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Review Article

Research Progress on Key Mechanisms and Translational Applications of Biomechanical Microenvironment Regulation in Fracture Repair

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Abstract Fracture healing is a highly coordinated spatiotemporal biomechanical process, in which the micro-mechanical environment precisely regulates bone metabolic balance and tissue regeneration by integrating mechanical perception and biochemical signal transduction.In recent years, with the rapid development of multi-scale biomechanical testing techniques, single-cell omics and biomimetic materials science, the “force-cell-matrix” coupling mechanism has been continuously revealed, providing new intervention targets and engineering strategies for the treatment of refractory fractures and bone defects. Based on a systematic review of domestic and international literature over the past 10 years, this article provides an overview of key cell populations such as osteoblasts, osteoclasts, vascular endothelial cells, and immune cells, as well as signaling pathways such as YAP/TAZ, Piezo1/2, Integrin-FAK-ERK, and RhoA/ROCK, focusing on the impact of the biomechanical microenvironment on fracture repair.

The new discoveries such as strain-hypoxia coupling promoting endochondral osteogenesis, shear force-driven angiogenesis and bone-blood coupling remodeling, and mechanical loading regulating immunophenotypic transformation were mainly discussed; The application progress and limitations of engineering strategies such as intelligent adjustable stiffness scaffolds, programmable microfluidic bioreactors, magnetic/acoustic/electrical mechanical stimulation devices, and 3D-bioprinting mechanical gradient construction in animal models and early clinical trials were further summarized. Therefore, in the future, efforts should be made to enhance the clinical transformation and verification of real-time mechanical-biological dual-signal monitoring based on multimodal in-situ imaging, individualized mechanical intervention optimization integrating cross-scale computational models and artificial intelligence algorithms, and the closed-loop system of “degradable materials - wearable loading devices - digital twins”.Clarifying the systematic mechanism of mechanical regulation of the fracture microenvironment and developing precise intervention techniques will provide new ideas and theoretical support for improving the healing quality of complex fractures, shortening the rehabilitation period and reducing the reoperation rate.

Keywords: Biomechanical microenvironment; Fracture repair; Mechanism; Translational application

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Fracture healing, as the self-repair process of the body for bone tissue damage, involves continuous stages such as inflammatory response, endochondral osteogenesis and bone remodeling, and runs through the multi-dimensional coordinated regulation of cells - matrix - blood vessels - nerves [1].

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Traditional studies have mostly focused on the roles of biochemical factors such as BMP, VEGF and inflammatory cytokines in bone formation. However, both clinical observations and animal experiments suggest that appropriate mechanical stimulation is one of the primary external factors determining the quality and speed of fracture healing [2]. Ilizarov's tensile stress theory at the end of the 20th century has demonstrated that macroscopic loading can induce bone regeneration. However, its large-scale application is still limited by the risk of complications and individual differences. In the past decade or so, with the breakthroughs in micro-nano mechanical measurement, single-cell sequencing and high-resolution in vivo imaging technologies, researchers have narrowed their focus from “holistic mechanics” to “biomechanical microenvironment” (BME). That is, the physical signals such as stress-strain distribution, compression-tension cycle, fluid shear force and matrix stiffness gradient within the local area of the fracture site, and reveal that they precisely drive the dynamic balance of the osteogenic - osteoclast - immune - vascular network through force-sensitive ion channels, mechanical transcription factors and Integrin-FAK signal axes [3]. At the clinical level, delayed union fractures and large bone defects remain intractable problems for orthopedic surgeons, with an incidence rate as high as 5% to 10%. They not only significantly prolong hospital stays and rehabilitation times but also cause huge medical burdens and functional disabilities [4]. For such cases, merely emphasizing the intervention of chemical or biological agents often has limited effects. How to activate the endogenous regenerative potential by precisely regulating the micro-mechanical environment without increasing the fixed strength or undergoing secondary surgery has become a research hotspot in bone repair and regenerative medicine [5]. Meanwhile, bionic materials science, 3D bioprinting, wearable mechanical intervention devices and digital twin technology are booming, providing an engineering foundation for the construction of adjustable stiffness scaffolds, mechanical gradient hydrogels and spatio-temporal controllable external stimulation systems, making “mechanical-biological dual targeting” a comprehensive strategy that can reach clinical application.

