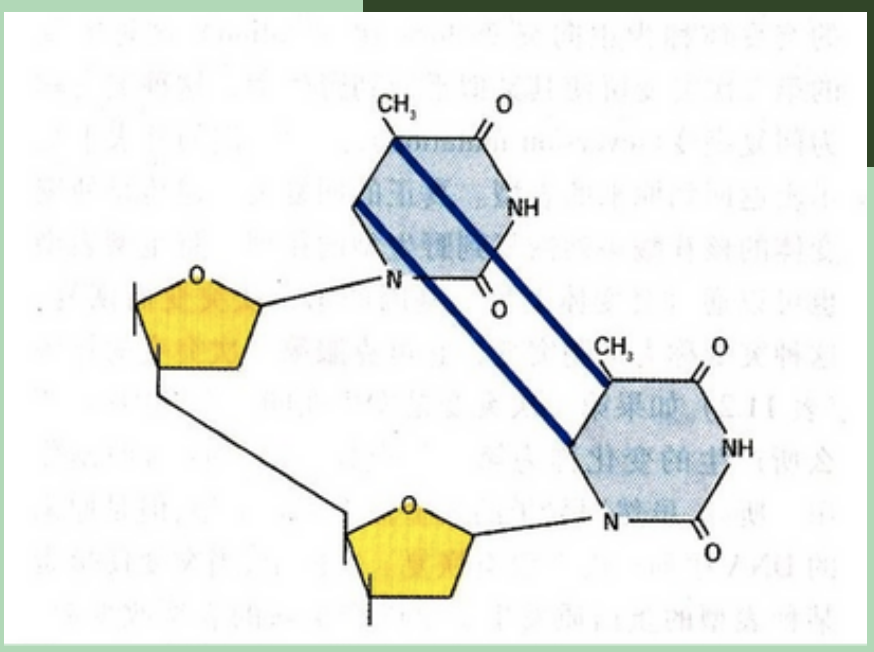

Figure 1. Pyrimidine dimer
In photoreactivation repair, photolyase will cleave two dark blue bonds.

(3) Biological damage

Biological damage refers to DNA damage caused indirectly in the process of biological metabolism. For example, oxygen free radicals or reactive oxygen species are produced in the metabolic process. Reactive oxygen species, one of the most common agents of biological damage, are generated inside cells and cause oxidative damage in DNA. At the same time, the stability of the DNA structure can be affected, leading to DNA mutations and other types of damage. In addition to this, hydrolysis is another common damage. Hydrolysis reactions can partially or completely cleave nucleotide bases from DNA strands. With the loss of the amine group on the pyrimidine ring, deamination will occur in the cell to produce other different kinds of purines and pyrimidines, such as xanthine. These internal factors may contribute to problems such as aging, disease, cell death, and neurodegenerative diseases. However, in addition to the products produced during the metabolic process that may cause DNA damage, errors may also occur during the process of DNA replication, transcription, and translation. Examples include pairing errors or mutations in transcription and regulatory factors during DNA transcription.

III. EFFECTS OF DNA DAMAGE

(1) Mutations and chromosomal abnormalities

DNA damage can lead to genetic mutations and chromosomal abnormalities. A genetic mutation is a permanent change in the DNA sequence that can affect the function of a protein and lead to disease. Chromosomal abnormalities are changes in the structure or number of chromosomes that can lead to fetal malformations, reproductive problems, or diseases such as cancer. Chromosomal abnormalities include chromosomal deletions, duplications, translocations, or structural abnormalities.

(2) Cell death

DNA damage can lead to apoptosis or necrosis. Apoptosis is a kind of programmed death, which is usually induced and executed by the cells themselves. Cell necrosis is a type of non-programmed death, usually caused by external factors. DNA damage may activate cell death pathways that allow damaged cells to die, thereby protecting other cells from the damaged cell.

(3) Cancer development

DNA damage is a major factor in the development of cancer. Cancer is caused by a series of genetic mutations that can increase the speed and error rate of cell division, leading to the development and spread of tumors. DNA damage may also lead to the development of precancerous lesions, which are early changes before tumors develop and may eventually develop into cancer.

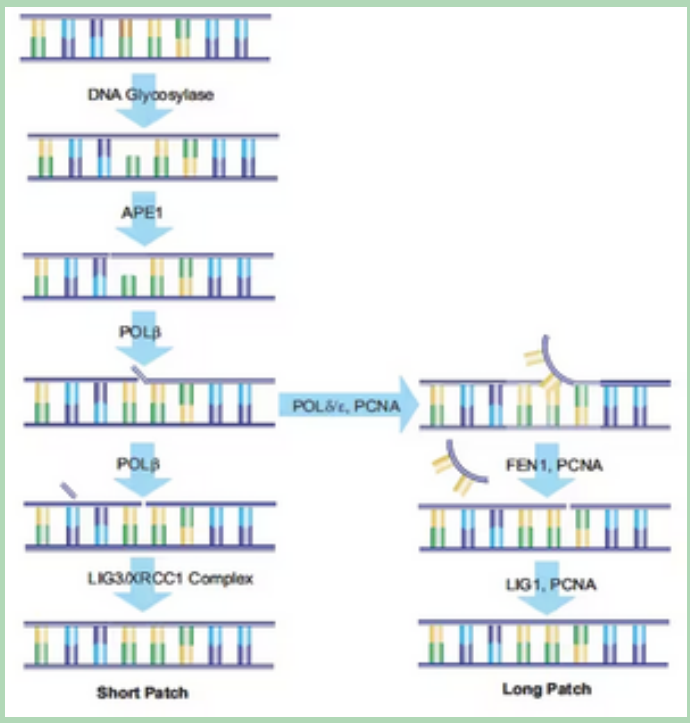

Figure 2. Schematic diagram of the short patch and long patch repair

IV. THE MECHANISM OF DNA REPAIR

(1) Photoreactivation and repair

Photoreactivation repair is the first DNA repair method discovered, mainly through the photolyase to decompose the pyrimidine dimer into two monomers, so that the DNA returns to normal. When this enzyme is irradiated with light with a wavelength of 300-600 nanometers, it will be activated and specifically repair pyrimidine dimers caused by ultraviolet rays. However, this repair method does not exist in higher mammals. Despite the limitations of this approach, the photoreactivation repair mechanism still plays an important role in organisms with this enzyme.

(2) Alkylation damage repair

Alkylation damage repair refers to the use of O6-methylguanine DNA methyltransferase (MGMT, also known as DNA alkyltransferase) to cut the methyl and ethyl groups from the guanine bases on the DNA structure, and the alkylation The damage is restored to normal state. This is a chemical rather than a catalytic reaction, and for every methyl or ethyl group removed, one MGMT molecule is consumed. Under the action of a low dose of an alkylating agent, it is possible to induce the repair activity of MGMT, which can transfer the methyl group from the base to the cysteine of the protein, and then complete the repair of DNA.

(3) Base excision repair

Base excision repair (BER) primarily repairs small base damage that does not significantly distort the DNA helical structure. This damage is usually caused by deamination, oxidation, or methylation. DNA glycosylase first excises the damaged base and then replaces the missing base with DNA polymerase. Base excision repair involves multiple enzymes to excise and replace individual damaged nucleotide bases. The repair method can be further divided into short patches and long patches. Short patches are used to repair one nucleotide, while long patches are used to repair nucleotide chains of two nucleotides or more. At present, whether cells choose short patches or long patches for repair is still under study.

(6) Double-strand break repair

Double-strand break repair, also known as recombination repair or template-assisted repair, is one of the most complex and time-consuming repair mechanisms because DNA double-strand breaks are among the most severe types of damage. Double-strand breaks in DNA cause the genomic sequences to be lost and require rearrangement. These breaks are repaired by non-homologous end joining (NHEJ) or homologous recombination (HR). This repair mechanism is activated upon DNA double-strand breaks and involves multiple enzymes and signaling pathways. However, this kind of repair cannot completely remove the damage, and the damaged DNA segment still remains on the parental DNA strand, but after multiple replications, the damage is diluted.

V. FACTORS AFFECTING DNA REPAIR

(1) Age

As we age, the ability of cells to repair gradually declines. Research has shown that age is an important factor affecting the efficiency of DNA repair. Older adults have slower DNA repair and are prone to DNA damage, which can lead to chromosomal aberrations and the development of diseases such as cancer.

(2) Environmental factors

Environmental factors are also important factors affecting DNA repair. For example, environmental factors such as ultraviolet radiation and chemical toxins can cause DNA damage and inhibit the ability of DNA to repair. At the same time, these environmental factors may also lead to mutations in DNA repair mechanisms, which in turn lead to a decrease in DNA repair ability and increase the risk of diseases such as cancer.

(4) Nucleotide excision repair

Nucleotide excision repair (NER) is commonly used by mammals as the main pathway used to remove bulky DNA lesions, such as those formed by ultraviolet light, environmental mutagens, and some cancer chemotherapy in DNA. This repair method is relatively complicated, and more than 20 kinds of proteins are involved in the repair.

(5) Mismatch repair

Mismatch repair is the repair of wrongly paired bases during DNA replication. DNA polymerase-delta, for example, has proofreading activity, and when an error is detected, these polymerases stop the DNA replication process, remove the erroneous nucleotides from newly synthesized strands, wait until the apparently incorrect nucleotides disappear, and then restart Copy process. Mismatch repair is essential to maintain the genomic stability of DNA.

