CAS Dominates China's Annual Top 10 Science Advances 2016

By SONG Jianlan (Staff Reporter)

A frequent contributor of the annual Top 10 science advances of China, CAS never fails the anticipation of the public. Sure enough, the spring of 2017 witnessed its one-more-time overwhelming victory: The Academy reaped 7 of the 10 places in the annual election of the top 10 science discoveries, as released by the Chinese Ministry of Science and Technology on February 20 in Beijing.

For 12 times, at the turn of a new year, the annual election reviews science research conducted over the previous year, and names the most significant discoveries/advances, aimed at promoting major advancement in fundamental research and increasing public awareness of science. Specifically, for the year of 2016, the election reviews results achieved between December 1, 2015 and November 30, 2016. At the first round, an expert panel covering different disciplines selected 30 candidates for final competition, and eventually the final winners were produced via an online ballot by as many as 2,000 illustrious scientists of the country, including Members of the Chinese Academy of Sciences and the Chinese Academy of Engineering, chief scientists of projects under the National Basic Research Program (dubbed "973 Program") and directors of State Key Laboratories.

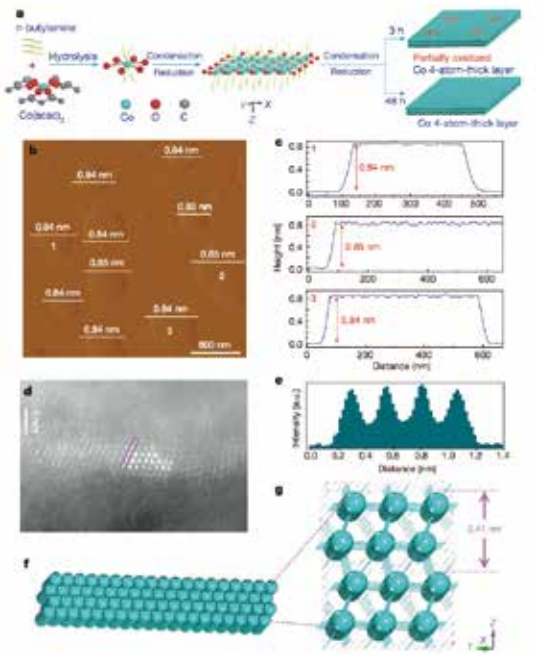
Dominating the list, CAS won the 1st to the 4th, the 6th, the 8th and the 9th places – CAS scientists participated in these seven winning projects either as principal investigators or as major contributors. Notably, of these advances, two (the 1st and the 2nd) contribute to green energy generation and carbon sequestration, and as many as five, to life sciences. As follows, the *Bulletin* is presenting a brief review of them.

1st Place: Novel Cobalt-based Catalyst Turning Carbon Dioxide into Liquid Fuel under Ambient Condition

What looks so effortless and ordinary for green plants has long baffled human beings: photosynthesis, an innate ability of chloroplasts to turn carbon dioxide into carbonhydrates, proves to be extremely difficult to realize in artificial synthesis under ambient conditions. This might explain why a discovery has attracted so much attention and, why it is ranked the first in the annual "greatest" list.

This discovery is made by a team led by Dr. XIE Yi and SUN Yongfu at the University of Science and Technology of China (USTC), an educational organ under the umbrella of CAS. In a paper published in *Nature* on January 7, 2016, the team reported their successful fabrication of two types of partially oxidized atomic cobalt layers effective in catalyzing the electroreduction process to turn carbon dioxide into liquid fuel – a reaction that facilitates the strategy to replace fossil feedstocks with cleaner energies, and meanwhile addresses climate warming by reducing CO_2 emissions and hence their adverse effects on climate.

