# Structure, Function, and Regulation of Biological Supramolecular Complexes: Postprint

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## Abstract

As the fundamental unit of life, cellular functions are not independently executed by individual biomacromolecules, but rather are carried out by supramolecular complexes formed through the interaction and dynamic assembly of tens of thousands of biomacromolecules. The supramolecular complexes defined herein refer to multi-subunit, multi-component complexes capable of relatively independently performing specific biological functions during life processes. On the one hand, cells utilize these complexes to ensure the correct expression of genetic information and maintain normal genetic functions; on the other hand, cells employ these complexes to exchange matter, energy, and information with the external environment, thereby sustaining the normal progression of life activities. Therefore, supramolecular complexes serve not only as the 'executors' of life activities, but also as the key to deciphering the mysteries of life.

## Full Text

Strategic Priority Research Program (Category B) of the Chinese Academy of Sciences
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## 1. Background and Significance

As the fundamental unit of life, cellular functions are not carried out by individual biomolecules in isolation, but rather by super-macromolecular complexes formed through the interaction and dynamic assembly of thousands of biomolecules. Here, we define super-macromolecular complexes as multi-subunit, multi-component assemblies that can independently perform specific biological functions during life processes. On one hand, cells utilize these complexes to ensure the proper expression of genetic information and maintain normal genetic functions; on the other hand, cells employ these complexes to exchange matter, energy, and information with the external environment, sustaining the normal progression of life activities. Therefore, super-macromolecular complexes serve as both the "executors" of life activities and the key to decoding the mysteries of life.

Studying the structure, function, and regulation of these executors of life activities represents a crucial pathway to unraveling life' s mysteries and mapping the blueprint of life. For instance, multiple Nobel Prize-winning works on RNA polymerase, the ribosome, and G protein-coupled receptors (GPCRs) have essentially revealed the fundamental principles of life activities through persistent research on specific biomolecular complexes. Consequently, resolving the structures of core super-macromolecular complexes will undoubtedly advance human understanding of the essence of life at the atomic level, triggering milestone scientific events and leading the development of modern life sciences. The Strategic Priority Research Program on "Structure, Function and Regulation of Biological Macromolecular Complexes" takes super-macromolecular complexes as its entry point, representing not only an essential path toward decoding the operational mechanisms of life' s machinery at atomic resolution, but also holding profound significance for leading the development of life sciences in China and enhancing innovation capacity and standards in the biomedical industry through original and source innovations. Just as the high-resolution structure determination of the ribosome will effectively facilitate the development of novel antibiotics, the structural elucidation of GPCR complexes will greatly promote the discovery of new drug targets, and the in-depth investigation of functionally important super-macromolecular complexes harbors immeasurable application value.

## 2. Progress Achieved

The program has focused on worldwide scientific challenges such as heterochromatin structural complexes, virus-receptor-host supercomplexes, and technological bottlenecks including micro-crystal diffraction, high-resolution electron microscopy three-dimensional reconstruction, and NMR dynamic conformational analysis. By integrating superior research teams to tackle these problems, the program has achieved a series of breakthrough innovations. Within two years of implementation, the program has published numerous high-level articles in top-tier international journals, including 13 in *Nature*, 1 in *Science*, 2 in *Cell*, and 56 important papers in *PNAS*, with related achievements reaching internationally leading levels and playing an important guiding role in the field.

(1) Targeting the frontiers of basic life sciences, research has been conducted on chromatin structure and function, as well as transmembrane exchange of matter and energy. The program has, for the first time internationally, elucidated important cutting-edge scientific problems such as the 30 nm chromatin higher-order structure (Figure 1 [Figure 1: see original paper]), photosynthesis supercomplex structure, and the mechanism of the CRISPR adaptive immune system, generating major international impact.

For example, the 30 nm chromatin fiber higher-order structure has been included in world-renowned biochemistry textbooks such as *Fundamentals of Biochemistry: Life at the Molecular Level* and *Lehninger Principles of Biochemistry*. *Science News* published a special issue article introducing the research on the CRISPR-Cas adaptive immune system mechanism, and related papers were selected by Cell Press as China' s top research of 2015.

(2) Guided by key scientific questions in population health, the program has conducted research on disease mechanisms and drug targets. It has revealed the molecular mechanisms of bacterial outer membrane lipopolysaccharide assembly and viral infections including hand-foot-and-mouth disease, hepatitis A, and Ebola, and developed specific inhibitors to block viral infection. These achievements have been reported by numerous domestic and international media outlets including People' s Daily Online and Xinhua Net, attracting widespread attention and discussion in the scientific community and being recognized by field experts as major breakthroughs in related areas. Additionally, important achievements have been made in several GPCR studies, overcoming major scientific challenges in cell signal transduction and providing a foundation for new drug development, which was selected as one of China' s top ten scientific and technological advances of 2015 by the Chinese Academy of Sciences and Chinese Academy of Engineering. Meanwhile, a series of breakthroughs in pyroptosis have revealed the key molecular mechanisms of cellular pyroptosis and inflammatory necrosis, providing novel drug targets for various autoinflammatory diseases. This work was selected by *Science Signaling* as a breakthrough research achievement of 2015 and included in China' s top ten scientific advances of 2015. The program also discovered new methods to enhance the anti-tumor immune function of T cells, providing important scientific evidence for the prevention and control of major diseases.

