National Report on Space Medicine Progress in 2010–2012

Li Yinghui, Liu Zhaoxia, Ding Bai, Liu Yue, Zhang Xiaoyou, Bai Yanqiang, Chen Shanguang

China Astronaut Research and Training Center, Beijing 100094

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Abstract

Accompanying the flourishing developments of manned spaceflight of our country, space medicine has achieved great development during the past two years in our country. In this paper, scientific research of space medicine and its application in China during 2010–2012 have been briefly introduced.

From 2010 to 2012, our manned spaceflight technology has been greatly developed. Unmanned rendezvous and docking mission has been successfully carried out, manually controlled rendezvous and docking test in space is about to be implemented, and long-term spaceflight have been scheduled.

Accompanying the flourishing developments of manned spaceflight of our country, space medicine, the key elements for astronauts' health ensuring in spaceflight, also shows a charming status. For the first time, the State Key Laboratory of Space Medicine Fundamentals and Application was set up and has begun to function in our country. Converged and led by our national mission, more and more institutions joined, and a radialized entity distribution has been formed, in which China Astronaut Research and Training Center (ACC) plays a core role. More comprehensive and intensive researches have been carried out, and great progress both in thoery and technology has been made.

1 Space Medicine Application Research for Rendezvous and Docking Manned Spaceflight Mission

Compared with the previous short term flights, space medicine faces more challenges in rendezvous and docking manned spaceflight mission. Firstly, astronaut health and high efficiency should be ensured for a longer period. Secondly, physical and psychological agility must be maintained to meet the needs of manual rendezvous and docking operation. Furthermore, Spaceflight experiments need to be explored to accumulate certain theory and technology of astronaut health and performance maintaining for future spaceflight.

1.1 Astronaut Health Ensurance Technology

There are some obvious new characteristics of rendezvous and docking manned spaceflight mission. Firstly, spaceflight duration will be prolonged to 2–3 weeks. Secondly, automatic rendezvous and docking mission will be elaborately monitored on the early flight day of 2nd and 3rd when the incidence of space motion sickness is high. Thirdly, Tiangong target vehicle will fly on-orbit in a tightly closed state for a long duration. Fourthly, our female astronauts will attend the flight crew for the first time. While the solar proton event incidence which increases the radiation risk to the mission might be high. To solve these problems, systematical health ensuring measures are designed as follow.

(1) To take integrative countermeasures on microgravity physiological effects. Regarding the cardiovascular weightlessness physiological effects as the key problem and giving the consideration to the risk of skeletal muscle atrophy at the same time, variety of countermeasure instruments have been developed. An Integrative countermeasure system with independent property rights which are composed of physical, exercise and

medicine protective technologies has been established correspondingly. Health and working ability of the astronauts in flight and during reentry will be ensured through the implementation of the protective measures, which will improve the blood re-distribution, alleviate the acute adaptation symptoms, exercise the cardiovascular regulation functions, and increase the muscle's static and exercise load. With the measures, cardiovascular function and physical ability will be maintained as maximum as possible, and muscle atrophy process will be slowed down as well. All the protective measures above have been verified by bed-rest experiments. For the first time, integrative countermeasures against the physiological effects of weightlessness will be systematically operated in orbit.

(2) By developing a wealthy of medical examination equipments which have the ability to detect physical fitness, cardiovascular function and oxidative stress levels in flight, regular assessments of the astronauts' health state in orbit will be realized.

(3) Systemic measures against space motion sickness and re-entry orthostatic intolerance, which include the methods of astronaut selection, training, work and rest regime constituting and medicine, have be developed by fully inheriting the successful experiences of the 7th Shenzhou spaceflight.

(4) As to the risk of solar proton events high-incidence during the mission days, the space environmental radiation forecast information tracking measure and the individual on-orbit radiation detection measure have been strengthened, and avoiding action which will be carried out on orbit when necessary, has been considered.

