OPEN ACCESS

EDITORIAL

Chiral biology: An unusual perspective on chirality-induced cell behaviors and life phenomenon

Chao Zhou,[1,2,4,*] **Yongfeng Ji,**[1,4] **Wanjun Liu,**[1] **Shunai Che,**[3,*] **and Cunyi Fan**[1,2,*]

[1]Department of Orthopedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200233, China

[2]Shanghai Engineering Research Center for Orthopedic Material Innovation and Tissue Regeneration, Shanghai 200233, China

[3]School of Chemistry and Chemical Engineering, State Key Laboratory of Composite Materials, Frontiers Science Center for Transformative Molecules, Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, Shanghai Jiao Tong University, Shanghai 200240, China

[4]These authors contributed equally to this work

*Correspondence: zh2c0211@163.com (C.Z.); chesa@sjtu.edu.cn (S.C.); cyfan@sjtu.edu.cn (C.F.)

Received: January 21, 2025; Accepted: April 11, 2025; Published Online: April 17, 2025; https://doi.org/10.59717/j.xinn-life.2025.100138

Citation: Zhou C., Ji Y., Liu W., et al. (2025). Chiral biology: An unusual perspective on chirality-induced cell behaviors and life phenomenon. *The Innovation Life* 3:100138.

Chirality, a geometric attribute wherein a structure is incapable of being superimposed onto its mirror image through translation and rotation due to the absence of Sn symmetry, is ubiquitous in nature, particularly within the realm of living systems.[1] Chirality is ubiquitous in biological systems composed of organic and inorganic materials, which play important roles in biosystems. One of the 125 most recent scientific questions asked by Science magazine is why does life need chirality? It can be understood from two levels, the first is that life is inherently chiral, most of the molecules that make up life are chiral, such as amino acids, proteins, polysaccharides, nucleic acids, cells and tissues. Why does life need to be assembled from chiral units? Secondly, the response of living bodies to external chiral substances requires recognizable chiral structures to be used by living bodies, otherwise it will have opposite effects or even toxicity, which is the result of selective recognition of external chiral substances by chiral living systems, and why life needs specific external chiral substances, such as chiral drugs.

Cells, as a basic structural and functional unit of organisms, have been proven to possess a chiral hierarchical organization due to the chirality of their organics. Due to the homochirality of organisms, which is mediated by cells, the selectivity of the recognition between chiral interfaces of exogenous materials and cells is a crucial factor in biological systems. Thus, the interaction between chirality and cells leads to unexpected cellular behaviors and life phenomena.[2]

In recent, the role of chirality in bionic scaffolds in biogenesis and tissue development has attracted much attention. For example, L-chirality can be recognized by integrin receptors and leads to the formation of focal adhesion, which activates mechanosensitive ion channel transient receptor potential vanilloid 4 to conduct Ca^{2+} influx. Consequently, the phosphorylation of serum response factor is biased by Ca^{2+} influx to promote the vascular endothelial growth factor receptor 2 signaling pathway, resulting in enhanced angiogenesis. After implanted in a rat rotator cuff tear model, L-CSO films strongly enhance vascularization at the enthesis, promoting collagen maturation, increasing bone and fibrocartilage formation, and eventually improving the biomechanical strength. Therefore, chiral tissue engineering scaffold materials have a broad application prospect in tissue damage repair.[3]

Chiral molecules with specific types of'handedness' will dominate over the other types in biological systems. For example, chiral amino acids exist mainly as L-enantiomers, whereas the D-enantiomers of carbohydrates are dominant in all living things. Such basic chemical components are fundamental for stereoselective protein formation. The chirality of these small molecules also affects biochemical processes, such as molecular binding, molecular synthesis and signalling in cell communication. Protein misfolding to form amyloid aggregates is the main cause of neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, Huntington's disease, etc). Chirality is a major factor controlling the folding structure of proteins. Therefore, chirality may be a precipitating factor in inducing certain diseases.[4] In addition, other research teams have found that mirror bacteria would likely evade many immunemechanisms mediated by chiral molecules, potentially causing lethal infection in humans, animals, and plants.[5]

The interdependent relationship between chirality and living organism leads us to propose the concept of "chiral biology", which is an interdisciplinary study of chiral phenomena in biological systems and its influence on life processes, which combines the knowledge of chemistry, biology, physics and medicine. Its core focus is on the generation, function, regulation and role of chiral molecules (molecules with asymmetric structures) in living organisms, as well as their

