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## Science China Life Sciences in 2011: a Retrospect

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Research in the field of life science is moving forward at a high pace. *Science China Life Sciences* is trying to reflect this trend as much as possible by publishing research articles of notable original discoveries. Here I am attempting to highlight some of the novel discoveries as reported in this journal in the

year 2011, a collection of the covers for the 12 issues are displayed in Figure 1. It is my hope that the retrospective summary presented here will help readers to gain an interest in this journal that was once highly prestigious at least for Chinese scientists to publish and to read.



Fig. 1 The cover collection of the 12 issues of *Science China Life Sciences* as published in 2011

### 1 Proteomics: cellular protein profiles and its alterations

The newly gained power of protein separation by two-dimensional gel electrophoresis or liquid chromatography, in combination with the effective characterization of unknown proteins by mass spectrometry are considered as the two technology developments that promoted the birth of proteomics, for which the nature of all proteins, as well as their posttranslational modifications and interactions are to be characterized in a particular biological source [1].

Chinese scientists actively participated in studies of proteomics, especially that of animal livers [2].

Some representative achievements in this field include the following. (1) Identification of organelle-, cell-, tissue- or condition-specific protein expressions, including unique proteins expressed in the mitochondria of a particular tissue [3-4], protein expression alteration of human epithelial ovarian

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cancer xenograft in immunodeficient mice subject to chronic psychological stress<sup>[5]</sup>, alteration of protein profiles for bacteria grown on different carbon sources<sup>[6]</sup>, protein profiles in apoptotic cells<sup>[7]</sup> and cancer cells<sup>[8]</sup>. (2) Revelation of protein biomarkers reflecting disease status and treatments, including the identification of plasma biomarker proteins for liver fibrosis<sup>[9]</sup>, immunoreactive proteins in bacterial pathogen *Brucella melitensis*<sup>[10]</sup>, an increase of  $\alpha$ -2-HS-glycoprotein level in the serum of chronic hepatitis B patients who are effectively treated with interferon  $\alpha$ 2b<sup>[11]</sup>, as well as identification of biomarkers in cancer<sup>[8]</sup>, in urine<sup>[12]</sup>, and during virus infection<sup>[13]</sup>. (3) Technology improvement in proteomics, including the increase of resolution of the protein profiles, especially those of low abundance, with two-dimensional gel electrophoresis<sup>[14]</sup>, improvement of methods for extracting proteins secreted in the culture media<sup>[15]</sup>, rapid identification of bacteria cultured in liquid media<sup>[16]</sup>, establishment of high throughput protein digestion by using immobilized proteases<sup>[17]</sup>.

## 2 Genomics: to gain a view of the complete genetic blueprints

Since the entire genomic DNA sequence of *Haemophilus influenzae* Rd, a Gram-negative bacterium that is an opportunistic pathogen, was successfully determined<sup>[18]</sup>, a great number of genomic sequences of other organisms of increasing complexity have been reported, which include more than 1 100 prokaryotes (archaea and bacteria) and 36 eukaryotes<sup>[19]</sup>. Scientists in China have participated in the human genome sequencing project<sup>[20]</sup> and independently determined the DNA sequence of the genomes of rice<sup>[21]</sup> and other species<sup>[22]</sup>. Recent progress in this field includes the following: complete sequences of the mitochondrial genome DNA of *Panthera*<sup>[23]</sup>, the sea cucumber<sup>[24]</sup>, and the genome of Gram-negative bacteria *Glaciecola mesophila* sp. nov. (using the BIGIS-4 sequencer system)<sup>[25]</sup>; improvement in methods sequencing all the exons in a genome (i.e., the exome)<sup>[26]</sup>; application of metagenome analysis in plankton ecological studies<sup>[27]</sup>; identification of combined partial DNA sequences from two genes (encoding EF-1 $\alpha$  and RBP2 proteins) as barcode of the fungus genus *Neonectri*<sup>[28]</sup>.

