

Exploring novel therapeutic avenues for arthritis precision medicine: The potential of mTOR-SIRT1, NRF2, GPX4 ferroptosis- and autophagy- related pathways and emerging technologies

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Editorial

Arthritis remains a common and debilitating disease affecting millions of people worldwide. Osteoarthritis (OA) and rheumatoid arthritis (RA) are among the most common forms of this chronic, degenerative disease, which is moving toward precision medicine [1-8]. Traditional treatment approaches have primarily focused on symptom management and pain relief, often failing to address the underlying molecular mechanisms that drive the progression of arthritis [9].

However, recent advances in biomedical research have opened new avenues for therapeutic intervention by targeting the key molecular pathways involved in the pathogenesis of arthritis. Emerging evidence suggests that modulation of critical signaling cascades such as mTOR, SIRT1, NRF2 and GPX4 holds great promise for the development of more effective and personalized treatment strategies [4,10].

In addition, the integration of cutting-edge technologies, including microphysiological systems (MPS) [11], artificial intelligence (AI) [12,13], single-cell analysis [3], digital twins [14,15], robotic biotechnology [16-18] and advanced 3D,4D/5D bioprinting [19,20] offers the potential to improve the understanding, diagnosis and treatment of this debilitating disease. By harnessing these innovative approaches, researchers and clinicians can explore new ways to improve the efficacy and precision of arthritis therapies, ultimately contributing to improved patient outcomes and quality of life.

This editorial explores the exciting prospects of combining the modulation of key molecular pathways with the implementation of these transformative technologies in the field of arthritis management. By reviewing recent advances and their potential impact, this article aims to shed light on the promising future of arthritis treatment and the opportunities for revolutionizing arthritis care.

Molecular Pathways and Their Therapeutic Potential

mTOR-SIRT1 pathway

The mTOR (mechanistic target of rapamycin) pathway is a central regulator of cell growth, metabolism, and survival and acts as a sensor of nutrient availability and cellular energy status [8,21]. In arthritis, dysregulated mTOR signaling contributes to increased inflammatory responses and impaired autophagy, exacerbating joint damage [8,22]. SIRT1 (sirtuin 1), an NAD⁺-dependent deacetylase, counteracts these effects by promoting autophagy and reducing inflammatory cytokine production, thereby increasing cellular resilience [23,24].

Modulation of the mTOR-SIRT1 axis is a promising therapeutic strategy. For example, the

mTOR inhibitor rapamycin has shown potential to reduce cartilage degradation and inflammation in preclinical models of arthritis [8]. Similarly, activation of SIRT1 using small molecules such as resveratrol has demonstrated protective effects against joint degeneration [25].

NRF2 pathway

NRF2 (Nuclear Factor Erythroid 2-Related Factor 2) is a transcription factor that regulates the expression of antioxidant and cytoprotective genes, providing a defense mechanism against oxidative stress. In arthritis, chronic oxidative stress leads to cartilage and synovial tissue damage. Enhancing NRF2 activity could attenuate oxidative damage and inflammation, thus providing therapeutic benefits [26].

Compounds such as sulforaphane, found in cruciferous vegetables, have been shown to activate NRF2 and reduce oxidative stress in arthritis models [27]. In addition, pharmacological NRF2 activators are being investigated for their potential to halt disease progression and improve joint function [28].

GPX4 pathway

GPX4 (glutathione peroxidase 4) is an essential enzyme involved in neutralizing lipid peroxides and preventing ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation [29,30]. In arthritis, ferroptosis contributes to chondrocyte death and cartilage degradation [31]. Increasing GPX4 activity may protect against oxidative damage and maintain cell viability [32].

Strategies to upregulate GPX4 include the use of selenium supplementation, as GPX4 is a selenoprotein, and small molecules that increase GPX4 expression [33]. These approaches hold promise for preserving joint integrity and function.

Innovative Technologies in Arthritis Research

The integration of advanced technologies is revolutionizing arthritis research and therapeutic development.

Microphysiological systems

Microphysiological systems, also known as "organs-on-chips," mimic the microarchitecture and functionality of human tissues *in vitro*. These systems enable high-throughput screening of drug candidates and provide detailed insights into tissue responses under physiological and pathological conditions [11,34].

For arthritis research, joint-on-a-chip models can mimic the complex interactions between cartilage, synovium and immune cells, allowing precise testing of therapeutic interventions and uncovering disease mechanisms [6,35,36].

Artificial intelligence (AI) and machine learning (ML)

AI and ML are transforming biomedical research by enabling the analysis of large datasets to identify patterns, predict outcomes, and optimize treatment strategies [12]. In arthritis, AI can be used to develop predictive models of disease progression, identify novel drug targets, and personalize treatment regimens based on patient-specific data [13]. For example, AI algorithms have been successfully used to analyze imaging data and quantify joint damage in arthritis patients, improving diagnostic accuracy and monitoring disease progression [37].

Single cell analysis

Single-cell analysis techniques allow the study of cellular heterogeneity within tissues, providing a detailed understanding of cell populations and their role in disease. In arthritis, single-cell RNA sequencing (scRNA-seq) can identify specific cell types and pathways involved in the disease, leading to the development of targeted therapies. Recent studies using scRNA-seq have uncovered previously unrecognized cell types and molecular signatures in arthritic joints, providing new insights into disease mechanisms and potential therapeutic targets [38].

