Annual Top 10 Science Advances of 2020 in China – To Honor and to Inspire

By YAN Fusheng and SONG Jianlan (Staff Reporters)

On February 27, 2021, the High Technology Research and Development Center (HTRDC) of the Chinese Ministry of Science and Technology released the "Annual Top 10 Science Advances" of 2020.

Topping the list is the collective efforts made by Chinese scientists to contain the coronavirus epidemic. The list extends to the explorations to the moon, to the deepest trench in the ocean and the highest mountain on the land. Among others, the list also embraces the reconstruction of the history of prehistoric Chinese populations informed by traces of ancient DNAs, as well as the history of marine invertebrates through an enormous collection of fossil species that span the Paleozoic through the Early Triassic.

The selection of the "Annual Top 10 Science Advances", led by HTRDC of the Chinese Ministry of Science and Technology, has been successfully held 16 times so far. By doing so it aims to promote scientific progress in major research fields and increase the public awareness of science.

Now, it is the time to tuck in.

1st

Fighting against COVID-19

Topping the list is the collective efforts made by Chinese scientists, from different disciplines and departments, to contain the coronavirus epidemic. In response to the sudden strike of the previously unknown virus, they have made prominent progress through widespread cooperation and perseverance.

Shortly after the onset of the virus outbreak, they isolated and identified the 'culprit' as a novel type of coronavirus, later termed as SARS-CoV-2, and shared its full genome sequence with the World Health Organization (WHO). These acts laid a foundation for the rapid advancement of diagnostic technologies and the development of drugs and vaccines.

Moreover, they also elucidated the cell invasion mechanism of SARS-CoV-2 on short notice and revealed its transmission mechanism, which provide important guideline for the authorities to establish effective public prevention and control strategies.

Inactivated vaccine against SARS-CoV-2.

With the aid from big data analysis, the efficacy of the taken measures against the COVID-19 epidemic can be accessed in real time. After confirming the infected with the self-developed nucleic acid-based or immunoassay-based diagnostic reagents, big data analysis also become handy in elucidating the tracks of the infected ones and confirming the close contacts, so that a precise and prompt quarantine can be initiated. Big data-aided quarantine has proven especially effective in preventing widespread infection.

The scientists also established mouse and monkey infection models to investigate how SARS-CoV-2 transmits *in vivo* and the damages it incurs by the way. Since SARS-CoV-2 does not infect mice in nature, they genetically engineered mice to carry the human ACE2 (hACE2) – the receptor used by SARS-CoV-2 for cell entry – to make them vulnerable. The hACE2 mouse can partially recapitulate the pathology of COVID-19 in humans, providing a valuable platform for testing potential vaccines and therapeutics.

Chinese scientists also revealed the clinical characteristics of COVID-19. Moreover, in the absence of specific drugs, they resorted to the wisdom of traditional Chinese medicine and integrated it with modern medicine to compile a national guideline for diagnosis and treatment of the viral infection. They kept updating the guideline with the latest R&D results and released a total of eight versions of this guideline in succession. Meanwhile, they elucidated fine structures of many key viral proteins, which inform why some compounds or drugs can inhibit the viral infection.

More importantly, to effectively prevent infection, they dedicated to develop different types of vaccines, including inactivated vaccines, viral vector vaccines, protein subunit vaccines and nucleic acid vaccines. The Chinese adenovirus vector vaccines took a lead in entering Phase 1 clinical trials, and so did inactivated vaccines in entering phase 3 clinical trials, which have been now approved and marketed with conditions.

Identification and creation of a series of neutralizing monoclonal antibodies targeting the viral spike protein and the receptor binding domain (RBD) have also been hotly pursued by Chinese scientists. For example, a recombinant monoclonal neutralizing antibody called "JS016", codeveloped by biopharmaceutical company Junshi Biosciences, the CAS Institute of Microbiology and others as a reward of treasure-hunting from the blood of a convalescent donor once infected with COVID-19 (*Nature* 2020, doi: 10.1038/s41586-020-2381-y), has entered Phase 2 trial.

The combination of these neutralizing antibodies forms an antiviral "cocktail" that also plays an important role in containing the infection.

Through unremitting efforts, selfless dedication, and rigorous and efficient scientific research, Chinese scientists have collectively provided a strong scientific support for China's major strategic achievements in fighting against COVID-19 epidemic, and made their contributions in tackling with this global crisis.

