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# The Application of Single-cell Omics in Developmental Biology: from Model Organisms to Humans

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Abstract With the rapid development of single-cell omics technology, its application in the field of developmental biology is becoming increasingly widespread. This article reviews the key role of single-cell omics techniques in research from model organisms to human developmental biology, revealing the importance of cell heterogeneity, dynamic monitoring of gene expression and epigenetic modifications, and constructing cross species developmental biology models. At the same time, the conservatism and diversity of single-cell omics technology in understanding human development, as well as its application in disease mechanism exploration, drug screening, and treatment strategy development, were also discussed. However, this technology still faces technical challenges such as sample preparation, data quality, and analysis complexity, as well as ethical challenges in the use and storage of human samples. This study aims to provide new perspectives and tools for the field of developmental biology, promote a deeper understanding of life processes, and provide strong support for future medical research and treatment.

Keywords Single-cell omics; Developmental biology; Model organisms; Human beings; Technology application

Developmental biology, as an important branch of biology, is dedicated to exploring the developmental process of organisms from single celled fertilized eggs to complex multicellular individuals. This process involves complex mechanisms of cell differentiation, tissue formation, organ construction, and ultimately individual formation. In recent years, with the rapid development of science and technology, especially the rise of single-cell omics technology, significant progress has been made in understanding the basic issues of developmental biology (Griffiths et al., 2018).

Single cell omics techniques, including single-cell transcriptomics, single-cell epigenetics, and single-cell proteomics, have brought revolutionary changes to developmental biology research (Griffiths et al., 2018). These technologies can analyze key information such as gene expression, epigenetic modifications, and protein expression of individual cells during development with unprecedented precision, thereby revealing heterogeneity between cells, cell fate determination, and intercellular interactions, distinguishing different types of cells and their gene expression patterns at different developmental stages. This helps to understand how cells work together to build complex tissues and organs.

From the research of model organisms such as mice, zebrafish, fruit flies, etc., single-cell omics technology has brought many breakthrough discoveries to the field of developmental biology (Irion and Nüsslein Volhard, 2022). These model organisms have advantages such as relatively simple developmental processes, short life cycles, and fast reproductive rates, making them ideal choices for studying fundamental issues in developmental biology. By conducting in-depth research on these model organisms, not only can we better understand the fundamental issues of developmental biology, but we can also provide important references and insights for human developmental biology research.

However, the ultimate goal of developmental biology research is to reveal the mysteries of human development. The application of single-cell omics technology in human developmental biology research is of great significance. By analyzing single-cell omics data during human embryonic development, tissue differentiation, and organ formation, we can gain a deeper understanding of the molecular mechanisms and regulatory networks of human



development (Peng et al., 2018), providing new ideas and methods for the prevention and treatment of developmental diseases. This study aims to review the application of single-cell omics technology in developmental biology, from model organisms to humans, and analyze the development of single-cell omics technology and its potential applications in developmental biology, in order to comprehensively and systematically demonstrate the achievements and prospects of single-cell omics application in developmental biology.

## 1 Application of Single-cell Omics in Model Organisms

### 1.1 Application in simple eukaryotic yeast

Yeast, as a simple but representative eukaryotic organism, has always received widespread attention in biological research. In recent years, with the rapid development of single-cell omics technology, yeast has become an ideal model organism for studying these technologies. Single cell omics technology provides unprecedented opportunities for yeast research, enabling scientists to gain a deeper understanding of gene expression, protein interactions, and metabolic processes within individual yeast cells.

In single-cell transcriptomics, the cell cycle and metabolic pathways of yeast have been extensively studied. Single cell RNA sequencing (scRNA seq) technology can accurately measure the gene expression patterns of individual yeast cells under different growth conditions and cell cycle stages. This helps to understand how yeast cells adapt to different environmental pressures and regulate their life activities.

In terms of single-cell proteomics, yeast also provides rich research cases. Single cell mass spectrometry technology can be used to identify the types and quantities of proteins within a single yeast cell (Bartolec et al., 2019), as well as their interactions. This helps to reveal the signaling pathways and regulatory networks within yeast cells. In addition, the genome of yeast is relatively small and easy to operate, and gene editing techniques such as CRISPR-Cas9 can be used to precisely knock out or insert specific genes (Figure 1), in order to study the role of these genes in yeast cell growth, metabolism, and differentiation.

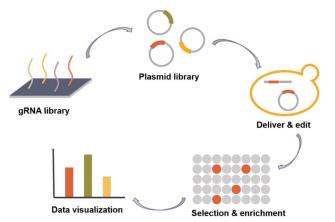


Figure 1 CRISPR/Cas9 tool for yeast library creation (Liao et al., 2022)

Single cell omics has the potential to revolutionize the complexity of yeast biology and its applications in biotechnology and systems biology. To understand the genetic and functional diversity within yeast populations, single-cell methods provide a more detailed and detailed perspective. Efremova and Teichmann (2020) studied computational methods for analyzing and integrating single-cell omics data in different ways, opening up new avenues for reconstructing gene regulation and signaling networks that drive cell identity and function. This is crucial for accurately understanding the genotype and phenotype heterogeneity within the yeast population.

Kaster and Sobol (2020) found that single-cell omics expands the understanding of microbial diversity and metabolic potential by providing information from individual organisms and the structure and dynamics of natural microbial communities in complex environments. This includes the current lack of representative deep lineage populations, highlighting their importance in microbiology and biotechnology research, particularly in relation to yeast research.



