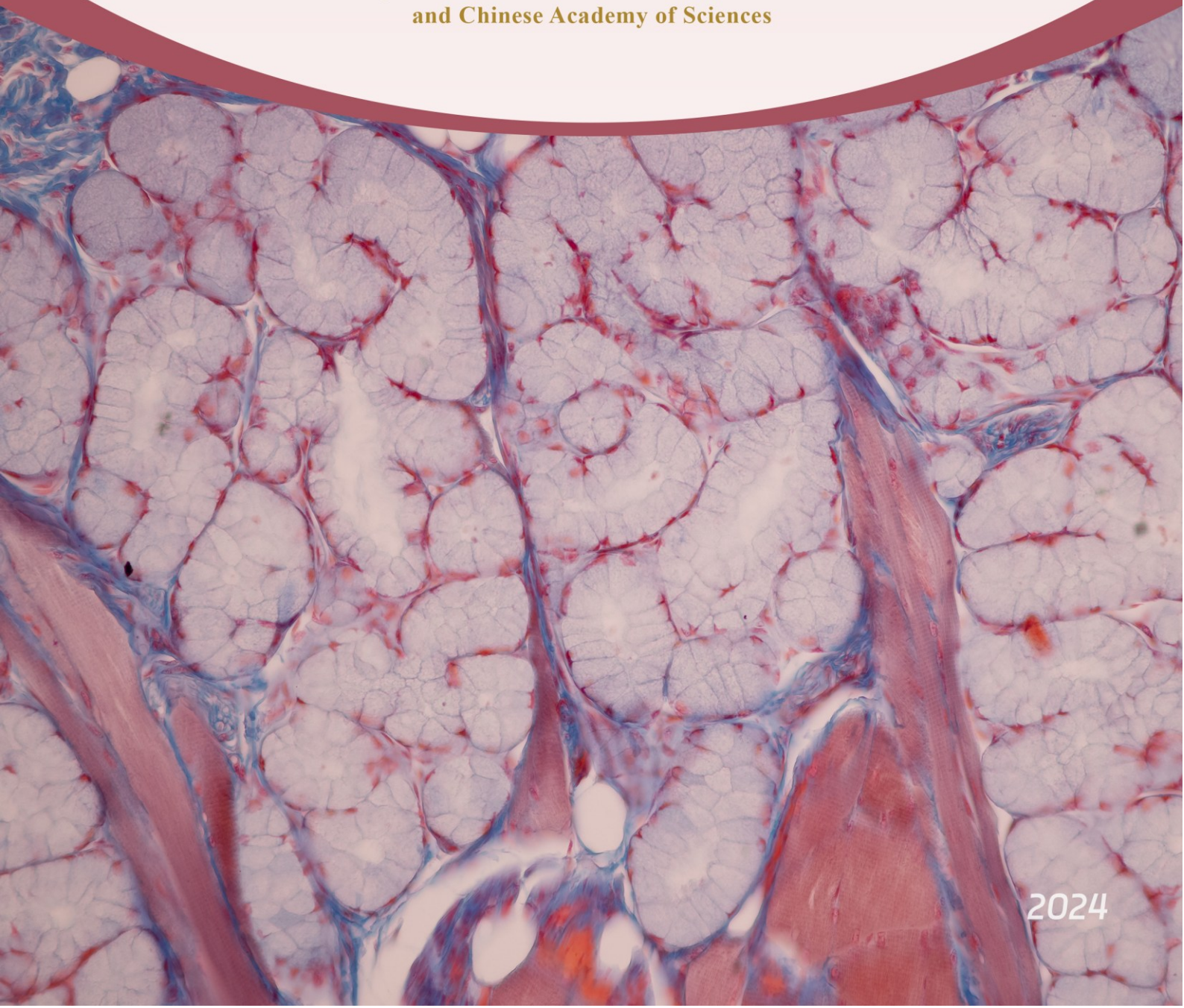
Frontier Interdisciplinary Strategy

Research Report on Frontier Development Strategy of Oral Homeostasis and Systemic Health

Frontier Development Strategy of Oral Homeostasis and Systemic Health Research Team

Funded by National Natural Science Foundation of China and Chinese Academy of Sciences



2024

Report Writing Group

Core Members:

Wang Songlin (Capital Medical University, Academician of the Chinese Academy of Sciences, Professor)

Bian Zhuan (Wuhan University, Professor)

Du Jie (Capital Medical University, Professor)

Fan Zhipeng (Capital Medical University, Professor)

Liu Guanghui (Institute of Zoology, Chinese Academy of Sciences, Professor)

Wang Yilong (Capital Medical University, Professor)

Zhang Chen (Capital Medical University, Professor)

Mao Shanhong (Capital Medical University, Professor)

Zhang Dong (Capital Medical University, Professor)

Zhou Jian (Capital Medical University, Professor)

Hu Lei (Capital Medical University, Associate Professor)

Abstract

Homeostasis is the fundamental mechanism by which organisms maintain internal stability, and its disruption is a critical trigger of diseases. This report elaborates the theoretical framework of "Homeostatic Medicine", proposing novel strategies for disease prevention and treatment through restoring systemic homeostasis. We highlight the role of oral homeostasis in systemic health, particularly the salivary gland-oral-gastrointestinal-systemic axis. Key findings demonstrate that dietary nitrate, via the nitrate-nitrite-NO pathway and the nitrate transporter Sialin, regulates NO homeostasis, mitochondrial function, and immune microenvironment, thereby sustaining the homeostasis of cardiovascular, metabolic, and neural systems. Dietary nitrate supplementation mitigates radiation-induced salivary gland dysfunction, enhances chemosensitivity in tumors, and ameliorates metabolic disorders. We advocate interdisciplinary collaboration to advance Homeostatic Medicine and develop novel therapeutics targeting the nitrate-Sialin pathway.

Content

Introduction

Homeostasis is a self-regulating dynamic equilibrium process through which biological systems remain stable while adapting to changing external conditions to maintain normal life activities. Homeostasis medicine is a science that studies the Homeostasis balance of molecules, cells, organs, and the whole body. It is a comprehensive subject based on the maintenance of Homeostasis balance to maintain human health and prevent diagnose and treat diseases. Homeostatic Medicine focuses on the whole, focusing on the role of homeostasis in health and disease, which is expected to provide new ideas and strategies for the maintenance of health and the diagnosis and treatment of diseases.

1. a comprehensive summary of the development of homeostasis medicine, definition, principles and connotation, scientific exposition of Homeostasis medicine theory.

2. Basic components and change rules of oral salivary gland/saliva, nitrate, and ecosystem were systematically combed. To investigate the effect of oral homeostasis on whole body health and propose the regulatory axis of the salivary gland – oral cavity – gastrointestinal – whole body health.

3. Explore the role of nitrate in regulating NO in the body through the nitrate-nitrite -NO pathway to maintain the homeostasis of the gastrointestinal tract, liver, bone, cardiovascular, brain, and other vital organs and its protective effect, and summarize the homeostasis regulation methods and diagnosis and treatment strategies.

4. Academic research framework of Homeostasis medicine.

1. Homeostasis Medicine

As an open system with energy metabolism function, can respond to stimulation and reproduction[1], the activities of the living body follow the second law of thermodynamics, there is a tendency for spontaneous disorder and entropy increase. To maintain an orderly and low-entropy state in the system, life experience continuously converts substances and energy in the high-entropy state in the environment into the low-entropy state for utilization, and discharges metabolic wastes out of the body[2]. In this process, the living body needs to maintain a relatively stable internal environment, namely, Homeostasis. Homeostasis is a dynamic balance process of self-regulation of living organisms. In the constantly changing external environment, organisms maintain the relative stability of the internal environment through this process, to maintain normal life activities, and ensure that the various systems of the body have good physiological functions. At the same time, the body through the Homeostasis regulation, deal with a variety of physiological stimulation and pathogenic factors on the body, adapt to the rapidly changing external environment, which is conducive to survival[3]. Once the Homeostasis balance is destroyed and the Homeostasis regulatory system is dysfunctional, a series of functional, structural, and metabolic changes will occur in the body, manifested as physical signs and behavioral abnormalities, resulting in the occurrence of diseases[4].

Therefore, based on maintaining the Homeostasis balance of the body, we propose the concept of "Homeostatic Medicine". Homeostasis medicine studies the role of Homeostasis in health and disease, and explores the rules and regulatory strategies of multi-level Homeostasis balance of molecules, cells, organs, and systems in the body, aiming to maintain health and diagnose and treat diseases. Compared with the conventional "symptomatic treatment", Homeostasis medicine, as a new system, focuses on the root causes of diseases and pays attention to the "causative treatment" for the destruction of Homeostasis, thus understanding health and diagnosing and treating diseases from a new perspective.

1.1 The development history of Homeostasis medicine

The Homeostasis view has been reflected in both Chinese and Western medical history. TCM pays attention to the concept of holism, which provides the soil for the generation of Homeostasis thought. As early as in the pre-Qin period, the Yellow Emperor's Internal Classic proposed that "Yin and Yang are secret, and spirit is the rule", and believed that the mutual regulation and relative balance of Yin and Yang were the symbol of personal health. Therefore, the therapeutic concept of "treating with equanimity for some time" was further proposed, and it was considered that maintaining this relative balance was the purpose and end point of clinical treatment, and it was pointed out that excessive treatment should be avoided to avoid breaking the balance of yin and yang[5]. As an important theoretical basis of traditional Chinese medicine, the idea of "harmony of Yin and Yang" has the same effect as the Homeostasis balance theory.

In the West, Hippocrates first proposed the "four humoral theory" to describe the balance of the human body, believing that the production and consumption of bile fluid, blood, mucilage, and black bile are in balance. When a certain body fluid is excessive or insufficient, or separated from other body fluids rather than mixed in the body, the body will show symptoms of diseases such as pain. According to this theory, clinical treatment is a process of "addition and subtraction", in which the needed body fluid is increased and the redundant body fluid is reduced to restore health. At the same time, the body can regulate itself to a certain extent, thus having a certain self-healing ability[6]. In the 19th century, Claude Bernard, a French physiologist, proposed the theory of "homeostasis", pointing out that living systems have internal stability. relatively constant temperature and blood glucose concentration can be protected from the external environment through certain regulation mechanisms. this internal stability is vital to the health of the body[7]. Based on Bernard, the American medical scientist Walter B. Cannon proposed that "slight instability is a necessary condition for the true stability of organisms". He introduced the concept of dynamic balance and believed that biological systems should meet two conditions simultaneously to maintain the relative stability of the internal environment

while adapting to environmental changes, i.e., internal stability within a certain range and the regulatory ability to maintain such stability. Cannon's view has been widely recognized, pointing out the direction for the Homeostasis research[8]. Charles R. Richet, a Bernard student, proposed that behavioral response was an important mechanism for regulating homeostasis[9]. Later, James Hardy (Heady DJ) proposed a model and pointed out the Homeostasis mechanism by comparing the actual value of the variable with the expected value or "set point" to maintain the physiological variable within an acceptable range[10].

