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REVIEW

CANCER INNOVATION

Mesoscience in cell biology and cancer research

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Abstract

Mesoscale characteristics and their interdimensional correlation are the focus of contemporary interdisciplinary research. Mesoscience is a discipline that has the potential to radically update the existing knowledge structure, which differs from the conventional unit-scale and system-scale research models, revealing a previously untouchable area for scientific research. Integrative biology research aims to dissect the complex problems of life systems by conducting comprehensive research and integrating various disciplines from all biological levels of the living organism. However, the mesoscientific issues between different research units are neglected and challenging. Mesoscale research in biology requires the integration of research theories and methods from other disciplines (mathematics, physics, engineering, and even visual imaging) to investigate theoretical and frontier questions of biological processes through experiments, computations, and modeling. We reviewed integrative paradigms and methods for the biological mesoscale problems (focusing on oncology research) and prospected the potential of their multiple dimensions and upcoming challenges. We expect to establish an interactive and collaborative theoretical platform for further expanding the depth and width of our understanding on the nature of biology.

KEYWORDS

mesoscience, biology paradigms, oncology, integrative paradigms

Abbreviations: cryo-EM, cryo-electron microscopy; DCs, dendritic cells; DPD, dissipative particle dynamics; EMMS, Energy Minimum Multiscale; LBM, lattice Boltzmann method;; LLPS, liquid-liquid phase separation; LSPS, liquid-solid phase separation; NET, nonequilibrium thermodynamics; TCR, T cell receptors; Tregs, regulatory T cells.

1 | THE CONCEPT AND ORIGINS OF MESOSCIENCE

Meso is rooted from Greek *mésos*, which means middle, and in the middle; is akin to Latin *medius*, which means mid. Mesoscale is traditionally termed as the space between the unit- and system-scale. The use of the term in meteorology was first seen in 1959 (Fujita, T. (1959) J. Meteorol. 16:454–66). In the view of mesoscale, the essence of universal connection between objects is a contradictory unity; and the essence of the development is the replacement of old systems with new ones [1]. The mesoscale characteristics between each stage or level is distinct from that of their adjacent scales, and the research at mesoscale is a linker that combines multi-level information, which will discover the unknowns between the knowns. Therefore, studying the features of objects from the aspect of mesoscale is also called mesoscience, which is a new scientific perspective, with universal applicability across the disciplines, for establishing the inner connection between macroscopic and microscopic scales. Mesoscale-driven exploration of the intrinsic relationship between every two scale units will be a distinctive atlas of the knowledge system in the future.

With the rapid development of scientific technology and the explosive expansion of knowledge in depth, collaborative and shared research has become the mainstream in contemporary science. Interdisciplinary and integrating research and applications are increasingly demanded to break the bottleneck in scientific frontlines. However, the specialization of each research field has also led to a prominent stratifications of information between disciplines and sub-divisions, which hinders further knowledge mining and scientific advancement that can only be achieved under conditions of efficient disciplinary integration. To discover the scientific connections between different research levels from a new perspective and to promote the depth and breadth of knowledge integration, we need to refine or reforge the knowledge systems by further exploring the intrinsic connections between each scientific unit. Furthermore, to energize the scientific and social values of current knowledge system and discover neoteric laws of interaction between research units, we need to update the connotation of knowledge and scientific connections among various disciplines.

In the traditional research paradigm of natural science, we generally learnt the macro-scale behavior of research objects, and then gradually delved into their micro-scale intrinsic mechanisms to establish the correlation between the macro-micro levels of facts using trans-dimensional evidence [2]. In fact, it is challenging to accurately explore the connection between macroscopic and microscopic research units because each scientific, at each level, is characterized by complex-stage and multi-scale, as well as different research methods and descriptive patterns. Specifically, the development of each scientific process undergoes multiple stages of high-dimensional structure, so the interactions or connections between other scientific units are also multi-scale. The accumulation of multi-dimensional and precise data and the weakness of cross-disciplinary analysis make the understanding of each research unit one-sided or even inaccurate, significantly obstructing existing knowledge to play roles in the scientific promotion and society service. Now, there is a clear understanding of the particle, atomic, molecular and macroscopic materials, and at the same time, knowledge of the scientific range between these scales, such as aggregates, dynamic properties of aggregates, and consequently their system-scale behaviors, is much neglected, and quite challenging [3].