Li et al. (2011) found that advances in "omics" technologies, including genomics, transcriptomics, proteomics, and metabolomics, have been applied to construct engineered strains of brewing yeast (Saccharomyces cerevisiae). This demonstrates the practical application of single-cell omics in improving strain characteristics in bioengineering processes, such as bioethanol production and brewing processes.

#### 1.2 Application of the multicellular model organism in the beautiful C. elegans nematode

*Caenorhabditis elegans*, abbreviated as *C. elegans*, is a multicellular model organism that occupies an important position in biological research. Its relatively simple nervous system and short lifespan make it an ideal choice for studying fields such as developmental biology, neurobiology, and cell biology (Figure 2). In recent years, with the rapid development of single-cell omics technology, *Caenorhabditis elegans* has played an increasingly important role in single-cell omics research.

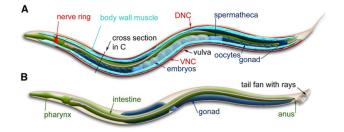


Figure 2 Lateral anatomy of *Caenorhabditis elegans* (Corsi et al., 2015) Note: A: hermaphroditic; B: male

The nervous system of *Caenorhabditis elegans* is relatively simple, consisting of only 302 neurons, which allows researchers to describe in detail the connectivity of each neuron. The use of single-cell omics techniques, particularly single-cell transcriptomics and single-cell proteomics, can reveal the functions and regulatory mechanisms of individual neurons in life processes. Li et al. (2020) found that single-cell RNA sequencing technology can analyze the gene expression patterns of different neurons at different developmental stages or under different environmental conditions, thereby gaining a deeper understanding of neural cell differentiation, development, and function.

Ma et al. (2017) found that the life cycle of *Caenorhabditis elegans* is very short, taking only about 3 days from fertilized eggs to adults. Moreover, its developmental process is highly conservative, and almost every individual can undergo similar developmental processes in the same time and space. In addition, *Caenorhabditis elegans* also has the characteristic of easy gene editing and genetic manipulation. This makes the *Caenorhabditis elegans* an important model organism for studying developmental biology. By utilizing single-cell omics techniques, it is possible to accurately track the gene expression, protein expression, and metabolic changes of individual cells during development, thereby revealing the molecular mechanisms and signaling networks involved in developmental regulation.

As a multicellular model organism, the nervous system and developmental process of the *Caenorhabditis elegans* are important models for studying developmental biology. Through single-cell omics technology, gene expression and protein interactions of individual neurons during development can be tracked. For example, using single-cell RNA sequencing technology, researchers have found that the gene expression patterns of different neurons in C. elegans exhibit spatiotemporal specificity during the developmental process from larval to adult stages. These genes are closely related to processes such as neuronal differentiation, synaptic formation, and function (Masoudi et al., 2021). In addition, single-cell proteomics techniques can also reveal the interactions and signaling pathways between neurons.

#### 1.3 Application of vertebrate model organisms in zebrafish

Zebrafish, as a vertebrate model organism, has been widely used in fields such as developmental biology, toxicology, disease modeling, and drug screening. In recent years, with the rise of single-cell omics technology,



the application prospects of zebrafish have further expanded, especially in understanding the complexity of life processes and fine regulatory mechanisms.

The fertilization and embryonic development process of zebrafish is an ideal model for studying fertilization and early embryonic development. Its developmental cycle is short, and embryonic development can be observed only a few hours after fertilization (Figure 3). Using single-cell omics techniques, especially single-cell transcriptomics, can accurately track gene expression changes at various stages from fertilized eggs to blastocysts, gastrulae, etc., thereby revealing the molecular mechanisms of fertilization process and the regulatory network of early embryo formation.

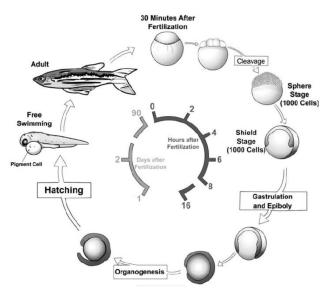


Figure 3 The life cycle of zebrafish (Costa and Shepherd, 2009)

The organ development process of zebrafish is also an important research direction in the field of developmental biology. Through genetic modification and single-cell omics analysis, the effects of different genes on organ development can be observed. For example, in pancreatic development, the Pdx1 gene is an essential gene for stabilizing pancreatic islet cells (Wang et al., 2018). By using single-cell RNA sequencing technology, the expression patterns of Pdx1 gene at different developmental stages can be analyzed, thereby gaining a deeper understanding of its impact on the number and function of pancreatic islet cells.

The nervous system development of zebrafish is very similar to other model organisms in vertebrates, but its growth rate is fast and it is still relatively simple in the early stages of nervous system development. This makes zebrafish an ideal choice for studying the mechanisms of neural development. By using single-cell omics techniques, the distribution sequence of neurons, the morphology and movement status of nerve cells, and the spontaneous activity of neurons can be studied, thereby revealing the precise process of neural system construction. The zebrafish experiment has the characteristics of fast and efficient in vitro experiments, as well as good correlation and high predictability in mammalian experiments, making it a unique advantage in drug screening and toxicology research.

Undoubtedly, zebrafish, as a model organism, has important value in single-cell omics research, providing scientists with in-depth understanding of biological systems and offering new strategies and methods for drug discovery and disease treatment.