From the perspective of life evolution, Homeostasis is an important symbol for organisms to distinguish from non-organisms and provides the basis for organisms to maintain a low entropy state. The intracellular fluid is rich in potassium ions, and the extracellular fluid is rich in sodium ions. The existence of cell membrane and sodium/potassium pump provides a structural basis for the homeostasis regulation of intracellular potassium ions and membrane potential, as well as the possibility for the electrical signal transduction of nerves and muscles[11]. With the complexity of the structure of living organisms, single-cell organisms begin to metabolize and cooperate to form the original Homeostasis regulation mechanism of intercellular signals, which constitutes the basis of biological morphogenesis and regeneration[12]. Thus, Homeostasis regulation exists in the key links of biological evolution and is an important factor in promoting biological evolution.

1.2 Homeostasis regulation, Homeostasis medicine, and Homeostasis science

Homeostasis balance is mainly regulated through a feedback system, which is usually composed of four main parts: variables, receptors, comparators or central processing units, and effectors. These parts form a closed loop of feedback signals [3]. In the process of negative feedback, the activity of the effector is opposite to the change of the variable, and it buffers the change of the variable. In the process of positive feedback,

the activity of the effector is the same as the change of the variable, and a control signal is amplified to achieve the effect of quickly changing the state of the body[13]. These four parts are the only necessary components of the feedback system. The feedback system in organisms is more complex and often involves the superposition and nesting of multiple feedback pathways. Another important mechanism for Homeostasis equilibrium is feed-forward regulation, which refers to the evaluation of an impending change in a variable before the actual change occurs and the advance adjustment [14], involves the Homeostasis system of multistage regulation, which can be the change of the environment information integration, to coordinate the physiological behavior of a variety of feedback system, the regulation can be unconscious, can also be controlled by the subjective consciousness[15].

Homeostasis regulation is a key regulatory mechanism in health and disease. A healthy body can maintain a good Homeostasis environment to ensure the normal function of various physiological systems. However, disease progression is usually accompanied by Homeostasis imbalance. Such changes adversely affect the body and eventually cause functional disorders and organic lesions. The body can maintain the physiological indexes within the specified range through Homeostasis regulation, but the specified range is not static. under specific conditions, the body can more effectively adapt to different requirements by adjusting the specified values of these physiological indexes, which is beneficial for the body to respond to certain extreme challenges.[9]. Normally, the body temperature is set at about 37. degree. c ., whereas in the state of inflammation or infection, the body temperature can be raised to 40. degree. c. to increase basal metabolic rate and fight infection, also known as "fever"[16]. After the removal of the stimulating factor, the prescribed value of the body temperature will return to normal, and this adjustment to the prescribed value is beneficial. However, persistent high fever can cause structural and functional damage to tissues and organs, and in severe cases, it can lead to multiple organ failure and even death. It can be seen that when the adjustment of the specified value deviates from the acceptable range, it will have an irreversible effect on the Homeostasis of the body, leading to pathological changes.

After centuries of research and development, Homeostasis theory has become an

important cornerstone of modern medicine. Integrating the concepts of traditional Chinese medicine and western medicine on Homeostasis in health and disease, we proposed the concept of "Homeostatic Medicine". Homeostasis medicine refers to a systematic study of the rules and mechanisms of homeostasis regulation from multiple levels, such as molecules, cells, organs, the whole body, and the external environment, and summarizes a series of methods and strategies to guide clinical treatment. Homeostasis medicine believes that the nature of the disease is an imbalance of Homeostasis. By studying the changes in Homeostasis in the process of disease, we are committed to eliminating the cause of the disease by restoring the Homeostasis balance, to achieve the purpose of alleviating or treating the disease. Homeostasis medicine research consists of three aspects: First, we have an in-depth understanding of the Homeostasis regulation mechanism and the role of Homeostasis regulation in maintaining health. Secondly, we analyze the causes and interference factors of Homeostasis imbalance in the disease process. Finally, we integrate the information obtained in the first two steps to restore the Homeostasis balance through reasonable intervention measures, to achieve the purpose of maintaining health and preventing diseases. Based on the critical role of Homeostasis in health and disease, Homeostasis medicine can be applied to various disease environments with a wide application prospect (Fig. 1).

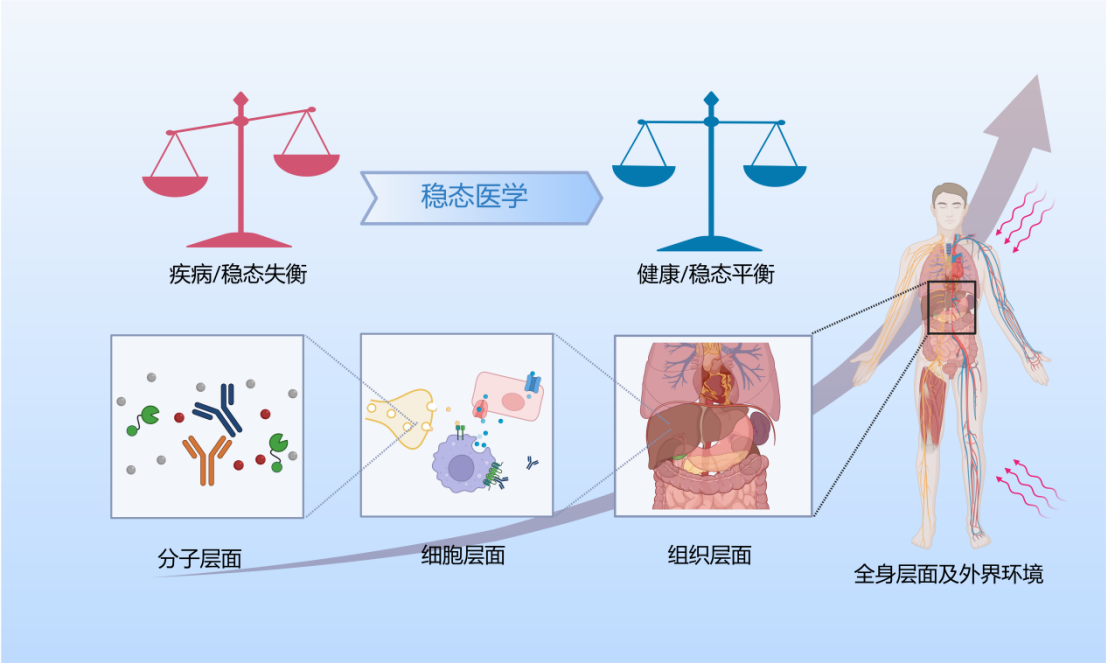


Fig. 1 Concept and content of Homeostasis medicine

Homeostasis is a broader concept based on the theory of homeostasis medicine and is not limited to biology and medicine. Homeostasis science research objects can be physics, biology, psychology, and even social science. Homeostasis theory summarizes various self-stabilizing phenomena in material exchange, energy transfer, and information exchange, i.e., information exchange with mutual antagonism between elements in various systems. The loop formed by this information exchange forms the basic form of system Homeostasis, making the system possess basic self-stabilizing ability. Through the thought of the Homeostasis theory, people can better understand the running law of all things in the world and reasonably use the Homeostasis thinking method to help the research and progress of various disciplines.

1.3 Concept of "50%" in Homeostasis

Under normal circumstances, the molecules, cells, and organs in the body will not exert their full physiological functions, and about 50% of their physiological potential is unused, i.e., the reserve function of the body. Only when coping with abnormal conditions or external challenges, can the physiological potential of these reserves be mobilized. This surplus reserve capacity gives the body the ability to cope with the overloaded

environment, which is conducive to the rapid recovery of the body's homeostasis [17]. The decline in reserve function will lead to a decrease in the body's ability to adapt to external stimuli, increased susceptibility to disease, and an extension of time to recover from disease. For example, aging will cause a decrease in the reserve capacity of tissues and organs of the body, leading to a decline in the function of the immune system, muscle system, nervous system, and other multiple systems[18].

The regulation of reserve function on Homeostasis is reflected in all levels of life activities of the body. The metabolic efficiency of the body depends on the number of enzymes and their activities. Excessive enzymes in organisms are the basis of the body's metabolic reserve, which can cope with the excessive activities required for more than the basic functions, and choose to improve to the maximum ability when needed, thus maintaining the balance in the body[19]. In nerve cells, the sodium and potassium pumps that maintain membrane potential also show large reserve capacity to ensure the Homeostasis of nerve ions under high-intensity neural activity[20]. At the cellular level, under health conditions, most cells in the human body are in a quiescent state of division. In response to adverse stimulation, these quiescent cells can quickly enter the cell cycle to repair the damaged tissues and functions[21]. At the organ level, for example, in the kidney, there is a large difference between the resting state and the glomerular filtration rate at maximum capacity. normally, the kidney only exerts about 50% of its potential. thus, in the case of renal impairment, serum creatinine and glomerular filtration rate (GFR) can remain normal until more than 50% of the nephron damage occurs[22].

The effect of reserve function on Homeostasis regulation is one of the research focuses in Homeostasis medicine. In theory, 50% recovery of body function can maintain Homeostasis[21]. Upholding the therapeutic concept of restoring 50% function of the body in Homeostasis medicine, is sufficient to achieve the purpose of maintaining Homeostasis and health by playing the reserve function of the body, and unnecessary excessive treatment can be greatly reduced.

1.4 Mechanism of Homeostasis regulation

1.4.1 Feedback regulation

The feedback regulation mechanism is the most important regulation system in Homeostasis regulation. The feedback system usually consists of four main parts: ① the variable to be controlled; ② receptors for detecting variables; ③ a comparator or a central processing unit that feeds back the signal detected by the receptor into the system and compares the detected value with a specified value; ④ The effectors used to adjust the required control variables. These parts form a closed loop of feedback signal. In the process of negative feedback, the activity of the effector is opposite to the change of variable, to buffer the change of variable. In the positive feedback process, the activity of the effector is the same as the change of the variable, so that a control signal is amplified to quickly change the state of the body. It is worth mentioning that these four parts are only necessary components of the feedback system. The feedback system in organisms is more complex and may involve the superposition and nesting of multiple feedback pathways [23].

Take the regulation of blood pressure as an example. Under normal circumstances, the blood pressure of the human body will be maintained in a relatively stable range through feedback regulation. The receptors in this Homeostasis system are baroreceptors located in the aortic arch and carotid sinus that respond to changes in arterial pressure. The solitary tract in the medulla oblongata of the brain processes signals fed back by baroreceptors and then acts on effectors located in blood vessels and the heart by regulating the neural activity of sympathetic and parasympathetic nerves. When blood pressure rises, baroreceptors are activated, and regulation of the nucleus of the solitary tract makes sympathetic nerve activity decrease, and blood vessel diameter increase. In addition, parasympathetic nerve activity increases and decreases heart rate and stroke volume, thus lowering blood pressure. On the contrary, when the blood pressure is below the equilibrium value, the opposite regulation will occur. This negative feedback

regulation can effectively buffer changes in blood pressure so that the body's blood pressure remains relatively stable throughout the day despite changes in environmental or behavioral conditions.

