ADVANCES AND CHALLENGES IN THE USE OF DECELLULARIZED EXTRACELLULAR MATRIX HYDROGELS FOR RENAL REGENERATION: A LITERATURE REVIEW

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ABSTRACT
Introduction: Chronic kidney disease (CKD) affects 8–16% of the adult population and is primarily treated with dialysis and transplantation, both of which have limitations. Advances in Tissue Engineering and Regenerative Medicine suggest the use of decellularized extracellular matrix (ECM) for renal regeneration. **Objectives**: To review the literature on renal hydrogels based on decellularized ECM, emphasizing their clinical applications and emerging challenges. **Methodology**: A literature review was conducted in PubMed (2015–2024), including peer-reviewed studies on renal hydrogels derived from decellularized ECM. **Results**: Six main studies were analyzed. Quinteira et al. (2024) developed porcine tissue renal hydrogels with therapeutic potential. Hiraki et al. (2018) replicated the renal microenvironment, preserving ECM proteins. Soranno et al. (2023) demonstrated improved renal function using injectable hydrogels. Guan et al. (2015) preserved renal vasculature but observed thrombosis after two weeks. Caralt et al. (2015) identified the Triton X-100/SDS protocol as the most effective for decellularization. Remuzzi et al. (2017) reported difficulties in cell distribution and viability. **Conclusion**: Decellularization and recellularization of renal ECM have shown significant advances, particularly with the Triton X-100/SDS protocol. However, challenges such as thrombosis and limited cell distribution must be overcome to enable the clinical application of renal hydrogels.

Keywords: Hydrogels; extracellular matrix; decellularization.

INTRODUCTION

Kidney disease results in the progressive loss of renal function, leading to toxin accumulation and homeostatic imbalance. Affecting 8–16% of the adult population worldwide, chronic kidney disease (CKD) is a major cause of morbidity and mortality. Currently, treatments for end-stage CKD are limited to dialysis and renal transplantation, both of which present significant limitations, including immune rejection and incomplete restoration of renal function. These constraints highlight the need to explore alternative therapeutic strategies.

Advances in tissue engineering and regenerative medicine have enabled the creation of whole organs for transplantation using decellularized extracellular matrix (ECM) derived from kidneys. This process removes donor cells while preserving the three-dimensional architecture and bioactive components essential for tissue regeneration. Despite progress, technical challenges remain, such as preserving renal vasculature and achieving efficient recellularization.

This study reviews the use of hydrogels derived from decellularized renal ECM, focusing on their applications in tissue regeneration and the challenges for clinical translation.

METHODOLOGY

This study conducted a literature review on the development of renal hydrogels using decellularized kidney ECM as a substrate. Searches were performed in PubMed and the Virtual Health Library (BVS) between July and August 2024, using the descriptors "hydrogels," "extracellular matrix," "decellularization," and "kidneys," according to the Health Science Descriptors (DeCS/MESH).

Original peer-reviewed articles published between 2015 and 2024 in English were included. Non-original studies, such as reviews and brief communications, as well as articles with incomplete data, were excluded, as they did not provide sufficient information for in-depth analysis of methods and results.

The critical analysis of the selected studies focused on the decellularization techniques applied, the characteristics of the resulting hydrogels, and the potential applications of these biomaterials in renal tissue regeneration.

RESULTS

Six main studies were selected for analysis, highlighting the development and characteristics of renal hydrogels based on decellularized extracellular matrix (dECM), with an emphasis on their application in tissue regeneration and the treatment of renal pathologies. Table 1 summarizes the main findings and methodological characteristics of each study.

Tabela 1: Estudos que avaliaram o desenvolvimento de MEC descelularizada associado a hidrogéis renais