Wagner et al. (2018) sequenced the transcriptome of over 90000 cells during zebrafish development, revealing the differentiation patterns of cells during axial patterning, embryonic layer formation, and early organ formation. These data and methods pave the way for comprehensive reconstruction of transcriptional trajectories during development.



Farrell et al. (2018) identified transcription trajectories in the data by generating single-cell transcriptomes of 38731 cells during early zebrafish embryogenesis using two complementary methods. These findings reconstructed the gene expression trajectory during embryonic development in vertebrates and highlighted the limitations and plasticity of cell type normalization.

Barriuso et al. (2015) used zebrafish as an animal model for human diseases, providing a platform for selecting personalized treatment options during drug discovery. Together with zebrafish transgenic tumor models, they represent an alternative tool for drug development. The transparency of zebrafish embryos and the recently developed colorless zebrafish provide valuable capabilities for researchers to directly observe cancer formation and progression in live vertebrate hosts.

# 2 The Application of Single-cell Omics in Human Development Research

### 2.1 Early human embryonic development

Early human embryonic development is a complex and intricate process that involves precise expression of numerous genes, protein interactions, and epigenetic modifications. Single cell omics techniques, especially single-cell transcriptomics and single-cell epigenetics, provide powerful tools for in-depth research on early human embryonic development.

Single cell transcriptomics technology can reveal the spatiotemporal specificity of gene expression in early human embryonic cells. Through single-cell RNA sequencing, researchers can accurately measure gene expression levels in individual cells and compare differences between different developmental stages or cell types. This helps to discover key genes and regulatory networks related to early embryonic development, further understanding the molecular mechanisms of human embryo formation.

Single cell epigenetic techniques can reveal epigenetic modification patterns in early human embryonic cells. Epigenetic modifications, such as DNA methylation, histone modifications, and non coding RNA, play important roles in embryonic development (Bednarczyk et al., 2021). Through single-cell epigenetic analysis, researchers can identify specific epigenetic markers in different cell types or developmental stages, thereby gaining a deeper understanding of the mechanisms of epigenetic regulation in embryonic development.

Single cell omics technology can also be combined with other high-throughput techniques, such as single-cell ATAC seq (for detecting chromatin accessibility) and single-cell chromatin conformation capture technology (for studying chromatin spatial structure), to comprehensively analyze key information such as gene expression, epigenetic modifications, and chromatin structure in early human embryonic cells. The application of these technologies will help reveal the complexity and fine regulatory mechanisms of early human embryonic development.

The use of single-cell genomics, transcriptomics, epigenomics, and proteomics, as well as these technologies, can help scientists gain a deeper understanding of cellular heterogeneity, developmental dynamics, and intercellular communication networks in early human development.

Efremova and Teichmann (2020) used computational methods to analyze and integrate different types of omics data from individual cells (such as genome, epigenome, transcriptome, and proteome data), which is crucial for understanding complex biological systems at the individual cellular level. By integrating multimodal data, these methods provide new avenues for high-resolution analysis of cell phenotype, developmental dynamics, and communication networks, which is crucial for understanding cell heterogeneity in multiple tissues and conditions.

Assou et al. (2011) Dynamic changes in gene expression during early human embryonic development: By analyzing gene expression in human eggs, embryos, and human embryonic stem cells (hESCs), different gene sets related to pluripotency, pluripotency, and reprogramming attributes were revealed. These analyses provide tools for understanding the molecular mechanisms and signaling pathways that control early embryonic development, and further discuss the clinical relevance of using non-invasive molecular methods for embryo selection.



#### 2.2 Human organ development and regenerative medicine

With the rapid development of single-cell omics technology, its application in human organ development and regenerative medicine is becoming increasingly widespread. Single cell omics technology can deeply study the molecular mechanisms at the cellular level, providing powerful tools for understanding the fine processes of organ development and the potential applications of regenerative medicine.

In terms of organ development, single-cell omics technology can reveal the diversity of cell types, intercellular interactions, and spatiotemporal changes in gene expression at different developmental stages. Li et al. (2016) systematically analyzed the molecular mechanism of growth plate development using single-cell RNA sequencing technology for the first time, providing new insights into unknown molecular cascade reactions. Researchers can identify key genes and signaling pathways related to organ development, thereby gaining a deeper understanding of the molecular mechanisms of organ formation. The results of this study enhance the understanding of bone growth and development regulation, and have potential implications for the treatment of bone diseases and the application of regenerative medicine. In addition, single-cell omics technology can also combine three-dimensional cell culture and organ chip technology to simulate the in vivo environment and further explore the complex process of organ development.

Single cell omics technology plays a crucial role in understanding the complexity of human organ development and revealing new strategies in regenerative medicine, providing powerful tools for future biomedical research and treatment methods. In the field of regenerative medicine, single-cell omics technology helps to discover potential regenerative mechanisms and cell types. Karthaus et al. (2020) found that stem cells or progenitor cells with regenerative ability can be identified through single-cell analysis, and their mechanisms of action in the regeneration process can be further understood. Single cell omics technology can also reveal the interactions and signaling networks between cells, providing important clues for the development of effective regenerative therapy methods.

It is worth noting that single-cell omics technology can also be combined with cutting-edge technologies such as gene editing and cell therapy, providing new therapeutic strategies for regenerative medicine. Silva et al. (2021) found that through gene editing techniques such as CRISPR-Cas9, researchers can precisely modify genes within cells to promote tissue regeneration and repair. Meanwhile, by combining cell therapy and tissue engineering techniques, modified cells can be applied for the repair and regeneration of damaged tissues.