1.4.2 Feedforward regulation

Another important mechanism for Homeostasis regulation of feed-forward regulation is the evaluation of impending changes before actual changes in the variable occur and the regulation in advance. This involves multi-stage regulation in a Homeostasis system, where the effector belongs to the first stage of the system and is mainly responsible for receiving higher-level regulation signals and regulating variables. Feedback regulation belongs to the second level, also known as autonomic regulation, which processes the signals detected by receptors and initiates regulation of the first level. The third level, located in the central nervous system, is responsible for processing the information transmitted from the second level and integrating the information on changes in the environment to coordinate the physiological behaviors of multiple feedback systems. This control can be unconscious, or under specific conditions by subjective consciousness [24]. Also, take the regulation of blood pressure as an example. In the face of danger or challenge, under the regulation of the central nervous system, cardiac output rate and blood pressure will be increased to cope with the upcoming environmental changes. This regulation belongs to the unconscious regulation. When the temperature drops, people actively add clothes to maintain the body temperature, and this regulation is completed with the intervention of consciousness.

1.5 Homeostasis medicine and disease prevention and treatment

1.5.1 Homeostasis medicine and oral disease

Oral flora is a diverse microbial community composed of more than 700 species, whose Homeostasis balance is crucial to oral health. It is known to include many species

such as Streptococcus, Actinomyces, and Veillonella[25]. Under healthy conditions, these oral bacteria maintain a Homeostasis between themselves coordinate with the oral environment, and do not cause oral diseases. However, under the stimulation of some factors, the proportion and number of microflora will change and the oral homeostasis will become imbalanced, which will lead to oral diseases such as dental caries and periodontal disease. Salivary gland dysfunction, poor oral hygiene, and poor dietary habits may all break homeostasis and become the cause of oral diseases[26]. Carbohydrate intake promotes the proliferation of acid-producing and acid-resistant bacteria, leading to decalcification of the enamel during dental caries progression. In the course of periodontal disease, the accumulation of biofilm and protein in the gingival sulcus provides an ideal environment for anaerobic and protein-dependent bacteria and promotes the reproduction of Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans[27].

1.5.2 Homeostasis medicine and tumor progress and treatment

Tumor progress is closely related to the imbalance of Homeostasis. The proto-oncogenes are a group of genes that play an important role in cell proliferation and differentiation. In general, the proto-oncogenes are strictly regulated by another group of genes, namely, tumor suppressor genes. The dynamic balance of the two genes is conducive to maintaining the number of cells in the body and the normal physiological function. However, under some stimulative factors, gene mutation breaks the balance between proto-oncogene and tumor suppressor genes, and the overexpression of proto-oncogene causes abnormal proliferation of cells to form tumors. Apoptosis, a programmed cell death program, plays a key role in the physiological processes of embryonic development and the dynamic balance of histiocytes. The Homeostasis regulation of apoptosis has a dual role in tumor development. On the one hand, apoptosis can inhibit tumor progression by recognizing and controlling programmed cell death of tumor cells. On the other hand, apoptosis can also promote tumor progression by stimulating repair and regeneration reactions in the tumor microenvironment. Therefore, simply promoting or inhibiting apoptosis is not conducive to the treatment of tumors [28].

In addition, redox homeostasis also participates in tumor progression. Reactive oxygen species (ROS) play a dual role in tumors. Appropriate concentration of ROS will stimulate tumor formation and support its development, while excessive concentration of ROS will lead to oxidative stress death of tumor cells. In this case, the regulation of homeostasis in tumor tissue is conducive to promoting tumor development. Therefore, inducing tumor cell death by destroying redox homeostasis in tumor tissue is also one of the ideas for treating tumors. In addition, there are other types of Homeostasis mechanisms in tumor tissues, such as the Homeostasis of immune-inflammatory signals, energy metabolism, and electrical signals [29].

At present, cancer is mainly treated by surgery, radiotherapy, chemotherapy, and immunotherapy, aiming to induce tumor cell death by reducing tumor size and blocking its invasion. Regulation of Homeostasis is an important part of tumor development and treatment. Therefore, regulating Homeostasis in the tumor microenvironment may be a feasible treatment. Homeostasis medicine combines Homeostasis regulation with tumor treatment to improve tumor resistance or destroy the Homeostasis of tumor tissue to inhibit its growth by restoring the Homeostasis imbalance of normal tissue, thereby improving the therapeutic effect of the tumor and reducing its side effects, thereby achieving the effect of achieving twice the result with half the effort. The application of pro-oxidants and antioxidants in tumors is a good example. In the early stage of the tumor, the redox homeostasis is destroyed, and oxidative stress promotes tumor progression. At this stage, the application of antioxidants will help inhibit tumors [30]. In the later stage of the tumor, to deal with the tumor cell death caused by oxidative stress, the anti-oxidative stress ability of the tumor tissue is enhanced, and the pro-oxidant can destroy the redox homeostasis of the tumor tissue to kill the tumor cells [31]. Therefore, targeted regulation of the Homeostasis of the tumor may be a more efficient option depending on the stage the tumor is in.

1.5.3 Homeostasis medicine and cardiovascular disease

Homeostasis plays a key role in the health and well-being of the cardiovascular

system. The cells of the vascular wall are very sensitive to changes in the mechanical environment. In healthy blood vessels, dynamic balance maintains mechanical biological stability through negative feedback loop regulation from multiple levels. The progression of cardiovascular disease is usually associated with over-regulation of mechanical biological balance or unstable positive feedback [32]. In short, the cardiovascular system will adapt to changes in the internal and external environment of the body through functional and structural changes. For example, a continuous increase in cardiac output leads to a dilation of the central artery, thereby reducing flow resistance and thus the workload of the heart. When tissue growth activity or local metabolic activity is increased, the angiogenic signal of the blood vessel at the site is activated, thereby increasing the local blood supply to meet the demand, and this regulating effect is conducive to maintaining the Homeostasis of the body. However, long-time vasoconstriction or vasodilation will cause changes in the geometry of the blood vessels, and the excessive dilation and thinning of the blood vessels will lead to aneurysm and arterial rupture. To enhance the vascular stress intensity, the degree of vascular fibrosis is increased. Excessive fibrosis will lead to decreased vascular elasticity and narrowing of the lumen, causing arteriosclerosis and hypertension, further increasing the load on the cardiovascular system. This abnormal positive feedback and tissue remodeling is one of the pathogenic mechanisms of cardiovascular disease [33].

1.5.4 Homeostasis medicine and metabolic diseases

The regulation of energy balance of the body is mainly regulated by the central nervous system, including the neuroendocrine center located in the hypothalamus and the nucleus of the solitary tract located in the lower brain stem. On the one hand, these neuroendocrine centers physiologically control metabolism by releasing thyroid-stimulating hormone-releasing hormone and adrenocorticotropic hormone-releasing hormone. On the other hand, serotonin can also regulate these nerve centers to regulate food intake. The lack of 5- HT will lead to anorexia and obesity, while the increase of central 5- HT will lead to anorexia and reduced energy intake [34]. In addition, the

interaction between the central nervous system and peripheral neurotransmitters such as leptin, ghrelin, insulin, and cholecystokinin is also an important part of energy metabolism homeostasis. Leptin is mainly secreted by adipocytes, and the amount of secretion is positively correlated with the amount of fat. Insulin is secreted by pancreatic β cells in response to the increase of blood glucose, and promotes the consumption and storage of glucose, thereby reducing blood glucose. Increases in the secretion of these hormones usually represent an excess of the body's energy reserves, so they also reduce appetite by regulating the central neuroendocrine system. Correspondingly, ghrelin is mainly produced by the stomach, and its secretion is increased when hungry to enhance appetite [35].

Obesity is a metabolic disease characterized by excessive accumulation of fat in the body and is associated with the increased prevalence of various diseases. As a disease controlled by multiple factors, obesity can be affected by a variety of regulatory mechanisms, including genetic factors, viral infection, insulin resistance, inflammation, intestinal microflora, circadian rhythm, and hormone regulation. In a word, metabolic homeostasis is the most important cause of obesity. Under normal circumstances, the foraging behavior of the human body is dynamically balanced, that is, the desire to eat increases when the energy reserve is reduced so that the food required to meet the physiological needs is ingested. Obese patients are often in a state of hedonism, that is, to promote sensory pleasure, even in the case of adequate energy reserves, will intake more than the energy balance of food. In addition, overeating will also change the sensitivity of the diet reward center to dopamine, further aggravating the destruction of energy metabolism homeostasis and promoting the progress of obesity [36].

Insulin resistance refers to a pathological state in which patients have reduced sensitivity to insulin and the uptake and utilization of insulin-mediated glucose by tissue cells such as the liver, skeletal muscle, and fat are reduced. In an inflammatory state caused by infection, stress, or injury, tumor necrosis factors reduce the sensitivity of fat and skeletal muscle to insulin to concentrate more energy on the immune system. In addition, during the inflammation, the expression of GLUT2 and glucokinase in

pancreatic β cells is inhibited, resulting in decreased sensitivity of the body to blood glucose levels and decreased insulin production. The above regulatory effects reduce the balance of tissue sensitivity to insulin and body sensitivity to blood glucose. Changes in the balance over a long period will cause irreversible decreases in insulin efficacy and the body's reduced sensitivity to increased blood glucose, eventually leading to insulin resistance. Therefore, homeostasis regulation is a key step in improving metabolic diseases [37].

1.5.5 Homeostasis medicine, immunity, and infectious diseases

Organisms are always in a challenging external environment. The immune system is the main defense line of the body against harmful external stimuli and antigens. In addition, the immune system maintains the balance of the body through immune monitoring, perception of metabolic changes, and control of inflammation caused by external stimuli. The immune system can be divided into innate immunity and acquired immunity. These immune systems do not work independently but interact with each other through a variety of cellular immune and humoral immune activities, and finally achieve the dynamic balance of the body's immunity. The disorder of immune homeostasis is closely related to diseases, and the development of diseases is the result of immune regulation failure [38].

Take the novel coronavirus (COVID-19), which is currently popular worldwide, for example. Its nature is also the destruction of immune system homeostasis. COVID-19 is an infectious disease caused by novel coronavirus 2(SARS-CoV-2) with acute respiratory failure as the main manifestation. SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE 2) and enter cells. In vivo, cells infected with Covid-19 are recognized by macrophages and dendritic cells. To remove the virus-infected cells as soon as possible, macrophages will produce a large number of pro-inflammatory cytokines and chemokines, leading to the further recruitment of neutrophils and other inflammatory cells to the infected site. Such excessive release of pro-inflammatory cytokines may lead to cytokine storms, leading to tissue damage, organ failure, and death [39]. Severe COVID-19 is most

common in older patients and is often associated with comorbid symptoms, while symptoms tend to be milder in younger patients. This is because the immune system goes through a complex process of maturation from birth to adulthood. The immune system of young adults is relatively sound, and with the aging of the body, the Homeostasis regulation of the immune system is changed. Compared with young patients, older patients have a lower response and clearance to viral infection, while the inflammatory response to infection is more aggressive. This immune feature is the main reason for the high critical illness rate and mortality rate of elderly patients with COVID-19 [40].