Classical case of mesoscale was an intermediate state of the process from Newtonian mechanics to quantum mechanics, that is, the quantization process, representing the gradual partitioning of objects until they approach the limit of scaling from geometrical optics to physical optics. Mesoscale or mesoscopy was first used to describe an electronic system close to phase coherence length that is associated with quantum coherence and transport [4]. Later, its principles and methods were gradually promoted and applied to the research of particle motion [5], solid-liquid phase change [6], and the development of functional materials [7, 8] in physical and chemical engineering, which markedly improved industrial efficiency. In a broad sense, mesoscale is not limited to the study of the absolute physical dimension but is a concept that refers to the specific scientific research between the unitary scale and the systemic scale, which applies to different disciplines, and is interdisciplinarities, including both natural and social sciences. The research at mesoscale covers the object with different volumetric sizes with a specific definition depending on the discipline units. In the natural sciences, elementary particles aggregate into atoms, molecules and even the earth and the universe at the hierarchical unit scale. Still the multi-scale cognitive structure makes interdisciplinary research a very challenging attempt. Similarly, social science also has multi-layered attributes, such as individuals, families, cities, countries, and so on [3]. Therefore, in the studies involving multiple units or disciplines, the investigation at the mesoscale level will be quite complex but indispensable. Mesoscale research is not only a challenge and bottleneck in all scientific fields, but also an opportunity for scientific breakthroughs.

2 | THE INTEGRATION OF MESO-SCIENCE AND BIOLOGY

Life science combines the knowledge of mathematics, physics and chemistry to explore the mechanisms behind life phenomena from the macroscopic level to the microscopic level. Cells are the basic units of life, composed of biological macromolecules such as proteins, nucleic acids, lipids, and, importantly, dynamic interactions between a large number of molecules. In organisms, cells are constructed into tissues or organs, which are further organized into various life systems to conduct the life activities of the body [9]. To study the life activity in depth, the traditional field of biology has gradually developed different branch disciplines, such as zoology, plant microbiology, cell biology, molecular biology and so on. Therefore, in the context of interdisciplinary integration, new opportunities and challenges have emerged, such as biochemistry, biophysics, biomedicine, and bioinformatics and other interdisciplinary research, providing an opportunity to re-integrate the laws of life in another kind of way.

Although the multi-level research hierarchy provides more diversified theories and perspectives for life research, it also raises the elusive scientific problems arising from the boundary scales of the various biological levels and disciplines. Breaking the inertial thinking and the bottleneck of knowledge and integrating the unit scale to truly achieve the assimilation of disciplines is particularly important. In traditional research methods, we have accumulated many scientific theories and mechanisms of biological units and events such as molecular structure, signaling pathways, organelles, and cell types. However, it was still difficult to draw a dynamic network containing biological synergies of each level [10]. Due to the dynamic nature of biological units and the elusive scientific space between them, it is challenging to describe and predict the properties of the parent unit or the overall unit from the perspective of a single biological unit. For example, as one of the essential components of cells, proteins not only play the role of building cellular structures in solid phase, but also act in various chemical reactions in the form of solution phase. Interestingly, some proteins in the liquid phase do not mix, and little is known about how these liquid-phase proteins affect the structure and behavior of cells. The separation of two immiscible liquids, such as oil and water, known as "liquid-liquid phase separation," is a fundamental concept in physics, chemistry and engineering that is critical to the function of many proteins. Phase separation is ubiquitous in cell biology, such as in enzymatic reactions, where substrate molecules are enriched in a specific phase, but reaction products are excluded from it; one example is the repair process after DNA damage, where the DNA repair-related polymerase PARP1 produces phase-separated droplets [11].

In addition to phase separation phenomena, many biological descriptions also reflect the mesoscale features of biological systems (other systems share common similarities), including nonlinearity, self-assembly, dissipation, intermittent, disorder, and so forth. While there is strong interest in what happens during these processes and what their characteristics are, little is understood about the ways in which this space is explored, especially in nonmathematical disciplines such as traditional biology and medicine. For example, bridging our understanding of the kinetic characteristics of genomic chromatin accessibility, the condensation and solidification of chromatin, the dynamic structure and function of non-membrane biomolecular clusters and their regulatory mechanisms, the structure of organelles and the significance of changes in their subcellular localization, and so forth, will advance our comprehension of complex systems. Thus if we can explore life phenomena between the hierachical units from a mesoscale perspective by integrating knowledge from different levels, we will produce a rapidly developing and forward-looking research field [12].