#### 2.3 Neurological development and diseases

The nervous system is one of the most complex and intricate systems in the human body, and precise regulation of its developmental process is crucial for the normal physiological functions of individuals. Meanwhile, abnormal development of the nervous system is often closely related to the occurrence of various diseases. Single cell omics techniques, especially single-cell transcriptomics and single-cell epigenetics, provide powerful tools for in-depth research on the molecular mechanisms of neurological development and diseases.

In terms of neurological development, single-cell omics techniques can reveal the molecular mechanisms underlying the differentiation, migration, and synaptic formation of neural cells at different developmental stages. Through techniques such as single-cell RNA sequencing, researchers can accurately measure gene expression levels in individual nerve cells and compare differences between different developmental stages or cell types. This helps to discover key genes and regulatory networks related to neural cell differentiation, migration, and synaptic formation, further understanding the fine processes of nervous system development. As Lake et al. (2016) developed a mononuclear sequencing technique for cells from the Bodeman region of the human brain. Through gene expression clustering, 16 subtypes of neurons were identified, which are consistent with the origin region and exhibit regional variations in both excitatory and inhibitory neuronal subtypes, defining different cortical regions.

In the field of neurological diseases, single-cell omics technology helps to reveal the molecular mechanisms and pathological processes of disease occurrence. Castro et al. (2022) found that single-cell omics techniques can



identify abnormal expression of disease-related genes and disrupted intercellular interactions in congenital brain developmental abnormalities, neuronal migration disorders, and neural tube closure disorders. This helps to gain a deeper understanding of the pathogenesis of diseases and provides important clues for early diagnosis and treatment of diseases.

Single cell omics techniques can also be combined with other high-throughput techniques. Rocks et al. (2020) discovered single-cell ATAC seq and single-cell chromatin conformation capture techniques to comprehensively analyze key information such as gene expression, epigenetic modifications, and chromatin structure in neurological diseases. The application of these technologies will help discover new therapeutic targets and develop more effective treatment methods.

#### 2.4 Cancer diagnosis and treatment

Single cell omics techniques, especially single-cell RNA sequencing (scRNA seq), have found widespread applications in cancer diagnosis and treatment. These technologies can provide unprecedented insights, enabling researchers to analyze the cellular and molecular mechanisms related to tumor occurrence, evolution, metastasis, and immune response with higher resolution and accuracy. Peng et al. (2020) summarized the latest single-cell multi omics technologies and discussed their potential applications in cancer biology, providing unprecedented insights into decoding cellular and molecular mechanisms related to tumor generation, evolution, metastasis, and immune response with higher resolution and accuracy. Strzelecka et al. (2018) focused on the use of single-cell omics in cellular and animal disease models as well as human patient samples, emphasizing the potential of these methods to further improve various pathological diagnoses and treatments, while discussing the advantages and challenges of implementing these technologies in clinical practice.

Peng et al. (2020) explored single-cell multi omics and its potential applications in cancer biology. They believe that single-cell multi omics technology is based on a combination of multiple single-cell single omics technologies, which can simultaneously analyze RNA expression, single nucleotide polymorphism, epigenetic modifications, or protein abundance, making it possible to gain a deeper understanding of gene expression regulation mechanisms. The application prospects of these technologies in cancer biology are being explored.

Liu et al. (2021) investigated the application of single-cell omics in tumor immunology. The tumor microenvironment (TME) is an ecosystem that includes multiple cell types such as cancer cells, immune cells, and stromal cells. The use of single-cell technology systematically outlined the multi omics states in TME, providing unprecedented resolution for the pathogenesis of cancer and abnormal tumor immune function.

Nath and Bild (2021) discussed the application of single-cell omics technology in cancer precision medicine. The development of single-cell technology enables the tracking of tumor heterogeneity and its use to reveal the biological processes of clone evolution, which is of great significance for the development of personalized treatment strategies. The single-cell multi omics method has broken through the limitations of previous data resolution and can provide a more detailed understanding of the evolutionary dynamics of tumor progression, immune escape, metastasis, and treatment resistance.

#### **3** Construction of Three Cross Species Comparison and Developmental Biology Models 3.1 Conservation and differences between model organisms and humans during development

Conservation refers to the core mechanisms and gene networks shared by different species during their developmental process. Model organisms, such as mice, zebrafish, fruit flies, etc., are often used in developmental biology research because they share high similarities in developmental mechanisms with humans. These model organisms exhibit significant conservatism compared to humans in terms of cell differentiation, organ formation, and signal transduction. Many genes and signaling pathways related to organogenesis and cell fate determination are similar in both model organisms and humans.

Veraksa et al. (2000) studied developmental pattern genes and their conserved functions, emphasizing the conserved functions of developmental pattern genes, such as the Hox gene system, which involves establishing



cellular identity along the anterior posterior axis in all higher animals. It also covers the role of the *Pax6* gene in eye development and the role of Nkx2.5 protein in heart development, emphasizing their correlation with human pathological conditions.

Irie and Kuratani (2011) compared transcriptome analysis to reveal the typical stages of vertebrate organogenesis. Through quantitative comparative transcriptome analysis of several model vertebrate embryos, the pharyngeal stage was shown to be the most conservative stage, indicating that gene expression profiles are most similar between different species during the pharyngeal stage, which may reflect the source of vertebrate basic body plans. These studies demonstrate the power of model organisms in revealing the genetic and molecular basis of shared development across species, including humans. They emphasize the importance of evolutionary developmental biology in understanding the diversity and commonalities of life forms, with profound impacts on human health and disease.