In addition, the immune system has an insufficient response. For example, HIV infection specifically attacks CD4+T cells in the human body to cause the body to lose immune function, eventually leading to a variety of infectious diseases and neoplastic diseases leading to systemic failure and death. However, excessive or abnormal immune responses may cause allergic reactions or autoimmune diseases. Thus, restoring the Homeostasis of the immune system is the key to the treatment of immune system diseases. The over-activation of B cells is one of the important pathogenesis of various autoimmune diseases such as systemic lupus erythematosus, Sjogren's syndrome, and rheumatoid arthritis. Such over-activation is related to the related signal disorder for regulating B cells. By inhibiting B cell activator (BAFF), hypoxia-inducible factor (HIF)-1α, and tumor necrosis factor receptor-associated factor (TNFR)-3, it helps to reverse the metabolic activity of B cells, leading to the reduction of their self-reactive B cell activity, thereby reducing their autoimmune symptoms [41].

References

[1] David L. Abel. Is Life Unique? [J]. Life, 2011, 2(1). DOI:10.3390/life2010106.

[2] Chirumbolo Salvatore, Vella Antonio. Molecules, Information and the Origin of Life: What Is Next? [J]. Molecules, 2021, 26(4). DOI:10.3390/molecules26041003.

[3] Billman George E. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology[J]. Frontiers in physiology, 2020, 11.

DOI:10.3389/fphys.2020.00200.

[4] López-Otín Carlos, Kroemer Guido. Hallmarks of health[J]. Cell, 2021, 184(7). DOI:10.1016/j.cell.2020.11.034.

[5] Maiese Kenneth. Cellular balance, genes, and the Huang Ti Nei Ching Su Wen[J]. Current neurovascular research, 2006, 3(4). DOI:10.2174/156720206778792920.

[6] Adolph E F. Early concepts of physiological regulations[J]. Physiological reviews, 1961, 41. DOI:10.1152/physrev.1961.41.4.737.

[7] Gross Charles G. Three before their time: neuroscientists whose ideas were ignored by their contemporaries[J]. Experimental brain research, 2009, 192(3). DOI:10.1007/s00221-008-1481-y.

[8] Steven J. Cooper. From Claude Bernard to Walter Cannon. Emergence of the concept of homeostasis[J]. Appetite, 2008, 51(3). DOI:10.1016/j.appet.2008.06.005.

[9] Maya E. Kotas, Ruslan Medzhitov. Homeostasis, Inflammation, and Disease Susceptibility[J]. Cell, 2015, 160(5). DOI:10.1016/j.cell.2015.02.010.

[10] Hardy J D. Control of heat loss and heat production in physiologic temperature regulation[J]. Harvey lectures, 1953, 49.

[11] Sieck Gary C. Physiology in Perspective: Homeostasis and Evolution[J]. Physiology (Bethesda, Md.), 2017, 32(2). DOI:10.1152/physiol.00002.2017.

[12] Torday John S. Evolutionary biology redux[J]. Perspectives in biology and medicine, 2013, 56(4). DOI:10.1353/pbm.2013.0038.

[13] David S. Goldstein, Irwin J. Kopin. Homeostatic systems, biocybernetics, and autonomic neuroscience[J]. Autonomic Neuroscience: Basic and Clinical, 2017, 208. DOI:10.1016/j.autneu.2017.09.001.

[14] Carpenter R H S. Homeostasis: a plea for a unified approach[J]. Advances in physiology education, 2004, 28(1-4). DOI:10.1152/advan.00012.2004.

[15] Goodman L. Regulation and control in physiological systems: 1960-1980[J]. Annals of biomedical engineering, 1980, 8(4-6). DOI:10.1007/BF02363432.

[16] Morrison Sf. Central control of body temperature[J]. F1000Research, 2016, 5. DOI:10.12688/f1000research.7958.1.

[17] Atamna Hani, Tenore Alfred, Lui Forshing, et al. Organ reserve, excess metabolic capacity, and aging[J]. Biogerontology, 2018, 19(2). DOI:10.1007/s10522-018-9746-8.

[18]Iliodromiti Stamatina, Iglesias Sanchez Carlos, Messow Claudia-Martina, et al. Excessive Age-Related Decline in Functional Ovarian Reserve in Infertile Women: Prospective Cohort of 15, 500 Women[J]. The Journal of clinical endocrinology and metabolism, 2016, 101(9). DOI:10.1210/jc.2015-4279.

[19] Eanes Walter F, Merritt Thomas J S, Flowers Jonathan M, et al. Flux control and excess capacity in the enzymes of glycolysis and their relationship to flight metabolism in Drosophila melanogaster[J] . Proceedings of the National Academy of Sciences of the United States of America, 2006, 103(51). DOI:10.1073/pnas.0607095104.

[20] Clare Howarth, Padraig Gleeson, David Attwell. Updated Energy Budgets for Neural Computation in the Neocortex and Cerebellum[J]. Journal of Cerebral Blood Flow & Metabolism, 2012, 32(7). DOI:10.1038/jcbfm.2012.35.

[21] Campana Lara, Esser Hannah, Huch Meritxell, et al. Liver regeneration and inflammation: from fundamental science to clinical applications[J]. Nature reviews. Molecular cell biology, 2021, 22(9). DOI:10.1038/S41580-021-00373-7.

[22] Ragnar Palsson, Sushrut S. Waikar. Renal Functional Reserve Revisited[J]. Advances in Chronic Kidney Disease, 2018, 25(3). DOI:10.1053/j.ackd.2018.03.001.

[23] GOLDSTEIN D S, KOPIN I J. Homeostatic systems, biocybernetics, and autonomic neuroscience, Auton Neurosci, 2017, 208, 15-28.

[24] GOODMAN L. Regulation and control in physiological systems: 1960-1980, Ann Biomed Eng, 1980, 8, 281-290.

[25] Deo Priya Nimish, Deshmukh Revati. Oral microbiome: Unveiling the fundamentals[J]. Journal of oral and maxillofacial pathology : JOMFP, 2019, 23(1). DOI:10.4103/jomfp.JOMFP_304_18.

[26] Philip D. Marsh, David A. Head, Deirdre A. Devine. Prospects of oral disease control in the future – an opinion[J]. Journal of Oral Microbiology, 2014, 6(0). DOI:10.3402/jom.v6.26176.

[27] Kilian M, Chapple I L C, Hannig M, et al. The oral microbiome - an update for oral healthcare professionals[J]. British dental journal, 2016, 221(10). DOI:10.1038/sj.bdj.2016.865.

[28] MORANA O, WOOD W, GREGORY C D. The Apoptosis Paradox in Cancer, Int J Mol Sci, 2022,

23.

[29] SHETH M, ESFANDIARI L. Bioelectric Dysregulation in Cancer Initiation, Promotion, and Progression, Front Oncol, 2022, 12, 846917.

[30] PANIERI E, SANTORO M M. ROS homeostasis and metabolism: a dangerous liason in cancer cells, Cell Death Dis, 2016, 7, e2253.

[31] CONKLIN K A. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness, Integr Cancer Ther, 2004, 3, 294-300.

[32] HUMPHREY J D, SCHWARTZ M A. Vascular Mechanobiology: Homeostasis, Adaptation, and Disease, Annu Rev Biomed Eng, 2021, 23, 1-27.

[33] TAKEBE T, IMAI R, ONO S. The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collabo ration on Drug Discovery and Development, Clin Transl Sci, 2018, 11, 597-606.

[34] KOLIAKI C, LIATIS S, DALAMAGA M, et al. The Implication of Gut Hormones in the Regulation of Energy Homeostasis and Their Role in the Pathophysiology of Obesity, Curr Obes Rep, 2020, 9, 255-271.

[35] MAKRIS M C, ALEXANDROU A, PAPATSOUSTSOS E G, et al. Ghrelin and Obesity: Identifying Gaps and Dispelling Myths. A Reappraisal, In Vivo, 2017, 31, 1047-1050.

[36] KESSLER R M, HUTSON P H, HERMAN B K, et al. The neurobiological basis of binge-eating disorder, Neurosci Biobehav Rev, 2016, 63, 223-238.

[37] KOTAS M E, MEDZHITOV R. Homeostasis, inflammation, and disease susceptibility, Cell, 2015, 160, 816-827.

[38] KENEDY M A. A brief review of the basics of immunology: the innate and adaptive response, Vet Clin North Am Small Anim Pract, 2010, 40, 369-379.

[39] ZHOU Y, FU B, ZHENG X, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients, Natl Sci Rev, 2020, 7, 998-1002.

[40] FULOP T, LARBI A, DUPUIS G, et al. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front Immunol, 2017, 8, 1960.

[41] MUBARIKI R, VADASZ Z. The role of B cell metabolism in autoimmune diseases, Autoimmun Rev, 2022, 21, 103116.

2. Effects of Oral Homeostasis on Systemic Health

Oral health is the cornerstone of whole-body health. Oral homeostasis is closely related to the occurrence and development of a variety of systemic diseases, serving as the prerequisite for maintaining health and the basis for disease prevention and treatment. The maintenance and imbalance of oral homeostasis involve the oral and maxillofacial system itself and its supporting systems, including saliva, microecology, oral and maxillofacial protection barrier, and many other known and unknown factors. The study on the relationship between oral homeostasis and whole body health will help to fundamentally clarify the internal mechanism of disease occurrence based on a unique perspective, provide an effective solution for clinical diseases, provide the driving force for the continuous progress of medical development, guide the development direction of science and technology in the future, and provide strong support for the construction of a world science and technology power.

The results of studies over the past twenty years have shown that oral health can directly affect whole-body health, with the following typical representative pathways:

1) Nitrite is an important system for maintaining the Homeostasis of the body through the cellular biological effects mediated by its metabolites nitric oxide (NO) and nitrate transport channel (Sialin)

Nitrate and nitrite have been previously considered to have a significant adverse effect on human health. However, the biological activity of nitrate as a natural dietary nutrient has been widely used. Nitrate ingested through the oral cavity is absorbed into the blood in the gastrointestinal tract and enters systemic circulation. About 25% of nitrate in the blood is ingested and transported to saliva through salivary glands so the concentration of nitrate in saliva is about 10 times that in blood.

The nitrate in saliva plays a protective role in maintaining the oral cavity, gastrointestinal tract, and even multiple organs of the whole body by being converted into nitrite and nitric oxide [1 - 5]. Nitric oxide (NO), as the second messenger of cells, plays an important role in maintaining the normal physiological function of the body at Homeostasis. Under physiological conditions, the body catalyzes the synthesis of nitric

oxide (NO) by endogenous enzymes (nitric oxide synthase (NOS). Under pathological conditions, the synthetic NO pathway of this endogenous enzyme is blocked, which will enable the exogenous nitrate-nitrite-nitric oxide (NO3-NO2-NO) pathway to provide the NO needed by the body.