2nd

Successful Unmanned Robotic Collection and Return of Lunar Samples by CE-5

Ranked second is *Chang'e*-5 (CE-5), the lunar mission that has successfully collected and returned lunar samples via unmanned robotic maneuver from around 384,000 km away.

Launched early morning on November 24 from the Wenchang Satellite Launch Center in Hainan Province, China by the CZ-5 (Long March-5) Y5 rocket, CE-5 navigated to the Moon and sent its lander-ascender complex onto the predetermined location to the north of Oceanus Prcellarum to collect samples of lunar rocks and soils. The complex automatically drilled a 2-meter hole, shoveled 2 kg lunar rocks and soils, and sealed them in an air-tight vessel. After a successful unmanned blasting off from the lunar surface, the ascender accurately docked onto the returner-orbiter complex in orbit, and passed the collected samples onto the latter. The sealed samples, kept in the returner, were subsequently carried by the orbiter back to the

The *Chang'e*-5 probe

Earth. On December 17, 2020, 23 days after CE-5's launching, the returner touched down on the snowy prairie of Inner Mongolia, China, marking the first return of lunar samples by humankind in 44 years.

This mission has made history by establishing multiple records, including China's first unmanned robotic collecting and sealing of extraterrestrial samples, first soft landing on and blasting-off from the surface of an extraterrestrial body, first unmanned docking and sample delivery in lunar orbit, first high-speed re-entry into terrestrial atmosphere from the Moon, and first safe return of lunar samples.

The success of CE-5 marks the glory ending of the finale of the Phase I of China Lunar Exploration Program (CLEP-I), dubbed "*Chang'e* Programme" after a legendary fairy dwelling on the Moon in Chinese mythology. This program features three stages of unmanned robotic missions, respectively focusing on orbiting, landing on, and returning samples from, the Moon.

CE-5 has set a milestone for China's lunar exploration, and will help humankind better understand related scientific issues, including the formation of the Moon and the evolution of the solar system.

3rd

Deep-sea Manned Submersible *Fendouzhe* Makes a New Record on Diving Depth

The development of deep-sea manned submersible *Fendouzhe* (Striver) is a major task in the field of deep-sea key technology and equipment outlined in the China's 13th Five-Year Plan, which was launched in 2016.

In June 2020, *Fendouzhe* went through the final assembly, integration and tank test. In July 2020, the submersible started its first stage of sea trials, and accomplished 17 dives with a maximum depth of 4,548 meters.

On October 10, 2020, *Fendouzhe* set sail for the second stage of sea trials in the Mariana Trench, the world's deepest natural trench in the western Pacific. During this expedition, *Fendouzhe* successfully completed 13 dives, eight of which exceeded a depth of 10,000 meters. At 8:12 a.m. (GMT+8) on November 10, the manned submersible set a new national record by diving to a depth of 10,909 meters.

Deep-sea manned submersible *Fendouzhe*.

The development of *Fendouzhe* was led by the China Ship Scientific Research Center (CSSC), which plays important roles in many aspects, including the submersible's design, development of key technologies and instruments, assembly and trials. The development of home-made *Fendouzhe* and its successful sea trial marked China's breakthroughs in deep-sea equipment and technologies. Notably, its cabin and buoyancy materials are more pressure-resistant compared with its predecessors.

Fendouzhe is the world's first deep-sea manned submersible that allows three crew members to accomplish multiple dives at the same time. Its successful sea trial marked a great leap in China's ability to perform deep-sea scientific research and exploration, as well as an important milestone in the advancement of marine high technology.

4th

Pinpoint Where DNA Begins to Replicate

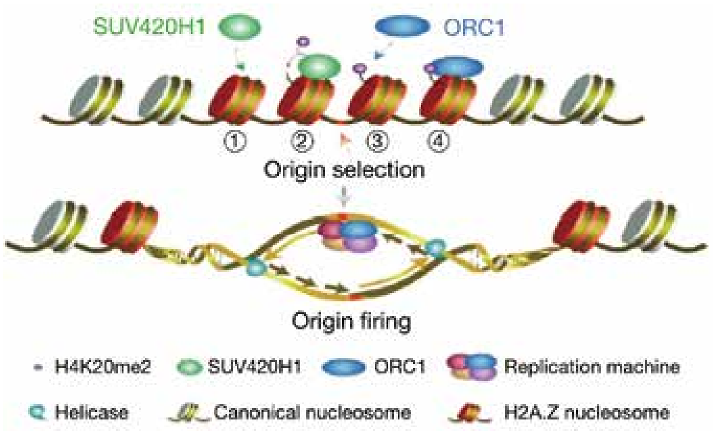
DNA replication is the basis for the accurate passing of human genetic material between cells. In eukaryotes, DNA replication starts at the replication origins, which are first licensed in G1 phase by prereplication complex and then selectively activated during S phase.