3 | MESOSCIENCE IN BIOLOGY (INCLUDING CANCER BIOLOGY)

In recent years, we have accumulated an increasingly astonishing amount of information on the fundamental theories and mechanism of biological events at each unit level. However, until today, we cannot map the dynamic networks composing the collaborative relationships among the units at the cell or organism level. Although, mesoscopic space exists between unitary scales, the biological rules are not easily or not suitable to be deciphered by conventional experiments and the techniques. Here, we discuss examples of biological units and highlight possible scientific challenges from the mesoscience perspective.

3.1 | Genome

Chromatin, the genetic material of eukaryotes, is a polymer of ribonucleoproteins (nucleosomes) that carry chemical signatures according to specific biological environments [13]. The multi-scale nature of the genome, resulting from the physicochemical heterogeneity of chromatin, poses a great challenge to resolve chromatin states and corresponding genome functions [14–16]. Phase separation is a thermodynamic process in

which a mixture of molecules disintegrates into dense and dilute phases to reach a state with the lowest free energy [17, 18]. It has been proposed that chromatin aggregation is a physiologically relevant liquid-solid phase separation process driven by chromatin self-interactions [19–21]. Also, under certain solution conditions, chromatin can also undergo liquid-liquid phase separation (LLPS) [22]. These chromatin stages have significant implication. Furthermore, next-generation multi-scale chromatin models attempted to use the atomic properties of nucleosomes to explain gene regulation and even phase separation of chromatin organization. All this knowledge lead to a paradigm shift in genomics research, bridging the gap between the atomic behavior of biomolecules and the genome-wide properties at the cellular nuclear scale [20, 23–25].

In the mesoscale view, genome transcription involves interactions of hundreds to thousands of nucleotides [26]. During transcription, DNA is organized into mesoscale structures by forming supercoiled structures and changing the location of DNA-packaging proteins in the genome [27–30]. Enhancer-driven transcriptional regulation is one of the major mechanisms mediating cell-type- and signaling-pathway-dependent transcriptional diversity [31, 32]. Acutely activated transcriptional enhancers had been found to regulate chromatin assembly into hierarchical mesoscale structures with distinct physical properties [33–35]. Live imaging of transcriptional processes and transcriptional regulators revealed that transcription factors and gene-regulatory proteins form dynamic clusters up to 300 nm at their transcription sites in the nucleus [36, 37]. Biophysical and biochemical techniques have shown that enhancer complexes are a new class of membrane-less nuclear structures [36, 38, 39]. Exploring the biological interactions among various transcriptional processes at the mesoscale level is crucial to elucidate both cell-type-dependent and species-dependent, common and unique principles of gene transcription.

3.2 | Plasma membrane and cytoskeleton

The fundamental mechanism underlying the division of different cellular processes at the cell surface is the establishment of plasma membrane heterogeneity, in which certain proteins, lipids and carbohydrates form specific membrane domains to perform different functions, such as signal transduction, material transport, and cellular adhesion [40]. Signaling proteins on the plasma membrane do not diffuse freely on the membrane surface, but function in the form of highly dynamic signaling nanoclusters, which are characteristic organization of the plasma membrane [41, 42]. At the mesoscale, nanoclusters contain microdomains that support pathogen binding, cell adhesion, and cell recognition [43–45]. For example, desmosomes are protein complexes with specific mesoscale lipid raft properties [46, 47], whose assembly, function, and disassembly all depend on raft dynamics. This dynamic process including anchoring keratin filaments to the plasma membrane through protein-protein interactions which mediate vital cell adhesion that enables tissues to resist mechanical stress [48, 49].

Similarly, the cytoskeleton is an integrated network of filamentous proteins that organizes the cytoplasmic network to maintain cell shape, facilitate cell motility and build the compartment required to segregate genetic material [50, 51]. From the mesoscale view, the eukaryotic cytoskeleton is formed by a non-covalent array of polymers, called microtubules [52, 53]. Thus, cells regulate the structure, assembly dynamics, and mechanics of microtubules by using a "microtubule protein code" that selects microtubule protein isoforms and exerting posttranslational modifications. This protein code, guides various microtubule morphologies and dynamics in different cell types, cellular cycles, and developmental stages [54–56]. Thus, the complex and diverse spatio-temporal microtubule modification patterns are a function of the expression levels, subcellular distribution, substrate specificity, and kinetic parameters of posttranslational tubulin-modifying enzymes [57, 58]. Consequently, deciphering the tubulin code is an interdisciplinary challenge that requires the combined efforts of physicists, chemists and geneticists.