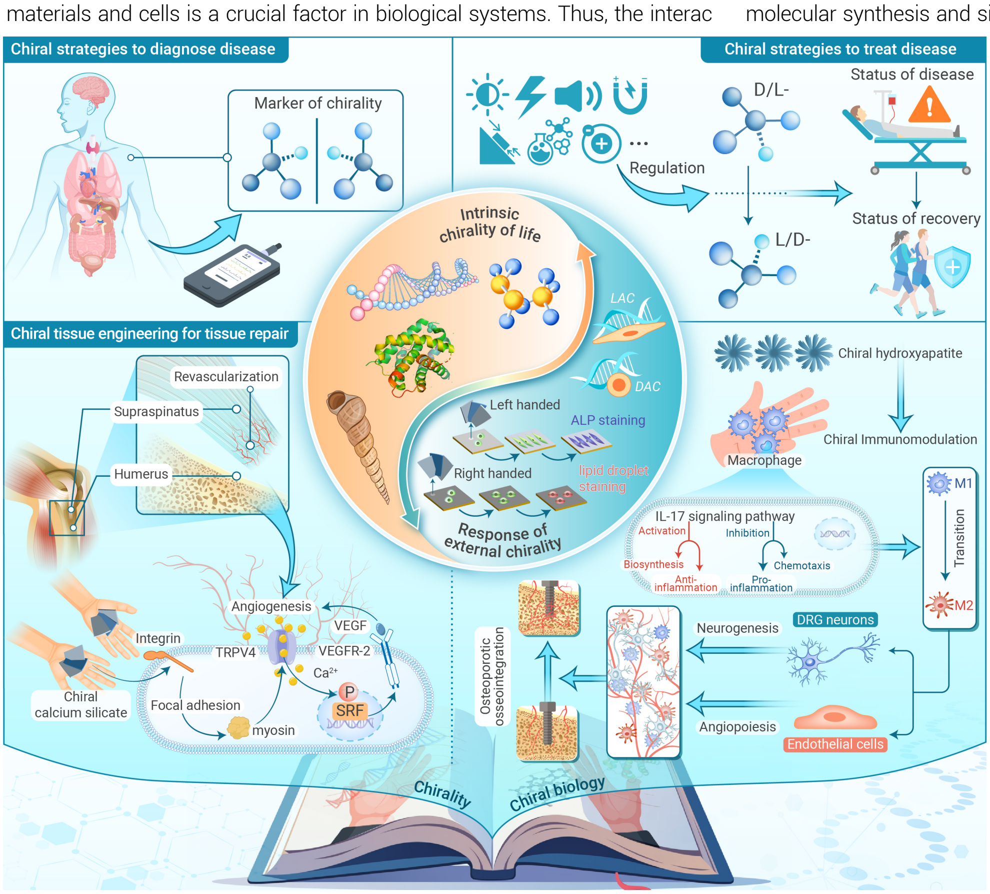

Figure 1. An unusual perspective of chiral biology Based on the intrinsic chirality properties of living organisms and their selective responses to external chiral substances, chiral strategies are expected to be applied to living systems in three directions.

interaction with external chiral substances. Based on the intrinsic chirality properties of living organisms and their selective responses to external chiral substances, three research directions for chirality applied to living systems were proposed to comprehensively evaluate the relationship between chirality and life (Figure 1).

(1) Chiral tissue engineering for tissue damage repair. Tissue engineering is a new discipline that combines cell biology and material science to construct tissues or organs in vitro or in vivo. It can also be understood as a discipline of bionic construction of living tissues. Three elements of tissue engineering: scaffold material, cell and growth information (protein factors and electrical signals). Cells and growth factors are components of life itself, which are consistent with living organisms, while most scaffold materials are introduced from the outside, and there are similarities and differences with the microenvironment of living organisms. Therefore, biomimetic materials are particularly important, and chirality is an important component of living organisms, so biomimetic chiral scaffold materials are the most important components of tissue engineering scaffolds. Compared with traditional tissue engineering, chiral tissue engineering has stronger biomimetic, histocompatibility and biological activity.

(2) Chirality detection for diagnosis and prediction of disease. The identification and detection of distinct biomarkers is important for the diagnosis of disease, evaluating disease progression and even the development of therapeutics. An advantage of biomarkers is that many of them are chiral, therefore, the detection of chirality can be used to identify disease-related biomarkers, and then achieve disease diagnosis.

(3) Chiral regulatory strategies for treatment and reversal of disease. Firstly, chiral molecules have different activities and therapeutic effects in living organisms. For example, different enantiomers of many drugs have radically different effects in the organism, and one enantiomer may be therapeutic while the other may be ineffective or even harmful. Through chiral structure regulation, chiral drugs with specific biological activities can be synthesized to improve the efficacy and safety of drugs. Second, chiral structures play a key role in biometrics and signaling. For example, the chiral structure of biological macromolecules such as proteins and nucleic acids determines their interactions and functions. By manipulating the chiral structure, biosensors and diagnostic tools with specific recognition functions can be designed, and drugs can be developed to treat and reverse diseases. Through a variety of means, chemical methods such as chirality induction and chirality transfer, physical methods such as external field stimulation and mechanical force, supramolecular self-assembly and biological methods, the precise regulation of chiral structure can be realized, so as to design chiral materials and functional devices with specific properties and realize disease treatment.