## 3 MicroRNA: small RNA that regulates cellular events

Since the first report of microRNA lin-4 in negatively regulating the expression of the LIN-14 protein in *C. elegans*<sup>[29]</sup>, a tremendous number of such regulatory RNA molecules have been identified in various living organisms<sup>[30]</sup>. Representative recent progress includes the revelation of Pns12 as an additional silencing repressor of rice gall dwarf virus<sup>[31]</sup>, the microRNA expression profile of the eye cancer uveal melanoma<sup>[32]</sup>, identification of novel microRNAs produced in the rat proximal sciatic nerve injury and regeneration<sup>[33]</sup> and ways to monitor the real-time activities of microRNAs in living cells<sup>[34]</sup>.

## 4 Protein structure, folding and *de novo* design

Since the report of the low-resolution structure of myoglobin<sup>[35]</sup> and hemoglobin<sup>[36]</sup>, determining the three-dimensional structure of proteins, understanding their folding mechanism and eventually designing new proteins are active fields in protein science. Representative progress in these fields includes the structure of the capsid particle formed by the hepatitis B core antigen N-terminal domain (truncated at residue 154) at a resolution of 7.8Å determined by cryo-electron microscopy<sup>[37]</sup>, structure of the histidine-containing phosphocarrier protein from a thermophile<sup>[38]</sup>, effective determination of protein complex structures (such as protein complexes involving the L27 domain of Lin-2 and Lin-7, myosin VI, the N-terminal PDZ domain of harmonin, or the SNARE protein Ykt6) with a combination of NMR spectroscopy and X-ray crystallography<sup>[39]</sup>, understanding of protein folding rate by applying a new parameter called the dynamical contact factor which was formulated based on quantum conformational transitions<sup>[40]</sup>, a more effective method to design DNA sequence specific zinc finger nucleases (for modifying the eukaryotic genomes) using the FoldX force field algorithm<sup>[41]</sup>.

## 5 Gene expression, regulation and manipulation

As units of heredity, genes carry the information to make and maintain an organism and pass the unique genetic traits to its offspring. Much effort is still being

made to unveil the expression pattern, regulation, function and manipulation of the individual genes in all types of organisms. Representative progress includes the revelation that the prohibitin 1 gene is significantly up-regulated in highly metastatic liver cancer cell lines but not in low-metastatic ones<sup>[42]</sup>, a global gene expression profiles of the fungus *T. rubrum* at different growth phases using cDNA microarray technology<sup>[43]</sup>, four members of the genes encoding LAP (leucine-rich repeats and PDZ) family proteins are widely expressed in the epithelial cells during the development of *Xenopus tropicalis* frogs and thus may play a role for tissue polarity as revealed by whole mount *in situ* hybridization<sup>[44]</sup>, genes encoding MAFbx and MuRF1 (two E3 ligases in the ubiquitin-proteasome system) are up-regulated in chicks by fasting, possibly leading to increased degradation of their corresponding target proteins<sup>[45]</sup>, expression pattern of the hunchback protein (a contributing factor in anteroposterior axial patterning for insects) during oogenesis and embryogenesis of locust *L. migratoria manilensis* was examined by immunohistochemical staining<sup>[46]</sup>; characterization of genes differentially expressed when treated with such environmental hormone toxicants as dichlorodiphenyltrichloroethane (DDT), tributyltin (TBT), and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD)<sup>[47]</sup>; a way to assemble the *de novo* transcriptome using different RNA-Seq read datasets and different strategies<sup>[48]</sup>, double-stranded RNA-mediated transient gene silencing studies reveal that the Cdc14 phosphatase is important for the sporangial development of a soybean root rot fungus pathogen<sup>[49]</sup>; overexpression of the gene encoding the activin-binding protein follistatin (*Fst1*) promotes zebrafish muscle growth by enhancing myofiber hyperplasia<sup>[50]</sup>; genomic position-ready marker-based linkage analysis identified the gene endowing rice blast resistant towards fungal pathogens<sup>[51]</sup>; successful development of black carp growth hormone gene transgenic allotetraploid fish with a highly increased growth rate<sup>[52]</sup>.