However, how these replication origins are selected remains largely unknown, which, to some extent, hinders our understanding of cancer occurrence and progression.

The research published in *Nature* on December 25, 2019, led by Dr. LI Guohong and Dr. ZHU Mingzhao from the Institute of Biophysics (IBP), Chinese Academy of Sciences, reported a precise mechanism that determines where DNA starts to replicate (doi: 10.1038/s41586-019-1877-9).

In this study, the scientists demonstrated that the histone variant H2A.Z can facilitate the licensing and activation of early DNA replication origins.

They first found that knocking down *H2AFZ* genes in HeLa cells led to cell growth defects. Through mass spectrometry, they then found that many subunits of prereplication complex were enriched on H2A.Z nucleosomes compared with canonical H2A nucleosomes, the repeating unit of chromatin made up of DNA wrapping around histone octamers. The result indicated the involvement of H2A.Z in the licensing of DNA replication origins.



The work model of origin selection (top) and origin firing (bottom). Top, H2A.Z nucleosomes bind SUV420H1 directly (step 1) to establish H4K20me2 on chromatin (step 2), which then recruits ORC1 (step 3) to bind to replication origins (red mark; step 4). Bottom, origin firing: the H2A.Z-SUV420H1-H4K20me2-ORC1 axis selectively licenses and activates early replication origins. (Image by Dr. LI Guohong's lab)

To reveal the probable interaction between H2A.Z and the prereplication complex, they then went through many *in vitro* biochemical analyses and found that H2A.Z-containing nucleosomes bind directly to the histone lysine methyltransferase enzyme SUV420H1. Their binding promotes H4K20me2 deposition, which further recruits origins recognition complex 1 (ORC1) to help seal the licensing and activation of DNA replication origins.

In addition, the scientists discovered that H2A.Z-regulated replication origins have a higher firing efficiency and earlier replication timing compared with other origins.

Taken together, their study describes a novel epigenetic regulation mechanism for DNA replication origin selection and offers a new way of understanding DNA replication regulation in eukaryotes.

5th

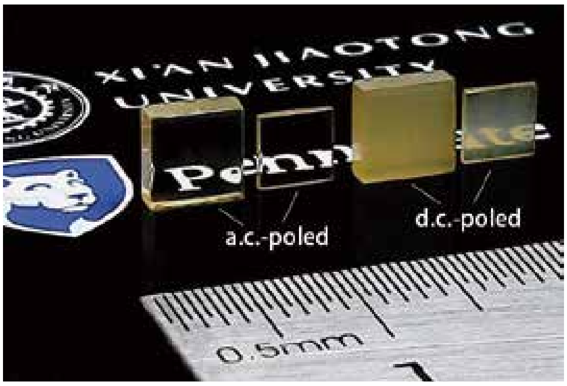
Transparent Ferroelectric Crystals with Ultrahigh Piezoelectricity

Piezoelectric materials show high electro-mechanical coupling, which means that they can generate large mechanical strains if an electric field is applied to them, and vice versa. This unique feature makes them very attractive in developing sensors, small motors and actuators – devices that convert external electrical stimuli into movement.

It is ideal to make piezoelectrics transparent so that they can find wide applications in coupled electro-optical–mechanical devices. However, simultaneously achieving high piezoelectricity and perfect transparency in piezoelectric materials has long been a challenge because most high-performance piezoelectrics are ferroelectrics that contain high-density light-scattering domain walls, which in return gives the crystals an opaque appearance.

This hurdle has now been overcome, as a research paper, entitled "Transparent ferroelectric crystals with ultrahigh piezoelectricity," was published in *Nature* on January 15, 2020. This breakthrough was made by a joint team led by Prof. XU Zhuo from Xi'an Jiaotong University.

