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PLURIPOTENT STEM CELLS AND CELLULAR INNOVATIONS: ADVANCING REGENERATIVE MEDICINE

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Abstract:

Human pluripotent stem cells (hPSCs) hold immense promise for regenerative medicine, with therapies for over 14 diseases and injuries advancing toward clinical trials. Applications include differentiating hematopoietic stem cells for blood disorders, generating liver and kidney organoids for organ failure, and leveraging exosomes to combat skin aging and inflammation. Complementary advances in structural biology, such as cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryo-ET), provide high-resolution insights into macromolecular interactions in situ, while microphysiological systems (MPSs) mimic organ physiology using hPSC-derived cells. Cell mechanics, including membrane dynamics and fibroblast heterogeneity (e.g., 15-30% of heart cells), further inform differentiation and tissue engineering. This review synthesizes hPSC-based therapies, exosome applications, structural biology, MPSs, cell mechanics, and tissue engineering, emphasizing their interconnected roles in addressing challenges like tumorigenicity, immunogenicity, and system complexity in regenerative medicine.

Keywords: Pluripotent stem cells, exosomes, cryo-EM, microphysiological systems, cell mechanics, tissue engineering, regenerative medicine.

INTRODUCTION. The transformative potential of human pluripotent stem cells (hPSCs) is driving progress in regenerative medicine, with cell therapies for more than 14 diseases, including leukemia, liver failure, and kidney failure, reaching or nearing clinical trials. hPSCs can differentiate into diverse cell types, such as hematopoietic stem cells and organoids, offering solutions for blood disorders and organ replacement [1]. Concurrently, mesenchymal stem cell (MSC)-derived exosomes, stable at 20°C for 6 months, provide low-immunogenicity alternatives, reducing reactive oxygen species (ROS) and matrix metalloproteinases (MMPs) in skin aging [2]. Structural biology advancements, particularly cryo-EM and cryo-ET, enable visualization of macromolecules in their native cellular context, bridging molecular and cellular insights [3]. Microphysiological systems (MPSs), or organ-on-a-chip models, replicate organ-level physiology using hPSC-derived cells, while cell mechanics, such as membrane-to-cortex interactions and cardiac fibroblast heterogeneity (15-30% of heart cells), regulate differentiation and tissue function [4, 5]. This review explores these interconnected fields, addressing challenges like tumorigenicity, immune rejection, and scalability, and highlighting their potential to revolutionize regenerative medicine and disease modeling.

Human Pluripotent Stem Cells in Regenerative Medicine. hPSCs, including embryonic and induced pluripotent stem cells (iPSCs), are advancing therapies for over 14 diseases and injuries, with clinical trials underway or imminent. For blood disorders like leukemia, hPSCs are differentiated into hematopoietic stem cells, offering a renewable cell source for transplantation. Similarly, liver and kidney organoids derived from hPSCs provide potential treatments for organ failure, addressing the shortage of donor organs. These applications face significant challenges, including the risk of tumorigenicity due to uncontrolled cell

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proliferation and heterogeneity in differentiated cell populations. To address these, sensitive in vitro systems, such as organ-on-a-chip models, are being developed to predict tumorigenic risks, while optimized differentiation protocols reduce variability [1].
The development of organoids and specialized cell types from hPSCs is a cornerstone of regenerative medicine. For example, hPSC-derived oligodendrocyte progenitor cells (OPCs) are being used for drug screening to treat myelin-related disorders like multiple sclerosis. High-throughput screens have identified small molecules that enhance OPC differentiation into oligodendrocytes by inhibiting enzymes in the cholesterol biosynthesis pathway, suggesting a universal mechanism for promoting remyelination. These findings underscore the potential of hPSCs to generate millions of cells for transplantation and drug discovery, but challenges remain in ensuring scalability and safety for clinical use [1, 6].