Autor/Ano	Objetivos	Métodos	Resultados
Quinteira R, et al. 2024[12]	Desenvolver um hidrogel a partir de células descelularizadas de tecido renal suíno para aplicação em bioimpressão e regeneração do tecido renal.	Descelularização do tecido renal utilizando Triton X-100. . Avaliação da viabilidade celular com ensaio Live/Dead. . Análise de citocinas inflamatórias em hidrogéis DKECM. 4. Análise histológica e SEM para verificar a integridade do biomaterial.	O hidrogel demonstrou capacidade de induzir polarização de macrófagos M1 e M2, sugerindo um equilíbrio entre sinais inflamatórios. Resultados promissores foram observados em modelos de doença renal aguda e crônica, indicando potencial para restauração da função renal.
Hiraki HL, et al. 2018[13]	Produzir um hidrogel replicando o microambiente do córtex renal.	Descelularização do tecido renal com solução de SDS a 1%, homogeneização e liofilização para isolar a MEC. Solubilização do MEC com ácido forte e pepsina. Gelificação do hidrogel com reagentes neutralizantes.	O hidrogel final preserva as proteínas nativas da MEC, proporcionando um ambiente fisiológico que suporta o crescimento de células renais. A matriz permite a modelagem de doenças como a fibrose renal
Soranno DE, et al. 2023[14]	Investigar a viabilidade de hidrogéis injetáveis como terapias para doenças renais, incluindo a melhoria da função renal e a redução da inflamação e fibrose.	Hidrogéis injetáveis foram desenvolvidos com materiais como quitosana, colágeno e ácido hialurônico, além de terapias encapsuladas, como células-tronco mesenquimais e fatores de crescimento. Estudos pré-clínicos em ratos e camundongos avaliaram essas formulações em lesões renais.	Hidrogéis aumentaram a sobrevivência celular, melhoraram a função renal e reduziram inflamação e fibrose em modelos de lesão renal aguda. Hidrogéis sozinhos também mostraram benefícios significativos na função renal e redução de inflamação.
Guan Y, et al. 2015[11]	Estabelecer um método eficiente de descelularização e recelularização de rins de ratos para regeneração renal.	Descelularização com SDS 0,5% preservando a estrutura 3D da MEC e a vasculatura. Recelularização com CTE de camundongos.	O arcabouço renal preservou a MEC e a vasculatura, permitindo adesão e proliferação de CTE. Os rins regenerados produziram urina e mantiveram a pressão arterial, mas apresentaram trombose nas veias renais após duas semanas
Caralt M, et al. 2015[15]	Comparar métodos de descelularização e otimizar arcabouços renais para bioengenharia.	Comparação dos métodos Triton X-100, Triton X-100/SDS e Tripsina-EGTA/Triton. Análise histológica e bioquímica. Recelularização e transplante em ratos.	O protocolo Triton X-100/SDS foi o mais eficaz, preservando a arquitetura renal e a integridade vascular, ideal para bioengenharia renal.
Remuzzi A, et al. 2017[16]	Explorar estratégias para regeneração renal utilizando bioengenharia em andaimes acelulares.	Descelularizacao de rins de ratos usando perfusão de SDS e recelularizacao com CTE em diferentes vias (artérias, veia, ureter). Avaliacao da distribuição celular, viabilidade e proliferação ao longo tempo	A recelularização foi limitada, com distribuição celular inadequada nos componentes renais. Houve proliferação inicial, mas a manutenção e distribuição celular ao longo do rim não foram eficazes, devido à baixa permeabilidade da matriz.

The analysis of the selected studies revealed significant advances in the development and application of renal hydrogels based on decellularized extracellular matrix (dECM). One study demonstrated that a hydrogel derived from decellularized porcine kidneys can induce macrophage polarization and shows potential for treating acute and chronic kidney diseases (12). Another study developed a hydrogel that replicates the renal cortex microenvironment, preserving native proteins and supporting renal cell growth, making it useful for modeling pathologies such as renal fibrosis (13). It was also highlighted that injectable hydrogels formulated with various materials and encapsulated therapies improved renal function and reduced inflammation and fibrosis in animal models (14). Another study showed that SDS-based decellularization preserved the 3D matrix structure and vasculature, allowing recellularization with embryonic stem cells, although long-term renal thrombosis was observed (11). A specific protocol was identified as the most effective for cell removal, architecture preservation, and maintenance of vascular integrity in transplantation (15). However, challenges were faced regarding limited cell distribution and maintenance of cell viability when using SDS perfusion and embryonic stem cells (16).

Furthermore, despite advances in decellularization and recellularization, maintaining renal functionality and preventing thrombosis remain significant challenges. Preservation of the structure and bioactive components is crucial for creating functional scaffolds, and the effectiveness of injectable hydrogels underscores the need for combined approaches to optimize renal regeneration. Comparisons of decellularization and recellularization methods highlight the importance of selecting protocols that preserve vascular integrity and kidney functionality, as well as the ongoing need for innovation to overcome technical limitations and improve clinical applicability.

CONCLUSION

This review highlights the advances in the use of renal hydrogels based on decellularized extracellular matrix (dECM), with the Triton X-100/SDS protocol proving effective in preserving tissue and vascular architecture. However, challenges such as limited cell distribution and thrombosis remain significant obstacles for clinical application. dECM-derived hydrogels have shown to be a promising alternative in animal models for improving renal function and reducing inflammation, but efficient recellularization and vascular complications still require improvement.

Future research should focus on refining these methodologies, seeking solutions that enable functional renal regeneration. Despite the challenges, decellularized ECM hydrogels offer a promising approach that could significantly contribute to the treatment of chronic kidney diseases.

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