Comparative genomics analysis of conservation studies to specific developmental stages emphasizes the importance of identifying common developmental mechanisms among different organisms for understanding human biology. Despite conservatism, there are also significant differences in the developmental processes between different species. These differences can be attributed to the timing, intensity of gene expression, or specificity of intercellular interactions. For example, certain genes may be expressed in specific species, while they are not expressed or have different expression patterns in other species (Uebbing et al., 2016). In addition, there may be differences in cell types, tissue structures, and organ functions among different species. These differences make model organisms limited in human disease research, drug screening, and other areas.

Gerri et al. (2020) studied a comparative perspective on human embryogenesis, using low input methods to study genetic and epigenetic mechanisms, as well as effective gene function assessment techniques, allowing us to directly study human embryos. These advances have transformed research on early embryonic development in non rodent species, providing a broader understanding of conservative and diverse mechanisms.

Workman et al. (2013) established neurodevelopmental sequence models in different mammalian species, which described the relationship between the asynchronous variability of neurodevelopmental events and their basic developmental relativity in 18 mammalian species (including humans, macaques, various rodent species, and six marsupials), and provided an empirical basis for identifying comparable mature states among different animals.

These studies indicate that although there are significant differences in genomes between species, key genes and molecular pathways during development are highly conserved in evolution. By studying these common developmental mechanisms in different biological models, we can deepen our understanding of human biology and reveal the genetic basis of some birth defects.

#### 3.2 Feasibility of constructing a cross species developmental biology model using single-cell omics

Single cell omics techniques, especially single-cell transcriptomics and single-cell epigenetics, provide unprecedented opportunities for the construction of cross species developmental biology models. These technologies can reveal key information such as gene expression, epigenetic modifications, and intercellular interactions of individual cells during development, providing a rich dataset for cross species comparisons.

Single cell omics techniques can capture the heterogeneity of individual cells and reveal the commonalities and differences in cell types among different species. By comparing the gene expression patterns and epigenetic modifications of the same cell type in different species, we can gain a deeper understanding of their conservatism and differences during development.

Single cell omics technology can dynamically monitor changes in gene expression and intercellular interactions. This helps to capture key events and regulatory mechanisms during the developmental process, and further reveals the commonalities and differences in developmental processes among different species. In addition, single-cell omics technology can also combine multiple omics data, such as proteomics, metabolomics, etc., to provide more comprehensive information. Wörheide et al. (2021) found that by integrating omics data at different levels, more

accurate developmental biology models can be constructed, and a deeper understanding of the commonalities and differences in developmental processes between different species can be gained.

Blencowe et al. (2019) discussed the challenges, opportunities, and progress in network modeling of single-cell omics data. They identified unique challenges and opportunities in single-cell omics data modeling and provided an overview of recently developed network modeling methods aimed at capturing dynamic networks, intracellular networks, and intercellular interaction or communication networks.

Strzelecka et al. (2018) used single-cell omics to analyze human diseases in model systems and clinical settings, focusing on the use of single-cell omics in cellular and animal disease models as well as human patient samples, emphasizing the potential of these methods to further improve various pathological diagnoses and treatments.

These studies indicate that although building cross species developmental biology models faces challenges, single-cell omics provides a unique opportunity to gain a deeper understanding of the complexity and dynamics of biological systems. By integrating and analyzing single-cell data from different species, researchers can uncover common and unique molecular mechanisms that control cell development and function.

### 3.3 Application of cross species developmental biology models in human diseases

Cross species developmental biology models play an important role in understanding the mechanisms of occurrence and development of human diseases. These models not only help reveal conservatism and diversity in human development, but also provide powerful tools for disease research.

Among them, the use of stem cell models, gene editing, and large-scale animal models is crucial in understanding the mechanisms of human disease occurrence and developing new therapies. Sterneckert et al. (2014) studied the use of stem cell models to study human diseases. Due to their self-renewal and differentiation abilities, stem cells are highly suitable for generating disease models and obtaining a large number of cells needed for drug development and transplantation therapy. Induced pluripotent stem cells (iPSCs) have been proven to be the most practical for simulating human diseases, and combined with gene editing techniques, models of genetically complex diseases can be generated.

Lin and Musunuru (2016) studied genomic engineering tools for constructing disease cell models, and comparative genomics methods and multi species biology are valuable tools for genetic analysis. Cross species connections, especially those between genes with human disease status mutations and their homologous genes in model organisms, can be particularly powerful because gene function data and experimental methods in model organisms can reveal the molecular mechanisms of diseases.

Rogers (2019) studied engineered large animal models to simulate human diseases. Although genetically engineered mice are the most commonly used species and have made significant contributions to understanding basic biology, disease mechanisms, and drug development, they often fail to accurately reproduce important aspects of human diseases, thus limiting their practicality as translational research tools. Developing disease models in species more similar to humans may provide a better environment for studying disease pathogenesis and testing new treatment methods.

By comparing the gene expression and regulatory mechanisms during development between humans and other species, scientists can discover key genes and signaling pathways associated with specific diseases. For example, disease models constructed using model organisms such as mice or zebrafish can simulate the process of human disease occurrence (Beck et al., 2021), thereby revealing the molecular mechanisms and pathophysiological processes of diseases.