There is a nitrate transport channel (Sialin) in the cell membrane of human cells, which actively transports extracellular nitrate to play a role in cells. Sialin is widely and highly expressed in the brain, liver, kidney, cardiovascular, thyroid, and other important organs [3 - 5].

Studies have shown that nitrate can protect the digestive system, maintain microbial homeostasis, delay aging, and improve motor function; Nitrates can play a therapeutic role in a variety of systemic diseases, including salivary glands and systemic protection of radiotherapy for head and neck cancer and nasopharyngeal carcinoma [6 - 8], adjuvant tumor therapy to increase cisplatin chemotherapy sensitivity [9], and alleviation of metabolic disorders and inflammatory status [5 - 7,10,11]. However, the following key scientific and core technical problems need to be solved urgently in this part of the research:

① Is the exogenous inorganic nitrate able to protect the brain, liver, kidney, cardiovascular, and other multiple organs of the whole body from structural and functional homeostasis under the conditions of aging and inflammation?

② What is the mechanism of nitrate maintaining the body's Homeostasis? The regulatory systems and means for maintaining homeostasis at the molecular, cellular, tissue, organ, and organism levels need to be further studied. Such as how nitrate transport and metabolism play an important role in maintaining mitochondrial function and metabolic reprogramming of key cells in tissues and organs, and whet the nitrate-signaling loop plays an immune regulatory role and its mechanism.

③ How to convert cutting-edge knowledge and achievements into independent research and development of new drugs based on nitrate, and promote the clinical application of drugs that maintain oral and systemic homeostasis.

2) The oral ecosystem is the first protection system for whole-body health

The oral ecosystem consists of ecological zones (oral tissues and organs), saliva in the mouth, and over 700 microorganisms in the mouth. The oral cavity is a reservoir of human bacteria and a potential habitat for respiratory and intestinal pathogenic bacteria. Oral microorganisms can enter the respiratory tract, intestinal tract, or blood circulation by inhalation, ingestion, and blood source, thus activating inflammation and immune response and regulating the innate and adaptive immune response of the host. At present, the research on the correlation between oral inflammation and systemic multisystem diseases by domestic and foreign scholars mostly focuses on clinical epidemiology, and research on the correlation mechanism is rare.

At present, the following key scientific and core technical problems need to be solved in this part of the research:

① The basic components and changing rules of components of the oral ecosystem need to be systematically studied;

② Effects of oral immune microenvironment on the oral ecosystem and its correlation with systemic inflammation-related diseases;

③ Effects of impaired salivary gland function on oral flora, intestinal epithelial cell homeostasis, and intestinal flora.

(3) the research basis and conditions in related fields in china

Homeostasis is a dynamic balance process regulated by the body, and it is the intersection point of body health and disease. Normal Homeostasis regulation is the basis for maintaining body health. The imbalance of oral Homeostasis regulation will cause body dysfunction and eventually cause systemic diseases, so maintaining oral Homeostasis is essential [12].

1) Nitrate-related NO and Sialin participate in the regulation of body homeostasis

The parotid gland is the main organ in four groups of salivary glands that transports nitrate from blood to saliva [3], and based on the model organ of the parotid gland, we found the existence of a nitrate transport channel (Sialin) in the human cell membrane. Sialin is widely and highly expressed in the brain, liver, kidney, cardiovascular, thyroid, and other important organs [4]. Nitrate can play a variety of physiological functions

through the nitrate-nitrite -NO pathway [5]. Oral nitrate can increase blood flow and regulate intestinal flora to protect the digestive system [7,10,13,14], affect fat metabolism to reduce obesity [11], increase the sensitivity of cisplatin chemotherapy to assist tumor treatment [9], etc. In addition, nitrate can significantly up-regulate the expression of a variety of cellular signaling pathways, including MAPK signaling pathway [6], PI3K-Akt signaling pathway, mTOR and Wnt signaling pathway [15], glutathione metabolism and cell cycle [16]. These signaling pathways play an important role in cell regeneration, cell metabolism, and disease progression.

In terms of nitrate transport channels, it was found that the increased concentration of nitrate in the body's blood was generally accompanied by the increased expression of Sialin in important organs, and the highly expressed Sialin [17] located in the cell membrane and organelles further regulated a series of cell biological functions. The supplementation of inorganic nitrate increases the expression of AQP5 in the salivary glands and improves salivation, thereby effectively reducing the fibrotic area and cell atrophy of the salivary gland tissue [18]. Nitrate can increase the expression of Sialin in acinar cells, thus further promoting the entry of nitrate into cells. This nitrate-sialin loop up-regulates the EGFR-AKT-MAPK signaling pathway to promote the proliferation of acinus and vessel elements and reduce apoptosis [6]. Nitrate upregulates the expression of Sialin in mesenchymal stem cells to improve mitochondrial function and reduce senescence [19]. Nitrate-sialin can protect against radiation-induced salivary gland cell injury by regulating autophagy in salivary gland cells [20]. Oral administration of nitrate can directly regulate the M1/M2 balance of macrophages and reduce inflammation in liver tissue, thereby alleviating non-alcoholic steatohepatitis [21]. Atomized nitrate can directly act on T cells to prevent and treat pulmonary fibrosis through a NO-independent pathway [22]. Therefore, the interaction between Sialin and nitrate has an important regulatory effect on the physiological functions of different cells, tissues, and organs.

Therefore, these latest research results suggest that nitrate and its transport channel Sialin are an important field for studying oral homeostasis regulation and whole body health in the future, and have high research value.

2) The oral microbiome is a critical hub linking local homeostasis with systemic health.

More and more attention has been paid to the study of human micro-ecological flora. The flora parasitic on various parts of the human body is a micro-ecological system formed by natural selection and symbiotic with the host. With the development of second-generation sequencing technology, there are more and more studies on the relationship between oral flora and systemic diseases. At present, our research group and studies in China and abroad have confirmed that the structural disorder of microflora microecology has a significant correlation with autoimmune diseases, metabolic diseases, tumors, and other diseases.

Chronic periodontitis is a disease characterized by inflammation of periodontal tissues and absorption of alveolar bone and is the main cause of tooth loss in adults. The incidence of chronic periodontitis is as high as 80% or more, and patients often suffer from an imbalance of micro-ecological flora. Bacteria infected with chronic periodontitis can enter the whole body through periodontal ligament blood, swallowing into the gastrointestinal tract or inhalation into the body's lungs, causing or aggravating cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease (COPD), colorectal cancer, esophageal cancer, diabetes, nervous system diseases and mental diseases and other diseases in the whole body. After one minute of oral treatment (such as tooth extraction, root canal treatment, periodontal surgery, or curettage), the microorganisms in the oral cavity can reach the heart, lung, and peripheral capillary system from the infected site, and periodontal intervention treatment helps to reduce the clinical symptoms and attack frequency of COPD [23]. Chronic periodontitis, a long-term chronic inflammation, causes an imbalance of oral flora, which may cause structural changes in the composition and proportion of oral flora, induce local oral and systemic inflammation, and thus affect whole body health. The salivary glands of the human body can produce up to 1.5 liters of saliva every day. When swallowing, many bacteria will enter the intestinal tract from the oral cavity and colonize the intestinal tract to change the composition of the intestinal flora, leading to the imbalance of the intestinal flora and

triggering an inflammatory reaction.

With the advance of microbial identification and classification technology, the understanding of the complexity and specificity of these microbial communities has deepened. A variety of samples including oral saliva, oral gingival crevicular fluid, dental plaque, sputum, blood, and urine were collected for detection using solid medium standardized culture technology, anaerobic culture system, PCR, Sanger sequencing, high-throughput sequencing analysis, and metagenomics [24]. Regarding oral flora and lung diseases, our research group has found that most of the microflora in the oral cavity of healthy people are the same. The Proteomics phylum was significantly increased in the periodontitis group and the COPD with periodontitis group [25]. This indicates that achieving a new balance or restoring the original balance between oral salivary bacteria may be a reasonable idea to solve clinical problems.

References

[1] Duncan C, Dougall H, Johnston P, Green S, Brogan R, Leifert C, Smith L, Golden M, Benjamin N. Chemical generation of nitric oxide in the mouth from the enterosalivary circulation of dietary nitrate[J]. Nat Med, 1995, 1(6): 546-551. doi: 10.1038/nm0695-546

[2] Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics[J]. Nat Rev Drug Discov, 2008, 7(2): 156-167. doi: 10.1038/nrd2466

[3] Xia D, Deng D, Wang S. Destruction of parotid glands affects nitrate and nitrite metabolism[J]. J Dent Res, 2003, 82(2): 101-105. doi: 10.1177/154405910308200205

[4] Qin L, Liu X, Sun Q, Fan Z, Xia D, Ding G, Ong H, Adams D, Gahl W, Zheng C, Qi S, Jin L, Zhang C, Gu L, He J, Deng D, Ambudkar I, Wang S. Sialin (SLC17A5) functions as a nitrate transporter in the plasma membrane[J]. Proc Natl Acad Sci U S A, 2012, 109(33): 13434-13439. doi: 10.1073/pnas.1116633109

[5] Ma L, Hu L, Feng X, Wang S. Nitrate and nitrite in health and disease[J]. Aging Dis, 2018, 9(5): 938-945. doi: 10.14336/ad.2017.1207

[6] Feng X, Wu Z, Xu J, Xu Y, Zhao B, Pang B, Qu X, Hu L, Hu L, Fan Z, Jin L, Xia D, Chang S, Wang J, Zhang C, Wang S. Dietary nitrate supplementation prevents radiotherapy-induced xerostomia[J]. elife, 2021, 10. doi: 10.7554/eLife.70710

[7] Wang W, Hu L, Chang S, Ma L, Li X, Yang Z, Du C, Qu X, Zhang C, Wang S. Total body irradiation-induced colon damage is prevented by nitrate-mediated suppression of oxidative stress and homeostasis of the gut microb iome[J]. Nitric Oxide, 2020, 102: 1-11. doi: 10.1016/j.niox.2020.05.002

[8] Chang S, Hu L, Xu Y, Li X, Ma L, Feng X, Wang J, Zhang C, Wang S. Inorganic nitrate alleviates total body irradiation-induced systemic damage by decreasing reactive oxygen species levels[J] . Int J Radiat Oncol Biol Phys, 2019, 103(4): 945-957. doi: 10.1016/j.ijrobp.2018.11.021

[9] Feng Y, Cao X, Zhao B, Song C, Pang B, Hu L, Zhang C, Wang J, He J, Wang S. Nitrate increases cisplatin chemosensitivity of oral squamous cell carcinoma via REDD1/AKT signaling pathway[J]. Sci China Life Sci, 2021, 64(11): 1814-1828. doi: 10.1007/s11427-020-1978-4

[10] Hu L, Jin L, Xia D, Zhang Q, Ma L, Zheng H, Xu T, Chang S, Li X, Xun Z, Xu Y, Zhang C, Chen