This article first Outlines the spatiotemporal process of mechanical-biological signal integration during fracture healing. Subsequently, the roles of signaling pathways such as YAP/TAZ, Piezo1/2, Integrin-FAK-ERK and RhoA/ROCK in bone, blood vessels and immune cells were expounded from three levels: “cellular sensation - signal transduction - effect execution”. Further focus on the design principles, animal experiments and preliminary clinical data of engineering strategies such as intelligent scaffolds, microfluidic bioreactors, magnetic/acoustic/electro-mechanical stimulation platforms and 3D-bioprinting gradient construction; Finally, the prospects and challenges of individualized mechanical intervention, multi-scale modeling empowered by artificial intelligence, and the “material-device-digital twin” closed-loop system in fracture treatment are prospected. By integrating the latest evidence from biomechanics, cell biology, materials science and clinical medicine, the aim is to provide new ideas and feasible transformation paths for the precise treatment of refractory fractures and large bone defects.

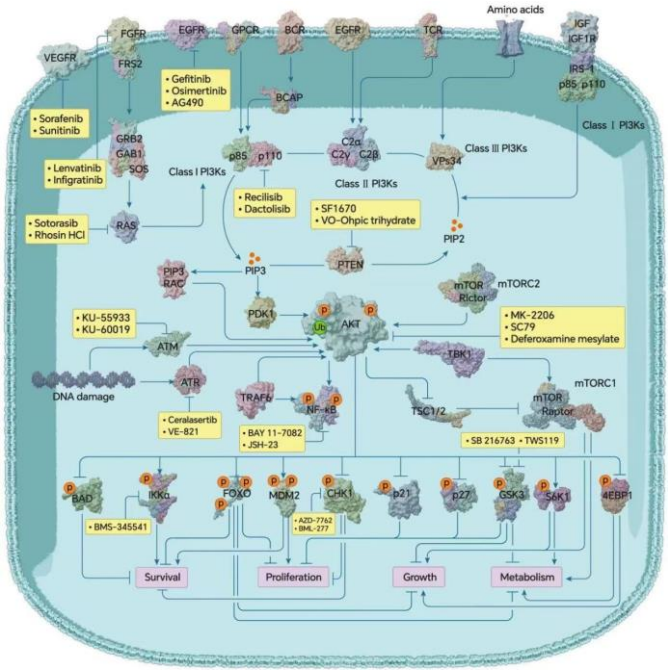

Figure 1: Schematic diagram of the PI3K/AKT axis.

1. Research on the Multi-scale Regulatory Mechanism of Biomechanical MicroEnvironment on Fracture Healing

The macroscopic load transfer at the fracture healing level needs to be transformed into mechanical signals recognizable by microscopic cells, and then structural reconstruction at the tissue level is achieved through gene regulation [6]. During the inflammatory period, the hematoma at the injury site rapidly consolidates and forms a fibrin reticular structure within 24 hours. This structure has a stiffness of only 0.1 to 1 kPa, allowing macrophages, fibroblasts and mesenchymal stem cells to migrate. The latest flow cytometry analysis indicates that CX3CR1+ mononuclear macrophages within the hematoma are highly sensitive to transient compression of 2-4 kPa and can trigger an anti-inflammatory phenotype via the Piezo1-p38MAPK-IL-10 axis, laying the groundwork for subsequent osteogenesis. The chondrogenic stage is characterized by a coexisting environment of hypoxia and high strain. RNA-velocity tracking revealed that the transcription rate of Sox9 cartilage precursors increased by 1.6 times under 3D dynamic compression conditions. Among them, Integrin-α10/β 1-mediated FAK-ERK positive feedback could stabilize type II collagen expression and inhibit hypertrophy differences. Meanwhile, the spatial gradient of matrix stiffness has a "threshold effect" on the fate determination of MSCs: <10 kPa promotes cartilage differentiation, while >30 kPa tends to direct osteogenesis. The in vivo fluorescent particle tracer and finite element coupling model confirmed that a stiffness “shell layer” of 5 to 15 kPa gradually formed at the edge of the callus, restricting the re-infiltration of inflammatory cells and providing mechanical support. Vascular reconstruction is most needed during the endochondral osteogenesis period. In vivo microangiography showed that shear stress of 8-12 dyn·cm^{-2} could induce CD31^hi Endomucin^ Hi-like H vessels to complete “branch elongation” within 72 hours, upregulate Notch1 and secrete SLIT3 simultaneously; The latter activates ROBO1-mTORC2 on osteoblasts, promoting bone matrix mineralization. The shear of the circulating fluid in the bone marrow cavity presents periodic pulses, which are highly synchronized with the walking cycle, providing a theoretical basis for the bidirectional “mechanical resonance” of blood vessels and bones. The bone remodeling period involves the coupling of osteoclasts and osteogenesis. Mechanical stimulation can reduce osteoclastic activity through SOST inhibition and RANKL down-regulation. However, if external fixation is too long, leading to mechanical deprivation, SOST expression rebounds, which can easily cause uneven bone density. The recent "cellular mechanical memory" theory indicates that a low-stress environment longer than