## 6 Bioinformatics and computational biology

Computational technology becomes indispensable in modern biology, and it helps us to store and analyze the astronomical information data in life sciences. It also helps us to unveil new principles and rules in the

life phenomenon. Representative progresses include the following: construction of the Tsdb database annotating transporters and transporter substrates<sup>[53]</sup>; the *Tetrahymena* gene expression database TGED annotating the microarray data of gene expression in *T. thermophila* cells during growth, starvation, and conjugation<sup>[54]</sup>; discrimination of different types of cancers by looking into the alteration of a group of genes involved in particular functional modules (e.g., viral genome replication, virion transport, cell cycle, signaling)<sup>[55]</sup>.

## 7 Stem cell self-renewal and differentiation

The successful reprogramming (reversion) of mature, differentiated cells into immature, pluripotent stem cell state<sup>[56-57]</sup> has greatly attracted people to work on the cellular and molecular basis for stem cells to self-renew as well as their potency to differentiate into many other types of cells. Representative progresses in this field include the following: a new strategy to derive induced pluripotent stem (iPS) cells from porcine fibroblasts, into which the four human reprogramming factors (*Oct4*, *Sox2*, *Klf4* and *Myc*) were transfected in one step using the VSV-G envelope-coated pantropic retrovirus<sup>[58]</sup>; myostatin inhibits adipogenic differentiation in porcine-muscle-derived mesenchymal stem cells, which can be alleviated by arginine supplementation<sup>[59]</sup>; a Molday ION Rhodamine-B-based labeling method was established for tracking bone marrow mesenchymal stem cells, using magnetic resonance imaging, in cynomolgus monkeys<sup>[60]</sup>.

## 8 Exploration of the neurons and central nervous system

The study of the nervous system dates back to the ancient times and has become an interdisciplinary science that involves chemistry, computer science, engineering, linguistics, mathematics, medicine, philosophy, physics, and psychology. Active research is performed in understanding the molecular, cellular, developmental, structural, functional, evolutionary, computational, and medical aspects of the nervous system. Representative progresses include the following: observation of the cross-talk between the N-methyl-D-aspartate (NMDA) and  $\gamma$ -aminobutyric acid type A (GABAA) receptors in cultured neurons of the rat central auditory system using whole-cell patch-clamp recording techniques<sup>[61]</sup>; neural correlates

revealed for the audio-visual modal interference inhibition in 10-year-old children as investigated by measuring the event-related potentials<sup>[62]</sup>; difference due to memory (Dm effect) of prospective memory (PM) shares similar characteristics with known Dm effects of other types of episodic memory after the very early stage of neural processing also by measuring the event-related potentials<sup>[63]</sup>; meditation promotes insightful problem-solving when people were kept in a mindful and alert conscious state<sup>[64]</sup>; event-related functional magnetic resonance imaging (fMRI) analysis of the brain indicates different roles of the left DLPFC (dorsolateral prefrontal cortex) and left APFC (anterior prefrontal cortex) in data-driven scientific discovery<sup>[65]</sup>; a novel simple diffusion delivery system invented for administering drugs into the brain via the interstitial space<sup>[66]</sup>; residues 4~17 in Huntingtin protein were found to be important for the protein to be localized in the cytoplasm<sup>[67]</sup>; presenilins seem to function as a low-conductance, passive ER Ca<sup>2+</sup> leak channels whose defect may derange Ca<sup>2+</sup> signaling in neurons and cause Alzheimer's disease<sup>[68-69]</sup>; high concentrations of copper significantly increase the paralysis rate of the A $\beta$  (1~42) worm while low concentrations of copper significantly decrease the paralysis rate of the A $\beta$ (1~42) worm<sup>[70]</sup>.