F, Wang S. Nitrate ameliorates dextran sodium sulfate-induced colitis by regulating the homeostasis of the intestinal microbiota[J] . Free Radic Biol Med, 2020, 152: 609-621. doi: 10.1016/j.freeradbiomed.2019.12.002

[11] Ma L, Hu L, Jin L, Wang J, Li X, Wang W, Chang S, Zhang C, Wang J, Wang S. Rebalancing glucolipid metabolism and gut microbiome dysbiosis by nitrate-dependent alleviation of high-fat diet-induced obesity[J] . BMJ Open Diabetes Res Care, 2020, 8(1). doi: 10.1136/bmjdrc-2020-001255

[12] Qin L, Wang S. Protective roles of inorganic nitrate in health and diseases[J]. Curr Med, 2022, 1: 4. doi: 10.1007/s44194-022-00002-1

[13] Jin L, Qin L, Xia D, Liu X, Fan Z, Zhang C, Gu L, He J, Ambudkar I, Deng D, Wang S. Active secretion and protective effect of salivary nitrate against stress in human volunteers and rats[J]. Free Radic Biol Med, 2013, 57: 61-67. doi: 10.1016/j.freeradbiomed.2012.12.015

[14] Li S, Jin H, Sun G, Zhang C, Wang J, Xu H, Zhang D, Wang S. Dietary inorganic nitrate protects hepatic ischemia-reperfusion injury through NRF2-mediated antioxidative stress[J]. FrontPharmacol, 2021, 12(616). doi: 10.3389/fphar.2021.634115

[15] Jiang H, Torregrossa AC, Potts A, Pierini D, Aranke M, Garg HK, Bryan NS. Dietary nitrite improves insulin signaling through GLUT4 translocation[J]. Free Radic Biol Med, 2014, 67: 51-57. doi: 10.1016/j.freeradbiomed.2013.10.809

[16] Jia M, Mateoiu C, Souchelnytskyi S. Protein tyrosine nitration in the cell cycle[J]. Biochem Biophys Res Commun, 2011, 413(2): 270-276. doi: 10.1016/j.bbrc.2011.08.084

[17] Li S, Gu J, Zhang D, Yu L, Wang S. Sialin subtype identification，distribution and function in human cells[J]. In preparation.

[18] Xu Y, Pang B, Hu L, Feng X, Hu L, Wang J, Zhang C, Wang S. Dietary nitrate protects submandibular gland from hyposalivation in ovariectomized rats via suppressing cell apoptosis[J] . Biochem Biophys Res Commun, 2018, 497(1): 272-278. doi: 10.1016/j.bbrc.2018.02.068

[19] Li X, Wang X, Zhang C, Wang J, Hu L, Wang S. Nitrate-Sialin loop in regulating cellular functional homeostasis through activation of mitochondrial function and metabolic reprogramming in mesenchymal stem cells[J]. In preparation.

[20] Wang X, Li X, Pan W, Feng X, Zhang C, Wang J, Hu L, Wang S. Nitrate regulates epithelial cell mitophagy to prevent radiation damage to salivary glands[J]. In preparation.

[21] Li S, Sun G, Wang Y, Jin H, Han X, Liu Y, Li C, Zhang C, Wu Y, Hu L, Hu L, Zhang C, Wang J, Zhang D, Wang S. Immunoregulation of intrahepatic bone marrow monocyte-derived macrophages by dietary nitrate prevents NAFLD[J]. In preparation.

[22] Pan W, Gu J, Xu S, Zhang C, Wang J, Xu J, Wang S. Aerosol inhalation of inorganic nitrate prevents pulmonary fibrosis[J]. In preparation.

[23] Li X, Kolltveit K, Tronstad L, Olsen I. Systemic diseases caused by oral infection[J]. Clin Microbiol Rev, 2000, 13(4): 547-558. doi: 10.1128/cmr.13.4.547

[24] Dewhirst F, Chen T, Izard J, Paster B, Tanner A, Yu W, Lakshmanan A, Wade W. The human oral microbiome[J]. J Bacteriol, 2010, 192(19): 5002-5017. doi: 10.1128/jb.00542-10

[25] Lin M, Li X, Wang J, Cheng C, Zhang T, Han X, Song Y, Wang Z, Wang S. Saliva microbiome changes in patients with periodontitis with and without chronic obstructive pulmonary disease[J]. Front Cell Infect Microbiol, 2020, 10: 124. doi: 10.3389/fcimb.2020.00124

3. Nitrate–nitrite–nitric oxide and Sialin are important factors for Homeostasis regulation

Nitric oxide, NO) is an important signaling molecule in mammals and plays a key role in maintaining the body's Homeostasis. For example, as a signaling molecule, NO can re-establish the appropriate autonomic-humoral balance by regulating the neuro-endocrine and autonomic nervous system and regulating the dynamic balance of the neuro-humoral system to play a protective role in the case of imbalance (such as dehydration, hemorrhage, and stress) in the body.[1]. In some cases, NO may exhibit a dual effect, for example, NO may inhibit tissue inflammation by inhibiting the recruitment of white blood cells[2], however, with the progress of inflammation, excessive NO can cause cell oxidative stress, but promote the progress of inflammation[3]. Therefore, in vivo, NO plays an important role in regulating the systemic homeostasis (Fig. 2).

The human body can synthesize NO endogenously through nitric oxide synthase (NOS), and when the synthesis of endogenous NO is impaired, the NO homeostasis can be maintained through the ingestion of exogenous nitrate-nitrite-NO.[4]. Exogenous nitrate is rapidly absorbed into the blood in the upper digestive tract, and about 25% of it is ingested by the salivary glands and enriched in saliva, which is secreted into the oral cavity again, known as the intestinal salivary circulation.[5]. The nitrate in saliva is reduced to nitrite by the nitrate reductase in the oral flora, which enters the gastrointestinal tract again along with swallowing and is absorbed into the blood to enter the body. It is reduced to NO by a variety of enzymes in the blood and tissues, a process known as the nitrate-nitrite -NO pathway[6]. Through the nitrate-nitrite -NO pathway, nitrate can regulate the Homeostasis in cells from multiple angles and play a variety of NO-like physiological functions, such as increasing gastrointestinal blood flow and regulating intestinal flora to protect the digestive system, affecting fat metabolism to reduce obesity, and increasing the sensitivity of cisplatin chemotherapy to assist tumor therapy. In addition, nitrate can significantly up-regulate the expression of a variety of cellular signaling pathways, regulate metabolism, promote cell regeneration, and inhibit disease progression, thus playing an important role in Homeostasis balance[6].

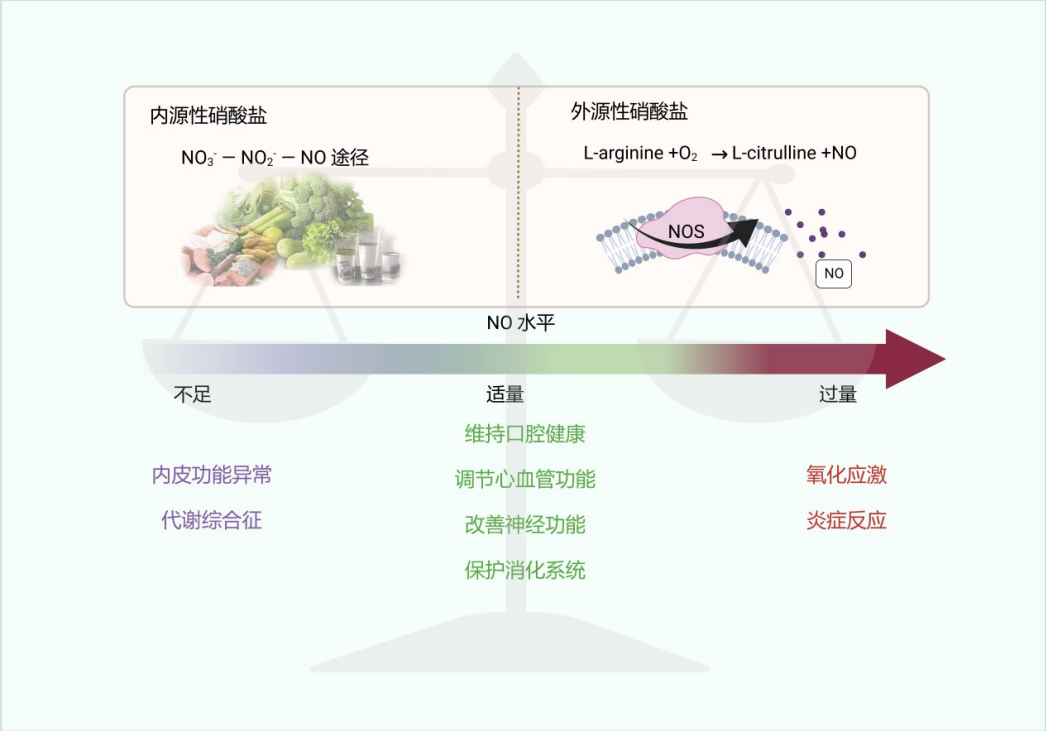


Fig. 2 Dietary nitrate regulates NO homeostasis and promotes systemic homeostasis

Sialin is a nitrate transport channel in the mammalian cell membrane and also exists in the cytoplasm, serving as a key protein for nitrate to exert its physiological function and maintain NO homeostasis[7]. The increased nitrate concentration in the blood of the body is usually accompanied by the increased expression of Sialin, an important organ, which causes a series of cell biological functions. On the one hand, Sialin is highly expressed in human salivary glands, so salivary gland function is one of the important factors affecting the physiological function of nitrate[7], on the other hand, nitrate can in turn regulates the function of the salivary gland. In ovariectomized rats with xerostomia, inorganic nitrate increased the expression of aquaporin AQP5 in the salivary glands and the secretion of saliva, and effectively reduced the fibrotic area and cell atrophy of the salivary gland tissue[7]. In the salivary gland radiation injury model of miniature pigs, nitrate was found to increase the expression of Sialin in acinar cells, thereby further promoting the entry of nitrate into cells. There was a positive feedback loop between nitrate and Sialin, which was conducive to the regulation of NO Homeostasis by nitrate to improve the Homeostasis of the body[7]. Recent studies have found that the nitrate transport channel, -Sialin, itself mediates a series of cellular biological functions,

including improving mitochondrial function and intracellular autophagy. Therefore, the nitrate-sialin loop-mediated cellular biological effects and the regulation of NO homeostasis by nitrate are important research directions for potential studies on homeostasis regulation in the future (Fig. 3).