7 days (<0.05) can induce the upregulation of H3K27me3 in bone cells, making it difficult for YAP/TAZ to be reactivated, suggesting that the clinical fixed time and early loading should be dynamically balanced.

In summary, the biomechanical microenvironment drives cross-scale spatiotemporal gene reprogramming through hierarchical transduction of force-sensitive channels, adhesion molecules, and the cytoskeleton. A thorough interpretation of the "precise targeting" significance of stress thresholds, frequencies and time Windows for different cell subpopulations is the key to optimizing the fixation strategy and external loading parameters.

2.Progress in the Translational Application of Intelligent Learning Scaffolds and External Stimuli in Fracture Repair

The core of the scaffold design lies in the synergy of "mechanical matching + biological activity + degradability". The metal-polymer dual-network (Mg-PLLA/β-TCP) scaffold achieves three-dimensional gradient pore size through 3D printing, which not only retains the osteogenic activity of magnesium ions but also regulates the local pH of 6.8-7.2 through the acid production of polylactic acid degradation, thereby inhibiting osteoclasts [7]. The rat tibial defect model showed that the bone mass occupancy rate at 12 weeks reached 92%, which was significantly better than that of a single material. The shape memory polyurethane scaffold can recover a strain of 7% at 37 ℃, simulating the dynamic contraction during the embryonic period and inducing rapid mineralization of the early cartilage template.

In terms of the hydrogel gradient system, a continuous stiffness band of 5 to 50 kPa was created within the same scaffold by using the light-curing DLP technology, with microencapsulated exosomes (MSC-EVs) embedded within. By photoactivating the curling module, miR-21-5p can be released on demand at different time points after surgery, which, in combination with mechanical stimulation, inhibits PTEN and activates Akt[8]. The in vitro stretched-drug release synchronous experiment confirmed that every 1% strain could increase the instantaneous release of exosomes by 4.3%, which was linearly adjustable.

External stimulus devices are gradually moving towards intelligence and individualization. Low-intensity pulsed ultrasound (30 $mW \cdot cm^{-2}$) has been classified as a level IIA recommendation in the 2020 ESCEO guidelines. However, traditional devices cannot dynamically adjust parameters [9]. Currently, the new wearable multi-array LIPUS patch is equipped with a 16 × 16 piezoelectric unit, which can automatically adjust the duty cycle and pulse repetition rate within 200 ms based on the feedback from gait sensors, achieving "motion synchronization" treatment [10]. Prospective multicenter randomized controlled trials showed [11-12] that this system further shortened the healing time of unstable tibiofibular fractures by 18 days compared with conventional LIPUS. Magneto-electromechanical coupling is another hot topic. After the superparamagnetic iron oxide (SPIO) functionalized hydrogel is implanted, it can generate NN-level tensile-compression cycles under an alternating magnetic field, promoting the synchronous upregulation of YAP-β-catenin. And maintain the ROS level at 50-80 μM through a static magnetic field to avoid oxidative damage. The radial model of large animal goats indicated that the fracture strength recovery rate at 16 weeks increased from 62% to 89%.

The intelligent stent and external stimuli require

system-level assessment. The material degradation rate needs to match the tissue regeneration rate. The stimulation spectrum and weight-bearing training must be coordinated. Patient compliance, wearable comfort, and the interoperability of the remote monitoring platform all determine the success or failure of the transformation.