### 9 Pathological viruses and bacteria: their relationship with the host organism and ways to contain them

The mechanism for the disease-causing pathological viruses and bacteria to enter their host organisms and finding ways to contain such pathogens is still a field of active research. Representative research progress includes: HSRG1, a virally induced protein expressed in HSV-1-infected cells, inhibits viral gene transcriptional elongation by interacting with cyclin T2, the regulatory subunit of the positive transcription elongation factor b<sup>[71]</sup>; the presence of antibody was found to "increase" mutations of virus genes encoding the epitopes as occurring in cultured host cells<sup>[72]</sup>; the serine residue at position 100 of the capsid protein VP1 of Encephalomyocarditis virus is important for its pathogenicity<sup>[73]</sup>; the two aspartate residues of the Ser-Asp-Asp motif in replicase are critical and essential for transcription of the porcine reproductive and respiratory syndrome virus<sup>[74]</sup>; the presence of cholesterol in the cellular membrane was found to be a key component for the porcine

reproductive and respiratory syndrome virus (PRRSV) to infect cells<sup>[75]</sup>; the staphylococcal nuclease was found to be able to prevent biofilm formation in bacteria<sup>[76]</sup>; scanning electron microscopy and transmission electron microscopy studies reveal that the insect antimicrobial peptide melittin exhibits its bacteriostatic effect by integrated into and causing defect on the phospholipid double layers of the plasmalemma and the endomembranes<sup>[77]</sup>; an improved method for the rapid identification and the precise determination of minimum inhibitory concentration of resistant strains in the bacterial population was established by using agar plates containing a linear gradient of antibiotic<sup>[78]</sup>.

### 10 The immune response: basic mechanism and medical applications

How animals recognize and neutralize pathogens is still being actively explored. Representative progress includes the following: ultrastructural examination and *in situ* hybridization reveal that the epidermis and alimentary canal epithelium as well as macrophages located in the coelom seem to play important roles in immune defense in amphioxus which is a cephalochordate representing the invertebrate-to-vertebrate transition<sup>[79]</sup>; humanized mouse liver model was successfully established from the Fah<sup>-/-</sup> Nod/Scid mice by treating it with immunosuppressant FK506 combined with gradual withdrawal of NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) before cell transplantation<sup>[80]</sup>; immuno-camouflaging red blood cells (from sheep) by grafting methoxypoly (ethylene glycol) on their membrane was found to reduce the risk of allo-immunization (*i.e.*, with shortened cell survival and mild fever) in mice<sup>[81]</sup>; combined immunization with DNA, AAV, and adenovirus vector vaccines induced effective cellular immunity against Epstein-Barr virus thus might constitute a sound vaccine strategy for the prevention and treatment of nasopharyngeal carcinoma<sup>[82]</sup>; DNA vaccines expressing hemagglutinin antigen of H1N1 and being delivered by electroporation were found to significantly increase the T cell and humoral immune responses and effectively protected the mice against a lethal challenge with seasonal H1N1 influenza virus<sup>[83]</sup>; a novel copper ion hapten was successfully synthesized and used to generate specific antibodies of copper ions which might be used for immunoassaying copper ions in environmental and food samples<sup>[84]</sup>; Rotavirus-like

particles were produced by co-expressing three capsid proteins (VP2, VP6 and VP7) of group A rotavirus in tobacco plants and orally delivered into mice for producing rotavirus specific antibodies<sup>[85]</sup>; a new immunomodulatory protein of 15.0 ku was purified from the medicinal mushroom *T. versicolor*, and found to markedly increase the proliferation of human peripheral blood lymphocytes<sup>[86]</sup>; HIV virus like particles were successfully produced in an eukaryotic cell line expressing the HIV-1 structure protein Gag and Env and found to be able to elicit specific humoral and cellular immune response after immunization without any adjuvant<sup>[87]</sup>.