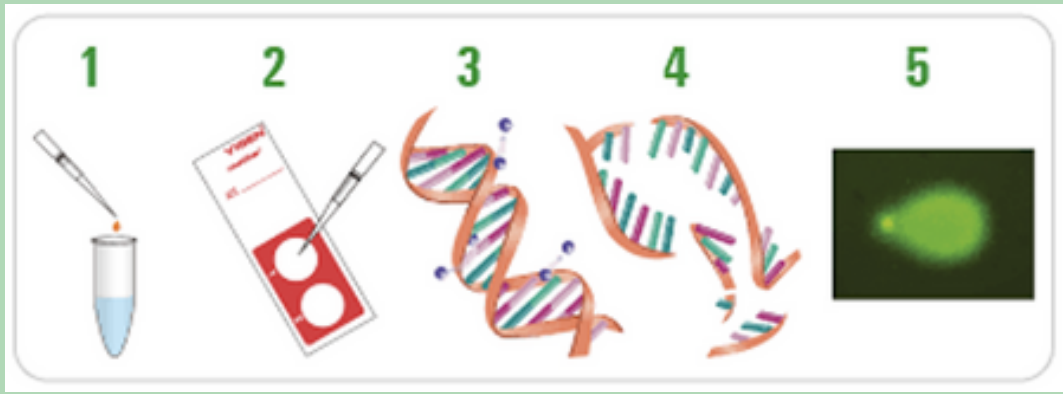

Figure 3. Comet assay simple operation process

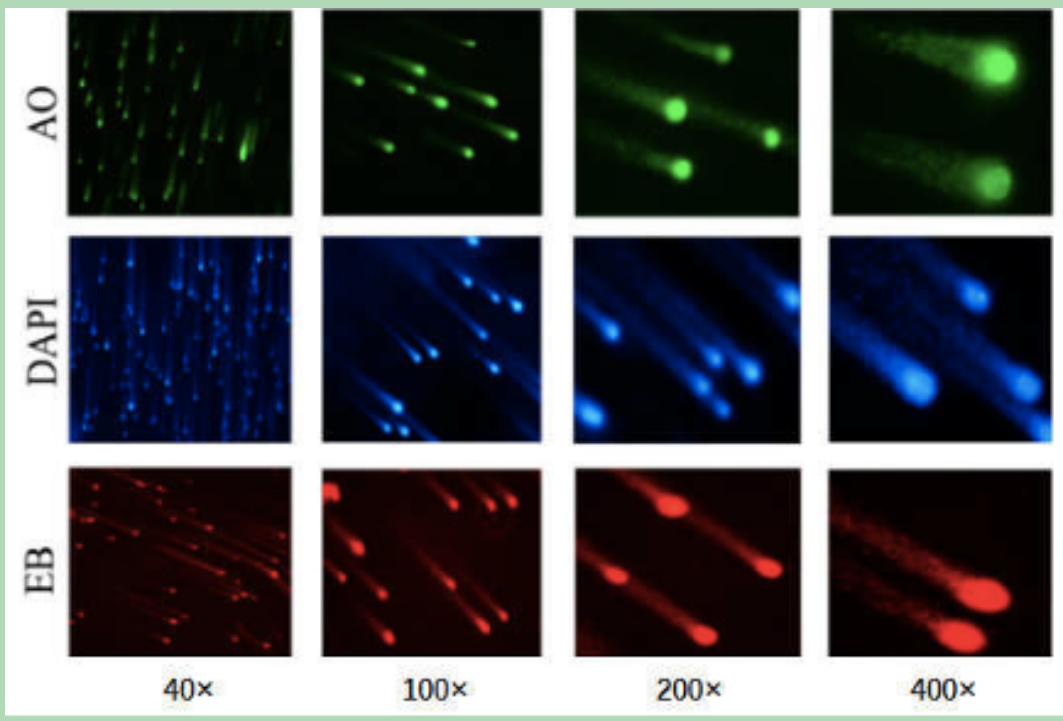

Figure 4. The result of the comet assay after image processing

3) Genetic factors

Genetic factors can also affect the ability to repair DNA. If an individual carries a mutation in a DNA repair gene, it can lead to a decrease in the ability to repair DNA, increasing the risk of DNA damage, mutations, and diseases such as cancer. For example, mutations in the BRCA1 and BRCA2 genes are among the main genetic causes of breast and ovarian cancer.

To sum up, age, environmental factors, and genetic factors all have an impact on DNA repair. In order to maintain good health, we need to avoid environmental pollution and exposure to harmful substances as much as possible, and at the same time pay attention to lifestyles such as exercise and a healthy diet to maintain a healthy DNA repair ability. In addition, genetic factors cannot be ignored. If there are related genetic mutations, they should be detected and treated in time to prevent or reduce adverse effects such as DNA damage and mutations.

(2) Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) is a cytogenetic technique that can be used to detect the presence of a specific nucleotide sequence on a gene body and to observe gene expression by detecting the expression of mRNA. Compared with other detection methods, the fluorescent in situ hybridization technology can directly observe the distribution of the target nucleic acid sequence in cells or tissues; it can also use different fluorescent proteins to simply color distinguish between different target sequences.

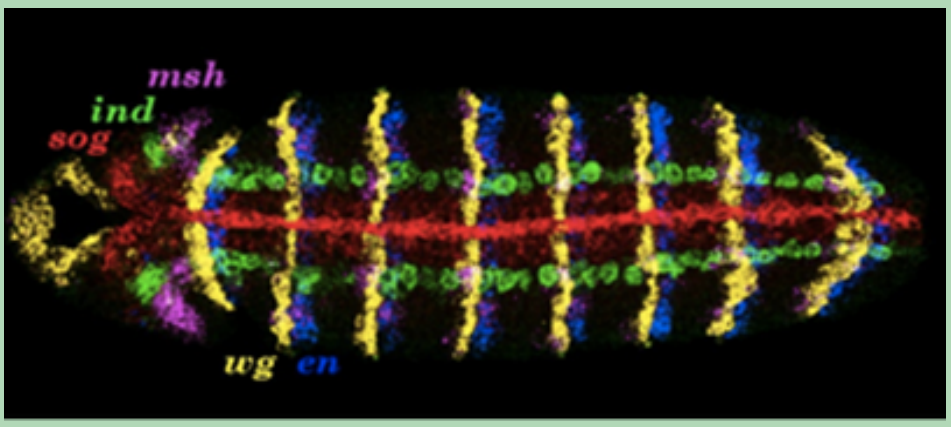

Figure 5. Schematic diagram of the simultaneous detection of the expression and distribution of five different gene products in Drosophila using the fluorescence in situ hybridization technique

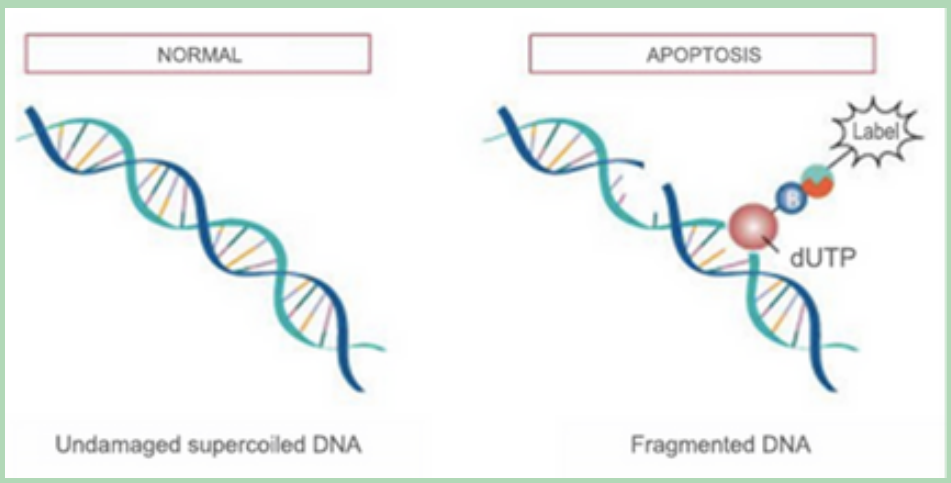

Figure 6. Schematic diagram of binding labeled dUTP to chromosomal DNA

VI. DNA DAMAGE DETECTION TECHNOLOGY

In this paper, four DNA damage detection techniques were selected from several DNA damage detection techniques, namely comet assay, fluorescence in situ hybridization, 8-OHdG detection, and TUNEL detection.

(1) Comet Assay

Comet Assay, also known as Single Cell Gel Electrophoresis (SCGE), is a fast, sensitive, and simple method for detecting DNA damage. In this test, cells are embedded in an agarose gel, and after electrophoresis, the DNA is stretched into a "comet tail," the length of which is proportional to the degree of DNA fragmentation. This test can be used to assess the extent of DNA damage from chemicals, radiation, and other environmental factors. No matter what factors induce DNA damage, DNA damage will affect its higher-level structure and make its supercoil lose. During electrophoresis, the damaged DNA will overflow from the nucleus and swim towards the anode, creating a tail band, while the undamaged DNA part remains spherical, and finally, the two together form a "comet". The fluorescence intensity of "comet" is related to the degree of DNA damage. Therefore, after "comet" fluorescent staining or silver staining, DNA damage in a single cell can be quantitatively detected.

(3) 8-OHdG detection

8-OHdG (8-hydroxy-2-deoxyguanosine) is a product generated by free radicals attacking DNA or free nucleotides in the body. Afterward, the oxidized deoxyribonucleic acid is cut out by the repair enzyme in the organism and enters the saliva, urine, and plasma, which are finally excreted from the body. However, the amount of 8-OHdG will be affected by the individual's specific lifestyle and habits, so the detection of 8-OHdG can also be used for oxidative stress health assessment.

(4) TUNEL detection

Normal cells have different repair systems to maintain DNA stability, and in the late stage of apoptosis, chromosomal DNA will begin to break and produce a large number of 3'-OH ends, so it can be passed through terminal deoxynucleotidyl transferase (TdT), bond the pre-labeled dUTP to it. Therefore, the situation of cell apoptosis can be reflected by observing the labeled dUTP. This method is called "terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling", or TUNEL detection for short. In simple terms, this is a method of detecting DNA fragments by labeling the ends of nucleic acids.

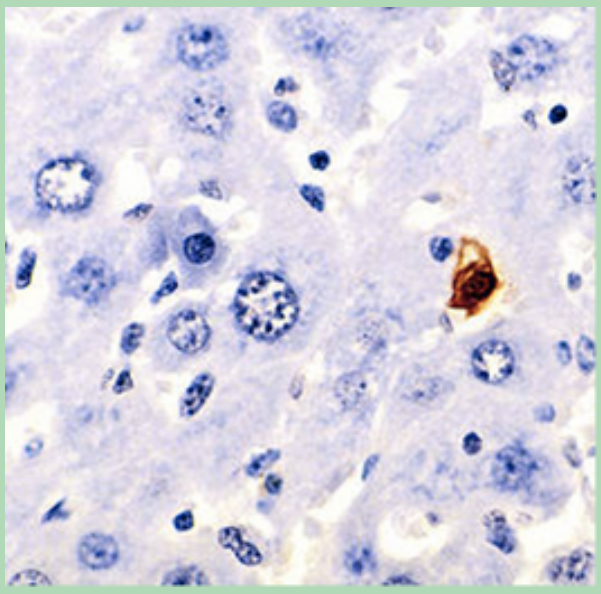

Figure 7. showing an apoptotic cell in a mouse liver by TUNEL assay

VII. CONCLUSION

DNA repair is a critical process for maintaining genome stability and preventing cancer and other diseases. DNA damage is unavoidable daily, but a timely repair can avoid its fatal consequences. Therefore, studying the mechanism of DNA repair and exploring how to promote or accelerate the DNA repair process is of great importance to human health and medical research.

With the continuous advancement of technology, more and more types of DNA damage have been discovered, and the repair mechanism is constantly updated. In future studies, we need to explore more DNA repair mechanisms, especially for some known but not yet thoroughly studied damage types. At the same time, the development of more advanced technologies, such as high-throughput sequencing and single-cell technology, will help to better understand the complex process of cellular DNA repair. In addition, studying the interplay between DNA repair and other cellular processes, such as cell cycle, transcription, and metabolism, will further expand our understanding of the DNA repair process. Ultimately, applying these research results to real life to promote more effective DNA repair and treat diseases will become the future direction of DNA damage and repair research.