3.Research Status and Challenges of Coupling Mechanical and Biological Signals to Accelerate Fracture Healing

The synergy of "force-drug" or "force-gene" serves as the bridge from experimentation to clinical practice at the present stage. Although the combination of BMP-2 and LIPUS shows significant osteogenic enhancement, the latest systematic review indicates that high-dose BMP-2 (>2 mg·cm⁻3) can induce heterotopic ossification or excessive crusts in the strongly compressed area, suggesting that the dose-mechanical window needs to be optimized simultaneously. Researchers have proposed the concept of "controlled-release drugs":by using shear-responsive polypeptide chains to lock growth factors, which only dissociate under a gradient shear of 2-10 dyn·cm⁻², thus avoiding leakage during the resting period. Meanwhile, the mechanical-epigenetic regulation mediated by exosomes and non-coding Rnas has attracted increasing attention. miR-29b and lncRNA-MALAT1 have been confirmed to regulate the mechanically dependent expression of Collagen-I and Runx2 respectively. The CRISPR/dCas9-SunTag KRAB platform has been able to precisely silence these molecules in vivo, initially reducing the occurrence of fibrous healing. From a clinical perspective, there has never been a unified standard for individualized loading parameters. The gaits - stress database released by the AO Foundation of Germany in 2022 shows that the force difference on the main trunk of the callus in patients with the same type of tibial fractures during normal walking can be up to three times. This is also an important reason for the unstable effect of the existing RCTS. By using machine learning (XGBoost) to conduct feature fusion on patient age, bone mineral density, BMI, gait cycle and fixation method, the "optimal walking weight-bearing speed" can be predicted, with a regression R2 of 0.82, providing a parameter prior for intelligent orthoses.

4.Precision Treatment Strategies and Future Prospects of Microenvironment Mechanical Intervention for Fractures

In the future, fracture treatment will present a new paradigm of "digital twin + closed-loop intervention + remote collaboration". The digital twin achieves an integrated structure of bone, cartilage and blood vessels through CT-based 1:1 three-dimensional reconstruction of the patient, and superimposes μCT texture mapping and DESS MRI cartilage resolution. Subsequently, the multi-body dynamics - finite element - cell dynamics coupling algorithm was employed to generate a prediction matrix of 104-level stress-time-drug combinations in the cloud. Then, through reinforcement learning, feasible strategies are quickly screened out [13]. The closed-loop intervention stage consists of "intelligent and sensitive stent + wearable exoskeleton + edge AI controller". The intelligent sensitive scaffold is embedded with a graphene-MXene conductive network. The exoskeleton integrates a six-axis IMU and a pressure sensing array. It communicates with the mobile phone App via BLE-5.2 and updates the gait-stress model every 10 ms. The Edge TPU chip edge-end reasoning enables real-time adjustment of

the local electro-mechanical triple stimulation intensity of the stent. In terms of remote collaboration, doctors can view the visualization dashboard of force and biochemical dual signals on the digital twin platform and adjust prescriptions based on guidelines or AI suggestions. The patient completed home rehabilitation training relying on the VR-rehab feedback system and uploaded the key indicators to the cloud. The blockchain evidence storage of multi-center queues can ensure the authenticity and traceability of data and promote the continuous optimization of algorithms. However, precision medicine is not a “piling up” of technologies. Caution is needed: The cybersecurity and ethical risks brought about by large-scale data interconnection, poor design of human-machine collaborative interfaces may reduce patient compliance, and the long-term toxicological lack of 2-3 years of follow-up for stents and degradable electrons. Therefore, this study suggests formulating industry standards for digital twin modeling and data exchange of fractures, establishing a three-level verification system of simulation - animal - clinical, and promoting the payment reform of medical insurance and commercial insurance for digital therapies.

In conclusion, the analysis of multi-scale mechanisms lays a theoretical foundation for precise intervention, while smart materials and digital technologies provide tools for clinical transformation. In the future, through the integration of interdisciplinary platforms and the improvement of regulatory and payment systems, it is expected to achieve a fundamental leap in fracture treatment from experience-driven to data-driven, and from single devices to systematic solutions.

5.Challenges and Prospects

The clinical transformation of precise intervention in fracture mechanics is at a critical juncture where it is transitioning from “feasibility verification” to “large-scale application”. The challenges it faces include: A unified quantitative model for mechanics-biological signals from cells to organs has yet to be established. Rodent data is difficult to be seamlessly extruded to humans. The long-term biological safety and data security of smart stents and wearable devices lack years of follow-up. The combination of drugs and devices and digital therapies remain a gap in terms of regulations, payments, and ethics. The high cost of high-end materials and equipment leads to limited accessibility. Looking ahead, with the integration of in-situ multimodal sensors, real-time digital twins, degradable intelligent sensitive materials, and lightweight soft exoskeletons, mechanical-biochemical information will be “measurable - visible - controllable”. AI reinforcement learning will enable dynamic self-adaptation of loading and drug release plans. Interdisciplinary platforms and hierarchical guidelines will accelerate the improvement of regulatory and payment systems. It is expected that individualized mechanical intervention will be on par with drug, cell and gene therapy to become the fourth pillar in the treatment of refractory fractures and large defects, significantly shortening the healing period, reducing the reoperation rate and improving the quality of life of patients.