3D, 4D, and 5D bioprinting

3D, 4D, and 5D bioprinting technologies allow for the fabrication of complex, multilayered tissue constructs that mimic the native architecture of human joints [19,39]. These technologies enable the creation of personalized, biocompatible grafts using patient-derived cells, potentially revolutionizing joint repair and regeneration.

For example, 3D bioprinting has been used to create cartilage tissue constructs with precise mechanical properties and cellular composition, showing promise for use in cartilage repair. Advances in 5D bioprinting continue to improve the functionality and realism of printed tissues, paving the way for more effective regenerative medicine [20].

Digital twin technology

Digital twin technology is the creation of a virtual model of a physical entity [15]. In healthcare, this means building a detailed digital replica of a patient's anatomy and pathology that can be used to simulate disease progression and treatment response [14].

Personalized treatment planning: Digital twins equipped with patient-specific data can simulate the effects of different therapeutic interventions, helping physicians choose the most effective treatment plan [40,41].

Predictive modeling: By integrating genomic, proteomic, and clinical data, digital twins can predict disease progression and flare-ups, enabling proactive management of arthritis [42].

Robotic biotechnology

Robotic biotechnology involves the use of robotic systems to perform complex biological tasks with high precision and reproducibility. In the treatment of arthritis, this can revolutionize both surgical and non-surgical interventions. Robotic surgery: Robotic systems can improve the precision of joint surgeries such as arthroplasty or synovectomy, leading to better outcomes and faster recovery times for arthritis patients [16]. Automated drug delivery: Robotic platforms can facilitate targeted drug delivery to inflamed joints, minimizing systemic side effects and maximizing therapeutic efficacy [17]. Finally, nanorobots can also be used [18].

Challenges and Future Directions

While the promising advances in modulating key molecular pathways and integrating innovative technologies have great potential to transform arthritis treatment, several challenges need to be addressed to fully realize the benefits of these approaches.

One of the key challenges is to accurately model the complex human joint environment *in vitro* [43]. The development of more

sophisticated and scalable microphysiological systems will be critical to faithfully recapitulate the cellular and biomechanical interactions within the joint, thereby allowing for more reliable preclinical testing and evaluation of new therapeutic strategies [8,44].

In addition, large-scale validation studies will be needed to confirm the efficacy and safety of emerging molecular and technological interventions [45]. Robust clinical trials incorporating real-world data and multi-omics analyses will be essential to establish the clinical utility of these innovative approaches and ensure their successful translation into routine patient care. In addition, the integration of multidisciplinary expertise spanning fields such as molecular biology, bioengineering, and data science will be critical to the effective implementation of these integrated approaches [46]. Navigating the ethical and regulatory considerations surrounding the use of advanced technologies, such as AI, digital twins and robotic biotechnology, will also be a critical aspect of the future development and deployment of these transformative solutions.

The limitations include lacking accurately modeling joint environments *in vitro*, the need for more advanced systems, and the necessity of conducting large-scale validation studies. Additionally, improved multidisciplinary collaboration and addressing ethical concerns are critical. The manuscript would also benefit from a discussion on ensuring that patient safety and data privacy remain top priorities.

Despite these limits and challenges, the continued integration of molecular pathway modulation with cutting-edge technologies holds great promise for revolutionizing the treatment of arthritis. By personalizing treatment strategies and increasing the precision of therapeutic interventions, these innovative approaches have the potential to significantly improve the quality of life for patients affected by this debilitating disease.

Future Research Directions Include

Advancing microphysiological systems

Developing more complex and dynamic models that can replicate the multifaceted nature of human joints, including mechanical loading and immune interactions [6,11,13].

Improving AI algorithms

Improving the predictive accuracy of AI models and integrating multi-omics data to provide a comprehensive view of disease mechanisms and treatment responses [47]. The Nobel Prize in Physics 2024 was awarded to both John J. Hopfield and Geoffrey E. Hinton for foundational discoveries and inventions that enable machine learning with artificial neural networks.

Combining single-cell and multi-omics technologies

Leveraging the power of single-cell analysis in conjunction with genomic, transcriptomic, proteomic, and metabolomic data to achieve a holistic understanding of arthritis [48].

Refining bioprinting techniques

Exploring novel biomaterials and printing methods to improve the durability, functionality, and integration of engineered tissues in joint repair applications [49].

Conclusion

In summary, modulation of key molecular pathways such as mTOR-SIRT1, NRF2, and GPX4, combined with the integration of innovative technologies such as microphysiological systems, artificial intelligence, single-cell analysis, digital twins, robotic biotechnology, and advanced bioprinting, holds great promise for revolutionizing arthritis treatment. These diverse approaches offer new hope for the development of more effective and personalized therapies, ultimately improving the quality of life for patients suffering from this debilitating disease.

The integration of targeted molecular pathway modulation with advanced technologies provides a powerful framework for improving arthritis care. For example, a digital twin model can incorporate patient-specific data on mTOR-SIRT1, NRF2, and GPX4 activity, allowing real-time simulation of how different therapies affect these pathways. Similarly, robotic systems can be programmed to deliver drugs that specifically modulate these molecular targets, improving the precision and efficacy of therapeutic interventions.

The combination of these innovative molecular and technological approaches holds great promise for the future of arthritis treatment. The personalization of treatment strategies and the increased precision of therapeutic interventions have the potential to transform the way arthritis is managed, offering new hope and improved outcomes for patients affected by this debilitating disease.

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