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CHINESE VERSION

English version is in the front

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http://www.ilpapaveroros soweb.it/article/onu-pesticidi-inutili-provocano-200000-morti-allanno

环境污染物与孕妇健康

简介

环境污染物在提到影响孕妇健康时就不得不提两个人们熟知的污染物质，细颗粒物（PM）和农药。随着环境污染和极端气候的出现，提到细颗粒物，为人们熟知的来源可能是汽车尾气，烟雾等，然而PM也可能存在于被人们所忽视的地方，比如道路粉尘和海盐等。农药是农业发展不可或缺的重要组成部分，然而就像蕾切尔《寂静的春天》的文中所提出二氯二苯基三氯乙烷(DDT)，尽管大多农药在被推出时宣称对人体无副作用，但是实际上农药所具有的高毒性，高生物积累性和高持久性的特点，都带来了潜在的糟糕的影响。孕妇在产前独立的空间所含有的细颗粒物，饮用水和食品中含有的农药都极大的影响了孕妇的身体状态和胎儿的生长发育进程。

细颗粒物与产妇健康

在世界卫生组织于2022年发布的第六个6000多个城市的第五个空气质量数据库的更新中发现，尽管各个国家都采取降低空气中颗粒物的含量，数据显示全世界绝大多数城市远超世卫组织规定的空气质量指南水平。同时，在评估的城市总人口中，只有约17%居住在空气质量符合此类水平的城镇。同时工业化的快速发展和GDP的断层式上升，可能意味着颗粒物排放量的增加。据2000年至2016年的数据表示，摩纳哥的年平均工业PM2.5排放量最低为3381公斤，而美国排放量最高为4，721，297，957千克。高排放量可能意味着潜在的全球健康风险。

细颗粒（PM）通常表征为PM2.5，质量浓度小于2.5μm，具有相对较小的粒径和较大的比表面积，吸附有害物质的能力较强，这使得重金属更容易富集。PM一直以来因其对可见度影响较大而备受关注，而最近一些研究表明接触空气中的颗粒物（PM）与孕妇的不良反应具有一定的相关性。在现有的研究中，PM主要通过三种可能的暴露途径进入人体：吸入，食物摄入和皮肤接触吸收。如果PM以吸入的方式进入体内，由于PM的粒径较小会以更高的速率更深入地穿透呼吸道，并积累在呼吸道细支气管和肺泡中或进入血液，引起一系列呼吸道和肺部疾病。同时，PM可能会从肺部间隙渗入，PM含有的不同重金属在体内会引发相关的炎症。有文献证明孕妇在妊娠晚期暴露在PM2.5的环境下，可能会导致孕妇和胎儿呈现促炎状态。PM中含有的重金属可以穿过胎盘，改变其功能和基因表达并被胎儿吸收，这是一个非常危险的信号，PM可能对胎儿营养和生长产生不利影响。环境中颗粒物增加被证明与出生体重、早产率呈正相关。产前和产后暴露于PM也被证明都与婴儿和孕妇哮喘的后期发展有关。甚至，PM与早产和流产也被证实具有一定的相关性。

农药与孕妇健康

农药一般包括多种除草剂、杀虫剂、杀菌剂等，是现代农业中不可或缺的一部分，在过去的数十年来，农药极大的提高了全球粮食产量。据估计，市场上近三分之一的农产品都是借助于杀虫剂生产的。有研究表明，全世界每年约有35亿公斤的农药喷洒在农田上。

在大量使用农药的同时，一些糟糕的事情出现了。

据研究发现全球74.8%的农业用地（约28万平方公里）具有一定的农药污染风险。在沿海地区的试样检测中在超过50%的样品中观察到农药残留。农药的使用常用于达到杀死害虫和控制杂草的目的，然而对植物和昆虫有毒性这一特点，也进一步引起了更多学者对农药是否对人类有危害健康的风险做出探讨。由于农药的高生物积累性，高毒性，高持久性的特点，在水、空气、土壤和食品中都可能检测到农药残留物，同时其生物积累性，农药在整个食物链上传递并积累，带来了极大的健康隐患。

有研究估计，全世界每年大约有3.85亿无意的、急性的农药中毒（UAPP）病例，包括大约11000人死亡。最近，多项研究证明在孕妇的体内外也检测到了农药及其代谢产物的存在。在法国孕妇头发中检测到了大量农药及其代谢物，标志着孕妇的农药暴露情况和程度。在83%的受试孕妇的血浆中检测到多种农药，并与怀孕期间空气样本中的农药具有一定程度上的一致性。在孕妇的尿液中检测到了有机磷农药和其代谢产物的残留新生儿出生体重的降低可能是农药带来的氧化损伤和遗传毒性增加的结果。暴露于一些农药可能会降低甲状腺素浓度，并且孕妇产前暴露于农药会导致不良的神经发育影响。因此孕妇可能更应该注意产前的环境成分和影响。

结论

在前几个部分的了解中，我们发现尽管各国施行新的污染物管理政策，但环境污染物仍然处于增加的状态，尤其是农药，每年推出的农药不计其数，然而人们对于是否农药不危害人体健康这一问题的观点却闭口不提。对于细颗粒物，可能人们对于细颗粒物的认知往往停留在雾霾这一形式，但是实际上PM10，PM2.5等环境颗粒物可以以多种形式注入人体。孕期的女性对所处的空气环境和食物标题等极为敏感，PM和农药的增加可能一定程度上提高了全球孕妇健康风险的经济压力。

肺结节诊治

随着大家认知的提高以及更加关心自己身体的健康，有越来越多的人们加入到了体检大军。然而不幸的是，许多人在体检中发现了自己竟然有肺结节。面对这个陌生的疾病显然有些不知所措。其实，只要得到合理的管理和诊治，肺结节并不可怕。那么什么是肺结节呢?

肺结节，是指肺内直径小于或等于3 cm的类圆形或不规则形病灶，可表现为密度增高的阴影，边界清晰或不清晰的病灶。不同密度的肺结节，其恶性概率不同，依据结节密度将肺结节分为三类：实性结节、部分实性结节和磨玻璃密度结节。其中，部分实性结节的恶性概率最高，依次为磨玻璃密度结节及实性结节。（CJLC NCBI，2016）。

察觉到一丝不安

36岁的小王（化名）正值身强力壮的花样年华，但由于家境贫困，无奈之下只能远走他乡在福建某化工厂上班。一个月前小王出现了咳嗽，没有发热。年轻的小王只以为是工作劳累休息休息就好，可女朋友却认为到当地社区医院检查检查更放心。经过CT检查发现小王右上肺多发磨玻璃结节，最大0.6cm x 0.5cm。一听自己肺上竟然长东西了，小王便立马联想到了肺癌，认为自己得了绝症。为了进一步给小王确诊，医生将他转至上级医院。

不幸中的万幸

转诊上级医院后，医生进行了增强CT检查，发现小王多发磨玻璃结节且边缘不规则。在与患者和家属沟通后医生决定执行胸腔镜右上肺楔形切除术。术中冰冻病理证实非小细胞肺腺癌，原位癌。所说肺癌死亡率极高，但如果能在IIA期以前切除肿瘤/结节的话，那么5年生存率是非常可观的，达到了60%以上，每往前推一期生存率增加10%。

是否应该手术

转诊上级医院后，医生进行了增强CT检查，发现小王多发磨玻璃结节且边缘不规则。在与患者和家属沟通后医生决 由于胸腔镜手术伤害极小，小王恢复非常好，没过两天就能沟通自如，甚至还向医生请教有那么多种肺结节，难道全部都要做手术吗？现在仅中国已知肺结节患者高达惊人的1亿2000万名。医生介绍说：并不是所有肺结节都需要手术。医生会根据密度，大小，形态，生长部位以及生长速度综合判断。当出现分叶，毛刺，胸膜凹陷症便提示有可能是恶性。部分实性结节实性成分>50%常提示恶性的可能。持续存在的磨玻璃结节大多为恶性，CT值高则恶性概率大。肿瘤标志物作用较小但当PET-CT SUV值大于2.5时恶性肿瘤可能性比较大。最后根据临床信息如年龄，职业，吸烟史和家族史综合决定。如恶性概率小，那么可以随访3/6/12个月。如果肺结节朝恶性发展那么建议立即手术，如果结节大小形态不变或进行抗炎治疗后结节缩小那么可以继续12个月随访。最后，建议年龄大于40岁，且吸烟大于每年400支/曾吸烟每年400支但戒烟时间不超过15年的，暴露于高危职业的（如石棉，化工）的，合并COPD的，有家族患有肿瘤史的，长期接触厨房，二手烟的人们每年至少做一次低剂量CT进行筛查（浙大一院，2023）。

定执行胸腔镜右上肺楔形切除术。术中冰冻病理证实非小细胞肺腺癌，原位癌。所说肺癌死亡率极高，但如果能在IIA期以前切除肿瘤/结节的话，那么5年生存率是非常可观的，达到了60%以上，每往前推一期生存率增加10%。

引用：(Qinghua ZHOU), 周 清华, et al. “中国肺部结节分类、诊断与治疗指南(2016年版).” PubMed Central (PMC), https://doi.org/10.3779/j.issn.1009-3419.2016.12.12.

Pic：Baidu 肺结节 public picture

SMART

病毒介紹—和伊波拉一樣恐怖的病毒：馬爾堡

一、 前言

1967年德國馬爾堡的一處實驗室突然爆發一種病毒，感染的人出現了高燒、腹瀉、出血等症狀，在31個感染者中有7人死亡，後來經調查發現，原來是實驗室進口了來自烏干達被感染的非洲綠猴，而有25名患者和這些猴子都有密切接觸，原本猴子是用來研究小兒麻痺疫苗，結果卻意外爆發疫情。

提到馬爾堡病毒就不得不提起伊波拉病毒，都是絲狀病毒，它們來源不明，人畜共患，會造成出血熱，患者初期主要出現發高燒、肌肉酸痛、頭痛，3～5天後全身出現紅疹、伴隨嘔吐、腹瀉、嗜睡、嚴重出血由於馬爾堡出血熱何期他傳染病的症，患者死因通常為休克及失血過多，病毒主要通過體液傳播（血液及唾液），在1967年德國的疫情中就有兩名醫生就是在抽血時不慎接觸患者血液而染病。世界衛生組織表示馬爾堡病毒在開發中國家的死亡率為88%～100%。目前沒有任何特效藥或疫苗，主要的治療方法為平衡患者的電解質、補充失血、治療併發症。

PHOTO BY BONNIE JO MOUNT/THE WASHINGTON POST VIA GETTY IMAGES

二、正文

（一） 病毒介紹

馬爾堡病毒被分類在單股反鏈病毒目，絲狀病毒科，馬爾堡病毒屬，形狀像絲線，長度為800～14000（nm），在長度為790（nm）時感染力最強，由7種蛋白質組成，是人類發現的第一種絲狀病毒。由於馬爾堡出血熱和其他傳染病的症相似難以區分，所以主要的確診方法有：TR-PCR、酶聯免疫吸附測試（ELISA）、抗原檢測試驗，因馬爾堡病毒有極高的生物危害風險，所以非滅活性樣本必須在C4級別的實驗室才可進行檢測。