In this study, the scientists reported a relatively simple method of using an alternating-current (a.c.) electric field to pole originally opaque ferroelectric crystals termed PMN-PT to simultaneously generate near-perfect light transmittance and ultrahigh piezoelectricity. These a.c.-poled PMN-PT can achieve ultrahigh piezoelectric coefficients exceeding 2,100 pC N^{-1}, which is far beyond the performance of the commonly used transparent ferroelectric crystals with piezoelectric coefficients of less than 40 pC N^{-1}.



Scientists from Xi'an Jiaotong University demonstrated that, when the poling (a process of applying an external electric field to the material to reorient unfavourably oriented domains, which can result in high piezoelectricity to the material) is carried out using alternating-current (a.c.) electric fields instead of using direct-current (d.c.) electric fields, a certain ferroelectric crystal, namely PMN-PT, shows near-perfect light transmittance and ultrahigh piezoelectricity. (Image by Dr. XU Zhuo's lab)

They also found that increasing the domain size leads to a higher piezoelectricity for certain PMN-PT crystals, challenging the conventional belief that decreasing the domain size always results in higher piezoelectricity.

This work presents a paradigm for achieving high transparency and piezoelectricity by ferroelectric domain engineering, and the transparent ferroelectric crystals reported here are expected to provide a route to a wide range of hybrid device applications, such as medical imaging, self-energy-harvesting touch screens and invisible robotic devices.

6th

The New Height of Mount Qomolangma

The elevation of the world's highest peak has been an issue of worldwide attention. The year 2020 witnessed the most accurate measurement and update of this landmark elevation by a team of Chinese scientists.

Highlighted in this survey are the state-of-the-art technologies and instruments indigenously developed by China that have played a central role in the process, represented by the *Beidou* Navigation Satellite System (CNSS) and advanced surveying equipment.

This round of survey and measurement obtained the first gravity value on the mount summit, setting a milestone in human history. This value is helpful for improving the accuracy of the elevation measurement. Despite the extreme weather conditions and severe environments, the team made breakthroughs in a series of scientific issues, and obtained data for aerial gravity, optical and laser remote sensing measurements, filling in knowledge gaps concerning the environment of the area surrounding the summit.

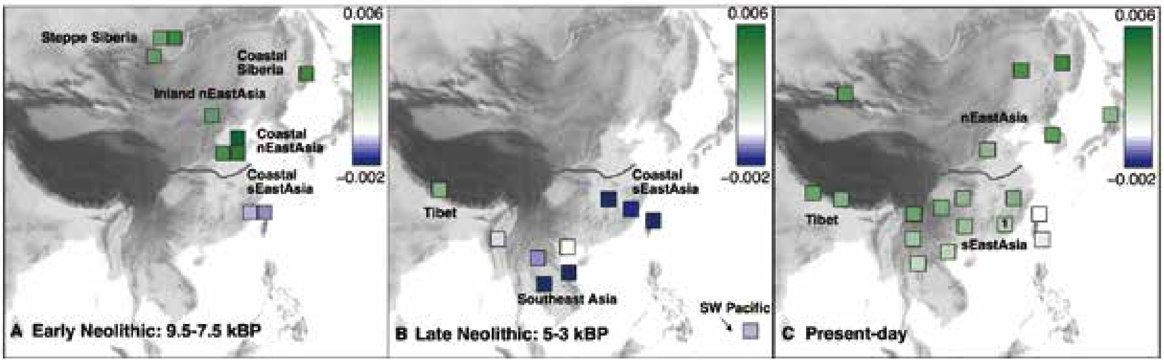
This survey updated the measurement for the geoidal surface of this area with a value 300% more accurate than the elevation obtained in 2005. In cooperation with Nepalese scientists, the team established the first geoidal surface for this area based on the global vertical datum, and first determined the elevation for the Everest summit as 8,848.86 meters above sea level. The data resulting from this survey has provided valuable first-hand materials for research in a series of areas, including eco-environmental preservation and recovery, natural resources management, geological research and survey, crustal movement monitoring, climate change, and glacier and permafrost research.

A surveyor sets up a marker on the top of the Mt. Qomolangma

7th

Missing Piece of East Asian Genetic History Revealed by Ancient Genome Analysis

In the field of ancient genome research, studies on East Asians, particularly those on prehistoric Chinese populations, are extremely scarce. Using advanced ancient DNA capture techniques, a team led by Prof. FU Qiaomei, a researcher at the Molecular Paleontology Lab under the Institute of Vertebrate Paleontology and



Ancient DNA analysis reveals the changes in northern and southern East Asian ancestry over time. (Credit: IVPP)

Paleoanthropology (IVPP), Chinese Academy of Sciences, retrieved ancient DNAs from 25 individuals dating back to 9,500–4,200 years ago and one individual dating back to 300 years ago from northern and southern East Asia.

