# Molecular Basis and Regulation of Cell Fate Plasticity Postprint

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## Abstract

Cells are the fundamental structural and functional units of life. All life activities of organisms, including growth, development, reproduction, and evolution, are based on cells. Multicellular organisms contain diverse cells with varied morphologies and functions, all of which originate from a single fertilized egg through proliferation and differentiation. Once generated, cells face various distinct fates, including division, proliferation, movement, differentiation, and death. Investigating and elucidating the essence of cellular life and the principles governing its activities constitutes an eternal theme in the life sciences.

## Full Text

## Preamble

**Strategic Priority Research Program (Category B) of the Chinese Academy of Sciences**
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**Molecular Basis and Regulation of Cell Fate Plasticity**

## 1. Background and Rationale

Cells are the fundamental structural and functional units of life. All biological processes—including growth, development, reproduction, and evolution—are based on cellular activities. Multicellular organisms contain diverse cell types with distinct morphologies and functions, all derived from a single fertilized egg through proliferation and differentiation. Once formed, cells face various fates such as division, proliferation, migration, differentiation, and death. Investigating and revealing the essence of cellular life and its activity patterns represents an eternal theme in life sciences. During organismal development from fertilized egg to individual, cells constantly face critical decisions about whether to

maintain their current identity and state or transform into alternative identities. The maintenance and transformation of cellular identity are controlled by both intrinsic genetic factors and extrinsic environmental cues. The interplay between these internal and external factors endows cell fate with variable and interchangeable characteristics.

Contemporary life science research grapples with fundamental mysteries surrounding cell fate plasticity: Why can a fertilized egg produce all cell types? Why do cellular morphology and function transform during organismal development? Why do certain specialized cells such as neurons and muscle cells stably maintain their characteristics once formed, while others retain plasticity? How do cells preserve homeostasis when confronted with environmental stress? Why can normal cells in an organism transform into cancerous or other pathological cells? Addressing these questions has become a frontier hotspot in basic life science research.

Analysis of current international trends reveals that research on "cell fate plasticity" predominantly focuses on neural plasticity and nervous system repair, immune cell differentiation and immunological diseases, and stem cells and regenerative medicine. Major funding agencies including the U.S. National Institutes of Health, U.S. National Science Foundation, and German Research Foundation have launched significant initiatives supporting basic and applied research related to cell fate plasticity. Although the overall field is experiencing rapid growth, concentrated and large-scale research programs remain limited, with relatively few funded projects, leaving the domain in a fragmented and nascent stage. If China can strategically deploy specialized research in "cell fate plasticity" at this critical juncture, it will seize a strategic initiative, consolidate and cultivate internationally leading innovative research teams, achieve multiple highly innovative, systematic, and internationally influential frontier accomplishments, and pioneer new directions in life sciences.

## 2. Scientific Questions, Project Layout, and Participating Units

### 2.1 Scientific Questions to be Addressed

This pilot special project focuses on the cutting-edge scientific question of "molecular basis and regulation of cell fate plasticity," with four primary research directions: "plasticity regulation of cell division modes," "plasticity regulation of cell proliferation, differentiation, and death," "plasticity regulation of cell fate under stress conditions," and the development and application of "novel technological methods for studying cell fate plasticity." The implementation of this project will systematically and comprehensively resolve a series of major scientific questions: Who determines cell fate? When and where is cell fate determined? How are cell fate maintenance and conversion decided, and what decisions are made? The project will elucidate the molecular basis and regulatory principles governing cell fate maintenance and transformation, decode the mysteries of cell

birth, aging, disease, and death, provide theoretical foundations and models for artificial intervention in cell fate, open new research directions in "cell fate plasticity," enrich theoretical systems, innovate research paradigms, lead the development of molecular cell biology, and form an outstanding research team with international influence.

### 2.2 Project Layout

This special project focuses on "molecular basis and regulation of cell fate plasticity," structured around four research directions that collectively aim to decode the mysteries of cell "birth, aging, disease, and death" regarding the plasticity of cell fate, including regulation of proliferation, differentiation and transdifferentiation, apoptosis and necrosis, senescence and pathological transformation. The project comprises four interconnected projects [Figure 1: see original paper].

**(1) Project One: Plasticity Regulation of Cell Division Modes.** Meiosis is the division process through which diploid cells become haploid gametes. Its precise execution is critical for ensuring reproductive health and population quantity and quality. However, how meiosis is initiated remains an unresolved question in life sciences. To address this, the project will investigate two directions: the molecular regulation of the transition from mitosis to meiosis and the control of meiosis progression.

**(2) Project Two: Plasticity Regulation of Cell Proliferation, Differentiation, and Death.** Upon formation, cells constantly face choices among proliferation, differentiation, or death. Whether cells divide into identical daughter cells, differentiate into distinct cell types, or progress toward pathology and death depends on comprehensive and complex regulation by both intrinsic and extrinsic factors. To reveal the regulatory mechanisms underlying cell proliferation, differentiation, death, and their plasticity, this project will pursue two directions: plasticity regulation of cell survival modes and plasticity regulation of tumor cells.