（二） 疫苗及相關藥物

世界衛生組織表示，目前正在開發單克隆抗體，在伊波拉病毒臨床研究中使用的瑞德西韋（Remdesivir）、法匹拉韋（Favipiravir）等抗病毒藥物可作為同情用藥。

Zabdeno (Ad26.ZEBOV)：此疫苗為抗埃博拉疫苗，在2020年5月被歐洲藥品管理局批准可作為預防馬爾堡病毒的疫苗。

Mvabea (MVA-BN-Filo)：此nRNA疫苗原本是抗埃博拉疫苗，疫苗中含有的MVA病毒（Vaccinia Ankara Bavarian Nordic ）經過修飾後可以產生絲狀病毒的四種蛋白質，在2020年5月和Zabdeno一同被歐洲藥品管理局批准作為預防馬爾堡病毒的疫苗。

以上兩中疫苗皆未在臨床實驗中得到證實。

三、結論

（一） 如何預防

1. 避免接觸患者遺體
非洲爆發了許多次疫情都是和當地的下葬風俗相關。患者遺體應在24小時內入殮並火化。

2. 避免和野生動物接觸
果蝠被認為是天然宿主，且在果蝠身上的馬爾堡病毒可以直接傳染給人類，所以要避免長期暴露在果蝠棲息的礦脈與洞穴，如果必須進入洞穴（如：工作、觀光）應戴手套並穿適合的衣物。

3. 保持手部清潔
手是最容易接觸到眼口鼻的部位，所以洗手是重要的防疫觀念。

4. 避免接觸患者體液
馬爾堡病毒在人類間的傳播是透過體液，所以要避免接觸被污染的環境和患者的體液，照顧患者應穿戴好防護裝備，也要避免和患者發生性行為直到確定體液無病毒為止。

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5. which are cancer precaution?
According to scientific research, 1/3 of cancers can be prevented, 1/3 of cancers can be cured if diagnosed early, and 1/3 of cancers can reduce pain and prolong life. i. Healthy diet: can bring vitamins and mineral elements to the body, used to enhance resistance ii. moderate exercise: enhance the metabolic capacity of cells, improve the function of the circulatory system and cardiopulmonary system iii. avoid excessive exposure to ultraviolet radiation or take sun protection measures iv. reduce exposure to outdoor and indoor air pollution.

癌症的发病机制

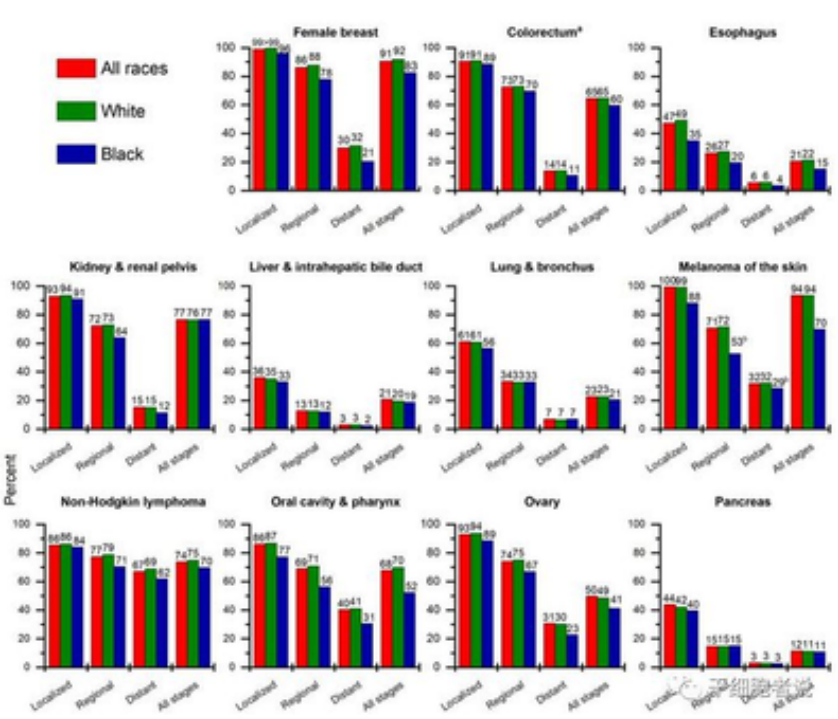
癌症的产生机制 VOCAB
肿瘤 TUMORS
化学致癌物 CHEMICAL CARCINOGENS
辐射 RADIATION
细胞癌变 CELL CARCINOGENESIS
淋巴系统 LYMPHATIC SYSTEM
癌症转移 CANCER METASTASIS

1. 什么是癌症

癌症又称恶性肿瘤，因人们身体内所有器官都是由细胞组成，当身体内细胞发生癌变后，便形成由大量癌变细胞组成的肿瘤。癌症是细胞对环境的适应能力的进化速度快于人体对细胞的掌控能力的进化速度而引起的。广泛癌症转移是癌症死亡的主要原因。

2. 为什么会引发癌症?

在日常生活中潜伏着许多致癌因子。致癌因子又可以分为物理致癌因子、化学致癌因子，和生物致癌因子。
物理致癌因子大多是γ射线、X射线，也就是紫外线和辐射。
化学致癌因子比较常见，比如尼古丁或黄曲霉素，这常见于坏了的花生、瓜子等。
生物致癌因子，例如由某些病毒、细菌或寄生虫引起的感染。



3. 癌症的发病机制

人类对肿瘤发病机制的认识经历一个漫长的过程，从过去单一和物理致癌、化学致癌、病毒致癌、突变致癌学说上升到多步骤、多因素综合致癌理论。最成功例子来源于美国霍普金斯大学Vogelstein实验室对结肠癌的研究。他们发现在结肠癌发生过程中所经历的增生、良性肿瘤、原位癌和浸润癌多步骤过程中，始终贯穿一系列分子事件变化。发现腺瘤中有Ras基因突变和抑癌基因APC和DCC丢失，在癌中有Ras基因突变以及抑癌基因APC、DCC、P53丢失。结肠肿瘤的发生似乎是由于抑癌基因APC的杂合性丢失而开始的。APC的缺失可以发生于生殖细胞或体细胞，导致逐渐增大的良性腺瘤。在良性腺瘤中常有其中一个细胞发生Ras癌基因突变而导致进一步克隆性发展。随后发生的抑癌基因DCC和P53缺失促进了良性到恶性发展过程。

4. 统计数据

在20年间，男性和女性的癌症死亡率总和下降了33%，癌症死亡人数的减少避免了大约380万人的死亡。对男性而言，前列腺癌占比最多，约有29%。对女性而言，其中乳腺癌最多，约占比31%。
据不完全统计，肺癌是第一致死癌症。数据显示，每天约有350人死于肺癌， 2023年，在127070例肺癌死亡病例中，约有103000例癌症将由直接吸烟导致，3560例癌症由二手烟导致。

mRNA 肿瘤疫苗
mRNA肿瘤疫苗属于核酸疫苗，它通过寻找可以编码肿瘤细胞抗原蛋白的氨基酸序列的基因。RNA肿瘤疫苗一般是翻译蛋白质，并以此为基础完成制备并注射入体内，通过人体细胞的蛋白质合成系统合成出特异性抗原蛋白，作为“靶标”，诱导人体产生对“靶标”的免疫，最终攻击肿瘤细胞。

优势：
短开发周期：MRNA疫苗的开发周期较短，因为一旦确定所需的MRNA序列信息，通过体外转录就可以实现快速、大规模生产。
双重免疫机制：MRNA疫苗具有双重免疫机制。除了编码抗原的MRNA能够刺激免疫应答外，MRNA本身也具有固有的免疫刺激特性。可以提高疫苗的免疫效果。
安全性： MRNA疫苗不会进入细胞核，因此不会导致潜在的基因组插入突变风险。

癌症的预防措施有哪些?

据科学研究发现，1/3的癌症是可以预防的，1/3的癌症如能早期诊断是可以治愈的，1/3的癌症可以减轻痛苦，延长生命。
I. 健康饮食：能带给身体维生素和矿物质元素，用来增强抵抗力
II. 适度锻炼：增强细胞的代谢能力，提高循环系统及心肺系统的功能
III. 避免过于暴露于紫外线辐射或采取防晒措施
IV. 减少接触室外和室内空气污染

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治疗肥胖症的方法

提尔西帕肽

作者: Leona

词汇

糖尿病是一种以高血糖为特征的代谢性疾病。高血糖则是由于胰岛素分泌缺陷或其生物作用受损，或两者兼有引起。长期存在的高血糖，导致各种组织，特别是眼、肾、心脏、血管、神经的慢性损害、功能障碍。

新每型周糖只尿需病注药射物一，次

背景

糖尿病是一种以高血糖为特征的代谢性疾病。高血糖则是由于胰岛素分泌缺陷或其生物作用受损，或两者兼有引起。长期存在的高血糖，导致各种组织，特别是眼、肾、心脏、血管、神经的慢性损害、功能障碍。

礼来（EliLilly）近日宣布，美国食品和药物管理局（FDA）已批准Mounjaro（tirzepatide）注射液，该药是一种新的、每周一次的GIP和GLP-1受体激动剂，辅助饮食和运动，用于改善2型糖尿病（T2D）成人患者的血糖控制。Mounjaro尚未在有胰腺炎病史的患者中进行研究，且不适用于1型糖尿病（T1D）患者。

值得一提的是，Mounjaro是美国FDA批准的第一个也是唯一一个GIP/GLP-1受体激动剂，该药同时代表着近十年来获批上市的首个新一类降糖药物。根据去年10月发布的三季度财报所披露的，礼来向FDA递交了一张优先审查凭证（PRV）来加速tirzepatide审查，该PRV可将审查周期缩短4个月。目前，tirzepatide也正在接受欧盟、日本和其他几个市场的监管审查。

糖尿糖是什么?

糖尿糖是一种慢性的代谢疾病，其特征为高血糖。在正常情况下，当人类进食后，身体所吸收的碳水化合物会被分解成葡萄糖，葡萄糖进入血液后会造成血糖上升，为细胞提供能量，同时葡萄糖亦能刺激胰岛素的分泌，而胰岛素是体内唯一降低血糖的激素，如果胰岛素无法分泌或者细胞对胰岛素不敏感的话，血糖将会降不下来，从而造成糖尿病。而高血糖会造成「三多一少」的症状，包括多饮、多食、尿频和体重下降。当体内长期存在高血糖，便会引起并发症，导致心脑血管疾病、截肢、失明、肾功能衰竭等问题。

糖尿病大概可分为四种类型，分别是一型糖尿病、二型糖尿病、特殊类型糖尿病以及妊娠糖尿病，但主要为一型以及二型糖尿病。一型糖尿病大多以儿童以及青年为主，他们是由于先天性的免疫问题而造成胰岛素分泌缺失，发病机制不明。二型糖尿病以成年人为主，是最为常见的类型，发病原因可能是由于遗传问题、生活方式以及环境因素等造成。

目前，糖尿病还没法治愈，但是可以通过合理的方法，提高患者的生活质量以及延长寿命。例如药物治疗和血糖监测等。药物治疗可分为口服药物以及注射药物，其中最先为人知的注射药物治疗是胰岛素。

图1 糖尿病的症状

Mounjaro(tirzepatide)是什么?