1.2 Space Medical Experiments on Orbit

Focusing on the human health monitoring and maintenance techniques, physiological effects of weightlessness and its cellular mechanisms, a number of space experiments will be carried out during rendezvous and docking mission:

(1) Research on Changes of Cardiovascular Function, Vestibular Eye Movement and Higher Brain Function During Space Flight

Target on the weightlessness physiological effects of cardiovascular dysfunction, vestibular dysfunction and higher brain function impairment, which have been proved to be the important risk affecting the health and working performance of astronauts during space flight, study on cardiovascular, vestibular, brain function changes during spaceflight will be carried out, and its on-orbit experimental equipment which can synchronously detect cardiovascular function, higher brain function and vestibular eye movement has been developed. This research will promote the systematic recognition on physiological effects mechanism, and provide the basis for the technological formulation of weightlessness countermeasures.

With its spaceflight apparatus, the head-down bed rest simulating weightlessness experiment results have showed that head-down bed rest can cause changes of hemodynamics, left and right heart function, vascular function, pulmonary circulation and cardiovascular regulation, also have a negative impact on the vestibular eye movements, reducing the depth and speed of brain cognitive processing with different tasks.

(2) Research on Cytology and Molecular Mechanism of Weightlessness Bone Loss

Focusing on diminished capacity of osteoblasts proliferation and differentiation caused by the change of responsiveness to important osteogenic factors such as IGF, integrin inhibitor effects on the reporter gene EGFP expression and alkaline phosphatase activity under the interfere with IGF-I to the OSE-MG63 cells will be carried out to study the impact of integrin on former osteoblasts Cbfa1 response to the IGF-I cytokine.

Effects of Clinostat Rotation on OSE-MG63 cell model whose EGFP fluorescence intensity and Luciferase activity could reflect the effects of microgravity on gene function showed that rotation will suppress the Cbfa1 transcriptional activity and reduce the expression of the integration-αvβ3 subunit and the IRS, a molecule in IGF-I signaling pathway, and its p85 phosphorylation, while overweight will have counterproductive.

For the technical difficulty raised by on-orbit weightless experiments for which variety of reagents will need to be added in turn according to the timing, noninvasive-multi sorts-micro reagent-standalone-timing-driven technology has been developed to meet with the complex on-orbit cell culture needs to realize the functions of cell activation, cell culturing, drug processing, cell fixing and disruption. For the first time in our country, the function integration unit has also been developed to realize the function of independent temperature controlling, tracing multi-fluid automatic dosing, microscopic images recording and multi-parameter synchronous monitoring, and as well as the establishing of the ground-based microgravity analog effects of dynamic rotation control system.

(3) Research on Bone Loss Countermeasure Based on the Principle of High Frequency and Low Amplitude Force

Bone loss is one of the major risks during long-term space flight. Instrument against bone loss based on the principle of high frequency and low amplitude force has been developed. Head-down bed rest experiments have verified that high-frequency, low amplitude force could significantly relive the bone density decline velocity of hip, proximal tibia and distal tibia compared with the stimulated weightlessness group. The simulated weightlessness

impacts on bone mineral density of the lower limb in different parts, bone metabolism regulating hormone, bone resorption and formation markers have been obtained also. Therefore, bone loss dynamic process during long term head down bed rest has been further understood, and the research level of bone loss early warning technology and countermeasure has been improved. The countermeasure instrument will be verified in our rendezvous and docking mission, which will provide a new idea for space bone loss countermeasure.

(4) Research on Human Biological Rhythm Changes and Oxidative Stress Monitoring Technology in Space Flight

As for the urgent needs for human risk assessment and health monitoring during space flight, biological rhythm disorders and high-stress effects has been focused on by one of our on-orbit research, of which monitoring technology of biological rhythm of sleep-activity cycle and oxidation level has been carried out in our country for the first time.

Oxidative stress related bio-molecular detection platform based on the SPR optical detection principle has been developed. Stabile and susceptible on-orbit testing technology which could detect the trace content of 3-nitro-Ge acid protein in urine during spaceflight has been established, which will provide a new technique for human health early warning and assessment in spaceflight, and will be very significant to astronauts' health ensuring, optimal alertness and neurological behavior performance maintaining.

