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Commentary

Harnessing mechanobiology to enhance cell therapy

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ABSTRACT

Recent developments in cell therapy have revolutionized medical treatment. While various methods of stimulation have been explored, the role of mechanical force has often been overlooked. Although mechanical loading is not easily visible, it can actively reshape organisms, and abnormal mechanical loading can lead to injury and disease. By leveraging the mechanobiology of cells, we can equip them with synthetic mechanosensors that can redirect genetic circuits to express protective factors, such as antibodies and cytokines, according to the mechanical force signal. The advancement of artificial intelligence (AI) presents a fascinating opportunity to redesign more complex mechanoreceptors, allowing cells to respond to intricate stimuli. Additionally, genetic engineering tools like CRISPR-Cas9, base editing, and prime editing enable the creation of multiple gene circuits for cells to react to complex mechanical environments. Advanced mechanical loading techniques, such as focused ultrasound, deliver signals in a confined spatial and temporal manner. Therefore, harnessing mechanobiology in cells can develop more flexible, personalized, and precise cell therapies.

Recent advancements in cell therapies, such as CAR-T therapy and stem cell treatments, have significantly reshaped clinical practices and inspired hope for patients suffering from debilitating or even life-threatening diseases, including cancer and rare diseases.[1] As of November 2024, over 20,000 cell therapy cases have been registered in clinical trials (https://clinicaltrials.gov/). The functions of cells are regulated by complex signaling networks that involve ions, proteins, biochemicals, and mechanical forces. However, mechanical forces are often overlooked in traditional analyses due to technical limitations. Although these forces can be difficult to observe in living systems, their impact is clear; they can deform cells or tissues. These forces are categorized as compressive, tensile, shear, bending, or torsional, based on the type of deformation they cause.[2] Daily exercise regularly applies mechanical stress to muscles, reshaping them, while excessive force can lead to injury and disease. In 1892, a German surgeon, Julius Wolff, noted the adaptation of trabecular structures in bone induced by daily physical loading, documenting this phenomenon.[3]

A variety of ion channels and receptors, transcription factors, cell adhesion molecules, cytoskeletal elements, and organelles, have been identified as mechanical sensors, which can "feel" the mechanical force.[4] When these sensors are activated, they can trigger downstream biological processes, such as protein phosphorylation, gene translation, and cell differentiation. For instance, the Notch receptor senses forces from neighboring cells that express ligand proteins, such as Jagged 1, 2, and Delta-like 1, 3, and 4.[5] This interaction extends the extracellular domain of the Notch protein, exposing a cleavage site for metalloproteases. Once cleaved, the intracellular domain is released to initiate downstream transcription. Mutations in the Notch1 protein are associated with bicuspid aortic valve disease (BAV).[6] Additionally, mechanical tension activates the expression of Engrailed-1 in fibroblasts, leading to scar formation. Inhibiting the mechanical sensor protein YAP promotes wound healing without scarring.[7] Extracellular matrix stiffness modulates the colon cancer invasion by regulating its mechanophenotypes and focal adhesions via YAP1 relocalization.[8] Chondrocytes dynamically

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express a range of receptors and channels, including TRP, VDCC, SOCE, SMOC, VDSC, and NMDAR, in response to various mechanical loads, such as compressive, tensile, shear strains, as well as hydrostatic and osmotic pressures.[9]

In addition to understanding the mechanisms behind force-induced diseases, mechanotransduction can also be utilized to enhance cell function. Cells can be genetically modified to sense the biophysical cues in the mechanoenvironment and translate these signals into cellular mRNA transcription and protein expression. The engineered Notch (synNotch) on T cell not only responds to the interaction with tumor cells but also averts tonic signaling and exhaustion, helping to maintain T cells in a naïve/stem cell memory state, which is superior to the normal chimeric antigen receptor (CAR) design.[10] With genetic engineering, the cartilage cell can express the TRPV4 ion channel, which activates synthetic gene circuits that produce the IL-1Ra antibody to remold the inflammation niche upon physiologic mechanical loading.[11] The TRPM8 ion channel can be stimulated by menthol. When stimulated, it initiates a synthetic gene circuit in HEK-293 cell that expresses insulin for the treatment of diabetes or activin type IIB to reverse muscle wasting.[12] Additionally, the Piezo1 ion channel can convert ultrasound waves into CAR expression in primary T cells, allowing for targeted destruction of tumor cells.[13] Furthermore, extracellular matrix stiffness can transcriptionally activate mechanosensitive promoter-driven mesenchymal stem cells (MSCs). In this process, YAP/TAZ transcription factors enter the nucleus and produce a convertase that catalyzes an anti-tumor pro-drug, thereby eliminating tumor cells.[14]

Mechanical loading is crucial for the successful integration of mechanobiology in cell therapy. The medical doctors need a general method that can remotely and non-invasively regulate genetic activities in the mechano-responsive cells within a confined local tissue space. Traditional physical exercise impacts the entire body, not differentiating between healthy and diseased tissues. One strategy to address this challenge and deliver targeted therapies is to modify the intrinsic mechanical microenvironment, which includes factors such as extracellular matrix synthesis and degradation, cell contractions, mechanosensors, and the downstream mechanotransduction pathways.[2] Alternatively, mechanobiomaterial can also mimic the biological mechanic niche to stimulate a mechanosensor.[15] Focused ultrasound (FUS) serves as a safe and non-invasive source of external mechanical loading, capable of reaching tissues deep within the body, up to tens of centimeters. The rapidly oscillating pressure of FUS waves creates cycles of mechanical loading and unloading. This technique can e. g. activate CAR expression and direct engineered T cells to target tumor cells at specific times and locations, providing greater safety compared to traditional CAR-T cells.[16]