The cross species developmental biology model provides an important platform for drug screening and the development of therapeutic strategies. By testing candidate drugs or treatment methods in these models, scientists can evaluate their efficacy and safety, and predict their therapeutic effects in humans. This method accelerates the drug development process and provides more options for clinical treatment.



By comparing the differences and conservatism of different species during development, scientists can better understand the differences between human individuals and provide guidance for personalized healthcare. For example, using cross species developmental biology models, scientists can evaluate the manifestations and developmental processes of specific diseases in different individuals (Vecchia et al., 2018), providing a basis for personalized treatment.

Cross species developmental biology models also have important application value for rare and hereditary diseases. By constructing corresponding disease models, scientists can delve deeper into the pathogenesis of these diseases and provide targeted treatment strategies for patients. These models can also be used for the development of cutting-edge technologies such as gene editing and cell therapy, providing new ideas and methods for disease treatment.

#### 4 Challenges and Prospects

In single-cell omics research, sample preparation is a crucial step that directly affects the quality of subsequent data and analysis results (Galazzi et al., 2018). At present, sample preparation still faces some technical challenges, such as cell acquisition, separation, labeling, and sequencing. How to efficiently and accurately obtain sufficient cells for certain rare cell types or specific tissues is an urgent problem to be solved.

The quality of single-cell omics data is crucial for subsequent analysis and interpretation. However, due to technical limitations and experimental conditions, there are often issues with noise, batch effects, and non-specific signals in the data. How to improve data quality and reduce technical errors is a direction that needs continuous efforts in the field of single-cell omics. Single cell omics data has extremely high dimensions and complexity (Naz et al., 2019), making it a huge challenge to extract useful information from it and provide effective explanations. Existing data analysis methods often struggle to cope with such complex data structures, requiring the development of more advanced and efficient analysis tools and methods.

In single-cell omics research, human samples are typically required. This involves a series of ethical issues such as privacy protection, informed consent, and data security. How to use and store human samples in a reasonable and compliant manner, ensuring the rights of researchers and the security of data, is a problem that must be taken seriously in research.

With the development of technology, integrating multiple omics information such as genomics, transcriptomics, and epigenetics will become an important direction for the development of single-cell omics. By integrating multiple omics data, scientists can gain a more comprehensive understanding of the state and behavior of cells during development and disease processes, providing richer information for revealing the mysteries of life activities.

The development of artificial intelligence and machine learning technology provides new opportunities for the analysis of single-cell omics data. By applying these technologies, we can more efficiently and accurately process and analyze large-scale single-cell omics data, extract useful information, and provide effective explanations. This will effectively promote the development of single-cell omics and make greater contributions to the progress of human health.

#### References

Assou S., Boumela I., Haouzi D., Anahory T., Déchaud H., Vos J., and Hamamah S., 2011, Dynamic changes in gene expression during human early embryo development: from fundamental aspects to clinical applications, Human reproduction update, 17(2): 272-290. <u>https://doi.org/10.1093/humupd/dmq036</u>

PMid:20716614 PMCid:PMC3189516

Barriuso J., Nagaraju R., and Hurlstone A., 2015, Zebrafish: a new companion for translational research in oncology, Clinical Cancer Research, 21: 969-975. https://doi.org/10.1158/1078-0432.CCR-14-2921

PMid:25573382 PMCid:PMC5034890



- Bartolec T., Smith D., Pang C., Xu Y., Hamey J., and Wilkins M., 2019, Crosslinking mass spectrometry analysis of the yeast nucleus reveals extensive protein-protein interactions not detected by systematic two-hybrid or affinity purification-mass spectrometry, Analytical chemistry, 92(2): 1874-1882. <u>https://doi.org/10.1021/acs.analchem.9b03975</u> PMid:31851481
- Beck E., Healey H., Small C., Currey M., Desvignes T., Cresko W., and Postlethwait J., 2021, Advancing human disease research with fish evolutionary mutant models, Trends in genetics: TIG, 38(1): 22-44.

https://doi.org/10.1016/j.tig.2021.07.002 PMid:34334238 PMCid:PMC8678158

Bednarczyk M., Dunisławska A., Stadnicka K., and Grochowska E., 2021, Chicken embryo as a model in epigenetic research, Poultry Science, 100(7):101164. https://doi.org/10.1016/j.psj.2021.101164

PMid:34058565 PMCid:PMC8170499

Blencowe M., Arneson D., Ding J., Chen Y., Saleem Z., and Yang X., 2019, Network modeling of single-cell omics data: challenges, opportunities, and progresses, Emerging Topics in Life Sciences, 3: 379-398. <u>https://doi.org/10.1042/ETLS20180176</u>

PMid:32270049 PMCid:PMC7141415

Castro L., Liu I., and Filbin M., 2022, Characterizing the biology of primary brain tumors and their microenvironment via single-cell profiling methods, Neuro-Oncology, 25: 234 - 247.

https://doi.org/10.1093/neuonc/noac211 PMid:36197833 PMCid:PMC9925698

Corsi A.K., Wightman B., and Chalfie M., 2015, A transparent window into biology: a primer on caenorhabditis elegans, WormBook, 200(2): 1-31.