2 Scientific Research

2.1 New Animal Model of Gravity Environment Simulation

Because of the similarity of morphology, physiology and biochemical metabolism characteristic between monkeys and human beings, medium and long term simulated weightlessness macaque model has been established to research the physiological limits to environments of hypergravity and impact under the condition of emergency return occasion after medium and long term spaceflight. According to the characteristics of the primates, head-down bed, animal bondage vest, animal urine collection device and the recreational facilities adapted to the ethics rule of animal experiments have been developed, nonhuman primates simulated weightlessness model and adaptive training measures have been established. The validity of the model has been confirmed by series characteristic physiological indexes, including blood volume, muscle circumference and muscle structure characteristic, *et al*. The establishing of the macaques simulated microgravity model will sound the aerospace medical research application system, and establish an integral and mutually supporting researching chain from cell, model animal to non-human primates, which will provide an extremely strong data base and technical supports for space medicine research.

2.2 Series Head Down Bed Rest Test

In order to research and develop an effective and comprehensive protection technology for our rendezvous and docking spaceflight missions, to obtain further understanding of the physiological and psychological changes during long-term space flight, and to accumulate some cogent accumulation of protective technology, series of head down bed rest experiments have been carried out during recent two years, which included 30 days head-down bed-rest experiments, 45 days head-down bed-rest experiment and first female 15 days head-down bed-rest experiment in China.

From these experiments, physiological and biochemical characteristic changes in different stages of cardiovascular function, bone metabolism, muscle atrophy, endocrine and immune regulation have been obtained. Three reaction types to orthostatic stress after long-term bed rest, composed of vasovagal syncope type, autonomic dysfunction type and orthostatic tachycardia syndrome type have been identified for the first time, and orthostatic tolerance evaluation system has therefor been enriched. By synchronously real-time detection of cerebral blood flow velocity and lower extremity blood flow velocity, temporal artery blood flow velocity decrease has been found to be more sensitive to the orthostatic stress compared with the middle cerebral artery, and technology of early warning to orthostatic decline and evaluation indicators of orthostatic countermeasure has therefor been enriched. Time dynamic changes of human cognition, decision making, movement, operation, and biological rhythms under long-term head down bed rest simulated weightlessness condition have been comprehended, and the physiological effects of human operational capacity and its mechanism in future long-term space flight have been understood. Moreover, the security of single and integrative protective measures and its effectiveness, the effectiveness of the traditional medicine syndrome diagnostic scale for aerospace medical problems have also been researched and verified. Furthermore, theory of traditional Chinese medicine pathogenesis hypothesis on physiological adaption to medium-and long-term spaceflight has been improved either.

For the first time, characteristic physiological effects of simulated weightlessness on Chinese adult women has been obtained, results of which have shown that after 15 days of head-down bed rest, female has appeared

a higher probability of orthostatic intolerance, more obvious decline in cardiopulmonary exercise function and lower limb muscle atrophy, L5/S1 lumbar disc space has been widened, and lumbar lordosis curvature has been decreased. As to the psychological aspects, individual emotional performance showing a dynamic change from being nervous and easily excited to calm, and the psychological inhibition ability process from damage to recovery.

2.3 Research on Mechanism of the Weightlessness Physiologica Effects and its Countermeasures

For the prominent medical risks of bone loss, muscle atrophy, cardiovascular dysfunction, oxidative stress and other physiological effects raised by long-term spaceflight, systematic studies on molecular mechanisms and its relationships, related countermeasures exploring have been carried out.

2.3.1 Bone Loss

As to the highlight problem of bone loss in long-term flight, aiming at the current research focus, studies on the osteoblast differentiation, and apoptosis mechanism of cytokine regulation, gene regulation, nuclear transcription factors, miRNA regulation and signaling pathways have been carried out. Countermeasures of strontiumsalt, Chinese traditional medicine, power stimulating and various kinds of exercises have been explored.