Exosomes: A Low-Immunogenicity Therapeutic Platform. MSC-derived exosomes are emerging as a safer alternative to live-cell therapies, with applications in skin repair and inflammatory diseases. Exosomes enhance fibroblast proliferation and migration, counteracting UVB-induced senescence by activating signaling pathways like MAPK, AKT, STAT3, and BRK1/2. They reduce ROS and MMP production, restoring extracellular matrix (ECM) components critical for skin integrity. Unlike hPSC-derived cells, exosomes exhibit low major histocompatibility complex expression, minimizing immune rejection risks. They can be cryopreserved at 20°C for 6 months without losing bioactivity and show no significant toxicity in preclinical studies, making them ethically and practically favorable [2].

Exosomes also play a role in intercellular communication, modulating inflammation and tissue repair. Their parental cell properties make them ideal for studying disease prognosis and developing diagnostic tools [7]. For instance, exosomes regulate epidermal cell proliferation, offering a non-invasive approach to skin rejuvenation [2]. However, challenges remain in standardizing exosome isolation, dosing, and storage, as well as understanding their full therapeutic potential in inflammatory diseases [7]. Ongoing research aims to elucidate these mechanisms, positioning exosomes as a versatile platform for regenerative medicine.

Structural Biology: Bridging Molecular and Cellular Insights. Advances in structural biology, particularly cryo-EM and cryo-ET, are revolutionizing our understanding of cellular processes. Cryo-EM enables high-resolution imaging of large macromolecular complexes, such as those involved in myoblast fusion, without the need for extensive purification required by traditional crystallography. Cryo-ET further allows visualization of these complexes in their native cellular environment, bridging structural and cell biology [3]. For example, studies of myoblast fusion have identified Myomaker and Myomenger as key proteins, with dynamin 2 and phosphatidylinositol 4,5-bisphosphate facilitating fusion pore expansion [8]. These insights inform therapeutic strategies for muscle regeneration and related disorders.

Structural biology also intersects with stem cell research by elucidating mechanisms of differentiation. For instance, reduced membrane-to-cortex attachment in embryonic stem cells, modulated by Ezrin activity, is essential for exiting naive pluripotency [9]. These findings highlight how structural changes at the molecular level influence cellular fate, providing a foundation for designing targeted therapies. However, challenges persist in connecting nanoscale (nanometers/microseconds) to microscale (microns/seconds) dynamics, necessitating improved imaging and analysis techniques [3].

Microphysiological Systems and Vascularization. Microphysiological systems (MPSs), or tissue/organ chips, leverage microfluidics and 3D cell cultures to mimic organ-level physiology, with hPSC-derived cells enhancing their relevance for disease modeling. MPSs are categorized into three types: self-assembled, interface-focused, and 3D biofabricated, each addressing vascularization challenges. Vasculature is critical for physiological accuracy, yet often overlooked in MPS design. hPSC-derived vascular cells improve the modeling of diseases like cardiovascular disorders, enabling precise drug testing and tissue engineering.

The integration of hPSCs into MPSs has accelerated studies of organ systems, from heart to liver, but system complexity remains a hurdle. For example, incorporating functional vasculature requires balancing cell types, ECM components, and microfluidic dynamics. Advances in hPSC differentiation protocols are addressing these challenges, enabling the creation of vascularized organoids that closely mimic native tissues. These systems complement structural biology by providing a platform to test molecular insights in a physiological context, advancing both research and therapeutic development[4].

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Cell Mechanics and Fibroblast Heterogeneity. Cell mechanics play a pivotal role in differentiation and tissue function. Cardiac fibroblasts, comprising 15-30% of heart cells, derive from epicardial cells through epithelial-to-mesenchymal transition (EMT), driven by retinoic acid and TGF-β. These fibroblasts express unique genes (e.g., GATA4, GATA6, HAND2), distinguishing them from other mesenchymal cells and supporting heart development and homeostasis [5]. Similarly, fibroblast heterogeneity, including universal and specialized subtypes, enables functional diversity in tissues, with universal fibroblasts serving as a progenitor pool [10].