As indicated by the team, the very green pathway to energy generation – the catalyzed electroreduction of CO_2 – has been bottlenecked by the impractically high overpotentials generally needed in the activating of CO_2 into $CO_2^{\bullet-}$ radical anion or other intermediates,



To evaluate the role of the two different catalytic sites, the USTC team fabricated two kinds of four-atom-thick layers: Co 4-atom-thick layers with and without surface oxide.

preventing the possibility of further conversion. To solve the problem, a better understanding of the activity of the catalytic sites was needed. The team's review

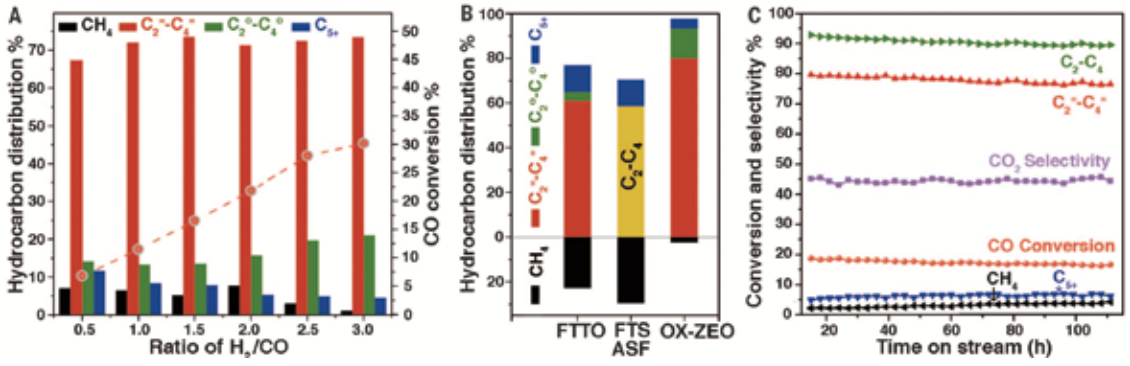
of previous research revealed that electrocatalysts based on oxide-derived metal nanostructures could enable CO_2 reduction at low overpotentials. It remained unclear how the electrocatalytic activity of these metals is influenced by their native oxides, mainly because some microstructural features that influence CO_2 reduction activity, such as interfaces and defects, are yet difficult to control. To evaluate the role of the two different catalytic sites, the team fabricated two kinds of four-atom-thick layers: pure cobalt metal, and co-existing domains of cobalt metal and cobalt oxide. Cobalt mainly produces formate ($HCOO^-$) during CO_2 electroreduction; they found that at lower overpotentials, surface cobalt atoms of the atomically thin layers have higher intrinsic activity and selectivity towards formate production than surface cobalt atoms on bulk samples. The team further discovered that partial oxidation of the atomic layers can further increase their intrinsic activity, and starting from this the team managed to realize stable current densities of about 10 milliamperes per square centimetre over 40 hours, with approximately 90 per cent formate selectivity at an overpotential of only 0.24 volts. This result outperformed previously reported metal or metal oxide electrodes evaluated under comparable conditions.

The team's work highlighted the role of correct morphology and oxidation state, concluding that this could "transform a material from one considered nearly non-catalytic for the CO_2 electroreduction reaction into an active catalyst". Furthering the understanding of the influence of both the atomic-scale structure and the presence of oxide, their findings have provided new opportunities for manipulating and improving the CO_2 electroreduction properties of metal systems, shedding light on how to fabricate highly effective and stable catalysts for the electroredection of CO_2.

2nd Place: A Short-cut from Syngas to Light Olefins

Light olefins, a family of chemicals pertaining to our everyday life due to its extensive application, have been mainly derived from oil. This keeps its producing costs at a high level and poses challenges to the environment as well as energy security of human society. Scientists have hence long sought to produce them from coal, a much cheaper natural resource whose recoverable reserves are much bigger than oil, to mitigate the impending energy crisis. An important result from this long-time effort is the Fscher-Tropsch synthesis (FTS), a gas-to-liquid technology to produce synthetic lubricants and synthetic fuels from coal. The only effective technology so far for direct conversion of synthesis gas (syngas) to light olefins, this technology has significant drawbacks, producing large amounts of by-products, and consuming large amount of water. To solve this problem, scientists worldwide have been working for over 50 years since its invention, and a variety of metal catalysts based on iron, cobalt, and ruthenium have been tested to this end. Despite the progress, the application of FTS remained limited, as a result of its low olefin selectivity and high methane selectivity, as well as severe carbon deposition.

The team led by Profs. BAO Xinhe and PAN



2nd Place: Selective conversion of syngas to light olefins. Illustrated here is the catalytic process of OX-ZEO.