As cytokine IGF-1 is very important to skeletal muscle reconstruction and adult stem cell proliferation and differentiation regulation, rat tail suspension model has been used to study the impact of different simulated weightlessness time on IGF-I selectively spliced MGF in muscle and bone. Results showed that two splice isoforms of IGF-I appeared certain degree of difference in the 4th and 7th tail suspension days, which suggested that tail suspension simulated microgravity impacted the IGF-I alternative splicing and affected the adult tissues cell death and renewal balance. The conclusion above will lead to a new view of the space re-adaptation disease development mechanisms.

Runx2 and Cbfa1, the important genes in regulation of bone mass cell differentiation and bone development, have been studied by osteoblast rotation culture mode whose Cbfa1 activity can be reflected by EGFP or Luc reporter gene. Results showed that rotation simulated weightlessness can inhibit Runx2/Cbfa1 activity, reduce the stimulating reactions to hypergravity, IGF-I, VD3 and BMP2, and inhibit the interaction between Runx2/Cbfa1 and VDR, the VD3 receptor. Rotation can also damage the actin cytoskeleton of MG63. Low concentrations of actin cytoskeleton disrupting agents CB can eliminate the BMP2 stimulating effect on Runx2/Cbfa1 activity, while the actin cytoskeleton stabilizing agent JAS can protect it in a certain extent.

Microfilament cytoskeleton has been found and proved to be involved in BMP2 inducing role on Cbfa1 activity besides the classic BMP2 signaling pathways. Important view has been proposed that actin cytoskeleton depolymerization might be the important regulation factor in the rotation inhibiting effects on BMP2 response to Cbfa1. Through application of the pre-established mouse simulated weightlessness bone loss model, using the ATF4 gene knockout mice, ATF4 molecule has been found to play an important role in the development process of the bone, and has been revealed to be a substrate of the Wnt pathway key kinase GSK for the first time. By inhibiting GSK phosphorylation levels, Wnt reduces the level of phosphorylation in ATF4, thereby enhances the stability of ATF4 in the body, and promotes the function of osteogenesis.

MicroRNA miR-214, specific binding ATF4 3′UTR and involving in the ATF4 cell protein expression regulation, has been screened. In vivo intervention study, results have showed that miR-214 inhibited the osteoblast function and affected the development process of the bone by reducing the body ATF4 protein levels. In vitro and in vivo experiments, results have showed that miR-214 antisense nucleic acid can enhance bone cell function, increase bone density, thus against the bone loss effect.

In addition, many other significant results have also been found. Skeletal unloading in rats induces an increase in Fas protein expression, thus increases the apoptosis of osteoblasts, osteocytes and bone marrow cells. Results of microarray analysis have revealed the differential expression pattern of microRNAs in microgravity, in which the expression levels of 2 miRs has been found to be increased and 5 miRNA to be decreased in simulated microgravity group. Among these genes, overexpression of miR-494 inhibits osteogenesis and inhibition of endogenous miR-494 promotes ostenblast differentiation. Disruption of the microfilament cytoskeleton induced by simulated microgravity can regulate the NO/NOS system to influence the signal transduction of the osteoblasts. Microgravity leads to a decrease in osteogenic potential of human bone marrow-derived mesenchymal stem cells by large gradient high magnetic field superconducting magnet model, LGHMF-MG shall affect the initiation of osteogenesis. Strontium ranelate can prevent bone loss by promoting bone formation, inhibiting bone resorption, increasing bone mass and bone strength, and decreasing the Fas expression to decrease the osteoblasts, osteocytes and bone marrow cells apoptosis. Chinese herbal prescriptions can relieve weightlessness osteoporosis and prevent the bone calcium distribution