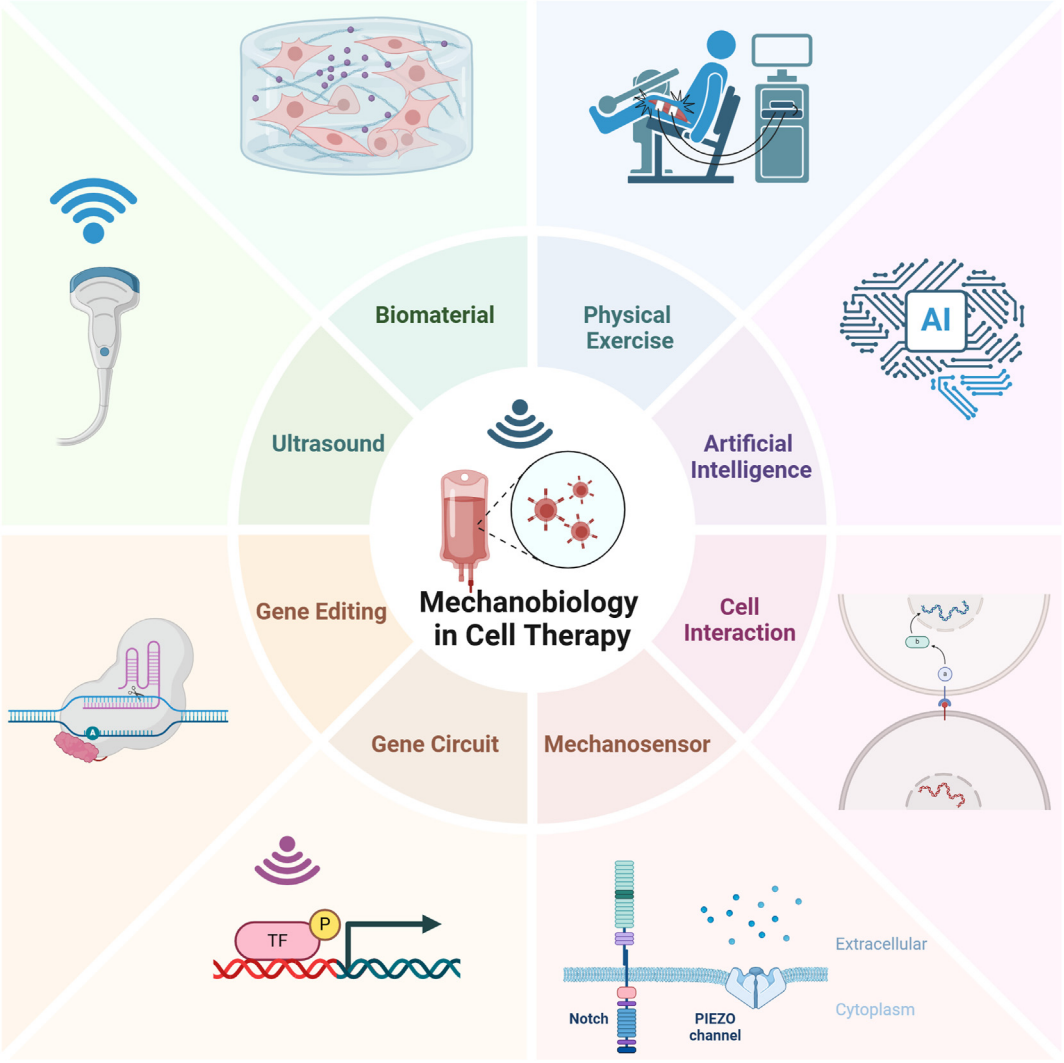

Fig. 1. Techniques for leveraging mechanobiology to improve cell therapy. Ultrasound, mechanobiomaterial, and physical exercise load mechanical force to the organism. Gene editing and gene circuit techniques redirect the cellular response. Mechanosensors respond to and transduce the force signals. Cell interaction transfers the force signals between cells. Artificial intelligence assists in the design of mechanically responsive cells. The figure is created in BioRender.

In conclusion, understanding the mechanisms and functions of mechanical loading in organisms can facilitate the design of novel cell therapies (Fig. 1). Additionally, with the help of artificial intelligence (AI), more specific and sensitive mechanical sensor proteins can be developed to convert mechanical signals into biochemical signals.[17] Furthermore, advanced genetic engineering techniques such as CRISPR gene editing, base editing, and prime editing enable us to redirect gene circuits in cells to respond to mechanical loading. Innovative methods of applying mechanical loading, including focused ultrasound, acupuncture, electric fields, and magnetic fields, can act as switches to provide controllable, safe, and non-invasive stimulation to engineered cells. Therefore, integrating mechanobiology has the potential to advance cell therapy, benefiting patients suffering from musculoskeletal diseases, cancer and genetic disorders.

CRediT authorship contribution statement

Peixiang Ma: Conceptualization, Funding acquisition, Writing – original draft. **An Qin:** Writing – review & editing. **Tobias Winkler:** Conceptualization, Writing – original draft. **Jie Zhao:** Conceptualization, Funding acquisition, Writing – original draft.

Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the manuscript, authorship, and/or publication of this article.

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