3.3 | Immune system such as T cell antigens

To protect the host and limit autoimmunity, mature T cells can differentiate between foreign antigen and self-antigens [59]. Traditional mammalian $CD4^+$ and $CD8^+$ αβ T cells engage in host defense by utilizing surface T cell receptors to detect corresponding ligands on pathogens or tumors [60, 61]. $CD4^+$ and $CD8^+$ αβ T cells, regulatory T cells (Tregs) and dendritic cells (DCs) constitute a minimal control system regulated by intercellular circuits [62–64]. Tregs, which are involved in the negative feedback on immune recognition, were found to recognize mesoscale T-cell antigens [65]. Small fluctuations in the control system will significantly affect antigen recognition at the mesoscale level, thereby altering T-cell response thresholds and autoimmune disease risk [66, 67]. Mesoscale studies of immune system regulation will open a new window for understanding the immune system and disease intervention.

3.4 | Mesoscientific characteristics of macro-biology

The above descriptions were all problems of mesoscientific biology in the traditional sense. As stated above, "mesoscale" is a relative concept, and conceptually expanding the definition leads to broader mesoscientific questions. As research has progressed, it has come to be understood that biological systems in traditionally defined in eukaryotes and prokaryotes interact in a way that intersects in space and time, rather than acting independently. The atypical mesoscale structure has led to some previously unnoticed mesoscientific problems. In the mitochondria of eukaryotic cells, mitochondrial DNA can form mitochondrial nucleoids, and various proteins are dispersed in the mitochondrial matrix in form of granules or anchored on the inner mitochondrial membrane surface, affecting processes such as oxidative phosphorylation and energy supply [68]. With the emergence and development of spatial transcriptome technology, it has been found that some mesoscale structures are formed between cells. Depleted $CD8^+$ T cells and tumor-associated macrophages had been found to be spatiotemporally interdependent and maintain each other's maturation through persistent antigen-specific synaptic contacts, constituting a microenvironment for immune escape [69]. Circulating tumor cells (CTCs) are tumor cells that shed from the primary tumor and infiltrate and circulate in the bloodstream. When CTCs are transported in the blood, most CTCs undergo programmed cell death due to loss of cell adhesion [70, 71]. However, a small fraction of CTCs forms CTC clusters that promote tissue invasion and tumor metastasis by interacting closely with platelets, neutrophils, macrophages, myeloid-derived suppressor cells or tumor-associated fibroblasts (CAFs), thereby evading the immune system [72–79]. Clusters of CTCs composed of distinct cellular fractions can be viewed as mesoscale structures between the immune system and tumors. CTC clusters can be isolated by microfluidic chips and nanotechnology to facilitate the study of CTCs as biomarkers for tumor diagnosis, prognosis, and therapeutic detection [80, 81]. In addition, some prokaryotic phenomena can be explained by applying mesoscientific hypotheses. Hu et al. (Hu (2022) Science 378(6615):85–9) applied the physics concept of "phase transition" to the study of gut microbiota. They found that only a small number of community-scale control variables are required to demonstrate a dynamic transition in microbial ecosystems from a stable equilibrium of all species coexistence to partial coexistence to persistent fluctuations in species abundance, enabling predictability of complex gut behavior in microbial ecosystems [82]. Based on the above findings, many biological questions can be further answered by mesoscientific models or concepts.

3.5 | Tumor microenvironment

The development of single-cell technology has brought us new knowledge about tumor composition [83]. Taking cancer as a whole, the tumor microenvironment has typical mesoscale features. Tumor cells interact with stromal cells, extracellular matrix, cytokines, and signaling molecules to dynamically coordinate the complex and diverse tumor microenvironment. These complex interactions make the tumor microenvironment the hallmark of cancer [84]. The stromal components of the tumor microenvironment are recruited from surrounding normal tissues. Stromal cells include mesenchymal cells, infiltrating immune cells, endothelial cells, and adipocytes. Tumors will reprogram the microenvironment to a state that preempts new metastases in distant organs by secreting exosomes or related factors [85]. All these tumor biological processes have a mesoscale scientific space. Attempts to use mesoscale mathematical models to build workflows for predicting tumor migration have led to advances in glioblastoma invasion and spread [86, 87]. Using atomic force microscopy to quantify the micromechanical characteristics of metastatic breast cancer and its surrounding bone microenvironment may shed new light on the mechanical characteristics of breast cancer bone metastases [88]. Tumors form a gradient hypoxic environment from the surface to the inside. In this context, mesoscale computational models can be used to simulate angiogenesis and oxygen transfer in the microcirculation [89–92]. Furthermore, given mesoscale computational models, morphological and kinetic reprogramming patterns of tumor cells and stromal cells by the extracellular matrix can also be explained [93, 94]. Mesoscale studies of tumor microenvironment may provide new clues and basis to developing novel tumor immunotherapy strategies.