Their research found that by 9,500 years ago, the primary genetic makeup of today's East Asians could have already taken shape in mainland East Asia.

Present-day mainland East Asians from the north and the south as well, as the research found, are genetically closer to northern Neolithic East Asians living along the Yellow River than to southern Neolithic East Asians on the southern coast of China. They almost all share a mixture of northern and southern ancestry from Neolithic East Asia, with northern ancestry playing a larger role. Population movement, particularly from north along the Yellow River southward, might have made a prominent part of East Asian prehistory after the Neolithic. Interestingly, the present-day Han people in all provinces, north and south, show a similar amount of northern and southern influences.

Another remarkable finding of the research is, present-day Austronesian speakers living across a wide swath of islands in Southeast Asia and the Southwest Pacific, who are genetically close to present-day mainland East Asians, show a remarkably close genetic relationship to Neolithic populations from the southern coast of China. Dr. FU and her team demonstrated unambiguous evidence showing that present-day Austronesian speakers have originated from a proto-Austronesian population derived from southern China at least by 8,400 year ago.

The history revealed by these 26 ancient humans has highlighted the prominent impact of population movement and mixture on human history, and meanwhile indicates a continuity tracing back 9,500 years. Unlike in Europe, the newly unveiled episode suggests that influences from Central Asia had no role in the formation of East Asian ancestry. Instead, the mixing largely has occurred regionally between northern and southern populations of East Asia.

The research has revealed a missing episode of human prehistoric migration, and has helped understand the formation of Chinese ancestry and updated the knowledge about the origin and evolution of the southern populations in East Asia.

8th

Big Data Mining Brings the History of Life into Sharp Focus

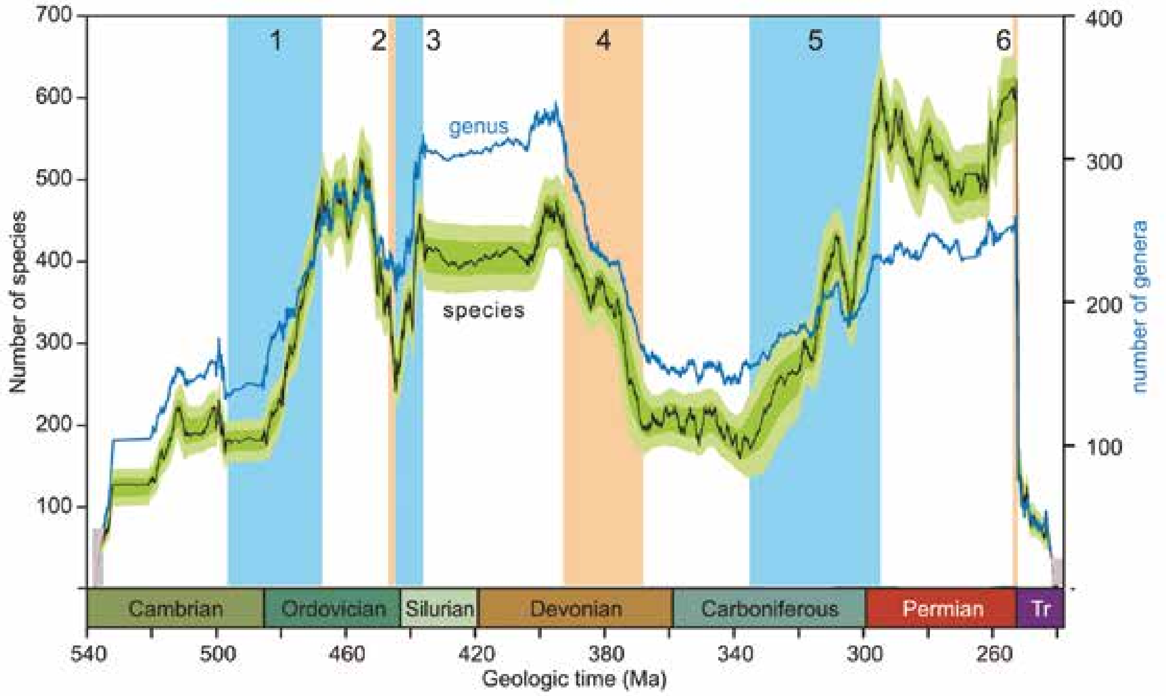
The origin and evolution of life is one of the world's biggest mysteries. More than 99% of the living organisms on earth are extinct, and rebuilding the history of biodiversity fluctuations through fossil record is one of the most important ways to gain insights to inform current biodiversity concerns.