https://doi.org/10.1895/wormbook.1.177.1

PMid:26087236 PMCid:PMC4781331

Costa A.D., and Shepherd I.T., 2009, Zebrafish development and genetics: introducing undergraduates to developmental biology and genetics in a large introductory laboratory class, Zebrafish in Education, 6(2): 169-177.

https://doi.org/10.1089/zeb.2008.0562

PMid:19537943 PMCid:PMC2774836

Efremova M., and Teichmann S., 2020, Computational methods for single-cell omics across modalities, Nature Methods, 17: 14-17.

https://doi.org/10.1038/s41592-019-0692-4

PMid:31907463

Farrell J., Wang Y., Riesenfeld S., Shekhar K., Regev A., and Schier A., 2018, Single-cell reconstruction of developmental trajectories during zebrafish embryogenesis, Science, 360: 6392.

https://doi.org/10.1126/science.aar3131

PMid:29700225 PMCid:PMC6247916

Galazzi R., Jesus J., and Arruda M., 2019, Sample Preparation Focusing on Plant Omics, Advances in experimental medicine and biology, 1073: 161-185. https://doi.org/10.1007/978-3-030-12298-0\_7

PMid:31236843

Gerri C., Menchero S., Mahadevaiah S., Turner J., and Niakan K., 2020, Human embryogenesis: a comparative perspective, Annual Review of Cell and Developmental Biology, 36: 411-440.

https://doi.org/10.1146/annurev-cellbio-022020-024900 PMid:33021826

Griffiths J., Scialdone A., and Marioni J., 2018, Using single-cell genomics to understand developmental processes and cell fate decisions, Mol. Syst. Biol., 14: e8046.

https://doi.org/10.15252/msb.20178046

PMid:29661792 PMCid:PMC5900446

Irie N., and Kuratani S., 2011, Comparative transcriptome analysis reveals vertebrate phylotypic period during organogenesis, Nature Communications, 2: 248. https://doi.org/10.1038/ncomms1248

PMid:21427719 PMCid:PMC3109953

Irion U., and Nüsslein-Volhard C., 2022, Developmental genetics with model organisms, Proceedings of the National Academy of Sciences of the United States of America, 119(30): e2122148119.

https://doi.org/10.1073/pnas.2122148119 PMid:35858396 PMCid:PMC9335277

Karthaus W., Hofree M., Choi D., Linton E., Turkekul M., Bejnood A., Carver B., Gopalan A., Abida W., Laudone V., Biton M., Chaudhary O., Xu T., Masilionis I., Manova K., Mazutis L., Pe'er D., Regev A., and Sawyers C., 2020, Regenerative potential of prostate luminal cells revealed by single-cell analysis, Science, 368: 497-505.

https://doi.org/10.1126/science.aay0267

PMid:32355025 PMCid:PMC7313621



Kaster A., and Sobol M., 2020, Microbial single-cell omics: the crux of the matter, Applied Microbiology and Biotechnology, 104: 8209-8220.

https://doi.org/10.1007/s00253-020-10844-0 PMid:32845367 PMCid:PMC7471194

Lake B., Ai R., Kaeser G., Salathia N., Yung Y., Liu R., Wildberg A., Gao D., Fung H., Chen S., Vijayaraghavan R., Wong J., Chen A., Sheng X., Kaper F., Shen R., Ronaghi M., Fan J., Wang W., Chun J., and Zhang K., 2016, Neuronal subtypes and diversity revealed by single-nucleus RNA sequencing of the human brain, Science, 352: 1586-1590.

https://doi.org/10.1126/science.aaf1204

PMid:27339989 PMCid:PMC5038589

Liao B., Chen X., Zhou X., Zhou Y.J., Shi Y.Y., Ye X.C., Liao M., Zhou Z.Y., Cheng L., and Ren B., 2022, Applications of CRISPR/Cas gene-editing technology in yeast and fungi, Arch. Microbiol., 204: 79. <u>https://doi.org/10.1007/s00203-021-02723-7</u>

PMid:34954815

Li J., Luo H., Wang R., Lang J., Zhu S., Zhang Z., Fang J., Qu K., Lin Y., Long H., Yao Y., Tian G., and Wu Q., 2016, Systematic reconstruction of molecular cascades regulating GP development using single-cell RNA-Seq, Cell reports, 15(7): 1467-1480. <u>https://doi.org/10.1016/j.celrep.2016.04.043</u>

PMid:27160914

- Li X.Y., 2011, Research progress of "omics" technologies and its application in construction of engineering strain of saccharomyces cerevisiae., China Biotechnology, 31: 139-144.
- Li Z., Tyler W., and Haydar T., 2020, Lessons from single cell sequencing in CNS cell specification and function., Current opinion in genetics & development, 65: 138-143.

https://doi.org/10.1016/j.gde.2020.05.043 PMid:32679535 PMCid:PMC7749065

Lin J., and Musunuru K., 2016, Genome engineering tools for building cellular models of disease, The FEBS Journal, 283(17): 3222-3231.

https://doi.org/10.1111/febs.13763

PMid:27218233 PMCid:PMC5881911

Liu J., Qu S., Zhang T., Gao Y., Shi H., Song K., Chen W., and Yin W., 2021, Applications of single-cell omics in tumor immunology, Front. Immunol., 12: 697412.

https://doi.org/10.3389/fimmu.2021.697412

PMid:34177965 PMCid:PMC8221107

Masoudi N., Yemini E., Schnabel R., and Hobert O., 2021, Piecemeal regulation of convergent neuronal lineages by bHLH transcription factors in Caenorhabditis elegans, Development, 148(11): dev199224.