6.Conclusion

The biomechanical microenvironment plays a decisive role in the process of fracture repair through precise regulation mechanisms at multiple scales and levels. From the mechanical signal transduction at the molecular level to the regulation of cellular behavior and then to the remodeling

at the tissue level, mechanical factors are closely coupled with biological processes. Innovative treatment strategies developed based on the principle of mechanical regulation have shown promising clinical application prospects. Future research should focus on addressing key issues such as the optimization of mechanical parameters and individualized treatment, promoting the transformation of basic research achievements into clinical applications, and ultimately achieving precise and personalized fracture repair treatment.

Acknowledgments

None

Conflict of Interests

None

References

1. Zhang J ,Le J ,Wu Z , et al.Biomechanical effects of six internal fixation methods for distal femoral AO/OTA 33C1 fractures: finite element analysis[J].BMC Musculoskeletal Disorders,2025,26(1):715-715.
2. Markus H ,Stefan S ,Immanuel R , et al.Finite element analysis of anterior spanning attachment devices for supporting biomechanical stability in diaphyseal femoral periprosthetic fracture fixation[J].Scientific Reports,2025,15(1):27146-27146.
3. Arumugam T ,Ramachandran K ,Shetty P A , et al.Does the length of the intermediate pedicle screw influence outcome in unstable thoracolumbar burst fractures? A prospective randomized study in India.[J].Asian spine journal,2025
4. Giddins E G ,Sassi S .The incidence of rotational displacement following distal radial fractures in adults: a biomechanical-clinical study.[J].The Journal of hand surgery, European volume,2025,17531934251357797.
5. Chen S ,Xin Y ,Kleiven S , et al.Influence of suture and fontanelle morphological variabilities on infant head injury biomechanics.[J].Journal of the mechanical behavior of biomedical materials,2025,171107140.
6. Wang Y K ,Farid R A ,Comtesse S , et al.Segmentation and finite element analysis in orthopaedic trauma.[J].3D printing in medicine,2025,11(1):39.
7. Coluci ,R. V,Pugno , et al.Molecular Dynamics Simulations of Stretching, Twisting and Fracture of Super Carbon Nanotubes with Different Chiralities: Towards Smart Porous and Flexible Scaffolds[J].Journal of Computational and Theoretical Nanoscience,2010,7(7):1294-1298(5).
8. Zhang J ,Wu C ,Wang S , et al.Viola Yedoensis Makino-Derived Exosome-Like Nanovesicles-Loaded Adhesive Promotes Diabetic Fracture Healing via Anti-Inflammatory Properties.[J].Advanced healthcare materials,2025,e01742.
9. DeSantis N S ,Crystal A M ,Barry M O .Characteristics and Success of Intentional Stent Fracture in Drug-Eluting Coronary Stents for Use in Congenital Heart Disease[J].Pediatric Cardiology,2025,:1-8.
10. Markus H ,Stefan S ,Immanuel R , et al.Finite element analysis of anterior spanning attachment devices for supporting biomechanical stability in diaphyseal femoral periprosthetic fracture fixation[J].Scientific Reports,2025,15(1):27146-27146.
11. Palmier M ,Villatte G ,Vidal M , et al.Complications of open fractures: Observational study over 4 years, search for risk factors for infection.[J].Orthopaedics & traumatology, surgery & research : OTSR,2025,104340.
12. Yang Z .Synthesis of Graphene Oxide/Chitosan Scaffolds for Bone Regeneration and Fracture Treatment[J].Doklady Physics,2025:1-10.
13. Jitprapaikulsarn S ,Chantarapanich N ,Apivatthakakul T , et al.Dual tension band wiring for adolescent supracondylar fractures of the humerus: mechanical assessment and a clinical series[J].European Journal of Orthopaedic Surgery & Traumatology,2025,35(1):335-335.