However, the paleobiodiversity reconstruction is a challenging task, suffering from low time resolution, coarse biological classification, and incapability of distinguishing sudden major biological evolutionary events.

Previous deep-time paleobiodiversity reconstructions achieved very limited temporal resolutions, generally no better than 8 to 11 million years. Such resolutions are often not precise enough to bring the history of life into shape focus.

Unsatisfied with such obscurity, a team of scientists, led by CAS member SHEN Shuzhong from Nanjing University, used machine learning and supercomputing to mine a database of more than 11,000 fossil species that span the Paleozoic through the Early Triassic. As a result, they succeeded in elucidating the rise and fall of marine species with the accuracy of about 26,000-year time intervals. This increased temporal resolution clarifies the timing of known diversification and extinction events. The study was published on January 17 in *Science*, entitled "A high-resolution summary of Cambrian to Early Triassic marine invertebrate biodiversity" (doi: 10.1126/science.aax4953).

"This new level of dating specificity is similar to moving from a system in which all people who lived in the same century are considered to be contemporaries to one in which only people who lived during the same



General trajectories of Paleozoic genus and species diversity of marine invertebrates. The color bars (as numbered, with biodiversification or radiation event in blue and diversity decline or extinction event in yellow) indicate many important evolutionary events. 1, the Great Ordovician Biodiversification Event (GOBE); 2, end-Ordovican mass extinction; 3, Early Silurian radiation; 4, Middle to Late Devonian diversity decline; 5, Late Carboniferous – Early Permian biodiversification event; 6, end-Permian mass extinction. (Image by SHEN Shuzhong's lab)

6-month period are deemed to be contemporaries," writes Peter Wagner, a palaeontologist and evolutionary biologist at the University of Nebraska-Lincoln, who was not involved in the work, in an essay published in the same issue.

This approach not only allows scientists to learn extra details about well-known major events, but also enables them to uncover some smaller-scale events that were once masked. Understanding these smaller-scale events, particularly the smaller-scale extinctions in short time range, may provide insights to the planet's current loss of biodiversity.

Sparked by this breakthrough, a revolutionary change to the study of evolutionary palaeontology might be on the horizon when even a finer resolution could be achieved.

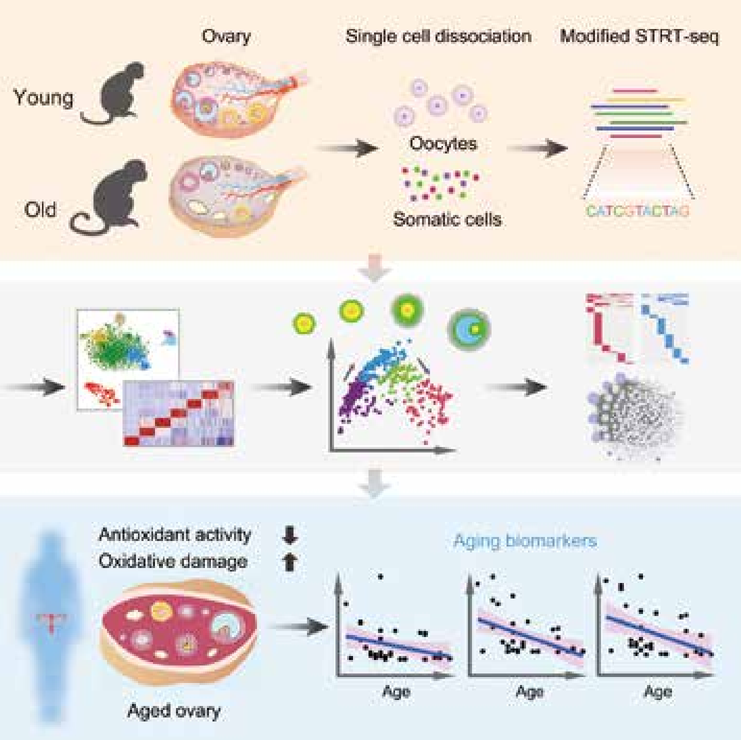
9th

Zoom in Multi-Organ Aging

Aging causes a functional decline in multiple tissues of the body, which in return increase the chances of getting various diseases.