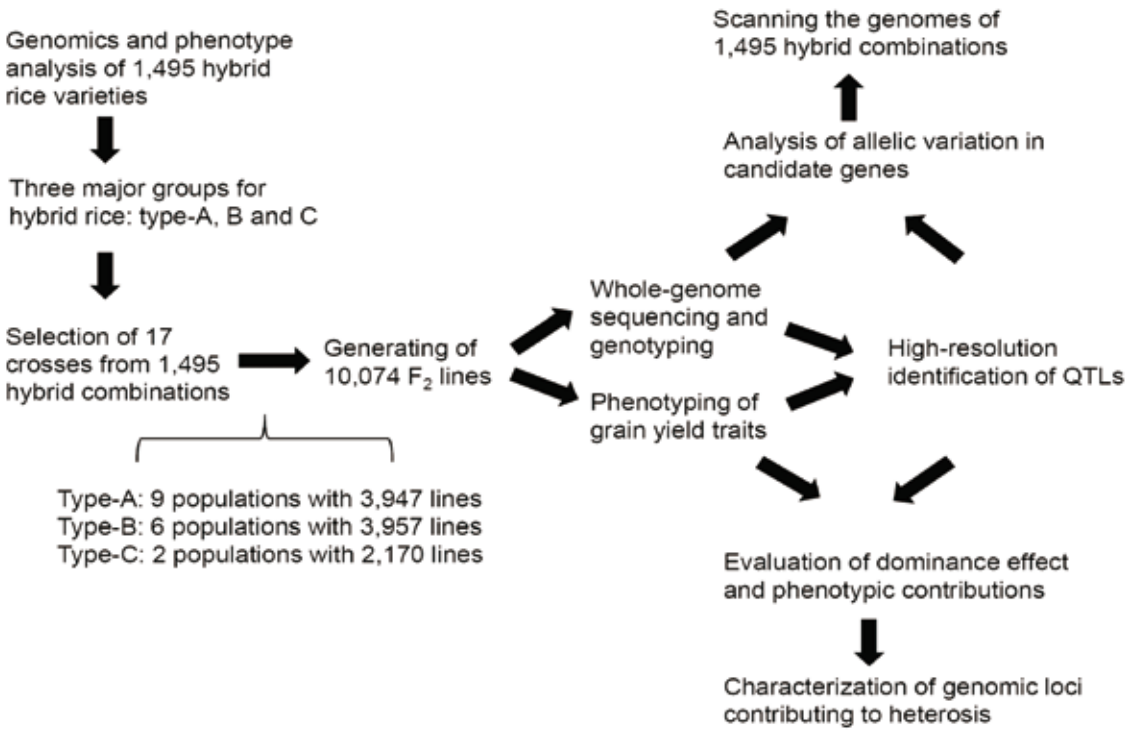
Xiulian at the CAS Dalian Institute of Chemical Physics targeted the problem inherent to the reaction mechanism of FTS, aiming to achieve the precise control of C-C coupling while suppressing over-hydrogenation and methane formation. They eventually succeeded, after long-term painstaking attempts, in developing a bifunctional catalyst affording two types of active sites with complementary properties, which made possible the one-step production of light olefins from coal-derived syngas, and hence proposed a new process named OX-ZEO (Oxide-Zeolite).

The new process proposed by the team greatly improves the olefin selectivity of FTS, raising the theoretical limit of C2-C4 hydrocarbons from 58% to over 80%. At the same time, the new process successfully prevents the involvement of water molecules, hence radically avoids the water-consuming problem. Furthermore, the composite catalyst and the process developed by the team might also allow the use of coal- and biomass-derived syngas with a low H_2/CO ratio, hence might promise its application in a broad range of areas.

Their result was published in the March 4 issue of *Science* in 2016. The magazine published a commentary in the same issue to highlight the amazing selectivity achieved by the new method.

3rd Place: Genomic Architecture of Heterosis for Yield Traits in Rice

Increasing grain yield has been a long-term goal in crop breeding as an effort to ensure global food security; and heterosis, the marvelous phenomenon in which a hybrid beats both of its parents to demonstrate better performance for a trait, has inspired an important strategy for breeding improved varieties. The genetic mechanism underlying this phenomenon, however, has long perplexed biologists. A team led by Profs. HAN Bin and HUANG Xuehui at the Shanghai Institute of Plant Physiology and Ecology (SIPPE), Shanghai



To examine the genetic basis of hererosis of rice, HAN's team at SIPPE conducted large-scale sequencing, genotyping and genetic mapping in 10,074 F_2 lines. (Images provided by SIPPE)

Institutes for Biological Sciences (SIBS), CAS won the third place by successfully unraveling the genetic basis of high-yielding heterosis.