and enhance the generation of collagen I. Sports promote the bone formation by promoting the expression of osteoblast specific transcription factor Osterix, and the moderate jump exercise is superior than swimming. Even though whole body BMD increases significantly by bicycle ergometer exercise training, lumbar spine BMD during 30d head down bed rest can't be maintained, and the lower limb muscular strength exercise training methods has significant protective effect both on whole body and weight-bearing bone BMD. Calcitonin can improve osteoblast proliferation and secretion functions via up-regulating IGF-1 mRNA expression in simulated microgravity. Resistance exercise can improve BMD, BV/TV, Tb.Th, and reduced Tb.Sp in femoral cancellous bone, which can counter bone loss effectively and mitigate the bone strength reduction induced by simulated weightlessness. Direct mechanical loading at 5N/10Hz and one minute per day can effectively prevent the bone loss caused by hind limb unloading.

2.3.2 Muscular Atrophy

Focusing on the responses and interactions of the important regulatory molecules and signaling pathways in weightlessness skeletal muscle atrophy, researches on TGF-β/myostatin signaling pathway, the NOS / NO regulatory mechanism have been carried out to study the weightlessness muscle atrophy mechanism and to explore some new effective countermeasures.

Skeletal muscle tissue-specific TβRII gene knockout model animal based on the Cre-loxp technology for the first time in our country has been established, which realized the ability of skeletal muscle tissue targeting blocking to Smad3 key signal transduction pathway upstream by activating phosphorylation. It has been found that skeletal muscle tissue-specific TβRII gene knock can combat slow muscle loss of quality, combat the fast and slow muscle fiber phenotype transformation, regulate muscle atrophy-specific gene, muscle differentiation specific genes and slow muscle development specific genes through the blocking effect of Smad3 phosphorylation activating signal pathway and its interaction to important signaling pathway of ERK1 / 2 and AMPK, which will provide a new idea for drug countermeasure research and development of weightlessness muscular atrophy.

Tail-suspension simulated weightlessness can elevate the expression of myostatin mRNA in rat soleus muscle, and induce an obvious progressive decreasing in the NT-3 expression level of its intrafusal fibers, which suggests that the NT-3 expression change may contribute to the proprioceptive adaptations to microgravity. Unloaded soleus has been proved to suffer from several structural and functional changes, which include decreasing in expression and activity of nNOS, increasing in expression and activity of calpain and the concentration of intracellular calcium, the lower RyR stability and the destruction of fiber ultrastructure. On the opposite, while the stretch loading is putted on the unloaded soleus, all of the above changes will attenuate significantly. These results suggests that passive stretch of muscle may be an available way against unloaded muscle atrophy through increasing the expression and activity of nNOS, keeping the RyR stability, inhibiting calpain activity, and decreasing the adnormal degradation of desmin and other. Vibration combined with Radix Astragali is an effective countermeasure for muscle atrophy induced by tail-suspension.

2.3.3 Cardiovascular Disorders

For cardiovascular disorders, studies on cardiovascular structure and functional remodeling and its regulatory mechanisms and protective countermeasure of artificial gravity under simulated weightlessness condition have been carried out, which mainly include of expression level changes of cardiac-specific functional genes and cardiac important nuclear transcription factor, post translational regulation changes of cardiac troponin I subunit, desensitization mechanisms of myocardial beta-adrenergic receptor, gene expression changes of cardiovascular center, apoptosis of vein endothelial cell, regulation changes and its signaling pathway of autophagy and cellular life cycle, responsibility change of arterial smooth muscle cell ion channels to vasoactive substances, countermeasure effects of artificial gravity combined with exercise protective measures, *et al*.