To reveal the molecular mechanisms of aging and find ways to rejuvenate cells and organs, a joint team of scientists, led by LIU Guanghui and QU Jing at the CAS Institute of Zoology (IOZ), ZHANG Weiwei at the CAS Beijing Institute of Genomic Research, and TANG Fuchou at the Peking University, have conducted a series of studies and made numerous interesting findings.

Aging elicits distinct and complex responses across different types of cells, tissues, and organs, which in return leads to increased gene expression heterogeneity even within cells of the same type. Due to this level of



Comparative analysis revealed that inactivation of antioxidant genes is linked to the aging of monkey and human ovaries. (Image by CAS)

complexity, in-depth mining of genes expressed across different cell populations in multiple organs is required.

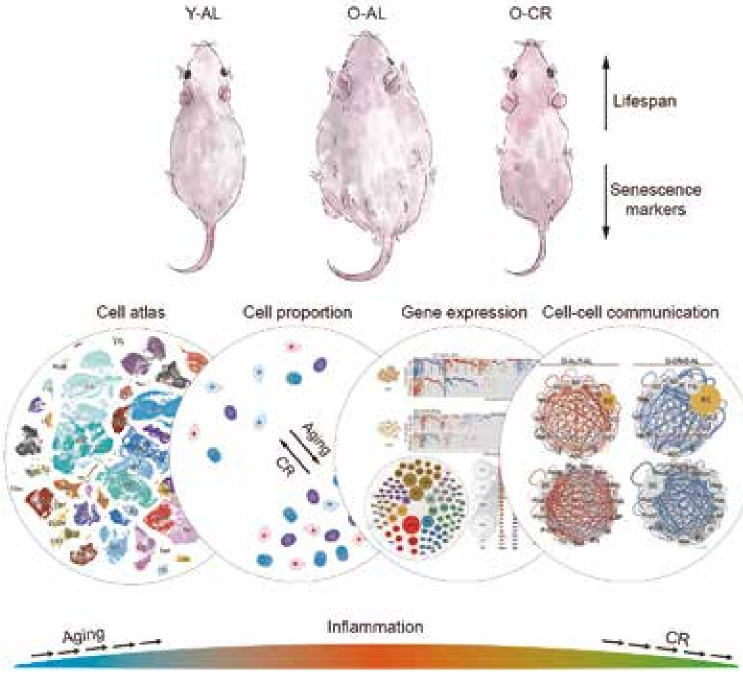
Enabled by single-cell isolation technique and high-throughput sequencing, scientists can now use a powerful technique, namely 'single-cell transcriptomic analysis', to assess the transcriptional features from individual cells, and are thereby able to identify a cell's inner nature by what it is doing, rather than by how it looks like. The high throughput of single-cell transcriptomic analysis allows such assessment to cover all prevalent cell identities in an organism.

The team surveyed the single-cell transcriptomic landscape of ovaries from young and aged cynomolgus monkeys, and identified cell-type-specific inactivation of antioxidant genes as the key transcriptional feature in primate ovarian aging (*Cell* 2020, doi: 10.1016/j.cell.2020.01.009). This finding derived that the ovarian functional decline, e.g., the female fertility decline with age, can be attributed to accumulative oxidative damage along the aging process. The newly revealed biomarkers and targets may serve well in developing protective intervention to age-related human ovarian disorders.

Similarly, the team also reported a single-cell transcriptomic survey of aortas and coronary arteries in young and old cynomolgus monkeys, and verified downregulation of FOXO3A, a longevity-associated transcription factor, as a key driver for arterial endothelial aging in primates, which informs clues for the treatment of age-associated vascular disorders (*Nature Communications* 2020, doi: 10.1038/s41467-020-15997-0).

More recently, the team sought to reveal the single-cell transcriptomic atlas of human skin aging (*Developmental Cell* 2021, doi: 10.1016/j.devcel.2020.11.002). Through single-cell RNA sequencing of human eyelid skin from healthy individuals across different ages, they identified eleven canonical cell types, as well as six subpopulations of basal cells. After further analysis, they uncovered progressive accumulation of photoaging-related changes and increased chronic inflammation with age. Notably, they found that genetic activation of HES1 (a transcriptional factor involved in the developmental process) or pharmacological treatment with quercetin can alleviate cellular senescence of certain skin cells.