4 | RESEARCH METHODS IN MESOSCIENCE BIOLOGY

According to Thea Newman, "mesoscale structure" can be adopted as a central conceptual framework for the study of various complex physical phenomena [95]. By incorporating biological research methods, we can also apply the concepts and models obtained from physical systems to biology, especially cancer. By combining experimental approaches from microscopical biology,

structural biology, and bioinformatics, we are able to build structural models of whole cells with molecular details. Emerging research techniques and methods are linking nanoscale molecular biology with microscale cell biology. This allows us to model and visualize the biological events at the mesoscale. Vibrant and dynamic digital cells or organisms can be created only by filling the mesoscale knowledge gaps in cell biology. Here, various methods for several mesobiological studies are presented.

4.1 | Microscopic imaging: Visual acquisition of raw images

Advances in microscopy techniques have provided opportunities for high-resolution characterization of internal cellular structures. To determine the atomic (or near-atomic) structure of biomolecules and biomolecular assemblies, cryo-electron microscopy (cryo-EM) has been developed to a level comparable to X-ray scattering techniques, becoming an important tool in structural and functional biology [96–98]. Cryo-EM is an indispensable new method in the field of molecular structure-based drug discovery that favors keeping the sample in its native state through rapid freezing techniques and avoiding protein crystallization steps. This process preserves valuable structural information for pharmacological targets [99]. In addition, optical microscopy techniques are rapidly advancing. Super-resolution microscopy overcomed the diffraction limitations of conventional optical microscopy, enabling cross-scale imaging from metal nanoparticles to single protein molecules to bilayer structures [100, 101]. Additionally, dynamic imaging capabilities are being added to new microscopy imaging techniques. Overall, these new methods of examining the internal structure of cells are the driving force behind many of the recent breakthrough discoveries in mesoscale science.

4.2 | Molecular composition and structural biology

Mesoscale models are a natural extension of the structural biology revolution [102]. While genomics provides the complete sequence information of proteins and nucleic acids that helps understand the molecular structure, proteomic techniques provide information on the properties and abundance of proteins in the different cell compartments [103]. In structural biology, structural models were built using data obtained through methods and procedures such as near-atomic and low-resolution imaging, cross-link confinement, and proteome identification [104]. Modeling platforms that simulate biological networks were combined with differential equations and graphical models to understand the structure and biological function of specific cellular regions such as nuclear pores [105–107]. For example, several research teams used transcription frequencies retrieved by chromosome conformation capture techniques to model bacterial chromosomes and eukaryotic chromatin [108–111]. Structural biology-oriented integrated modeling techniques had also been applied to explore organelle structures, such as synaptic vesicles and photochromic vesicles [112, 113]. Thus, the integration of physical with biological approaches has significantly advance our understanding of complex interaction in biological systems.

4.3 | Computational biology: Digital processing under statistical laws

Biological processes consist of a large number of complex, multidimensional, multiscale systematic events that obey specific biological laws with stable endpoints. Using physical and mathematical methods, biological processes can be described in a hierarchical organizational framework to enable virtual engineering of processes [114]. For physical systems that are not in thermodynamic equilibrium but can be represented by corresponding nonequilibrium variables, the range of the variables used to characterize systems in thermodynamic equilibrium, that is, the nonequilibrium thermodynamics (NET) methods, can be utilized [115]. NET had been used to describe how biological organisms develop disease and how cancer develops and occurs metabolically and genetically [116–118]. The mesoscale model “Energy Minimum Multiscale” (EMMS Model), abstracted from gas-solid fluidization, proposed a possible general principle of competitive compromise (EMMS principle), also had the mechanistic nature of bio-applicability [1]. In an ecosystem, the mechanisms of functional biological units are coordinated and compromised in competition to form a biological system composed of multi-scale dynamic structures. Dynamic stability, as the result of a competitive compromise, unifies and coordinates all levels of units and mesoscales regional laws. For cancer research, each stage of tumor progression is a process in which new biological properties emerging in tumor cells cooperate and compromise in competition to reach a new stable stage (Figure 1). Due to the mesoscale, tumor formation is just an evolutionary process that reflects the law of compromise in competition.