Results showed that cardiac-specific functional genes of ANP, α-actin, α-MHC have been significantly decreased under the rotation culture simulated microgravity condition. The protein level of their key transcription factor, MEF-2C, GATA4 and NKX2.5, haven't been significantly changed. However, its transcriptional activity has been decreased significantly. Calpastatin expression has been significantly decreased and calpain activity has been significantly increased after tail-suspension, the calpain activity inceasing may enhance cTnI degradation in the myocar-dium of tail-suspended rats. The depressed responsiveness of the β-adrenoceptor stimulation can cause the depression of cardiac function during weightlessness, Depressed β-adrenoceptor responsiveness may not be due to the downregulation of β-adrenoceptor itself, but to the impaired postreceptor events such as Gs protein/adenylyl cyclase /cAMP/ protein kinase A/Ca^{2+} cascades, The impaired function of AC and L-type Ca^{2+} current may be partially responsible for the depressed responsiveness of the β-adrenoceptor stimulation, which may be partially responsible for the depression of cardiac function. Simulated microgravity by clinostat can induce human pulmonary microvascular endothelial cells prophase apoptosis. The mitochondial signal transduction pathway has played an important role

in it, and the change of F-actin can take part in the cell apoptosis either. Simulated microgravity can also induce the autophagy of human umbilical vein endothelial, of which Beclin1 and PI3k might be the key signals. Simulated weightlessness can induce the adaptational change of CaL in cerebral VSMCs and increase its responsibility to Ang Ⅱ. Short-arm centrifuge and aerobic exercise are necessary conditions to improve cardiac function and cardiovascular autonomic nerve modulation. One hour intermittent (1−2G) artificial gravity with 40W work load exercise per day can successfully eliminate the changes in cardiovascular function, autonomic nerves regulation, the compliance of popliteal vein and exercise capacity.

2.3.4 Oxidative Stress

The mitochondrias in different tissues and cells appear different degrees of structural changes under the condition of weightlessness, which can cause the occurrence of oxidative stress and result in functional changes. Oxidative stress is an important reason leading to the occurrence of various diseases. Results have showed that an important cellular redox regulatory protein Trx in neuroblastoma cells can regulate the redox state of actin cytoskeleton and affects its structure, and thus involves in cell proliferation and apoptosis regulation. The combination of Trx and actin has been proved both in extracellular His-pulldown experiments and cells coimmuno-precipitation experiments. Trx 62 of Cys has a key role in the combination of them. It has been initially confirmed that Trx as a new actin-binding molecules involves in the redox regulation of the actin cytoskeleton by regulating actin Cys residues in the redox state and inhibition of oxidative stress caused by microfilament depolymerization, thus maintaining the shape of the actin skeleton and functional integrity.

Targeting at the problem of increasing level of oxidative stress level and declining in cognition caused by medium and long term space flight, two types of flavonoid monomer have been found to possess the protective effects. Luteolin can inhibit nerve cells oxidative stress caused by micro-gravity via inhibition ROS-NO pathway, and be able to significantly inhibit the microtubule binding protein Tau phosphorylation. These findings will provide certain theoretical foundation for natural flavonoids in fight application against neurodegenerative diseases induced by stress factors.

2.3.5 Others

A number of simulated weightlessness physiology effects on other tissues and their mechanisms have been carried out.

(1) Lung Tissue

A decline in lung function to certain extent has been found in healthy males under simulated weightlessness. The significant decrease of resistance in the pulmonary arteries and pulmonary circulation is mainly caused by the changes of pulmonary arterial pressure and may be the cause of the orthostatic intolerance and the decrease of exercise capability after simulated weightlessness. Pulmonary arteries with diameter less than 50μm are the main targets influenced by the simulated weightlessness of tail-suspension. Simulated microgravity by clinostat can induce human pulmonary microvascular endothelial cells prophase apoptosis. The mitochondial signal transduction pathway plays an important role in the apoptosis of human pulmonary microvascular endothelial cells by simulated microgravity, PI3K-Akt and NF-κB also take part in its mechanism. The decreased expression and depolymerization of F-actin might also take part in the cell apoptosis. Research on rat lung tissue extracellular matrix regulatory factors change and its role in lung fibrogenic-like change mechanism caused by simulated weightlessness have also been carried out.

(2) Digestive System

Simulated weightlessness may depress the structure of regenerative gastric mucosa, delay the healing of ulcer, and increase EGF level in gastric juice. The percentage of normal rhythm and total power of dominant frequency in EGG has been decreased significantly by HDBR. MTL concentration in arterial blood is significantly increased in rats under simulated weightlessness, whereas NO and gastrointestinal hormone hasn't changed remarkably.