**(3) Project Three: Plasticity Regulation of Cell Fate Under Stress Conditions.** How cells maintain homeostasis under stress and how they restore stability after homeostatic disruption represent critical decisions. To investigate how cellular identity and function undergo plastic changes under metabolic stress, tissue damage, or pathogenic infection, and how these changes determine whether organisms recover homeostasis or develop pathological deterioration, this project will explore two directions: plasticity regulation of tissue cell stress responses and plasticity regulation of immune cells.

**(4) Project Four: Novel Technological Methods for Cell Fate Plasticity Research.** The rapid development of life sciences depends on innovative technological methods in molecular and cellular research. Super-resolution imaging, single-cell biology, systems biology, and synthetic biology constitute indispensable technical platforms for revealing cell fate plasticity. This project will develop novel methodologies in two directions: super-resolution imaging

combined with single-molecule/single-cell analysis, and artificial chromosome construction and stable inheritance techniques.

The overall implementation roadmap illustrates how these four projects collectively advance the field [Figure 2: see original paper].

### 2.3 Participating Units

This special project is implemented under the leadership of the Chinese Academy of Sciences, 依托 the Center for Excellence in Molecular Cell Science/Institute of Biochemistry and Cell Biology (IBCB) through integrated collaborative operation, forming a comprehensive layout for molecular cell science research. Research teams with distinctive yet interconnected and cross-disciplinary expertise have been established in Shanghai, Hefei, Beijing, and other locations, creating a highly innovative scientific workforce led by academicians and supported by Distinguished Young Scholars, Young Thousand Talents, and Hundred Talents Program members, providing ample human resources for project implementation.

Founded in May 2000 through the integration of the former Shanghai Institute of Biochemistry and Shanghai Institute of Cell Biology, IBCB is one of China' s most influential national research institutions in life sciences. Through half a century of development and the arduous efforts of several generations of scientists, the institute (and its predecessors) has achieved groundbreaking results with major international impact, including the artificial synthesis of bovine insulin, total synthesis of yeast alanine tRNA, fertilization and parthenogenetic maturation of oocytes, and artificial breeding of domestic fish, earning multiple first-class National Natural Science Awards and National Science and Technology Progress Awards. The institute enjoys high scientific and social prestige domestically and attracts significant international attention. IBCB currently hosts three major research clusters: the State Key Laboratory of Molecular Biology, the State Key Laboratory of Cell Biology, and the National Protein Science Center (Shanghai), covering five frontier areas including gene regulation, RNA and epigenetics, protein science, cell signal transduction, cell and stem cell biology, and mechanisms of cancer and other major diseases, providing a crucial foundation for project implementation. Over the past five years, the project host and participating units have achieved representative results in multiple research directions related to "molecular basis and regulation of cell fate plasticity," with publications in top-tier journals such as *Science*, *Nature*, and *Cell*, and three research achievements selected as China' s "Top Ten Scientific Advances" of the year.

## 3. Expected Outcomes

The special project will achieve a series of pioneering, systematic, and internationally influential major frontier accomplishments in the field of "cell fate plasticity," striving for milestone scientific breakthroughs.

**(1) Plasticity Regulation of Cell Division Modes.** The project will elucidate the principles governing the transition from mitosis to meiosis, explain the molecular basis for crossover site selection during homologous chromosome exchange, and reveal the clinical significance of meiotic gene mutations. It will clarify the mechanisms maintaining genetic stability in haploid cells and design and establish protocols for haploid cell lines that stably maintain their haploid state.

**(2) Plasticity Regulation of Cell Proliferation, Differentiation, and Death.** The project will discover important novel mechanisms regulating the plasticity of cell proliferation, differentiation, and death, and establish a relatively complete molecular regulatory network. In the study of tumor cell plasticity, it will achieve key discoveries that provide valuable new insights for disease prevention and treatment. It will identify critical nodes and molecules in the regulatory network of cell fate plasticity, providing targets for artificial intervention and drug screening, and obtain small molecule compounds or antibodies with potential application value for inhibiting tumor cell proliferation and metastasis or for directionally inducing or inhibiting cell death.

**(3) Plasticity Regulation of Cell Fate Under Stress Conditions.** The project will systematically map metabolic regulatory networks, identify key nodes, and provide more precise strategies for improving metabolic diseases. It will discover molecular mechanisms regulating plasma membrane damage repair, elucidate the cytological mechanisms of damaged cell clearance and reconstruction, and develop novel rehabilitation methods using animal models of stress conditions such as muscle atrophy. It will achieve major original breakthroughs in understanding the mechanisms of immune cell fate plasticity, exploring novel targeted genes or diagnostic markers for blocking tumor growth, pathogenic microbial infection, and autoimmune diseases.

**(4) Novel Technological Methods for Cell Fate Plasticity Research.** The project will establish new technological methods for studying protein machinery dynamics and cytoskeletal assembly in cell fate determination, such as super-resolution optical microscopy of protein machinery activity, signal remodeling fluorescence molecular tracing, and chemical small molecule screening for signal remodeling intervention, advancing the development of 2–3 high spatiotemporal resolution imaging technologies. It will establish an online cell dynamics database related to cell division fate plasticity, create theoretical models for cell division fate selection and transition mechanisms to provide candidate models and new theories for experimental verification, and construct mouse and human artificial chromosomes containing compact structural-functional units capable of stable inheritance.

*(Implementing Unit: Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences)*

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