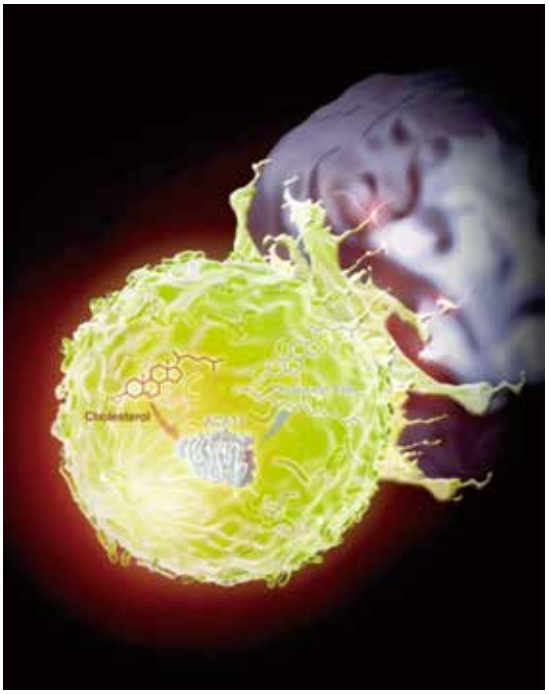
To examine the genetic basis of heterosis for yield in rice, the team generated, sequenced and recorded the phenotypes of 10,074 F_2 lines from 17 representative hybrid rice crosses. They classified modern hybrid rice varieties into three groups, representing different hybrid breeding systems. The researchers failed to find any heterosis-associated loci shared across all lines; however, they did find within each group a small number of genomic loci from female parents explaining a large proportion of the yield advantage of hybrids over their male parents. For some of these loci, they found evidence for partial dominance of heterozygous locus for yield-related traits and better-parent heterosis for overall performance when all of the grain-yield

traits were considered together. Published in *Nature* on September 29, 2016, these results are thought to have informed on the genomic architecture of heterosis and rice hybrid breeding. (For more detail, please refer to the report on page 244, issue 4, 2016 of *BCAS*.)

4th Place: Antitumor Therapy Based on Modulation of Cholesterol Metabolism

Antitumor therapies mediated by T-cells, a type of white blood cells that mature in the thymus or tonsils and play a central role in cell-mediated immunity, are among the four most powerful weapons against tumors. Despite their great success in clinical practice, current antitumor therapies based on signaling regulation are not effective to some patients, and this plight has called for new developments in this area to benefit a wider group of patients. The winner of the fourth place features a therapy hinged on awakening the antitumor response latent in a kind of T-cells, the $CD8^+$ T cells.

The activity of $CD8^+$ T cells is suppressed in the tumor microenvironment, and reactivating the cytotoxicity of them is of great clinical interest in cancer immunotherapy. On March 31, 2016, a team led by Profs. XU Chenqi and LI Boliang at the Institute of Biochemistry and Cell Biology (SIBCB), SIBS reported in *Nature* a new mechanism, by which the antitumor response of mouse $CD8^+$ T cells can be potentiated by modulating cholesterol metabolism. The team revealed that inhibiting cholesterol esterification in T cells by genetic ablation or pharmacological inhibition of ACAT1, a key cholesterol esterification enzyme, could lead to potentiated effector function and enhanced proliferation of $CD8^+$ but not $CD4^+$



With their discovery of a new mechanism to potentiate the antitumor activity of $CD8^+$ T cells (also known as killer T cells), a joint team led by Profs. XU Chenqi and LI Boliang at the Institute of Biochemistry and Cell Biology (SIBCB), SIBS, CAS won the 4th place of the 2016 top 10 science advances.

T cells. The team successfully verified that this could be a result from the increase in plasma membrane cholesterol level of $CD8^+$ T cells, which causes enhanced T-cell receptor clustering and signaling as well as more efficient formation of the immunological synapse. They found that ACAT1-deficient $CD8^+$ T cells were better than wild-type $CD8^+$ T cells at controlling melanoma growth and metastasis in mice, and tried to use the ACAT inhibitor avasimibe, which was previously tested in clinical trials for treating atherosclerosis and showed a good human safety profile, to treat melanoma in mice. In the end, they observed a good antitumor effect. Also, they demonstrated that combined therapy of avasimibe plus an anti-PD-1 antibody showed better efficacy than monotherapies in controlling tumor progression; and ACAT1, an established target for atherosclerosis, is therefore also a potential target for cancer immunotherapy.