## 11 Development and evolution: study at the molecular, cellular and individual levels

The processes through which a single fertilized cell develops into a complex animal or plant individual in days or months, or an ancient common ancestor evolves into the current forms of life over successive generations in approximately 3.8 billion years still attracts much research interest. Representative progress includes the following: scanning electron microscopy Raman spectroscopy studies on the shell structure of pearl oyster *Pinctada fucata* reveal that the annual growth lines in bivalve shells might be formed as a result of a discontinuity in the shell microstructure induced by "jumping development"<sup>[88]</sup>; two novel members of the Smad family signaling proteins, AmphiSmad1/5/8 and AmphiSmad4, were identified in the invertebrate amphioxus and their expression pattern suggests many important roles of them in the morphogenesis of a variety of tissues especially notochord and gonad<sup>[89]</sup>; the molecular variation of deduced tyrosine kinase domain amino acid sequences of insulin receptors IRa and IRb in Cyprinidae suggests that they may function differently in regulating the development and growth of this large family of freshwater fishes<sup>[90]</sup>; analysis of molecular, morphogenetic and morphological data suggests the discocephalids might represent a taxon intermediate between euplotids and hypotrichs and thus proposed to elevate the suborder Discocephalina to ordinal status within the subclass Hypotricha<sup>[91]</sup>; temporal and spatial expression pattern study suggests that Pod1, as a member of the basic helix-loop-helix family of transcription factors, is not only needed for the onset of sexual differentiation, but also plays an important role in gonadal development in the teleost *Nile tilapia*<sup>[92]</sup>.

## 12 Human diseases: diagnosis and treatment

How to effectively diagnose and treat human diseases, particularly those of cardiovascular and cancer, has always been an area of research that attracts great interest in life science research. Representative achievements in this field include the following. Linking branched PEG with TNF- $\alpha$  via a cathepsin B-sensitive valine-citrulline dipeptide was found to improve the anticancer efficacy TNF- $\alpha$ <sup>[93]</sup>; prediction of the Graves' disease (one common human autoimmune disease) achieved a 72.9% accuracy by using a combination of 17 single nucleotide polymorphisms<sup>[94]</sup>; intracellular calcium overload was found to interfere multiple membrane ion currents, cause abnormalities of cellular electrical activity and may thus cause ventricular arrhythmias<sup>[95]</sup>; the water extract of HangAmDan (a crude extract of nine Korean medicinal substances of animal and plant origin) was found to markedly reduce the length of blood vessel formed in a chick chorioallantoic membrane system<sup>[96]</sup>; a fusion protein consisting of an anti-CD20 scFv fragment and the peptide moiety of the anti-tumor antibiotics lidamycin was found to be able to kill the CD20-positive B cell lymphoma in mice<sup>[97]</sup>; a surface-enhanced Raman spectroscopy (SERS) plasma analysis combined with multivariate analysis revealed cancer-specific biomolecular differences and may thus be developed into a way to detect gastric cancer in a non-invasive manner<sup>[98]</sup>; a computer-aided dual S-shaped logistic model was developed to automatically quantify the characteristic kinetic curves obtained from dynamic contrast enhanced magnetic resonance imaging and effectively distinguished malignant from benign breast tumors<sup>[99]</sup>; metabolite profiles of intact tumor tissues measured with high-resolution magic-angle spinning proton nuclear magnetic resonance spectroscopy in conjunction with pattern recognition were found to provide a potentially useful tool for the rapid and accurate classification of human brain tumor grades<sup>[100]</sup>; mice cardiac remodeling studies indicate that intermittent  $\beta$ -AR stimulation leads to more severe cardiac dysfunction and fibrosis than sustained exposure to a  $\beta$ -AR agonist<sup>[101]</sup>.