In plants, cell wall mechanics regulate growth and stress responses, with primary cell walls (rich in cellulose, pectins, and hemicelluloses) providing extensibility via non-covalent interactions. Secondary cell walls, deposited in specialized cells, enhance structural integrity [11]. These principles inform animal cell mechanics, where techniques like scanning force microscopy and optical tweezers reveal how lipid membranes and cytoskeletal dynamics influence cell fate [12]. For example, membrane tension gates embryonic stem cell differentiation, with reduced cortex attachment driving pluripotency exit [9]. These insights connect cell mechanics to hPSC applications, informing tissue engineering strategies.

Tissue Engineering and Nanoencapsulation. Tissue engineering using hPSCs addresses limitations of organ transplantation, such as immunogenicity and donor shortages. Allogeneic and xenogeneic transplants face immune rejection and pathogen risks, while artificial materials lack biocompatibility. hPSC-derived tissues, grown through histological engineering, mimic natural structures and functions, offering a promising alternative [13]. For example, hPSC-derived cardiac tissues could replace damaged heart muscle, reducing reliance on costly, immunogenic transplants [5, 13].

Single-cell nanoencapsulation, inspired by natural cryptobiosis, protects cells with durable, permeable shells, enhancing survival under harsh conditions. First-generation shells were passive, but active shells now regulate cellular metabolism, endowing cells with new properties . These shells, applied to microbial and mammalian cells, support tissue engineering by improving cell viability and function. However, challenges in scalability and shell degradation persist, requiring further research to optimize their clinical potential [14]. These advances connect to hPSC therapies by enabling robust cell delivery systems for regenerative applications.

Exosomes in Inflammatory Diseases. Beyond skin repair, MSC-derived exosomes show promise in treating inflammatory diseases due to their paracrine effects. Exosomes act as nanocarriers, modulating target cell activity and inflammation through intercellular communication. Their parental cell properties make them ideal for diagnostic and prognostic applications, but their complex roles in inflammation require further study. Key challenges include optimizing isolation, transport, dosing, and storage of exosomes, as well as identifying optimal donor and tissue sources. Addressing these will unlock exosomes' full potential as a novel therapy for conditions like autoimmune diseases, complementing hPSC-based approaches [7].

Bone Remodeling and Stem Cell Applications. Bone remodeling, a dynamic process involving osteoclasts and osteoblasts, maintains skeletal integrity and adapts to environmental changes. hPSCs can generate bone-forming cells, offering in vitro models for studying bone diseases like osteoporosis . These models, combined with MPSs, enable high-fidelity disease modeling and drug testing [4, 15]. For instance, hPSC-derived osteoblasts can be used to study bone matrix deposition, while osteoclasts model resorption processes [15]. These applications connect to broader hPSC therapies, addressing skeletal disorders and supporting tissue engineering efforts.

Oligodendrocyte Progenitor Cells in Neurological Disorders. OPCs, derived from hPSCs, are critical for treating neurodegenerative and psychiatric disorders. Expanded in culture, OPCs generate millions of cells for transplantation and drug screening. Small molecules identified in these screens target cholesterol biosynthesis enzymes, promoting oligodendrocyte formation and remyelination. However, it remains unclear whether these therapies are universally effective or context-specific, necessitating further disease-specific studies. OPCs' dynamic roles in development and disease connect to structural biology insights, as their differentiation is influenced by cellular mechanics and molecular interactions [3, 6].

CONCLUSION. The convergence of hPSCs, exosomes, structural biology, MPSs, cell mechanics, and tissue engineering is transforming regenerative medicine. Therapies for over 14 diseases leverage hPSC-derived cells and organoids, while MSC exosomes, stable at 20°C for 6 months, offer low-immunogenicity solutions

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for skin repair and inflammation. Cryo-EM/ET provides molecular insights, MPSs mimic organ physiology, and cell mechanics, including cardiac fibroblast heterogeneity (15-30% of heart cells), inform differentiation and tissue function. Challenges like tumorigenicity, immune rejection, and scalability persist, but innovations like organ-on-a-chip models, active nanoshells, and optimized exosome protocols are addressing these hurdles. By integrating these fields, regenerative medicine is poised to deliver precision therapies for complex diseases, from neurological disorders to organ failure.

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