This study unveiled the key role of metabolic modulation, and moreover, identified the ACAT1 as a new target for potential therapies, expanding the application of small-molecule ACAT1 inhibitors. On publication of the above results, both *Nature* and *Cell* acclaimed the discovery in special commentaries as new hope for development of new anti-tumor drugs.

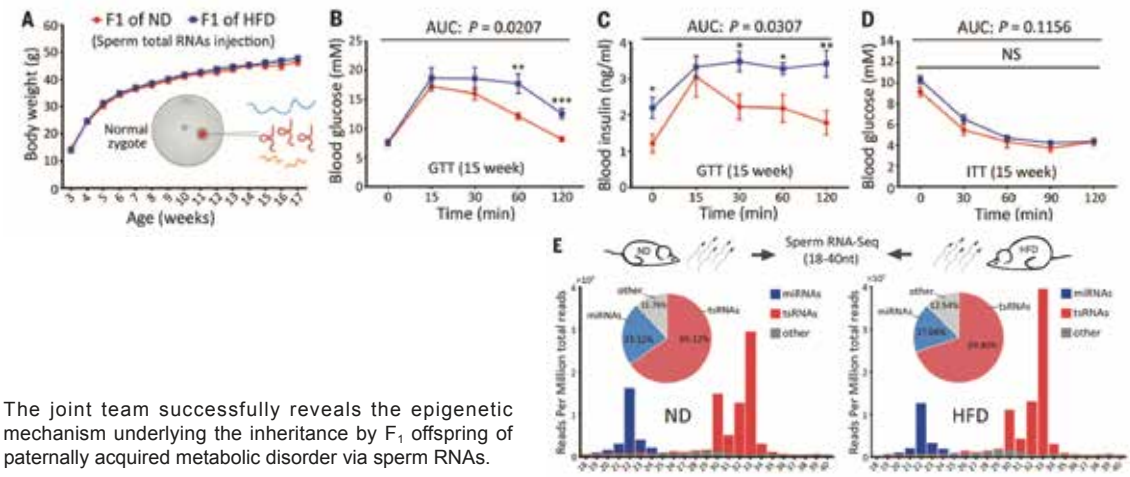
(For more detail, please refer to the report on page 51, issue 1, 2016 of *BCAS*.)

6th Place: Sperm tsRNAs Revealed as Paternal Epigenetic Factor in Intergenerational Inheritance of Acquired Metabolic Disorder

Like father, like son – this can even be true for obesity, as increasing evidence indicates that metabolic disorders like obesity in offspring can result from the father's diet. In other words, sperms can "remember" such diseases and pass them on to the offspring. How does the sperm "remember" such disorders? Inheritance of such acquired disorders involves the memory and transmission of epigenetic information occurring beyond the DNA sequence. Given its far-reaching implications to human health, the underlying epigenetic mechanism has been a target of intense attention from scientists.

A joint team led by Profs. ZHOU Qi and DUAN Enkui at the Institute of Zoology (IOZ), CAS and Prof. ZHAI Qiwei at the Institute for Nutritional Sciences, SIBS, CAS revealed in detail the role of sperm transfer RNA–derived small RNAs (tsRNAs) as a "memory capsule" in intergenerational inheritance of an acquired metabolic disorder, and took the 6th place of the ranking.

In their research published in *Science* on January 22, 2016, the team reported their observation in a paternal mouse model, which had been given a high-fat diet (HFD), that a subset of tsRNAs, mainly from 5′ transfer RNA halves and ranging in size from 30 to 34 nucleotides, exhibited changes in expression profiles and RNA modifications. Injection of sperm tsRNA fractions from HFD males into normal zygotes, as found by the



The joint team successfully reveals the epigenetic mechanism underlying the inheritance by F_1 offspring of paternally acquired metabolic disorder via sperm RNAs.