(3) Committed to developing new technologies and methods in life sciences, the program has concentrated efforts on biological imaging. It has established technical methodology systems for super-resolution fluorescence microscopy and high-resolution three-dimensional electron microscopy, and developed advanced equipment and platforms such as the photoelectric fusion super-resolution biological microscopy imaging system, providing powerful technical support and development momentum for super-macromolecular complex research.

Based on these achievements, the project "Structure and Function Relationships of Eukaryotic Membrane Proteins and Protein Complexes" was selected as a landmark major progress of the Chinese Academy of Sciences during the 12th Five-Year Plan period, marking important phased achievements of this program.

## 3. Originality and Innovation

Since its implementation, the program has achieved a series of internationally leading breakthroughs, solving several worldwide scientific challenges in the field.

(1) Elucidation of the 30 nm chromatin higher-order structure. For the first time internationally, the program resolved the high-precision three-dimensional cryo-electron microscopy structure of the 30 nm chromatin fiber (11 Å), revealing a novel left-handed double-helical structural model of the 30 nm chromatin fiber. This represents a major breakthrough in deciphering the higher-order structure of 30 nm chromatin—the carrier of "life information." On April 25, 2014 (the 61st anniversary of the discovery of the DNA double helix), this major achievement was reported as a Research Article in the top-tier journal *Science* (Figure 1). Following publication, the work received widespread attention from the academic community, with multiple commentaries and special reviews in related journals, and was quickly included in several classic textbooks of biochemistry and cell biology both domestically and internationally. Popular and science media including CCTV, Xinhua News Agency, and *Chemical & Engineering News* also gave high-level attention and coverage to this achievement. The work has been highly praised: "The 30 nm chromatin structure is one of the most fundamental questions in molecular biology, puzzling researchers for over 30 years," and our results represent "one of the most challenging structures resolved to date" and "an important step forward in understanding how chromatin is assembled." This research achievement represents a major breakthrough on the significant scientific problem of 30 nm chromatin fiber higher-order structure and demonstrates that China has reached an internationally leading level in chromatin structure research.

(2) Major progress in photosynthesis supercomplex structure research. Using single-particle cryo-electron microscopy, the program resolved the three-dimensional structure of the higher plant (spinach) photosystem II-light-harvesting complex II super-membrane protein complex (PSII-LHCII supercomplex) at 3.2 Å resolution. This structure is currently the highest-resolution (3.2 Å) three-dimensional structure of a super-membrane protein complex resolved by single-particle cryo-electron microscopy. This research was officially published online as an Article in *Nature* on May 19, 2016 (Figure 2 [Figure 2: see original paper]). Elucidating the mysterious and intricate structure of plant photosystem II will help understand the working principles of this supramolecular machine and has long been a hot and challenging topic in structural biology, as well as a highly anticipated three-dimensional structure of a super-macromolecular complex in photosynthesis research. The results reveal for the first time the overall structural features and arrangement patterns of subunits in this highly complex supramolecular system, which is of great significance for further

understanding energy transfer dynamics and photoprotection mechanisms at the molecular level in the PSII-LHCII supercomplex.

## 4. Recommendations for Future Development

(1) Promoting discipline development and academic status enhancement. Through the implementation of the program, numerous research achievements have been obtained. It is recommended that the Chinese Academy of Sciences and relevant national departments continue to provide focused deployment and stable support in this direction, such as further support for related research directions through the National Key R&D Program' s key special project on "Protein Machinery and Life Process Regulation," to fully leverage the guiding role of the program, continuously produce high-level research results, promote major theoretical and technological innovations, and advance the development of the super-macromolecular complex structure and function research field in China.

(2) Promoting talent team building. The program has leveraged the advantages of multidisciplinary talent and organizational coordination within the Chinese Academy of Sciences to initially establish an interdisciplinary joint research system. It is recommended that through mechanisms such as the NSFC "National Innovation Research Group Science Fund," the Ministry of Science and Technology "Ten Thousand Talents Program—Key Area Innovation Team," and the CAS talent team program, the concept of cross-disciplinary cooperation be more fully utilized to establish frontier interdisciplinary topics, recruit young talents with technical expertise from within and outside the Academy as needed, and form mission-oriented interdisciplinary joint research teams to lead discipline development.