(3) Immune System

Small molecule metabolites regulation mechanism research of simulated microgravity physiological effects on immune system have been carried out based on metabolomics analysis.

(4) Blood System and Others

Simulated microgravity environment can make the leukemia K562 cells arrest at G0/G1 cell cycle phase, which may be caused by the decreased ERK1/2 phosphorylation. Furthermore, researches on microgravity physiological effect and its initial mechanism of vestibular, central nervous system, psychology and cognition, digestive system and reproductive system *et al*. were also carried out.

2.4 Space Radiation Environment Measurements and Biological Effects

According to the characteristic of space radiation and the radiation safety evaluation needs for manned space flight, further study has been carried out to establish the space radiation measurement and evaluation platform, the space radiation dose data of unmanned rendezvous and docking mission has been further accumulated on the basis of all past flight data.

Some new progress has made in terms of radiation metrology methodology and mechanism of radiation damage repair. China body signs space radiation dose calculation of the human body mode has been established by image segmentation, non-uniform rational B-spline, three-dimensional reconstruction technology based on the male and female body signs data according to the research results of the 863 Chinese digital data item, which has solved the key technologies of great magnanimity images registration, big organ three-dimensional reconstruction, and the human body model cosine *et al*. These key technologies will lay the foundation for radiation simulation accuracy improvement.

U2OS and MCF7 cell model of heavy ion induced chromosome damage and UV radiation induced chromosomal damage cell model have been established. By means of gene chip technology, upward or downward of the factors involved in DNA repair and epigenetic effects including PR-Set7/SET8 have been filtered out. It has been found that SET8, the histone H4-K20-specific methyl transferase, is responsible for the single methylation modification for histone H4-K20 protein, which played an important role in gene expression regulation, cell cycle, DNA repair, cell proliferation, apoptosis and other biological processes. It can stabilize p53 by p53-K382 methylation. In UV-treated cells, SET8 is ecruited to sites of DNA damage relying on the interaction with PCNA, and is degradated after being ubiquitinated by CRL4CDT2 E3 ubiquitin ligase complexes. It can also promote the transformation between epithelial cell-mesenchymal cells and give the Twist transcription factor dual transcriptional functions.

As a result of the theoretical studies on space radiation protection mechanisms through the mechanism of interaction between plasma and magnetic field as well as expansion of the magnetic field, relationships between the various physical parameters in magnetic expansion has been discussed and its principle verification test has been carried out, new methods of active protection has been suggested.

3 Mars 500 International Collaborative Research

Mars 500 is an advanced large international cooperative project, a psychosocial experiment conducted by Russia, Europe and China in preparation for manned spaceflight to the planet Mars. ACC participated in this project with one Chinese crew member and three scientific research experiments, which played a positive role for the success of the project in terms of technological contributions to crew members' support and scientific research progress.

Aiming at the future applications and based on the scientific research and characteristics, three experiment projects of China named as traditional Chinese medicine research in long-term closed environment, oxidative stress response and circadian rhythm patterns under long term isolation and confinement environment, mood state and body language changes under long-term confinement and multi cultural environment, respectively, have been selected according to the Mars 500 project's special characters. All the three experiment projects have obtained valuable data of human physiological and psychological responses in the extreme long time isolated environment, and these results will provide great guidance to subsequent long-term manned spaceflight.

(1) Application of epigenetic theory and technology for the first time among the international field of aerospace medicine, a systematic study of human stress and rhythm changes in law and its molecular mechanism under the long-term closed flight condition has been conducted. Epigenetics is the frontier to explore the environmental factors that affect human health secrets. The quality of sleep, circadian rhythm parameters of oxidative stress parameters, DNA methylation events in circulating blood cells by illumina high-density and high-precision gene chip measurement have been monitored in different stages of the mission, respectively, in the stages of flight to Mars, landing on Mars and return to Earth. Results have suggested that the promoter region of the Wnt pathway relevant genes of the human blood cells are significantly methylated under the long-term confined condition. It will explain the law of human stress and rhythm changes under long-term closed conditions in the epigenetic point of view, and provide an unique perspective for the important scientific study of human adaptation mechanisms to the environmental factors.