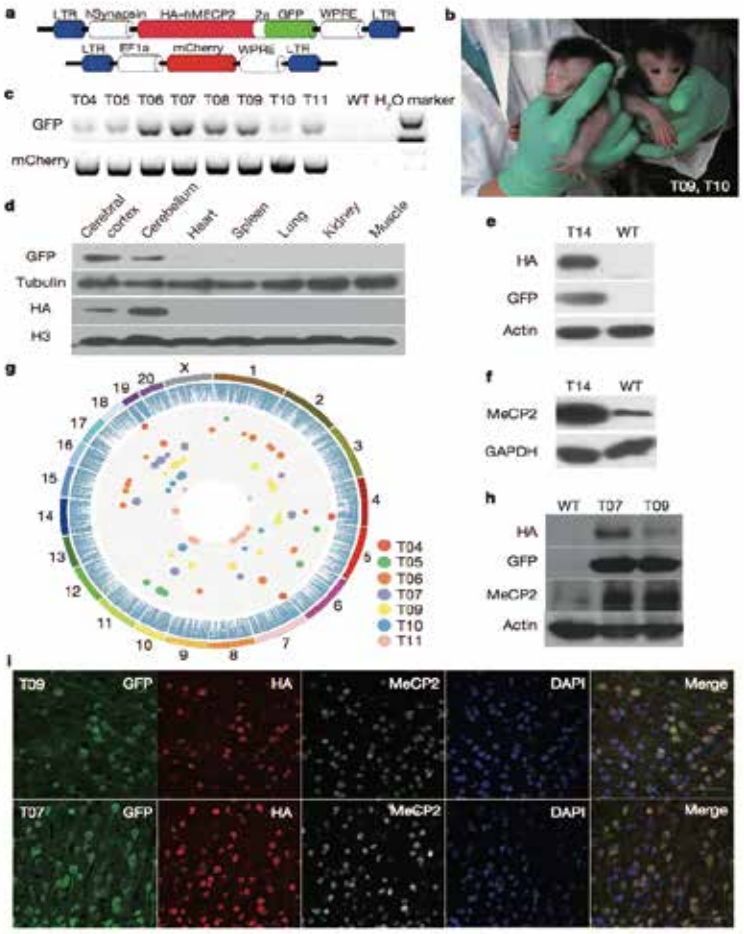
team, generated metabolic disorders in the F_1 offspring, and altered gene expression of metabolic pathways in early embryos and islets of them. Moreover, such change was not related to DNA methylation at CpG-enriched regions. Hence, the team concluded, sperm tsRNAs takes the role of a paternal epigenetic factor that may mediate intergenerational inheritance of diet-induced metabolic disorders.

Focusing on sperm RNA and exploring the intergenerational inheritance of acquired traits, this study represents a brand-new perspective, and has been widely cited and commented since its publication.

8th Place: First Nonhuman Primate Model for Autism

Autism, a neurodevelopmental disorder frequently found in teenagers, has aroused great concern worldwide due to its increasing occurrence in recent years. It is estimated that nearly 100 thousand people in China suffer from this disease, typical syndromes include impaired social interaction, verbal and non-verbal communication, and restricted and repetitive behavior. So far, no effective therapy or interference treatment is available for it, due to the poor pathological understanding of the disease.

A newly established non-human primate model of this disease might facilitate the research and development of future therapies and intervention treatments. A team led by Profs. QIU Zilong and SUN Qiang at the CAS Institute of Neuroscience (ION), SIBS, CAS succeeded in overexpressing in monkeys the Methyl-CpG binding protein 2 (MeCP2), a human-source protein associated with autistic phenotypes, and found in the subsequent molecular genetic research and behavioral analysis that these transgenic monkeys demonstrated autism-like restricted and repetitive behaviors, as well as impaired social interaction. Furthermore, they succeeded in speeding up the reproductive cycle of the monkey via testis allograft, and obtained the second generation of MECP2 transgenic monkeys, which manifested the same autism-like phenotype in social interaction as its parental generation.



The ION team won the 8th place with their success in constructing *MECP2* transgenic monkey and brain-specific expression of transgenes.

This study was published in *Nature* on February 4, 2016. Aside from implications to autism research, their results also demonstrate the feasibility and reliability of using genetically engineered non-human primates to study brain disorders.