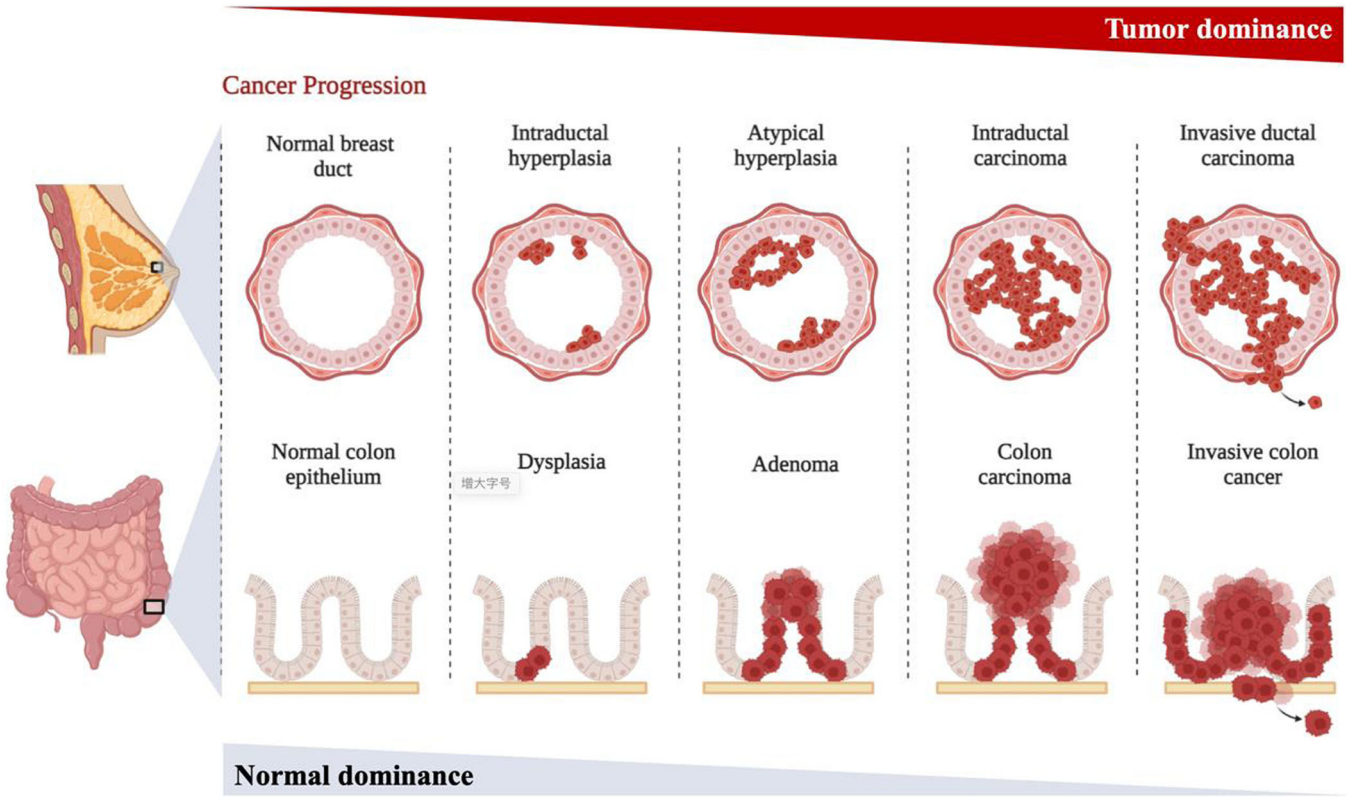

FIGURE 1 Competition between normal cells and tumor cells during tumor progression

5 | FUTURE APPLICATIONS OF MESOSCIENCE IN BIOLOGY AND ONCOLOGY

Introducing mesoscale concepts and models to biological research may revolutionize our traditional understanding of cellular structure and function, and thus their applications. As discussed earlier, mesoscale models have been applied to the study of the genomes, plasma membrane cytoskeletons, cell surface receptors, and so forth, filling the knowledge gaps of traditional methods in cell biology and molecular biology. In the future, the mesoscale models in the cellular environment will provide logical new thinking for scientific hypotheses, preliminary models for simulating and interpreting the experiments, and new opportunities for drug development [102].