Mounjaro(tirzepatide)注射剂是由礼来公司(Eli Lilly)所研发的，在2022年5月被美国食品及药物管理局(FDA)批准用于治疗2型糖尿病患者。该药物是近十年来获批上市的新型降糖药物，也是第一以及唯一一个葡萄糖依赖性促胰岛素多肽（GIP）和胰高血糖素样肽（GLP-1）受体双重激动剂。GIP和GLP-1两者皆是人体胃肠道黏膜上所分泌的天然多肽，可以调节胰岛素和胰高糖素的分泌，还能增加饱腹感，有减重作用，达到降糖以及减重双重效果，患者只需每周进行一次注射就可保持血糖平稳。Tirzepatide一共推出了六种剂量（2.5mg、5mg、7.5mg、10mg、12.5mg、15mg），同时患者对于针头的恐惧，礼来公司也推出了自家专利，一款自动注射器装置—预装注射笔隐藏针头，针头会被「隐藏」起来，患者在使用时视觉上不会看到针头存在，针头用完即弃，为患者提供便捷、安全的注射过程。

总结

Mounjaro(tirzepatide)注射剂的好处在于其便利性，因为患者只需每周进行一次注射便可控制血糖水平，同时预装注射笔隐藏针头亦为患者提供安全且便利的方式去注射药物，令使用者增加依从性，降低对于注射药物时的恐惧。Tirzepatide除了是降糖药物外，它也是一种很强劲的减肥药物，但是由于tirzepatide为受体双重刺激剂，所以可能会比单靶点GLP-1的副作用更大，对于肥胖严重，或者是使用GLP-1后血糖控制不佳的患者，可以考虑使用tirzepatide。

图2 Mounjaro(tirzepatide)注射剂

在安全性以及有效性方面，礼来公司就tirzepatide展开了一系列全球性临床实验，其中包括为期40周的全球3期SURPASSO-2临床实验。在本次实验中，对比于使用索马鲁肽（semaglutide），tirzepatide对2型糖尿病患者在降低血糖的效果最为显着。受试者在注射15毫克的tirzepatide后，平均A1C（糖化血红蛋白）下降了2.46%，同时体重也减轻了12.4公斤，与注射semaglutixe相比，体重减轻了近两倍。如果注射5毫克的tirzepatide，则A1C会下降2.19%，而体重会减轻7.8公斤。与其他对照组相比，例如度拉糖肽(dulaglutide)、甘精胰岛素(Insulin Glargine)、德谷胰岛素(Insulin Degludec)、赖脯胰岛素(Insulin Lispro)等，tirzepatide在降低血糖以及减轻体重方面的效果也不错，尤其体重减轻有较大显着。

需要注意的是tirzepatide 尚未在有胰腺炎病史的患者中进行研究，而且该药物并不适用于1型糖尿病患者。以及使用tirzepatide时常见的副作用包括恶心、腹泻、呕吐、便秘等。

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introduction

人们已经在种系和胚胎和诱导多能干细胞中可以控制动物细胞的多样性分化，但在蛔虫、苍蝇、鱼或啮齿动物模型系统中尚未发现天然存在的成体多能干细胞。在这些动物种，真涡虫扁虫和空腔动物拥有特殊的成体干细胞群，统称为新生细胞，其中包括克隆新生细胞的多能亚群，具有使全身再生和明显无限的组织稳态的能力。目前人们虽然已经在新生细胞中鉴定出多能性调节因子并使用 RNA 干扰进行了研究，但缺乏可靠的培养方法和转基因方式限制了其发育出成人干细胞多能性的可能性。

关键词

电穿孔法
纳米萤光素酶
转染
地中海圆头涡虫

Current situation:

目前主要使用遗传转化策略：通过新生细胞增殖和分化进行无性繁殖，然后将这些细胞移植到缺乏新生细胞的宿主中（例如，在致死性辐射后），以在辐射后一个月内重新填充干细胞并拯救宿主。因此，在移植前将 DNA 或 RNA 转化为新生细胞可以产生转基因涡虫，并随后在理解动物多能性控制方面取得重大突破。但目前还没有报道描述新生细胞的更进一步发展和基因改造。目前缺少的是一种建立多能新生细胞的一种稳健的培养方法，该方法还需要能够有效筛选外源 DNA 或 RNA 的成功递送和转基因表达。

建立标准化的新成纤维细胞培养条件:

研究人员首先筛选了23种不同类型的培养基，包括报道的配方和其稀释版本，以更好地匹配适合涡虫细胞的渗透压。
对于细胞的生存能力，研究表明，在除CMFB（有或没有5%CO2条件）外的所有培养基中，都有高的细胞生存能力和低百分比的死细胞。在这些活细胞中，通过定量smedw-1+X1（FS）细胞的数量可以评估新成纤维细胞所占的比例。在稀释的（d）Grace's、IPM、Knock-Out DMEM、dL15、dKnock-Out-DEM、dSchneider's和dDMEM培养基中，与所有其他条件相比，存在更多的smedw-1+新成纤维细胞，并且这些新成纤维细胞都被证实是可存活的。这些新成纤维细胞也能够持续至少三天。这七种培养基被确定为本研究剩余部分的重点。
接下来，研究人员评估了培养的新成纤维细胞在体外分裂的能力。延时显微镜成像显示，新成纤维细胞确实发生了分裂。然而，只有在IPM、KnockOut DMEM和dL15培养基中观察到对称和不对称的细胞分裂，并且它们也比其他四种培养基具有更多的增殖细胞。在体外评估之后，还评估了体内分裂的能力。这种能力存在于在IPM、KnockOut DMEM、dL15、dKnockOut DM EM、dSchneider和dDMEM培养基中培养的那些细胞中，尽管对于所有这些培养基，这一能力在三天后都显著降低。最后，细胞的多能性通过拯救致命辐射的有性地中海圆头涡虫宿主的能力评估。对于此，在KnockOut DMEM中生长的细胞表现出最高和最强大的宿主拯救能力。

确立可移植新成纤维细胞的替代来源

然后，研究人员旨在丰富新成纤维细胞用于培养。研究发现，SiR-DNA/CT共染色方法在丰富smedw-1+新成纤维细胞方面表现出与Hoechst 33342分选方法相当的性能。通过这种共染色方法获得的细胞被命名为SiRNeoblast细胞。此外，这些SiR-DNA染色的细胞在染色后仍然可以在体内分裂，这在Hoechst 33342分选的细胞中是不可能的。在体外观察分裂的SiRNeoblasts的染色体分离动力学在试验条件下证实了细胞分裂的发生。总之，基于SiR-DNA/CT双标记的细胞分选可以用于分离新成细胞，并且这些分离的SiRNeoblasts可以被维持并作为未来的供体细胞。

电穿孔方式的外源性信使核糖核酸递送

在优化体外培养条件后，研究人员评估了不同条件将外源分子递送到新成细胞中用于涡虫遗传转化。右旋糖酐FITC进入X1细胞的最佳递送条件是100-120V。然而，施加电压对细胞是有害的，在移植到受过致命辐射的宿主中后，没有细胞在受到超过100V的电压后仍形成集落。使用SiRNeoblasts代替X1细胞表明，SiRNeoblasts在施加电压后更具活力，能在之后持续一天以上。然后，研究人员评估了外源性信使核糖核酸是否可以通过电穿孔传递到成核细胞中。引入tdTomato信使核糖核酸的最佳方式是在110V下，能很好地保持多能性和活力。此外，成功与否并不取决于RNase A的存在与否。

纳米荧光素酶mRNA在分化SiRNeoblasts细胞中的表达

为了检测tdTomato mRNA的表达，研究人员参考了先前的研究，其中报道了纳米荧光素酶mRNA在涡虫细胞中的表达。因此，他们怀疑NanoLuc报告基因可以提供对新生代细胞中转基因表达的跟踪。他们观察到NanoLuc存在表达，并且在具有5%CO2环境的修饰KnockOut DMEM中培养的SiRNeoblasts中的表达水平高于在没有补充剂的相同条件下生长的细胞。至于将NanoLuc mRNA递送到新成细胞中的方法，只有在TransIT转染后才能检测到NanoLucs信号，而在电穿孔中不能检测到。与TransIT转染相比，电穿孔始终达不到递送的效率和成功率。令人惊讶的是，没有一种其他mRNA（NanoLuc、smed-histone3.3-2xflag、mCherry或NanoLuc-mCherry）能够在新生代细胞中成功递送，并表达到通过蛋白质印迹法可检测的水平。此外，NanoLuc信号几乎完全转移到体细胞中，这表明涡虫新成纤维细胞能在分化前阻止外源核酸进入。

Discussion

无法对真涡虫进行基因改造对研究这种多能性和全身再生的高度通用模型构成了长期障碍， 其中主 要技术限制包括确定维持多能新生细胞的最佳培养条件，并确定将外源核酸输送到这些细胞中的有效方法。实验人员在这项工作中开发的细胞培养系统解决了前一个问题，并能够进一步测试外源物质传递的策略，例如荧光共轭葡聚糖和 mRNA。首先，使用 SiRNeoblasts 可确保新生细胞的纯度和活力，从而使筛选转基因递送策略相对容易。其次，转染和翻译的低效率也可能是由于培养细胞的代谢活性相对降低。添加补充剂后观察到的NanoLuc mRNA 翻译增强，说明 mRNA 的摄取和翻译取决于满足培养的新生细胞的代谢要求。第三，鉴于新生细胞实际上是涡虫的选择单位，而且这些动物的生存能力在很大程度上取决于它们的正常功能和生存能力，因此这些细胞进化出强大的分子机制来保护它们的基因组免受外来核酸破坏是合乎逻辑的酸。总之，研究人员描述了用于在体外维持克隆形成、多能新生细胞的 FACS 分离策略和原代细胞培养条件在短期内与受致死辐射的宿主的移植、再增殖等。

SMART MAGAZINE PRODUCTION

Author：Icey

SMART

INTRODUCTION

2020年10月7日傍晚，诺贝尔委员会宣布，埃马纽埃尔·卡彭蒂耶（Emmanuelle Charpentier）和詹妮弗·杜德纳（Jennifer A. Doudna）荣获2020年诺贝尔化学奖，以表彰她们研发出的CRISPR-Cas9基因编辑方法。这一里程碑式的科技创新被誉为基因编辑领域的重要突破。利用这一技术，动植物以及微生物的DNA可以背精准改变，更重要的是为癌症等疾病提供新的治疗方案，基因编辑的强大力量为各方面的研究做出突破。

