ROS-responsive nanocellulose hydrogels as platforms for drug delivery

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INTRODUCTION: Pathological increases in reactive oxygen species (ROS) disrupt redox balance, causing oxidative stress and damage to essential biomolecules. Such ROS elevation is characteristic of neurodegenerative, cardiovascular, and inflammatory diseases, tumorigenesis, and the host response to implanted biomaterials. These differences between normal and pathological ROS levels motivate the development of ROS-responsive materials for diagnostics, targeted therapy, and controlled drug release.[1] Wood-derived cellulose nanofibrils (CNF) have emerged as attractive biomaterials for hydrogels and drug-delivery systems due to their biocompatibility, tunable mechanics, and high chemical functionality.[2] In this work, we exploit these properties by functionalizing CNF with ROS-sensitive linkers to enable ROS-triggered drug release in pathological microenvironments

METHODS: Oligoproline was selected as the ROS-sensitive linker and covalently grafted onto CNF via amidation of the nanofibrils' carboxyl groups. The peptides were designed with terminal cysteines with the aim of crosslinking the fibers via disulfide bond formation (Fig 1). To evaluate the influence of linker length, hydrogels were prepared using oligopeptides with 5- and 10- proline units (P_5 and P_{10}). The viscoelastic properties of the resulting oligoproline-CNF hydrogels were characterized under physiological (PBS, pH 7.4) and oxidative conditions (H_2O_2/Cu(II) in PBS). Hydrogels were loaded with lysozyme and ROS-triggered release profiles were assessed to determine the materials' responsiveness.

RESULTS: The results showed that linker length did not affect the degree of peptide substitution on the CNF, but it significantly influenced the kinetics of fiber crosslinking. Rheological analysis revealed that P_{10}-CNF required approximately 3–4 days to reach a crosslinking level comparable to P_5-CNF. Upon exposure to oxidative conditions, cleavage of the oligoproline linkers produced measurable decreases in storage modulus, mesh size, and crosslinking density, confirming that the ROS-sensitivity of oligoproline was preserved after covalent immobilization onto CNF. Lysozyme was used as a model protein to evaluate the hydrogels as ROS-responsive drug-release systems. The hydrogels demonstrated enhanced protein release under oxidative conditions relative to physiological conditions, indicating effective ROS-triggered network degradation. Comparison between P_5-CNF and P_{10}-CNF further showed that the release rate increased with linker length.

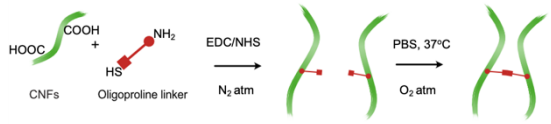

Fig. 1: Schematic representation of the strategy used to crosslink cellulose nanofibrils (CNFs) with oligoproline as the ROS-sensitive linker.

DISCUSSION & CONCLUSIONS: This work demonstrates that oligoproline-functionalized CNF hydrogels retain ROS-responsiveness while offering tunable crosslinking kinetics through control of linker length. Although peptide substitution on CNF was independent of oligoproline length, longer linkers slowed network formation but subsequently enhanced ROS-triggered degradation and protein release. These findings indicate that oligoproline chain length provides a useful design parameter for tailoring the release profile of the hydrogels under oxidative conditions. Overall, the study highlights wood-derived CNF as a versatile platform for engineering bio-based, ROS-responsive hydrogels, and supports their potential for targeted drug delivery in pathological tissues characterized by elevated ROS.

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REFERENCES: [1] Q.H. Xu et al. Macromolecular Bioscience (2016):16, 635-46. [2] X.R. Ong et al. Small Science (2023):3, 2200076.