(2) Combining the characteristics theory and technology of traditional medicine and aerospace medical research, a new way of thinking has been provided to the medical supports for the future long-term manned space flight. Basic information of 6 volunteers involving symptom grading scale information, typical pulse manifestation, tongue manifestation and face manifestation have been collected by four diagnostic methods of inspection, listening and smelling, inquiry, palpation and pulse taking using digital traditional Chinese medical diagnostic equipment. Combined with the comprehensive analysis of the results of the blood parameters and cerebral cognitive function, physical identification and syndrome differentiation have been carried out to clear the health status of the volunteers and their potential health risks. Furthermore, the physical condition of the volunteers has been estimated holistically and comprehensively from three aspects involving extent of fatigue, autonomic nervous functional status and health evaluation. Results have showed that different volunteers appear different characteristic of symptoms during

the experiment as a result of their respective constitution differentiation. Health status shows the development trend of mingled deficiency and excess syndrome to deficiency syndrome, or deficiency syndrome to mingled deficiency and excess syndrome. All the volunteers are in mild and moderate fatigue status generally, their sympathetic nerve excitability increased in early days after entering the cabin, and with adaptation to the environment, their autonomic nervous function status tended to be balanceable on the whole.

The study has obtained the dynamic changes of physical identification and syndrome differentiation under the long-term closed environment, has revealed the characteristics and laws of the overall functional status in the different stages, has systematically explained the TCM machine and intervention principles and measures of the whole functional status attributed to the 520 days long-term closed environment. It will provide valuable technical information for the TCM preventive treatment technology for future long-term manned spaceflight.

(3) Research on non-verbal communication changes under long-term confinement and multi-cultural environment has been carried out to reserve the techno-logy of psychological supporting in long-term spaceflight and psychology and communication restoration skills after space flight. The WHO Profile of Mood State (POMS) and Affective Picture Test has been examined in experiment training phase, and in every 30 days to 60 days during formal experiment in the cabin. Body language has been analyzed by observing the every two weeks video data of breakfast together with all crew in cabins. Results have showed that most members kept stable emotion in the long-term and confined simulation mars flight. Due to lots of stress of selection and training course, there are more negative emotions in the crew. There are close relations between mood states and professional experience, social experiences, and cultural difference in the crew. The dominance dimension of Affective Picture test means one feel himself in controlled disadvantage or in in-control predominance when facing the picture. The high-low-high dominance scores change pattern may be correlated with crew members' self-confidence, in-control feel to success of mars flight mission. The decline time of breakfast may be due to that the crew members have gradually showed their individuality and living habit. The body language has more indeterminacy and more context-dependent than verbal. So, the more use of gesture may be associated with the more familiarity and compatibility with the flight time in crew.

4 Considerations for Future

Following-up the requirements of crew health protection in subsequent long-term spaceflight, Chinese aerospace medicine research strategy must be planned, which focus on declining the human system risks and revealing the inherent key scientific issues of those risks. To gain those purposes above, a more advanced risk assessment system and a innovative and effective protection technology system for human system shall be established to reserve theory and technology for long-term space flight, by means of accumulating the data of space environmental effects and psychological changes obtained from theoretical and technical researches which targeting on the long term on-orbit habitation and health-maintenance. On the other hand, by using the unique space station experimental platform, taking full advantage of the rapid development of science and technology, also the experts resources in our country, inheriting and carrying forward the advantages of our traditional medicine, carrying out some international cooperation, batches of intelligent, multi-functional, personalized health detection technology will be developed, self-rehabilitation measures based on Chinese traditional medicine will be founded, family diagnosis and treatment technology and personalized health care level will be improved, and the public medicine will be accordingly promoted.

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