9th Place: TET-mediated DNA Demethylation Controls Gastrulation by Regulating Lefty–Nodal Signaling

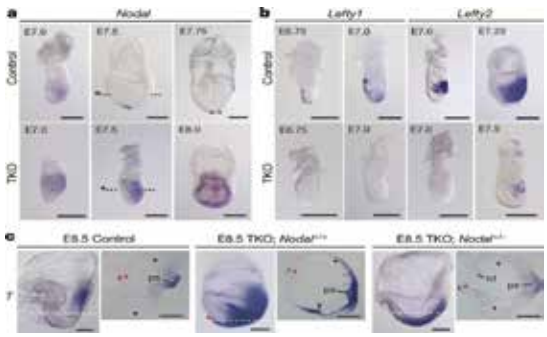
The ninth place was taken by a breakthrough in understanding the possible mechanism underlying congenital defects, a fundamental issue in developmental biology that has long baffled scientists.

The development of an organism from a one-cell zygote is a marvelous process and involves very complicated genetic and epigenetic regulations for cell growth and differentiation. Errors in early stages of this process can lead to severe developmental abnormalities, resulting in congenital defects and diseases. Prof. XU Guoliang at SIBCB and his colleagues and cooperators have invested great, continuous efforts into this field, striving to understand the process and role of DNA methylation/demethylation in mammalian development, which are pivotal in cell reprogramming, a mysterious and crucial epigenetic scenario regulating the early development of embryos, and hence imply a lot in early development of embryos. Published on October 27 in *Nature*, the winner advance represents the latest stepping stone lain down for further progress, resulting from a cooperative research joining forces from Prof. SUN Xin's group at Wisconsin University in USA and Prof. TANG Fuchou's group at Peking University, China.

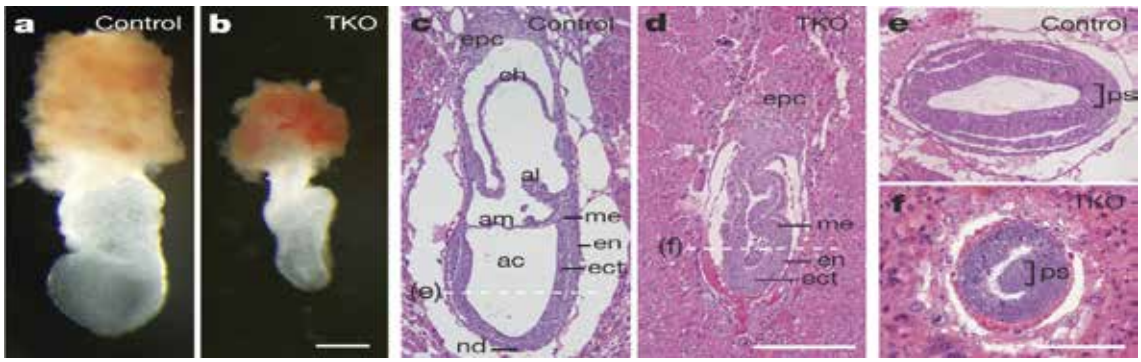
The work focuses on the fatal consequence in embryonic development caused by inactivation of all three members of the Ten-eleven translocation (TET) family of dioxygenases, namely TET1, TET2 and TET3. Previous research revealed that oxidation of 5-methylcytosine by TET can lead to DNA demethylation. It is understood that cytosine methylation plays important roles in several processes, such as genomic imprinting and X-chromosome inactivation, the functional significance of cytosine methylation and demethylation in mouse embryogenesis remained insufficiently studied, however. In their latest work, XU and his cooperators successfully obtained Tet-null embryos and demonstrated that inactivation of all three Tet genes in mice leads to gastrulation defects, which contribute to embryonic death.

Working to further understand how the inactivation works, the joint team unveiled in ensuing experiments that the TET1/2/3 worked in coordination and TET-mediated oxidation of 5-methylcytosine modulates Lefty–Nodal signaling by promoting demethylation in opposition to methylation by DNMT3A and DNMT3B.

For the first time, these findings revealed a fundamental epigenetic mechanism in embryonic development where dynamic DNA methylation and demethylation play crucial roles in the regulation of key signaling pathways, shedding new light on fundamental principles of developmental biology.



The joint team demonstrated in their latest work that increased *Nodal* expression in *Tet*-null embryos leads to patterning defects.



The joint team revealed that *Tet*-null embryos display gastrulation defects.