## 13 Plant biology: basic research and agricultural applications

The study of plant is essential not only for us to

understand the nature of life, but also key for us humankind to feed ourselves and to make our environment more livable. Representative progress includes the following: overexpression of the tocopherol cyclase OsVTE1 was found to increase the tolerance of rice to salt stress by efficiently scavenging reactive oxygen species while its suppression by RNAi makes rice more sensitive to salt stress<sup>[102]</sup>; a new method was developed to estimate such rice parameters as leaf area index and green leaf chlorophyll density by using stepwise multiple regression models and support vector machines to process remote sensing data<sup>[103]</sup>; the secretion of Na<sup>+</sup> takes precedence over K<sup>+</sup> in the multicellular salt glands of *T. ramosissima* and *T. laxa*, bush plants that grow widely in sandy wastelands and in saline-alkali areas of arid and semiarid regions<sup>[104]</sup>; survival analyses of the symbionts isolated from the lichen *E. pusillum* under desiccation and starvation stress unveiled that the mycobiont (the fungus) can survive for seven months under desiccation stress in combination with starvation stress, and for eight months under starvation stress alone. The phycobiont (the photosynthetic partner) can survive for two months under desiccation stress<sup>[105]</sup>; levels of ergot alkaloids (ergine and ergonovine) formed in endophyte-infected drunken horse grass (*Achnatherum inebrians*) was found to be dramatically affected by the defoliation (mowing) frequency or intensity<sup>[106]</sup>; a four-year field experiment revealed that the soil biological properties and quality will be significantly affected by treating with different types of fertilizers (*i.e.*, phosphorus, potassium or nitrogen, or a combination of them) in a sudangrass and ryegrass rotation system<sup>[107]</sup>; solution culture studies indicate that while shoot growth (indicating the nitrogen use efficiency) has improved for the Chinese maize (*Zea mays* L.) hybrids released between 1973 and 2009, their root growth has only improved under high nitrogen conditions<sup>[108]</sup>; transcriptional profile and gene suppression studies demonstrate that glutamate synthases play essential roles in carbon and nitrogen metabolism and thus indispensable for the efficient nitrogen assimilation process in rice<sup>[109]</sup>.

#### 14 Biomedical engineering: improving medicine through bioscience guided designs

Medical diagnostic and therapeutic has been greatly advanced by research conducted in the field of biomedical engineering, or unique engineering designs

based on what we have learned in modern life sciences. Representative progress includes the following: computer simulation and cadaveric studies on the foot arch deformation and stress distribution after plantar fascia release indicate that all the four plantar ligaments, particularly the plantar fascia, play an important role in stabilizing the normal foot arch, a revelation that would help understand the biomechanical behavior of the foot subjected to different injuries<sup>[110]</sup>; cytotoxicity and hemocompatibility experiments performed under both *in vitro* and *in vivo* conditions demonstrate that the g-HA/PLA composites, prepared by grafting L-lactic acid oligomers on the surface of hydroxyapatite (HA) particles which is then further blended with poly (L-lactide) (PLA), are a promising and safe material with potential applications in tissue engineering<sup>[111]</sup>; rheology (flowing behavior) studies demonstrate that the capacity of the red blood cells to go through the microvessel stenosis is affected by the Reynolds number (a dimensionless number measuring the ratio of inertial forces to viscous forces and quantifying the relative importance of these two types of forces for a given flow condition) of the plasma flow as well as the surface-to-volume ratio of the cell and at a constant inlet flow rate, an increased plasma viscosity will improve the transit of the cells<sup>[112]</sup>; superparamagnetic iron oxide nanoparticles were found to be internalized into macrophage cells through multiple endocytic pathways, distributed to daughter cells during mitosis, degraded in the lysosome with free iron being released into the intracellular iron metabolic pool, while the intact nanoparticles being potentially exocytosed out of the cells and that they do not induce cell damage and thus may be utilized as a drug delivery tool<sup>[113]</sup>; brain-computer interfaces were successfully constructed, through which the rat prefrontal cortex neurons are able to control a one-dimensional machine by using an encoding method<sup>[114]</sup>.

#### 15 Additional comments

Undoubtedly, great efforts will be needed to make *Science China Life Sciences* a journal to which authors are willing to publish their novel scientific discoveries and readers are willing to go through it for life scientists in China and worldwide. I am not sure whether this dream will ever become true if English is still the dominant language for scientific communication in the world, but it will certainly

become so when the Chinese language takes the turn. Nevertheless, nothing is impossible and where there is a will, there is a way.

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