In addition to describing traditional biological activities, mesoscience extends further into disease areas such as oncology. The tumor is not only an organism with a definite development endpoint that strictly follows the principle of life activities, but also an abnormal organism that metastasizes at the development endpoint and can further metastasize as the disease progresses. It maintains the same hierarchical unit as a normal organism in its structural and functional patterns, but its cellular activity in mesoscale space between adjacent hierarchical units is altered, resulting in a comprehensive disorder of the structure and behavior between cancer cells and their normal counterparts in mesoscale space. Both the mesoscale space and entropy at each level are expanded in cancer compared to the corresponding putative non-cancer state. In this view, cancer can be seen as a disease with disordered properties in mesoscale space that is overexploited. This may be the reason why after decades of efforts, we still searching for the true nature of the differences between tumors and normal tissues at a single scale level. Tumor is a disease with high spatiotemporal heterogeneity and disordered biological phenotypes, which may reflect abnormalities at mesoscale levels, such as epigenetic modifications, transcriptional regulation, alternative splicing events, etc. Therefore, there is an urgent need to introduce a new paradigm that leverage our understanding of the complex relationships in biological systems. By bringing mesoscience concepts to tumor biology research, for example, using evolutionary models and bynamic systematic theories we could verify the principle of compromise in competition (competitive coordination) and the spiral of compromise in competition (i.e., the evolution of cancer). Suppose the biological processes can be virtualized and engineered, biological research will usher in a revolutionary era of controllable, predictable, and even manufacturable biological processes. Precise intervention or even reversal of cancer is then possible.

6 | FUTURE DIRECTIONS AND CHALLENGES OF MESOSCIENCE IN BIOLOGICAL RESEARCH

Mesoscale space is not a scale space created by the imagination of theoretical researchers, but a scientific existence that has been verified in practice or is being verified by scientists and engineers with the help of rapid technological development and understanding of the real world, and is more and more widely recognized by broad disciplinary research fields. Mesoscale research is a more adventurous study of the common nature of the various disciplines, reflecting the complexity of multiphase reactions with materiality and abstraction [1]. As a foundational branch of natural science, biology is not only the basic elements of other disciplines, but also indispensable for social development and improving the quality of human life. Mesoscale biological research is a new field of modern biological exploration, which is of great significance but also full of challenges.

6.1 | Challenges to traditional scientific theories

Traditionally, biological research explored individual units such as biomacromolecules, cells, tissues, individuals, species, and biospheres, but no biological research can be studied alone at a scale. For example, genetics research focuses on both microscopic molecular genetics and macro-ecological genetics, while immunological research addresses interactions between ligands and receptors and immune responses at the organ or individual level, and oncology research covers everything from molecular mechanisms to cancer incidence in the population. With the introduction of mesoscience into biological research, experts realized that the subdivision in biological research is dynamic and continuous, and research areas between units were mostly neglected [1]. For what is currently known or recognized theories, the introduction of mesoscience has produced a "double-edged sword" effect, which can not only complete the traditional understanding with a novel vision, but also revise or subvert the traditional biological principles. As mentioned above, working from a mesoscience perspective, the researchers found that the condensed chromatin in the interphase nucleus exhibits solid-like properties, providing mechanical strength to the interphase nucleus and facilitating the spatial organization of nucleus by concentrating the binding sites of chromatin-binding proteins [20]. This was an important completion for cell cycle and transcription studies. Cellular compartmentalization is one of the essential features, and different organelles or subcellular organelles are strictly restricted to their functional locations. Mesoscience researchers have investigated how cellular compartmentalization uses measures of phase separation to modulate cellular function, thereby having a major impact on the known functions of organelles or subcellular organelles [119]. As a result, combining mesoscience with biology often leads to some surprising new conclusions that will be vigorously challenged by widely accepted traditional theories and by peer review from scientific colleagues. Of course, these challenges also put forward higher requirements for subsequent mesoscale biological research.