Chiral applications based on chiral biology, such as the research of chiral tissue engineering, the detection and diagnosis of diseases by chiral molecular markers, and the treatment of diseases by chiral regulation technology, have shown great application prospects. However, many challenges still need to be addressed: (1) Although there are many methods to prepare chiral materials, methods that can produce chiral materials with high purity are yet to be developed, special attention should be paid to the structure and chiral purity control of the prepared chiral materials. Our group has developed a coordination-induced self-assembly method for chiral molecules to realize the controlled synthesis of chiral structures. However, the purity of chiral ee values still needs to be further improved. Ion cluster crosslinking polymerization can precisely control the properties and structure of synthetic materials. If the chiral ion clusters can be obtained by combining chiral molecules, and then cross-linked and polymerized to form chiral structural materials, it may be possible to achieve precise regulation of chiral purity. Secondly, the adaptability of chiral materials to the living microenvironment needs to be further improved. Biological microenvironment is often a complex system with multi-scale, multi-level and multi-component. On the basis of taking into account the chiral microenvironment, the adaptation of hierarchy, size and composition should also be considered. (2) There are many kinds and different contents of chiral biomarkers in organisms, which indicator changes can indicate the occurrence of diseases? This is a very challenging problem. However, the detection results of many diseases can be found that different markers have specific expression content and location. By establishing a database of association between diseases and these specific markers, rapid screening and early detection of diseases can be achieved. Secondly, the current detection methods are limited, such as liquid chromatography and circular dichroism spectroscopy, but their detection sensitivity is limited. Therefore, the development of high-sensitivity detection equipment is the most urgent task at present. At the same time, it can also be used in combination with other equipment to achieve the purpose of accurate detection. In addition, the existing detection methods are based on in vitro testing of samples, but whether the samples change after take out is worth considering. Therefore, there is an urgent need to develop methods and equipment that can perform in vivo testing. (3) The chiral regulation strategies of chiral substances have also been extensively studied, but the chiral regulation strategies for chiral biomarkers and living tissues still need to be developed. In vitro, the chiral structure of a substance can be regulated by temperature, metal ions, pH, ion concentration, solution polarity, etc. But in vivo, can we learn from similar regulation methods to achieve chiral structure regulation of chiral substances in vivo? Extensive studies are warranted.

With the change of global environment and population aging, the incidence of human diseases is also increasing, which puts forward higher requirements for the diagnosis and prevention of diseases. The discovery and development of disease markers will provide more ways for disease diagnosis and treatment. The chiral applications based on the changes of chiral matter in living organisms and the selective response of living organisms to chiral matter is a promising approach. This editorial suggests that chirality biology, as a new discipline, comprehensively studies the relationship between chirality and living organisms, and ultimately uses chirality as a tool for living organisms, such as chirality tissue engineering, chirality strategies for diagnosing diseases, and chirality strategies for treating diseases. The above comments encourage the development of specific chiral biomaterials to achieve chiral regulation of life activities or phenomena. In addition, tools and methods for the detection of chiral substances in the body can be developed to achieve real-time monitoring of changes in chiral substances in the body of life. The construction of in situ carrier chirality detection technology is helpful to realize rapid and efficient diagnosis of diseases. At the same time, we can also develop chiral regulation strategies to achieve the regulation and reversal of pathological chirality for the treatment of diseases. In this editorial, the concept of chiral biology provides an unusual perspective for studying the deep mechanism of interaction between chirality and life. The application of chirality to diagnose and treat diseases is an innovative exploration that needs to overcome many difficulties. In order to cope with the health risks brought about by global environmental change and population aging, the relationship between chirality and life needs to be comprehensively and deeply studied as a special discipline - chiral biology.

REFERENCES

1. Bonner W.A. (1995). Chirality and life. Origins Life Evol. Biosphere. **25**:175–190. DOI:10.1007/BF01581581
2. Zhou C., Zhang S., Ai J. et al. (2022) Enantioselective interaction between cells and chiral hydroxyapatite films. Chem. of Mater. **34**:53–62. DOI:10.1021/acs.chemmater.1c02417
3. Cai Z., Qu C., Zhou C., et al. (2024) Hierarchical chiral calcium silicate hydrate films promote vascularization for tendon-to-bone healing. Adv. Mater. **31**:2404842. DOI:10.1002/adma.202404842
4. Liu Y., Wu Z., Armstrong D.W., et al. (2023) Detection and analysis of chiral molecules as disease biomarkers. Nat. Rev. Chem. **7**:355–373. DOI:10.1038/s41570-023-00476-z
5. Adamala K. P., Agashe D., Belkaid Y., et al. (2024) Confronting risks of mirror life. Science **386**:1351-1353. DOI: 10.1126/science.ads9158

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 82402770), Emerging Interdisciplinary Research Program of Shanghai Municipal Health Commission (No. 2022JC035). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. We would like to express our sincere gratitude to professor Hongshi Ma for their invaluable consultations, guidance, and inspiration throughout the development of this work.

DECLARATION OF INTERESTS

The authors declare no competing interests.