(3) Enhancing international influence. Through approximately two years of cultivation, the program has demonstrated excellent development momentum and will undoubtedly achieve more high-level research results in the future. It is recommended to actively conduct domestic and international academic exchange activities to strengthen the promotion of achievements and enhance international influence. Simultaneously, it is suggested that through programs supporting international organization appointments by the Ministry of Science and Technology, NSFC, and Chinese Academy of Sciences, program leaders be promoted to become internationally influential leading talents, enhancing the influence of Chinese scholars on the international stage and actively promoting the development of related fields.

(Program hosted by: Institute of Biophysics, Chinese Academy of Sciences)

**Expert Perspectives**

Researching the structure, function, and regulation of cellular super-macromolecular complexes is one of the important pathways to unraveling the mysteries of life and mapping the blueprint of life. Currently, structural biology is experiencing rapid development, and China has strong competitiveness in this field, with the potential to become a global leader. The Strategic Priority Research Program on "Biological Super-macromolecular Complexes," hosted by the Institute of Biophysics, Chinese Academy of Sciences, comprises research teams from multiple CAS institutions. From the perspective of protein science, it addresses a series of major scientific questions in modern biology, including genetics, genomics, immune response, and virology. The project team is also attempting to develop new technologies and establish technical systems for high-resolution structural and dynamic conformational studies of super-macromolecular complexes to enhance the team' s research capabilities. This project is very timely, and the participating scientists have achieved tremendous results in such a short period, producing a series of important scientific achievements with worldwide impact, which is rare internationally. It will not only promote the development of Chinese research internationally but also contribute to global scientific progress. It is hoped that the Chinese Academy of Sciences can provide greater support for this project to continue generating world-leading scientific achievements.

**Wang Xiaofan**, tenured chair professor at Duke University Medical Center, member of the Overseas Expert Advisory Committee of the Overseas Chinese Affairs Office of the State Council. He is the first Asian associate editor of the Journal of Biological Chemistry, a major journal in biochemistry, and serves as a reviewer or editorial board member for more than 30 top international journals including *Cell* and *Nature*. He is a leading figure among overseas Chinese biologists and served as president of the Society of Chinese Bioscientists in America (SCBA) from 2012 to 2013, the first scholar born in mainland China to hold this position. The Wang Xiaofan laboratory has made remarkable achievements in transforming growth factor family proteins and cancer development, DNA damage, angiogenesis, metastasis, and related cancer biology, publishing over 90 papers, including more than 20 in *Cell*, *Nature*, *Science*, *PNAS*, and other top journals.

The greatest feature of the Strategic Priority Research Program on "Biological Super-macromolecular Complexes" is its success in tackling a series of fundamental biological questions and elucidating biological mechanisms through the structural determination of key complexes. To a large extent, this represents the core talent, technology, and capabilities of Chinese scientists in this frontier field. The program focuses on the key scientific question of "assembly and regulation of biological super-macromolecular complexes and their relationship to cellular life processes," studying super-macromolecular complexes related to chromatin structure and function, viral transmembrane invasion, and transmembrane exchange of matter and energy to deeply understand the communication mechanisms between cells and the external environment. Simultaneously, it supports the development of new light sources, imaging, and dynamic spectroscopy frontier technologies to provide technical support and promotion for super-macromolecular complex research.

This program is of great significance, with relevance to almost all areas of life sciences and medicine. Although established just over two years ago, the program has achieved remarkable results, and its progress in the life sciences will place China' s scientific research at the forefront internationally. In an era where cryo-electron microscopy is revolutionizing atomic-level resolution, the application of structural biology methodologies and interdisciplinary approaches has profoundly impacted the development of structural biology. The Chinese Academy of Sciences has timely recognized this change and quickly established a position on the international stage. The program integrates X-ray crystallography and advanced nuclear magnetic resonance fields, organically assembling a group of outstanding scientists, which provides a guarantee for the production of excellent results. If the Chinese Academy of Sciences can provide stable and sufficient funding support for such projects, I believe more world-class, high-impact scientific achievements will be produced in the future.

**Fu Xiangdong**, tenured professor in the Department of Cellular and Molecular Medicine at the University of California, San Diego, member of the American Association for the Advancement of Science, RNA Society, Leukemia & Lymphoma Society, and Ray Wu Society for biomedical sciences. He is a "Chang Jiang Scholar" (lecture professor) appointed by the Ministry of Education (sixth batch). He graduated from the Department of Virology at Wuhan University in 1982 and received his Ph.D. in biochemistry from Case Western Reserve University in 1988, followed by postdoctoral research at Harvard University from 1988–1992. He has long been engaged in RNA functional genomics research, including mRNA precursor splicing and regulatory mechanisms in eukaryotic cells, related developmental processes and disease pathogenesis, the function of splicing factor SR protein families, and SR protein modification regulation. He has published 158 SCI papers, including 9 in *Cell*, 10 in *Nature*, 2 in *Science*, 33 in *Nature/Cell* sub-journals, and 14 in *PNAS*. He is a top international scientist in the RNA research field.

*Note: Figure translations are in progress. See original paper for figures.*

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