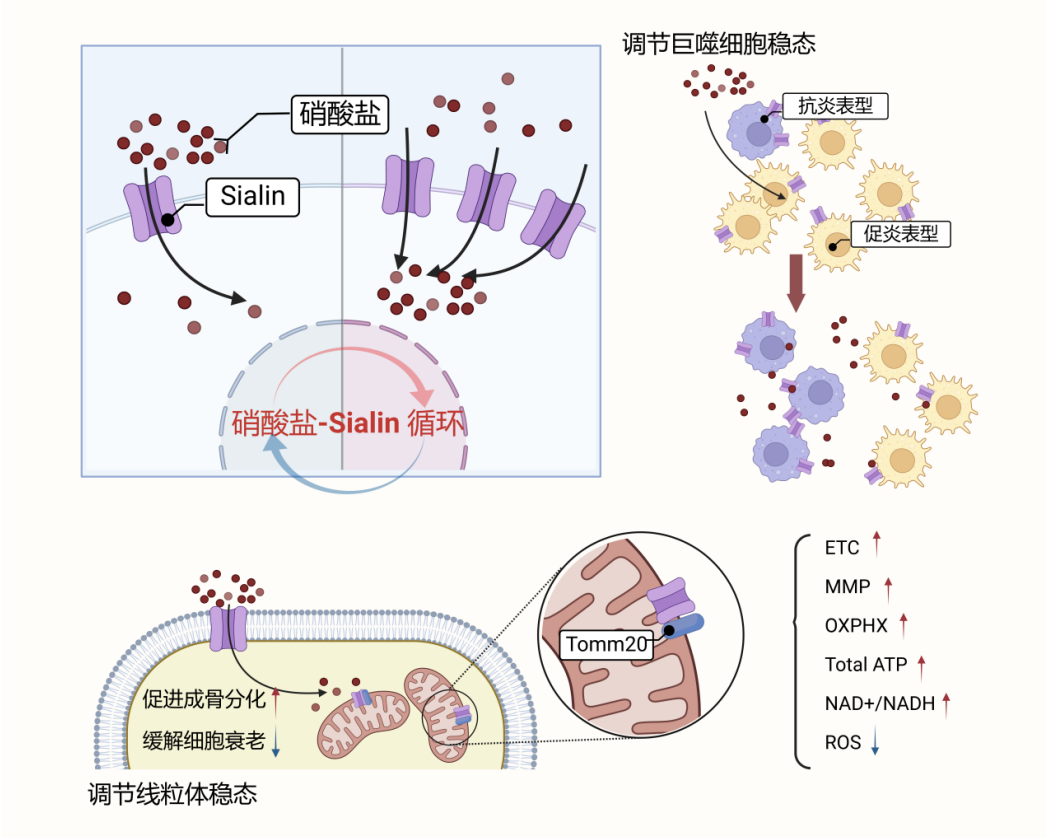


Fig. 3 Role of nitrate -sailin positive feedback cycle in regulating cell homeostasis

Nitrate can inhibit oral diseases and promote oral health by regulating the Homeostasis of oral flora. Dietary nitrate can inhibit the acid-producing ability of dental caries-related bacteria by increasing the pH of saliva, to play a role in caries prevention[8]. Eating beetroot juice for two weeks increased the concentration of nitrates and nitrites in saliva and increased the pH of saliva from 7.0 to 7.5[8]. In addition, nitrate intake reduces the level of caries-associated bacteria such as streptococcus, coccidioides, and actinomycetes[9,10], increases the use of lactic acid in nitrate-reducing bacteria such as mucositis[11]And helps inhibit the progression of dental caries. Nitrate can also reduce the number of a variety of periodontal pathogens, showing anti-periodontitis potential. In vitro, nitrates reduced levels of clostridium, Prevost, and porphyromonas in the saliva of

healthy donors[12], and these bacteria are thought to be associated with gingivitis, and periodontitis[13]. Intake of nitrate reduced the levels of Prevost, Sclerotinia, Bacteroides, and Fusobacterium in the saliva of healthy subjects. For patients with periodontitis, supplementation of lettuce juice rich in nitrate for two weeks significantly changed the composition of subgingival microorganisms and reduced gum inflammation[14].

Organic nitrates represented by nitroglycerin are often used to reduce blood pressure or treat congestive heart failure and function as NO donors. However, drug resistance occurs after long-term use, which may lead to endothelial dysfunction and increase long-term cardiovascular risk.[15]. Inorganic nitrates can also be used as NO donors to maintain NO homeostasis through the nitrate-nitrite -NO pathway, showing beneficial effects in a variety of cardiovascular diseases[4]. Compared with organic nitrates, inorganic nitrates do not cause adverse reactions such as syncope or postural hypotension and have no obvious drug resistance after long-term use. A relatively obvious antihypertensive effect can still be observed after one year of use.[16]. Furthermore, inorganic nitrates showed more pronounced antihypertensive effects in hypertensive patients with impaired endothelial function compared to healthy volunteers, suggesting that inorganic nitrates contribute to the improvement of endothelial homeostasis disorders[17].

Inorganic nitrates can improve NO homeostasis in tumor tissues and reduce the expression of Redd1, thus improving the sensitivity of oral squamous cell carcinoma to chemotherapy.[18]. In addition, the inorganic nitrate showed a good protective effect on tumor radiation injury, which could effectively alleviate the decreased function of salivary glands after radiation injury in rats, and alleviate colitis in rats after whole-body radiation by regulating the Homeostasis balance of intestinal flora[19], is expected to improve the Homeostasis balance to improve the quality of life of tumor patients after radiotherapy.

Dietary nitrate pretreatment can transport NO to the vascular system through the nitrate-nitrite -NO pathway and reduce the inflammatory response of leukocytes induced by acute chemokines[20]. In atherosclerosis-susceptible mice, the intake of inorganic nitrates saved NO homeostasis, and inhibited acute and chronic inflammation by inhibiting neutrophil activation and up-regulating the interleukin -10-dependent anti-

inflammatory pathway, resulting in the reduction of biologically available endothelial-derived NO and the related reduction of macrophage content and inflammatory state in atherosclerotic plaques, playing a good anti-inflammatory role[21].

In addition, nitrate, as a NO donor, had a certain inhibitory effect on pathogenic bacteria. inorganic nitrate could alleviate enteritis induced by dextran sodium sulfate, improve colon length, and maintain mouse body weight by regulating the Homeostasis of intestinal flora[22]. Inorganic nitrates can improve metabolic diseases, and their beneficial effects may be related to the maintenance of NO homeostasis and the regulation of microbial homeostasis. In mice with impaired NO synthesis due to eNOS deficiency, inorganic nitrates reduce body fat and improve glucose homeostasis[23]. In addition, by activating the NO pathway and regulating the intestinal microflora, inorganic nitrates can also reduce mouse obesity induced by a high-fat diet and improve glucolipid metabolism disorders[24]. Epidemiological studies have shown that eating leafy vegetables rich in dietary nitrates can reduce the risk of type 2 diabetes[25], and the habitual use of mouthwash to interfere with the conversion of nitrate to nitrite may lead to glucose metabolism disorders in overweight adults[26].

References

[1] Krukoff T L. Central actions of nitric oxide in the regulation of autonomic functions[J]. Brain research. Brain research reviews, 1999, 30(1). DOI:10.1016/S0165-0173（99）00010-7.

[2] Kubes P, Suzuki M, Granger D N. Nitric oxide: an endogenous modulator of leukocyte adhesion[J] . Proceedings of the National Academy of Sciences of the United States of America, 1991, 88(11). DOI:10.1073/pnas.88.11.4651.

[3] Król Magdalena, Kepinska Marta. Human Nitric Oxide Synthase-Its Functions, Polymorphisms, and Inhibitors in the Context of Inflammation, Diabetes and Cardiovascular Diseases[J]. International journal of molecular sciences, 2020, 22(1). DOI:10.3390/ijms22010056.

[4] Kapil V, Khambata R S, Jones D A, et al. The Noncanonical Pathway for In Vivo Nitric Oxide Generation: The Nitrate-Nitrite-Nitric Oxide Pathway[J]. Pharmacological reviews, 2020, 72(3). DOI:10.1124/pr.120.019240.

[5] Duncan C, Dougall H, Johnston P, et al. Chemical generation of nitric oxide in the mouth from the enterosalivary circulation of dietary nitrate[J]. Nature medicine, 1995, 1(6). DOI:10.1038/NM0695-546.

[6] Lundberg Jon O, Weitzberg Eddie, Gladwin Mark T. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics[J]. Nature reviews. Drug discovery, 2008, 7(2). DOI:10.1038/nrd2466.

[7] Qin Lizheng, Liu Xibao, Sun Qifei, et al. Sialin (SLC17A5) functions as a nitrate transporter in the plasma membrane[J] . Proceedings of the National Academy of Sciences of the United States of America, 2012, 109(33). DOI:10.1073/pnas.1116633109.

[8] Barbara Hohensinn, Renate Haselgrübler, Ulrike Müller, et al. Sustaining elevated levels of nitrite in the oral cavity through consumption of nitrate-rich beetroot juice in young healthy adults reduces sal ivary pH[J]. Nitric Oxide, 2016, 60. DOI:10.1016/j.niox.2016.08.006.

[9] Anni Vanhatalo, Jamie R. Blackwell, Joanna E. L'heureux, et al. Nitrate-responsive oral microbiome modulates nitric oxide homeostasis and blood pressure in humans[J]. Free Radical Biology and Medicine, 2018, 124. DOI:10.1016/j.freeradbiomed.2018.05.078.

[10] Mia Burleigh, Luke Liddle, David J. Muggeridge, et al. Dietary nitrate supplementation alters the oral microbiome but does not improve the vascular responses to an acute nitrate dose[J]. Nitric Oxide, 2019, 89. DOI:10.1016/j.niox.2019.04.010.

[11] Rosier Bob T., Palazón Carlos, García Esteban Sandra, et al. A Single Dose of Nitrate Increases Resilience Against Acidification Derived From Sugar Fermentation by the Oral Microbiome&#13[J] . Frontiers in Cellular and Infection Microbiology, 2021, 11. DOI:10.3389/fcimb.2021.692883.

[12] Rosier B T, Buetas E, Moya-Gonzalvez E M, et al. Nitrate as a potential prebiotic for the oral microbiome[J]. Scientific reports, 2020, 10(1). DOI:10.1038/s41598-020-69931-x.

[13] Abusleme Loreto, Dupuy Amanda K, Dutzan Nicolás, et al. The subgingival microbiome in health and periodontitis and its relationship with community biomass and inflammation[J]. The ISME journal, 2013, 7(5). DOI:10.1038/ismej.2012.174.

[14] Jockelschneider Yvonne, Schlagenhauf Ulrich, Stölzel Peggy, et al. Nitrate-rich diet alters the composition of the oral microbiota in periodontal recall patients[J]. Journal of periodontology, 2021, 92(11). DOI:10.1002/JPER.20-0778.

[15] Tarkin Jason M, Kaski Juan Carlos. Vasodilator Therapy: Nitrates and Nicorandil[J]. Cardiovascular drugs and therapy, 2016, 30(4). DOI:10.1007/s10557-016-6668-z.

[16] Münzel Thomas, Daiber Andreas, Mülsch Alexander. Explaining the phenomenon of nitrate tolerance[J]. Circulation research, 2005, 97(7). DOI:10.1161/01.RES.0000184694.03262.6d.