https://doi.org/10.1242/dev.199224 PMid:34100067 PMCid:PMC8217713

Ma X., Zhao Y., Jia F., Song Y., and Xie Y., 2017, Utilization of Caenorhabditis elegans in laboratory teaching of genetics, Yi chuan=Hereditas, 39(8): 763-768. Nath A., and Bild A., 2021, Leveraging single-cell approaches in cancer precision medicine, Trends in cancer, 7(4): 359-372.

https://doi.org/10.1016/j.trecan.2021.01.007

PMid:33563578 PMCid:PMC7969443

- Naz A., Obaid A., Ikram A., Awan F., Nisar M., Paracha R., and Ali A., 2019, Systems-level understanding of single-cell omics, Single-Cell Omics, 1: 433-456. https://doi.org/10.1016/B978-0-12-814919-5.00020-8
- Peng A., Mao X., Zhong J., Fan S., and Hu Y., 2020, Single-cell multi-omics and its prospective application in cancer biology, Proteomics, 20(13): 26. https://doi.org/10.1002/pmic.201900271

PMid:32223079

Peng G., Cui G., Ke J., and Jing N., 2020, Using single-cell and spatial transcriptomes to understand stem cell lineage specification during early embryo development, Annual Review of Genomics and Human Genetics, 21: 163-181.

https://doi.org/10.1146/annurev-genom-120219-083220

PMid:32339035

Rocks D., Jarić I., Tesfa L., Greally J., Suzuki M., and Kundakovic M., 2020, Cell type-specific chromatin accessibility analysis in the mouse and human brain, Epigenetics, 17: 202-219.

https://doi.org/10.1080/15592294.2021.1896983

PMid:33775205 PMCid:PMC8865312

Rogers C., 2016, Engineering large animal species to model human diseases, Current Protocols in Human Genetics, 90: 15.9.1-15.9.14.

https://doi.org/10.1002/cphg.18

PMid:27367161 PMCid:PMC4957131

Silva J., Meyenberg M., and Loizou J., 2021, Tissue specificity of DNA repair: the CRISPR compass, Trends in genetics : TIG, 37(11): 958-962. https://doi.org/10.1016/j.tig.2021.07.010

PMid:34392967



Sterneckert J., Reinhardt P., ang Schöler H., 2014, Investigating human disease using stem cell models, Nature Reviews Genetics, 15: 625-639.

https://doi.org/10.1038/nrg3764

PMid:25069490

Strzelecka P., Ranzoni A., and Cvejic A., 2018, Dissecting human disease with single-cell omics: application in model systems and in the clinic, Disease Models & Mechanisms, 11(11): dmm036525.

https://doi.org/10.1242/dmm.036525 PMid:30401698 PMCid:PMC6262815

Uebbing S., Künstner A., Mäkinen H., Backström N., Bolívar P., Burri R., Dutoit L., Mugal C., Nater A., Aken B., Flicek P., Martin F., Searle S., and Ellegren H., 2016, Divergence in gene expression within and between two closely related flycatcher species, Molecular Ecology, 25: 2015-2028. https://doi.org/10.1111/mec.13596

PMid:26928872 PMCid:PMC4879514

Vecchia E., Mortimer N., Palladino V., Kittel-Schneider S., Lesch K., Reif A., Schenck A., and Norton W., 2018, Cross-species models of attention-deficit/hyperactivity disorder and autism spectrum disorder: lessons from CNTNAP2, ADGRL3, and PARK2, Psychiatric Genetics, 29: 1-17. <u>https://doi.org/10.1097/YPG.000000000000211</u>

PMid:30376466 PMCid:PMC7654943

Veraksa A., Campo M., and McGinnis W., 2000, Developmental patterning genes and their conserved functions: from model organisms to humans, Molecular genetics and metabolism, 69(2): 85-100.

https://doi.org/10.1006/mgme.2000.2963 PMid:10720435

Wang X., Sterr M., Burtscher I., Chen S., Hieronimus A., Machicao F., Staiger H., Häring H., Lederer G., Meitinger T., Cernilogar F., Schotta G., Irmler M., Beckers J., Angelis M., Ray M., Wright C., Bakhti M., and Lickert H., 2018, Genome-wide analysis of PDX1 target genes in human pancreatic progenitors, Molecular Metabolism, 9: 57-68.

https://doi.org/10.1016/j.molmet.2018.01.011

PMid:29396371 PMCid:PMC5870105

Wagner D., Weinreb C., Collins Z., Briggs J., Megason S., and Klein A., 2018, Single-cell mapping of gene expression landscapes and lineage in the zebrafish embryo, Science, 360: 981-987.

https://doi.org/10.1126/science.aar4362

PMid:29700229 PMCid:PMC6083445

Wörheide M., Krumsiek J., Kastenmüller G., and Arnold M., 2021, Multi-omics integration in biomedical research-A metabolomics-centric review, Analytica chimica acta, 1141: 144-162.

https://doi.org/10.1016/j.aca.2020.10.038

PMid:33248648 PMCid:PMC770136

Workman A., Charvet C., Clancy B., Darlington, R., and Finlay B., 2013, Modeling transformations of neurodevelopmental sequences across mammalian species, The Journal of Neuroscience, 33: 7368-7383.

https://doi.org/10.1523/JNEUROSCI.5746-12.2013

PMid:23616543 PMCid:PMC3928428