CRISPR-细菌的战斗武器

CRISPR（Clustered Regularly Interspaced Short Palindromic Repeat), 是2002年，Jansen实验室通过生物信息学在细菌和古菌等原核生物基因组中发现的一段重复DNA序列。这些序列来自以前感染原核生物的病毒的DNA片段。CRISPR-Cas系统的运作机制于2011年被完整揭示。当病毒入侵细菌时，细菌能够捕捉到外来的DNA片段并且将其整合到自身基因组的CRISPR 序列中。当病毒再次入侵时，CRISPR转录生成前体crRNA (pre-crRNA)，之后便会形成cr-RNA。cr-RNA会识别病毒的基因组同源序列，介导Cas蛋白与其进行结合并切割。这是细菌和古细菌漫长的生物演化过程中形成的一种适应性免疫防御，因此是原核生物与病毒进行战斗的免疫武器。这也便是CRISPR-Cas9 基因编辑技术的起源。

图1：诺贝尔化学奖得主Emmanuelle Charpentier和Jennifer A. Doudna

基因剪刀——改写生命密码

编辑基因是深入探索生物内部系统的重要因素，这在一开始被研究者们认为是不可能的。正是“基因剪刀”CRISPR-Cas9技术突破了这一瓶颈。它的工作方式就像剪刀一般，切割DNA，之后重新编排基因代码。

2012年，两位科学家，也就是2020年诺贝尔得主首次将CRISPR-Cas系统运用于基因编辑技术。pre-crRNA可以通过碱基互补配对与tracrRNA形成RNA双链，tracrRNA是由重复序列区转录而成，具有发卡结构的RNA，而pre-crRNA是由整个CRISPR序列转录而成的大型RNA分子。随后，pre-crRNA，tracrRNA以及Cas9编码的蛋白将会组合选取对应的间隔序列RNA，并最终获得成熟crRNA。由此得到了crRNA，tracrRNA与Cas9的复合物。这一组合可以对DNA进行精准打击，通过扫描DNA序列识别与crRNA互补的序列，定位到位于DNA的PAM（protospacer adjacent motif）区域。此时DNA双链便会解开并于crRNA进行互补，Cas9在此时发起进攻，剪切DNA链，形成双链裂断（DSB）。这便是CRISPR-Cas9的作用原理。而它的基因编辑技术就是通过人工设计的sgRNA，也是guideRNA，来识别目标基因组序列，引导Cas9进行切割。损伤会造成基因敲除或基因敲入，从而对DNA进行编辑。

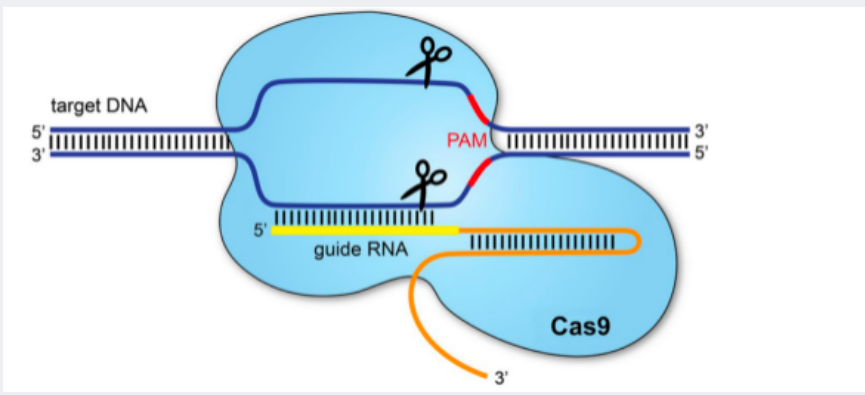


图2：基因编辑

未来展望

CRISPR/Cas9技术在未来有广泛的应用展望。首先，在基因疾病的治疗方面，CRISPR/Cas9可以精确地编辑人类基因组，纠正人类基因的缺陷，从而为基因疾病的治疗开辟新的途径。CRISPR/Cas9还可以用于生物农业领域，通过编辑植物和动物基因组，提高作物和牲畜的生产率和品质。此外，CRISPR/Cas9还可以用于环境修复，利用基因编辑技术改良环境污染物降解菌的能力，加速环境污染治。CRISPR/Cas9技术的未来应用前景非常广阔，将深刻影响人类健康、粮食安全、环境保护等领域的发展。

损伤及修复
DNA

作者: Katherine

关键字：分子生物学、DNA 损伤、DNA 修复

一、前言

DNA 是生命的基础，负责维护细胞的正常生命周期和功能。然而， DNA 很容易受到各种内部和外部因素的损伤。因此，了解DNA损伤和修复对于维护健康至关重要。

DNA 损伤是指 DNA 分子发生的任何改变，包括断裂、碱基损伤和交联等。这些损伤会导致基因突变、细胞死亡和异常增殖，从而导致疾病的发生。因此，了解 DNA 损伤的重要性是不言而喻的。

DNA 修复是指通过一系列机制恢复受损 DNA 的完整性和功能。这些修复机制可以大致分成三种类型：直接修复、碱基切除修复和重组修复。直接修复是指修复一些简单的DNA损伤，比如烷基化和光损伤等。碱基切除修复则是修复一些常见的 DNA 损伤，比如氧化损伤、异构化和单链断裂等。重组修复则是修复复杂的 DNA 损伤，比如双链断裂等。这些修复机制将在后面的段落做近一步的说明，了解这些修复机制能够帮助我们预防 DNA 损伤和疾病的发生。

目前已发现的人类遗传性疾病约有4000多种，其中不少皆与DNA修复缺陷有关。 1874 年，皮肤科医生 Moriz Kaposi ，首次描述着色性干皮病（Xeroderma Pigmentosum, XP）。他发现患者的皮肤干燥、有黑色斑点，且对阳光极为敏感。大约 100 年后， James Cleaver 发现着色性干皮病的发生，与 DNA 的修复缺陷有关。而这也是第一个发现的 DNA 修复缺陷性遗传病。

二、DNA 损伤的原因

DNA 虽然受到了人体的层层保护，但其实 DNA 还是很容易受到各种内部和外部因素的干扰而导致损伤，进而影响 DNA 的完整性和功能。 DNA 损伤的原因可大致分为三种，分别是化学损伤、物理损伤、生物损伤。

（一）化学损伤

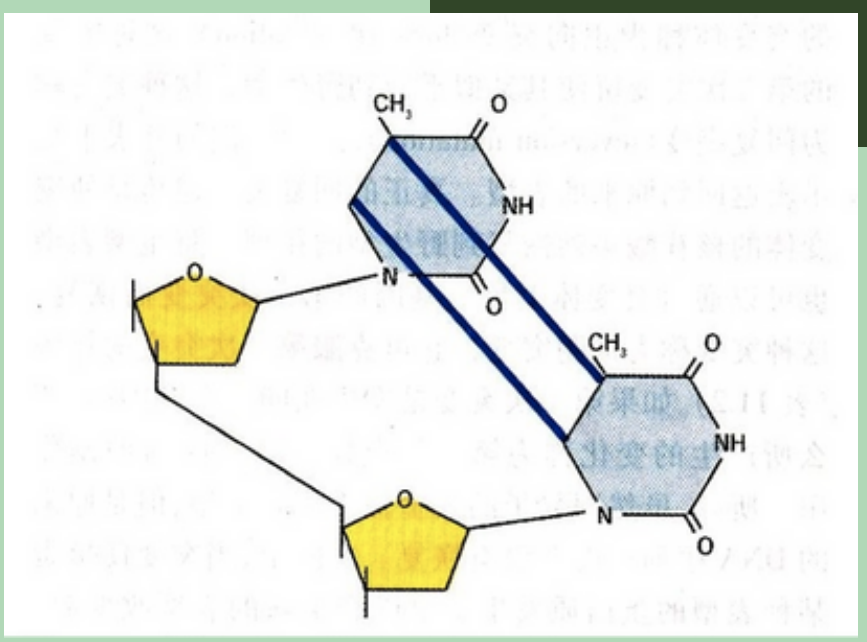
化学损伤是指由化学物质引起的 DNA 损伤。常见的化学损伤包括氧化损伤和烷基化。氧化损伤通常是由自由基和其他氧化物质所引起，这些物质会导致 DNA 分子中的碱基发生氧化反应。烷基化则是由含有烷基基团的化学物质引起的，这些化学物质会在 DNA 分子中引入异构化和碱基缺失。这些化学损伤会导致基因突变和细胞死亡等不良后果。

（二）物理损伤

物理损伤是指由物理因素引起的 DNA 损伤，例如紫外线（200 ～ 300 纳米波长）辐射、电离辐射（X 射线）是最常见的物理损伤因素。紫外线辐射会诱发 DNA 链中相邻的嘧啶键结，行程嘧啶二聚体。电离辐射会在细胞内产生自由基来引发 DNA 突变，自由基会产生活性氧（ROS）并导致双螺旋中的单链和双链断裂。

（三）生物损伤

生物损伤是指生物代谢过程中，间接造成的 DNA 损伤。例如代谢过程中产生的氧自由基或活性氧等。活性氧是最常见的生物损伤因素之一，它会在细胞内部产生，并引起 DNA 中的氧化损伤。同时，DNA 结构的稳定性也会受到影响，导致 DNA 突变和其他类型的损伤。除此之外，水解反应也是另一种常见的损伤。水解反应可以部分或完全从 DNA 链上切割核苷酸碱基。随着嘧啶环上胺基的丢失，细胞内将发生脱氨作用，产生其他不同种类的嘌呤和嘧啶，例如黄嘌呤等。这些内部因素可能会导致衰老、疾病、细胞死亡和神经退行性疾病等问题。不过除了代谢过程中产生的产物可能导致 DNA 损伤以外， DNA 复制、转录和转译的过程中，也有机率发生错误。例如 DNA 转录过程中，发生配对错误或是转录和调节因子的突变等。



图一、
嘧啶二聚体在光复活修复中，光裂合酶将切割两个深蓝色的键

三、DNA 损伤带来的影响

（一）突变和染色体异常

DNA 损伤可能导致基因突变和染色体异常。基因突变是指 DNA 序列发生了永久性改变，可能会影响蛋白质的功能，导致疾病的发生。染色体异常是指染色体结构或数量的改变，可能会导致胎儿畸形、生殖问题或癌症等疾病。染色体异常包括染色体缺失、重复、移位或结构异常等。

（二）细胞死亡

DNA 损伤可能导致细胞凋亡或坏死。细胞凋亡是一种程序性死亡，通常是细胞自身感应并执行的。细胞坏死则是一种非程序性死亡，通常由外部因素引起。 DNA 损伤可能会激活细胞死亡通路，使受损细胞死亡，从而保护其他细胞免受损伤细胞的影响。

（三）癌症发展

DNA 损伤是引起癌症发展的一个主要因素。癌症是由一系列基因突变引起的，这些突变可能会增加细胞分裂的速度和错误率，导致肿瘤的发生和扩散。 DNA 损伤还可能会导致癌前病变的发生，这些病变是肿瘤发生前的早期改变，可能最终发展成癌症。