The team also investigated how caloric restriction



Single-cell transcriptomic analysis in aging rats reveals that caloric restriction (CR) can attenuate aging-related changes in cell type composition, gene expression, and core transcriptional regulatory networks. (Image by CAS)

(CR), a well-reported method capable of extending heathspan and lifespan in studied animals, pulls off the trick to delay aging in rats (*Cell* 2020, doi: 10.1016/j.cell.2020.02.008). They built comprehensive single-cell and single-nucleus transcriptomic atlases across various rat tissues undergoing aging and CR. The results showed that CR can alleviate aging-related accumulation of proinflammatory cells in various tissues, and attenuates aging-associated cell-type-specific gene expression changes.

All these studies provide a wealth of molecular information about aging in multiple organs and inform richly the development of therapeutic strategies against aging-related disorders.

10th

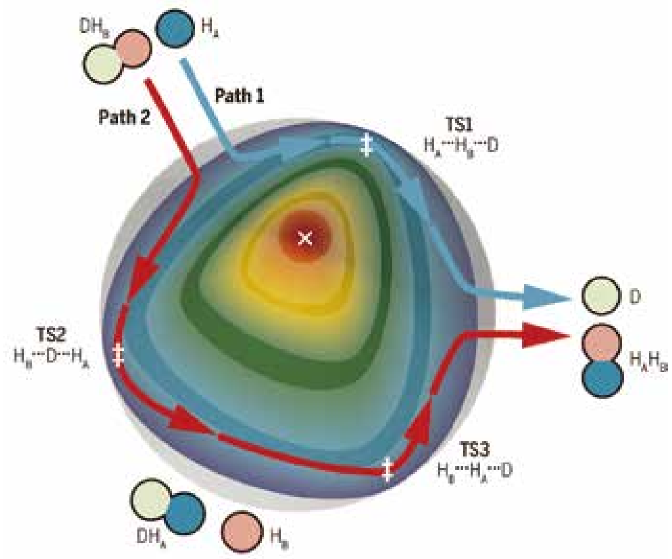
Quantum Interference Observed between Two Different Pathways of the Same Reaction

Understanding quantum interferences (QI) is essential to the study of chemical reaction dynamics. However, a QI phenomenon in a chemical reaction is not easy to observe. As a result, a thorough understanding of a chemical reaction could be obscured from view.

As appeared on May 15, 2020 in *Science*, a team of Chinese scientists, jointly led by CAS member YANG Xueming, CAS member ZHANG Donghui, Dr. SUN Zhigang and Dr. XIAO Chunlei at the Dalian Institute of Chemical Physics (DICP), Chinese Academy of Sciences (CAS), reported an interesting case of quantum interference in a hydrogen exchange reaction, $H + HD \rightarrow H_2 + D$ (doi: 10.1126/science.abb1564).

In the experiments, they observed strong oscillations in the energy dependence of the differential cross section (DSC) for the H_2 ($v' = 2, j' = 3$) product (where v' is the vibrational quantum number and j' is the rotational quantum number) in the backward scattering direction.

In order to understand the origin of these oscillations, they carried out quantum dynamics calculations and analysis. The calculations showed that there are two possible topologically distinct reaction pathways around the conical intersection: One goes clockwise through just one transition state (ST1), and the other passes through two transition states (TS2 and TS3) in an opposite direction (see the figure); the analysis pointed to the conclusion that the observed oscillations can only be attributed to the QI between the two reaction pathways.



Two distinct topological paths lead to the same products in the H + HD reaction. The red and blue lines that encircle the conical intersection (×) represent schematically two possible paths leading to the $D + H_2$ products, and the three transition states (‡) are TS1, TS2, and TS3. (Image credit: *Science*)

“To the best of our knowledge, such a QI pattern in the form of energy-dependent DCS oscillations between two topologically distinct reaction pathways in a chemical reaction has not been observed and understood previously,” writes the team in the published work, “…the observed interference pattern also provides a sensitive probe of the geometric phase effect at an energy far below the conical intersection in this reaction, which resembles the Aharonov-Bohm effect in physics, clearly demonstrating the quantum nature of chemical reactivity.”