6.2 | Research platform construction

Interdisciplinary research platforms are also one of the major barriers to mesoscale biological research. As mentioned before, mesoscale was first validated and applied in the study of stochastic processes in physics and chemistry, and subsequent mesoscale research was mainly conducted in the fields of physical and chemical engineering, although it has been reported, but it is still emerging in the biological sciences [120, 121]. Some scientists intuitively believed that mesoscale studies in biology are that somewhere between the molecular and cellular scales, on the order of 10 nm to 0.1 μm in length. As mesoscience is gradually integrated into other disciplines, the definition of this physical scale is being redefined. Mesoscale atomic details are often too small to be dissected by microscopy, and too large and inhomogeneous to be examined by X-ray crystallography and nuclear magnetic resonance spectroscopy [122]. For instance, the cell tomography methods provide the most detailed view of experiments at this level and have had many successes in the localizing macromolecules such as ribosomes to whole cells [123]. However, while this mesoscale atomic resolution view is useful for hypothesis generation, scientific communication, and simulation, its visualization resolution is still insufficient for smaller and smaller research scales [122]. In recent years, cryo-electron tomography and super-resolution microscopy, combined with modeling and simulation, have played a significant role in bridging different scales [124]. There are relatively successful research models, including phase separation, which is ubiquitous in cell biology, and LLPS has become a classic paradigm for how membrane-less organelles participate in different cellular activities [125]. Furthermore, by combining Bessel Focusing Module into two-photon fluorescence mesoscopic microscopy, the researchers achieved fast volumetric imaging of mesoscale neural activity in synapsis resolution [126]. In conclusion, mesoscale studies in biology must be conducted on integrative research platforms. As such, we must find ways to integrate multiple types of data in different scales into a

spatial model for comprehensive analysis, better communication, and more accurate simulation.

6.3 | Exploration of research mode

Shared and integrated science are shifting global scientific research, and global academic communications are adapting to open access models. The development of multiscale research methods is a prerequisite for mesoscale research. As such, many questions arise; for instance, how can we create a comprehensive model that integrates data management, model generation, and mesoscale characterization tools into biological research applications? How can we facilitate effective dialog among scientists, engineers, and computational mathematicians to achieve the goals of mesoscale research in biology? Furthermore, is mesoscale research in biology a bottom-up (micro to mesoscale) or a top-down approach (macro to mesoscale) approach [127]? Answers to these questions may require decades of significant effort and generations of exploration.

6.4 | Disease-related mesoscience research

Disease-oriented biological research is critical in integrating of modern biology and medicine. Although many mesoscience research methods objectively described a biological problem, such as subcellular organelle localization and function [125], chromosome replication, and transcription [20], and so forth, they have yet to achieved scientific translation, nor have they involved the relationship to human disease. Tumor is one of the most important problems endangering human health. Under the severe pressure of tumor prevention and control, mesoscience-based oncology research is still rare. Data from the cancer genome, transcriptome, proteome, and epigenome have been extensively analyzed at different scales to molecularly characterization of various tumors, but little is known about the molecular landscape at the mesoscale. For instance, researchers found that mesoscale features of the genome include unique DNA secondary structures (e.g., DNA stem-loop structures) that are uncommon in the genome and recurred in many cancer patients. One example is the APOBEC3A protein, which has a strong mutational preference for DNA stem-loop structure and contributes to cancer recurrence. This finding not only challenges the assumption that recurrent mutations are drivers of tumor, but also demonstrates the importance of incorporating mesoscale signatures into cancer genome analyses [128]. Another example of mesoscience studies is the function of Treg in autoimmune disease, where it divides its nearby microenvironment into two phases in a negative feedback manner to perturb the signal integration of activated T cells. However, part of the framework remains hypothetical and more support from interdisciplinary knowledge is needed to refine this immune response predictive models [129]. These are some examples of mesoscience research in disease biology.

The complexity and heterogeneity of disease-related molecules make it extremely difficult to develop comprehensive analytical models and design efficient experiments based on Trial-and-Error testing. All physiological activities of organisms are inseparable from the complex humoral environment, which makes the analysis of molecular bio-fluids exceptionally difficult. To address this problem, computational biology offers unique advantages for modeling specific biomedical systems, such as the mesoscale algorithms dissipative particle dynamics (DPD) and lattice Boltzmann methods, which examine biologically related dynamics. They can track the movement of individual molecules and allow precise reconstruction of molecular structure and properties. Although they have been extensively and successfully validated with experimental data, including direct comparisons with specific biomedical and bioengineered systems, several important questions remain open and need to be answered to facilitate further practical applications of these methods [127].

One of the important goals of biological research is to explore and reveal all steps from genotype to macrophenotype, and to achieve research translation as much as possible. At present, mesoscale biological research seems to play an irreplaceable role in bridging the "black hole" of knowledge. In this context, comprehensive mesoscale biological research has just started, and higher requirements have also been placed on researchers. Only by building a more complete research platform and efficient research model, to maximize the cross-integration and functional sharing of scientific research results, can we expect forward-looking progress and lay a solid foundation for promoting scientific research innovation and transformation.

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Not applicable.

INFORMED CONSENT

Not applicable.

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