四、DNA 的修复机制

DNA 的修复机制有很多种，随着人类的研究，也发现愈来愈多种机制。本文选了六种较常见的修复机制进行说明。

（一）光复活修复

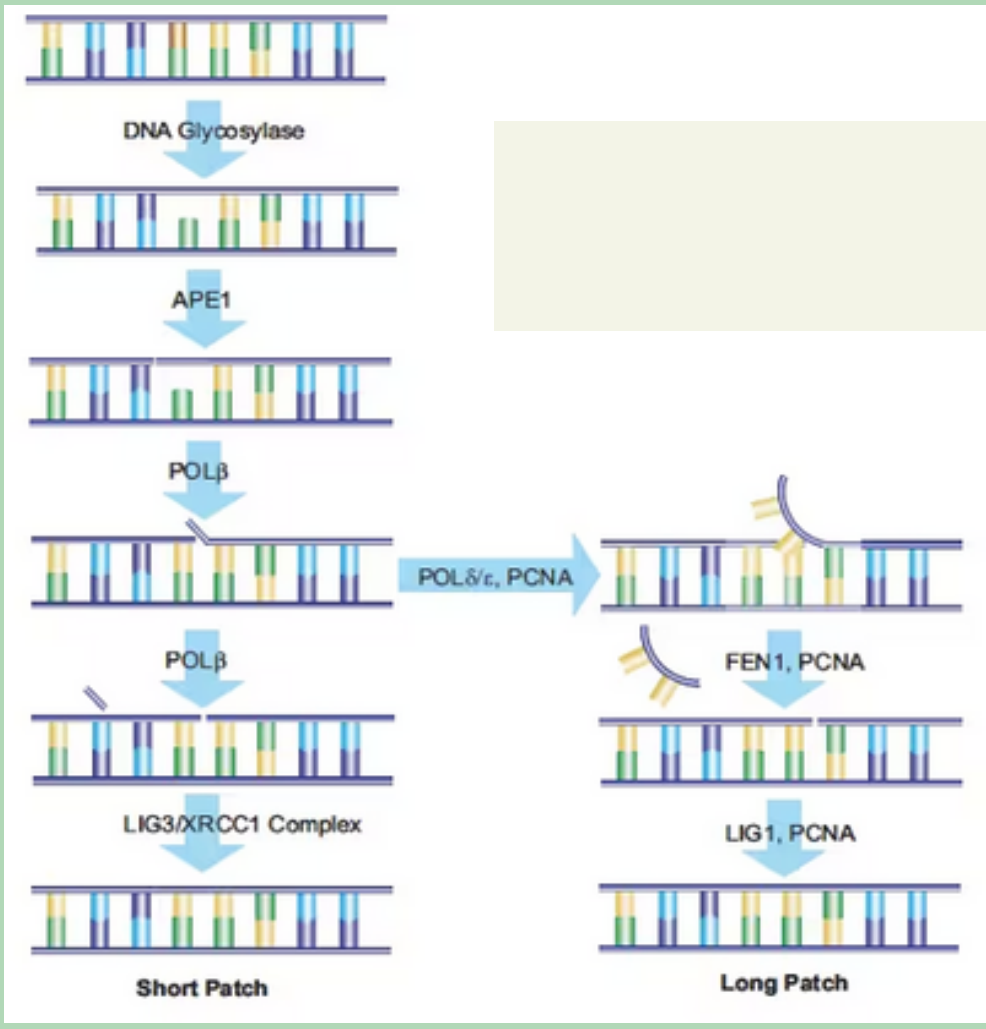
光复活修复是最早发现的 DNA 修复方式，主要是透过光裂合酶将嘧啶二聚体分解为2个单体，使 DNA 回复正常。当此酶受到 300 ～ 600 奈米波长的光照射就会被活化，专门修复由紫外线造成的嘧啶二聚体。不过此种修复方式不存在于高等哺乳类中。尽管这种方式具有局限性，但光复活修复机制在具有此种酵素的生物体中，仍扮演了很重要的角色。

（二）烷基化损伤修复

烷基化损伤修复是指利用 O6-甲基鸟嘌呤 DNA 甲基转移酶（MGMT，又称DNA 烷基转移酶）从 DNA 结构上的鸟嘌呤碱基切割甲基和乙基，将烷基化的损伤还原为正常状态。这是一种化学反应而不是催化反应，每去除一个甲基或乙基，就会消耗一个 MGMT 分子。在低剂量烷化剂作用下，即可能诱导出 MGMT 的修复活性，能将甲基从碱基转移到蛋白质的半胱氨酸上，进而完成 DNA 的修复。

（三）碱基切除修复

碱基切除修（BER）主要修复未显著扭曲 DNA 螺旋结构的小碱基损伤。这种损害通常由脱氨作用、氧化作用或甲基化作用引起。 DNA 糖基化酶首先会切除损伤的碱基，然后用 DNA 聚合酶将缺失的碱基替换回来。碱基切除修复涉及多种酶来切除和替换单个受损的核苷酸碱基。修复方式还可以更近一步分成短补丁与长补丁。短补丁用于修复一个核苷酸，而长补丁用于修复两个核苷酸（含）以上的核苷酸链。目前，细胞究竟选择短补丁还是长补丁来修复，仍在研究中。



图二、短补丁和长补丁的修复的示意图

（四）核苷酸切除修复

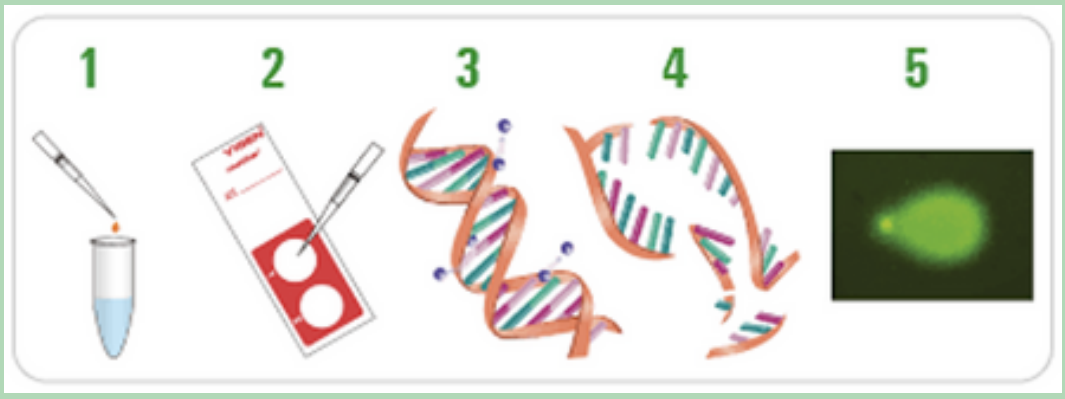
核苷酸切除修复（NER）通常用是哺乳动物用来去除大体积 DNA 损伤的主要途径，例如由紫外线、环境诱变剂和 DNA 中的一些癌症化疗形成的损伤。此种修复方式较为复杂，共有超过20种的蛋白质参与修复。

（五）错配修复

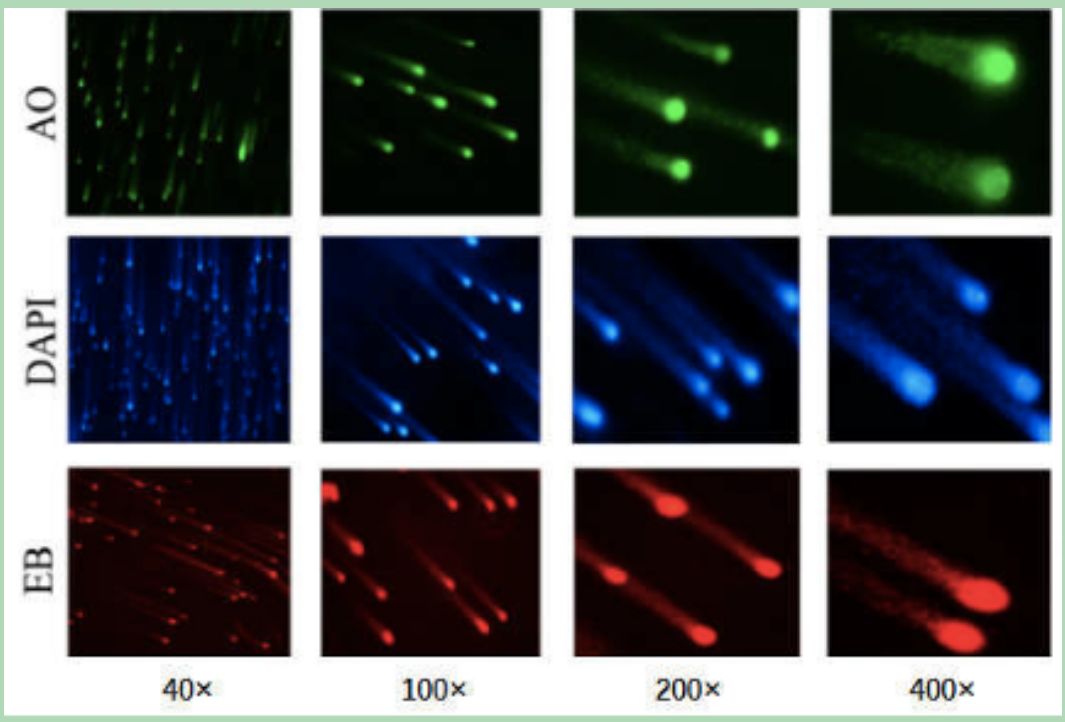
错配修复是指修复 DNA 复制时，配对错误的碱基。例如 DNA 聚合酶-δ 具有校对活性，当检测到错误时，这些聚合酶会停止 DNA 的复制过程，从新合成股上去除错误的核苷酸，直到明显不正确的核苷酸消失，然后再重新启动复制过程。错配修复对于保持DNA的基因组稳定性至关重要。

（六）双链断裂修复

双链断裂修复又称为重组修复或模板辅助修复，是一种最为复杂和耗时的修复机制，因为 DNA 双链断裂属于最严重的一种损伤。 DNA 中的双链断裂会导致基因组序列丢失，并且需要重新排列。这些断裂通过非同源末端连接（NHEJ）或同源重组（HR）修复。这种修复机制在 DNA 双链断裂时被激活，涉及多个酶和信号通路。不过此种修复不能完全去除损伤，损伤的 DNA 段落仍然保留在亲代 DNA 链上，但经多次复制后，损伤就被冲淡了。



图三、彗星实验简易操作流程



图四、彗星实验经图片处理之结果

（一）彗星试验

彗星试验（Comet Assay）又称单细胞凝胶电泳（SCGE），是一项可以快速、灵敏、简便的检测 DNA 损伤的方法。在此试验中，细胞被包埋在琼脂糖凝胶中，电泳后，DNA会被拉伸成一条“彗星尾”，尾部的长度与DNA的断裂程度成正比。这种试验可以用于评估化学物质、辐射和其他环境因素对DNA的损伤程度。不论是何种因素诱发 DNA 损伤， DNA 损伤后皆会影响其高级结构，使其超螺旋松散。电泳时，损伤的 DNA 将从细胞核中溢出，朝阳极方向泳动，产生一个尾状带，而未损伤的 DNA 部分则保持球形，最终二者共同形成 "彗星"。 "彗星"的荧光强度与 DNA 的损伤程度相关，因此将"彗星"荧光染色或银染色后，可以定量检测单个细胞中的 DNA 损伤。