[17] Kapil Vikas, Khambata Rayomand S, Robertson Amy, et al. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study[J]. Hypertension (Dallas, Tex. : 1979), 2015, 65(2). DOI:10.1161/HYPERTENSIONAHA.114.04675.

[18] Feng Yuanyong, Cao Xuedi, Zhao Bin, et al. Nitrate increases cisplatin chemosensitivity of oral squamous cell carcinoma via REDD1/AKT signaling pathway[J]. Science China. Life sciences, 2021, 64(11). DOI:10.1007/s11427-020-1978-4.

[19] Cecilia Jädert, Joel Petersson, Sara Massena, et al. Decreased leukocyte recruitment by inorganic nitrate and nitrite in microvascular inflammation and NSAID-induced intestinal injury[J] . Free Radical Biology and Medicine, 2012, 52(3). DOI:10.1016/j.freeradbiomed.2011.11.018.

[20] Khambata Rayomand S, Ghosh Suborno M, Rathod Krishnaraj S, et al. Antiinflammatory actions of inorganic nitrate stabilize the atherosclerotic plaque[J] . Proceedings of the National Academy of Sciences of the United States of America,

2017, 114(4). DOI:10.1073/pnas.1613063114.

[21] Liang Hu, Luyuan Jin, Dengsheng Xia, et al. Nitrate ameliorates dextran sodium sulfate-induced colitis by regulating the homeostasis of the intestinal microbiota[J] . Free Radical Biology and Medicine, 2020, 152(prepublish). DOI:10.1016/j.freeradbiomed.2019.12.002.

[22] Matafome Paulo, Seiça Raquel. The Role of Brain in Energy Balance[J]. Advances in neurobiology, 2017, 19. DOI:10.1007/978-3-319-63260-5_2.

[23] Carlström Mattias, Larsen Filip J, Nyström Thomas, et al. Dietary inorganic nitrate reverses features of metabolic syndrome in endothelial nitric oxide synthase-deficient mice[J] . Proceedings of the National Academy of Sciences of the United States of America, 2010, 107(41). DOI:10.1073/pnas.1008872107.

[24] Linsha Ma, Liang Hu, Luyuan Jin, et al. Rebalancing glucolipid metabolism and gut microbiome dysbiosis by nitrate-dependent alleviation of high-fat diet-induced obesity[J] . BMJ Open Diabetes Research & Care, 2020, 8(1). DOI:10.1136/bmjdrc-2020-001255.

[25] Carter Patrice, Gray Laura J, Troughton Jacqui, et al. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis[J]. BMJ (Clinical research ed.), 2010, 341(7772). DOI:10.1136/bmj.c4229.

[26] Kaumudi J. Joshipura, Francisco J. Muñoz-Torres, Evangelia Morou-Bermudez, et al. Over-the-counter mouthwash use and risk of pre-diabetes/diabetes[J]. Nitric Oxide, 2017, 71. DOI:10.1016/j.niox.2017.09.004.

4. Academic research framework of Homeostasis medicine

4.1 Hold the first Homeostasis medicine academic conference in China

On June 16, 2023, jointly sponsored by the Beijing Laboratory of Oral Health and National Key Laboratory of Oral Disease Prevention and Treatment, Chinese Journal of Oral Medicine, Science Bulletin, Science Bulletin, Medicine Plus, International Journal of Oral Science, Current Medicine, and Ziyang, Yagu, Sichuan, China are co-sponsors. The "First China Academic Conference on Homeostasis Medicine" sponsored by People's Health Publishing House was held in Beijing. More than 200 well-known experts and scholars from across the country gathered to discuss the new concept of Homeostasis medicine as well as its new developments and trends.

At the opening ceremony, Academician Qiang Boqin of the China Academy of Sciences fully affirmed the research value and development prospect of "Homeostasis medicine", and encouraged participants to make joint contributions to deepening research in new fields of this subject. Academician Wang Songlin of the China Academy of Sciences shared his thoughts on the Homeostasis medicine system, the development of Homeostasis medicine and Homeostasis science. Du Xian, editor-in-chief of People's Health Publishing House, and Yang Jin, deputy editor-in-chief of People's Health Publishing House, respectively expressed their welcome to the participants, showing their high recognition of Homeostasis medicine and Homeostasis science, stressing the importance for participants to exchange world-class research results and jointly promoting the development of Homeostasis medicine. Professor Wang Shan, the executive editor of Science Bulletin, Science Bulletin, and Medicine Plus, agreed with Homeostasis medicine—a new strategy for maintaining health and preventing and treating diseases and said that the magazine would strongly support new strategies and concepts of Homeostasis medicine. Members of the Eastern Division of Zhou Xue reviewed the research process of academician Wang Songlin's team in maintaining body

Homeostasis by nitrate and looked forward to more innovative results. The opening ceremony was presided over by a member of the Wang Ningli Department. He emphasized the scientificity, cutting-edges, and importance of the meeting, and advocated innovation and interdisciplinary cooperation to drive the further development of the field of Homeostasis medicine.

The keynote report entitled "Homeostasis medicine-a new strategy for maintaining health and preventing and treating diseases" was delivered by Academician Wang Songlin. It introduced in detail the important roles of nitrate-nitric oxide and nitrate transport channel Sialin and its subtypes in protecting the body and maintaining the body's Homeostasis. According to the system research, the concept and connotation of Homeostasis medicine were proposed. Homeostatic Medicine systematically studies the rules and mechanisms of homeostasis regulation from multiple levels such as molecules, cells, organs, the whole body, and the external environment, and creates a series of methods and strategies to guide the maintenance of body health and the diagnosis and treatment of clinical diseases.

Guest presentations included a report by Zhou Xuedong, a member of the Department of Oral Microecology and Oral Diseases, a report by Jiang Tao, a member of the Department of Neurohomeostasis in the Diagnosis and Treatment of Gliomas, a report by Shi Yufang, a member of the European Academy of Sciences, on immune homeostasis and health, a report by Professor Du Jie on cardiovascular homeostasis and diseases, a report by Wang Ningli, a member of the Department of Glaucoma and Biomechanics, and a sharing by Professor Chen Qian of recent research results on the mechanisms of periodontal homeostasis maintenance and remodeling. In addition, many experts have conducted research on "The mechanism of dentin hypersensitivity", "Homeostasis of cardiovascular system", "Effects of non-impacted third molar on periodontal health of adjacent teeth", "Sharing medical cases of cerebrovascular disease Homeostasis", "Mood disorder and Homeostasis medicine", "Role of macrophage Homeostasis in immune microenvironment of glioma", "ACE2 and glycolipid and energy metabolism Homeostasis", "Biological materials and immune Homeostasis", "Framework nucleic

acid drugs and Homeostasis research", "Periodontal homeostasis and atherosclerosis", "Regulatory mechanism of bone homeostasis", "The role of hypoxia-induced apoptotic bodies in maintaining bone balance", "Dental developmental homeostasis-The homeostasis mechanism of dental plate replacement in the jawbone microenvironment" provided in-depth exchange of hot issues in the field of homeostasis medicine and explored the challenges and opportunities for the development of homeostasis medicine.

4.2 Invited to do at the international academic conference Homeostasis Medicine invited report

Upon special invitation, Academician Wang Songlin gave a special lecture on Homeostasis medicine at the 35th Anniversary Meeting of the Sino-Japanese Shichuan Medical Scholarship Program, introducing China's progress in this field to international colleagues on the concept, connotation, and strategy of Homeostasis medicine, to expand China's international influence in this field. In addition, he also give special presentations at the China Conference on Redox Biology and Medicine, the National Higher Medical Textbook Construction and Innovative Development of Medical Education, and the 2023 Annual Meeting of Expert Consultation at the People's Health Publishing House, the first Academic Publishing Annual Meeting of the China Publishing Association, and the Academician Forum at the Dongshan Lecture Hall in Xiangxiang, Hunan, to promote the development of homeostasis medical science.

4.3 Wrote the textbooks of "Nitrate and Homeostasis " and " Homeostasis Medicine and Homeostasis Studies"

In 2024, the People's Medical Publishing House, in collaboration with Academician Wang Songlin, published the monograph *Nitrate and Body Homeostasis*. This work systematically summarizes the groundbreaking achievements made by Academician Wang Songling's team over two decades in the field of nitrate research. The book presents a scientific breakthrough that challenges conventional wisdom. For the first time, it comprehensively details the team's research journey in fundamentally questioning the

traditional view that "nitrate causes cancer." It meticulously documents the discovery process of the human cell membrane nitrate transporter channel (sialin), scientifically demonstrates the crucial physiological role of nitrate in maintaining homeostasis in the digestive, cardiovascular, and nervous systems, and reveals its potential applications in radioprotection, metabolic disease intervention, and anti-aging – effectively rehabilitating the biological functions of nitrate. Drawing on four decades of clinical and research experience, Academician Wang Songling systematically elaborates on his original "Homeostatic Medicine" academic framework within the book. He provides an in-depth analysis of the logic behind selecting research directions, formulating scientific questions, overcoming technical bottlenecks, and designing clinical translation pathways, offering a methodological paradigm for interdisciplinary medical research. The monograph has garnered significant international academic influence. Recognizing its immense scientific and social value, the prestigious international publisher Springer has initiated plans for a global English edition release. This publication will foster global academic collaboration and serve as a vital guide for medical professionals, researchers, university faculty, and students.

4.4 Homeostasis medicine development Suggestions

First, innovative ideas – to lead innovative thinking and promote the progress of health science through the new perspective of "Homeostasis medicine";

Second, cutting-edge results-the most active academic leaders in various fields demonstrated cutting-edge interdisciplinary research results, which injected confidence into the participants;

Third, cross-integration – It involves multiple disciplinary fields, and analyzes, abstracts, advances, and recognizes "Homeostasis medicine" in different fields and directions, thus showing the broad application prospect of "Homeostasis medicine".

Fourth, academic leadership – to promote the establishment of academic organizations, which will have a positive role in promoting the development of "Homeostasis medicine".

Fifthly, international communication-internationalization of the concept of Homeostasis medicine to promote the international development of Homeostasis medicine

Summary

Homeostasis balance is the symbol of body health, and normal Homeostasis regulation is the foundation for maintaining body health. Homeostasis regulation plays an important role in the health and disease of different systems. Homeostasis imbalance will lead to body dysfunction and eventually disease. Based on the previous medical science, Homeostasis medicine proposes a new medical system, which is committed to maintaining health and preventing diseases by regulating Homeostasis. It is expected to provide a new idea and strategy for medical research and disease treatment, with a broad development prospect. The regulation of NO homeostasis is closely related to the homeostasis of multiple systems in the body. Inorganic nitrate is an important substance for regulating NO homeostasis, which can exert a variety of beneficial physiological effects through the nitrate-nitrite-NO pathway. At the same time, the nitrate transport channel -Sialin, which exists in the cell membrane and cell cytoplasm, can mediate a series of cell biological functions and participate in the regulation of body homeostasis. Therefore, nitrate-nitrite-NO and Sialin-mediated cell biological functions are important mechanisms for homeostasis regulation, which deserve to be focused on in the research of homeostasis medicine.