五、影响 DNA 修复的因素

（一）年龄

随着年龄的增长，细胞的修复能力会逐渐下降。研究表明，年龄是影响 DNA 修复效率的一个重要因素。老年人的 DNA 修复速度较慢，容易发生 DNA 损伤，从而导致染色体畸变和癌症等疾病的发生。

（二）环境因素

环境因素也是影响 DNA修复的重要因素。例如，紫外线辐射和化学毒素等环境因素可以导致 DNA 损伤，并抑制 DNA 修复的能力。同时，这些环境因素也可能导致 DNA 修复机制的突变，进而导致 DNA 修复能力下降，增加发生癌症等疾病的风险。

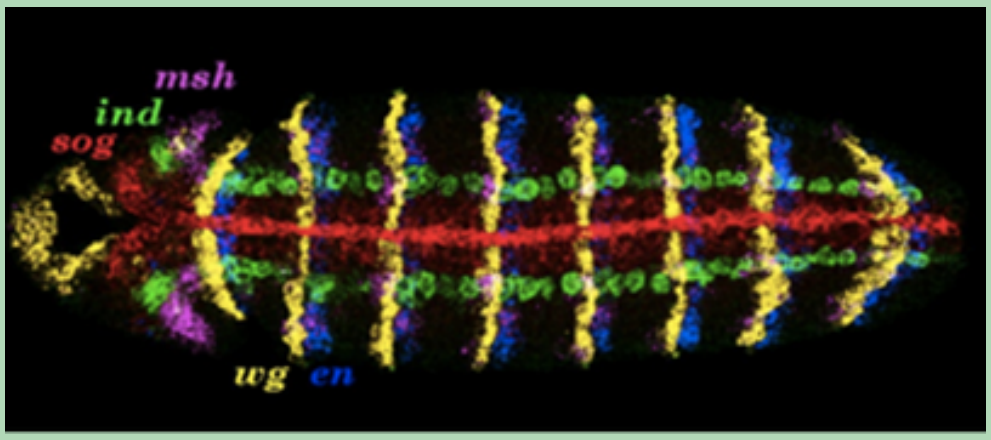
（三）遗传因素

遗传因素也会影响 DNA 修复的能力。如果个体携带的 DNA 修复基因突变，就会导致 DNA 修复能力下降，增加DNA 损伤、突变和癌症等疾病的风险。例如， BRCA1 和 BRCA2 基因突变，就是导致乳腺癌和卵巢癌的主要遗传因素之一。

综上所述，年龄、环境因素和遗传因素都会对DNA修复产生影响。为了维护身体健康，我们需要尽量避免环境污染和有害物质的接触，同时注重锻炼和健康饮食等生活方式，以维持健康的DNA修复能力。此外，遗传因素也是不可忽视的，如果存在相关遗传突变，应及时进行检测和治疗，以预防或减少DNA损伤和突变等不良影响。

六、DNA 损伤检测技术

本文从数种 DNA 损伤检测技术中，选择了其中四种 DNA 损伤检测技术，分别是彗星试验、萤光原位杂合技术、8-OHdG 检测和 TUNEL 检测。



图五、使用萤光原位杂合技术同时检测五种不同基因产物于果蝇体内的表现与分布示意图

（三）8-OHdG检测

8-OHdG（8-hydroxy-2-deoxyguanosine）是体内自由基攻击 DNA 或游离核苷酸所生成的产物，其后经由生物体内之修补酵素，将受到氧化之去氧核糖核酸切出，进入唾液、尿液、以及血浆，最终排出生物体外。不过8-OHdG的量会受个人特定的生活方式和习惯影响，所以8-OHdG的检测也可用于氧化压力健康评估。

（四）TUNEL 检测

正常的细胞会有不同的修复系统以维持 DNA 的稳定性，而细胞凋亡晚期时，染色体 DNA 会开始断裂，产生大量的 3’-OH 末端，因此可透过末端去氧核苷酸转移酶（TdT），将预先标记好的 dUTP 键结上去。因此能够透过观察标记的 dUTP，反映细胞凋亡的情形，此方法被称为"末端脱氧核苷酸转移酶脱氧尿苷三磷酸切口末端标记"，简称为 TUNEL 检测。简单来说，这是一种通过标记核酸末端，从而检测 DNA 片段的方法。

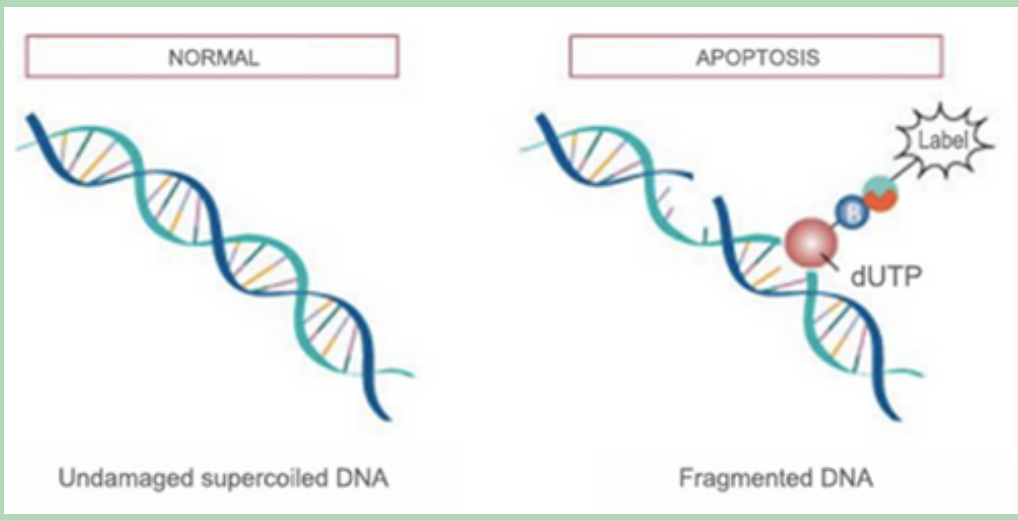
七、结论

DNA 修复是维持基因组稳定性、预防癌症和其他疾病发生的关键过程。 DNA 损伤在日常生活中不可避免，但及时修复能够避免其引发的致命后果。因此，研究 DNA 修复机制以及探索如何促进或加速 DNA 修复过程，对人类健康和医学研究至关重要。

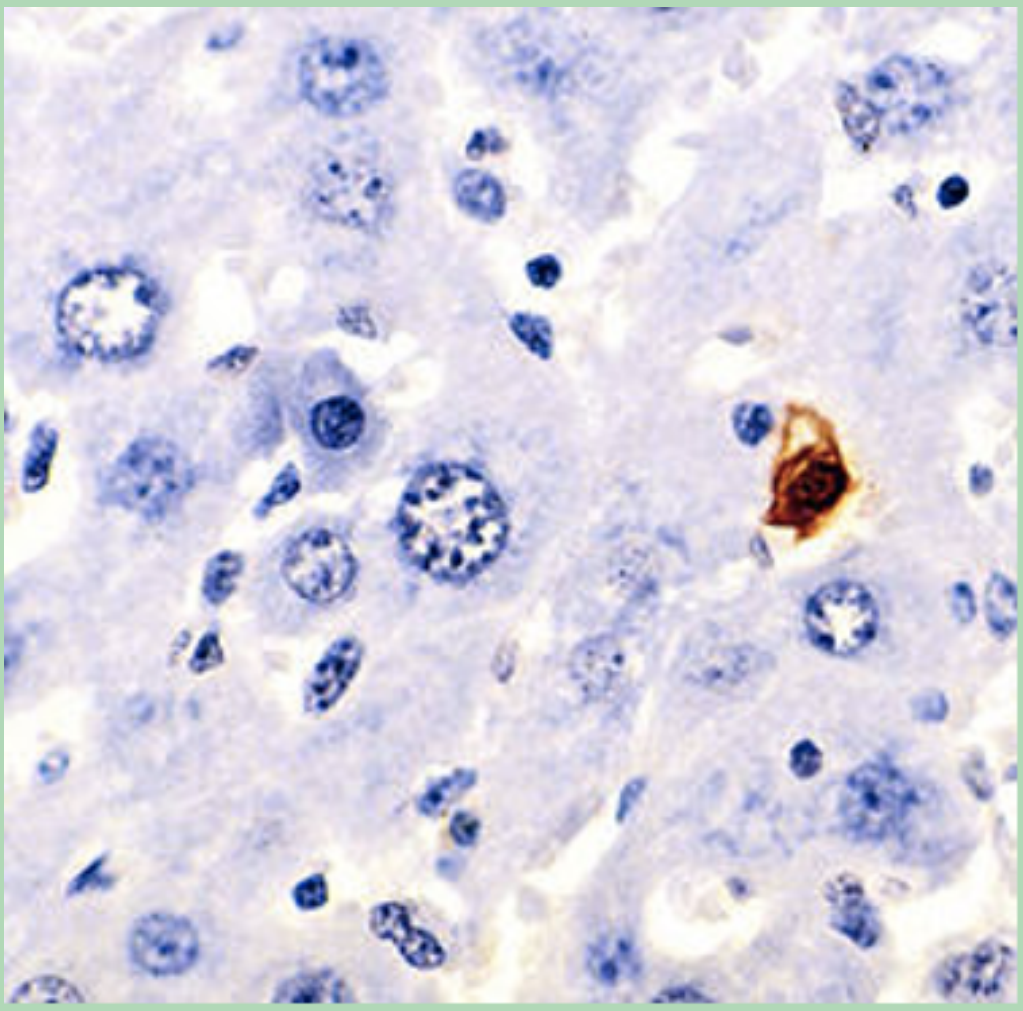
随着技术的不断进步，越来越多的 DNA 损伤类型被发现，并且修复机制也在不断更新。在未来的研究中，我们需要探索更多的 DNA 修复机制，特别是对于一些已知但尚未彻底研究的损伤类型。同时，发展更先进的技术，如高通量测序和单细胞技术，有助于更好的理解细胞 DNA 修复的复杂过程。此外，研究 DNA 修复与其他细胞过程之间的相互作用，如细胞周期、转录和代谢等，将进一步拓展我们对 DNA 修复过程的了解。最终，将这些研究成果应用到实际生活中，促进更有效的 DNA 修复和治疗疾病，将成为 DNA 损伤与修复研究的未来方向。

（二）萤光原位杂合技术

萤光原位杂合技术（FISH）是一种细胞遗传学技术，可以用来检测基因体上面特定核苷酸序列的存在，亦可藉由检测 mRNA 的表现量来观测基因的表现。相较于其他检测方法，萤光原位杂合技术更能够对目标核酸序列在细胞内或是组织内的分布有视觉性的直接观察；还可以利用不同的萤光蛋白，简单的以颜色来分辨不同的目标序列。



图六、将标记的 DUTP 键结到染色体 DNA 上之示意图



图七、以TUNEL检测展示出小鼠肝脏中的一个凋亡细胞

八、参考资料

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