2024 CMBEC46
Toronto, ON
May 28-30, 2024
CMBES/SCGB

The Role of Oxygen in ECM remodeling

Nadia Abzan[1,2], Zoya Versey[2,3], William Willmore[2,4], Leila B. Mostaço-Guidolin[1,2]

[1] Carleton University/Systems and Computer Engineering, Ottawa, Canada
[2]Tissue Engineering and Applied Materials (TEAM) Hub, Ottawa. Canada
[3] Carleton University, Health Science, Ottawa, Canada
[4]Carleton University/Biochemistry, Biology and Chemistry, Ottawa, Canada

Abstract— **The extracellular matrix (ECM) regulates several cellular functions via different signals. The structure and composition of the ECM change in various diseases. The mechanisms of ECM alternations and the role of oxygen in ECM remodeling is poorly understood. We are establishing *in vitro* models that simulate the ECM microenvironment to investigate the effect of oxygen in ECM remodeling.**

Keywords— **ECM remodeling, Collagen, Hydrogels, Hypoxia.**

I. Introduction

Within tissues, ECM plays a crucial role by maintaining structural integrity and guiding various cellular functions via mechanical and biochemical cues [1]. Alterations in the local oxygen concentration have been observed to alter the ECM structure (regulation of collagen, crosslinking enzymes, matrix metalloproteinases and tissue inhibitor matrix metalloproteinases), and mechanical stability as well as cellular functions in many diseases [2,3]. Since the interactions between the ECM and tissue-resident cells, the mechanisms that drive ECM remodeling and the role of oxygen in this process remain unclear, we are establishing *in vitro* models that simulate the ECM microenvironment to investigate the role of oxygen in ECM production and remodeling.

II. Methodology

We are developing *in vitro* 2D models of collagen-rich hydrogel matrices containing healthy fibroblasts (HFL-1) in normal condition (21%O_2) and hypoxia (5%O_2). Next, the role of oxygen in the collagen expression and synthesis pathway are investigated. Finally, the remodeling of the ECM by altering the fibroblast environment (modifying hydrogel composition, mechanical cues alternations, and adjusting the oxygen concentrations) is assessed. Alternations in ECM-associated protein profiles are assessed by mass spectrometry and Western blotting. The mechanical properties of the remodeled hydrogel matrices are mapped using tensile and tension-compression analyses. Hydrogels are also assessed by nonlinear optical and confocal microscopy (NLOM, CM), which allow us to analyze the 3D structural composition of the remodeled ECM components (particularly collagen) as well as cellular morphology and differentiation.

III. Results

In normal oxygen concentration, fibroblasts remodel the hydrogel collagen into fibers, by packing fibrils. It leads to the contraction of the hydrogels and formation of denser collagen bundles, as assessed by NLOM. However, in hypoxic conditions, our preliminary results present fragments of collagen and less contracted hydrogels. We hypothesize that in hypoxia, the transition of fibroblasts into myofibroblasts as well as the post-translational modifications of collagen molecules result in the reduction of collagen fiber crosslinking, therefore modifying tissue structure.

IV. Conclusions

The results from the present work will provide us with significant details about the mechanisms by which ECM regulates cellular behavior as well as the role of oxygen in these mechanisms. Identification of cell-ECM interactions can contribute to the novel therapeutic approaches for various fibrotic diseases.

Acknowledgment

This work is supported by NSERC-DG to LM-G (RGPIN-2021-04185) and WW (RGPIN-2017-06414).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] L. T. Saldin, et al., “Extracellular matrix hydrogels from decellularized tissues: Structure and function,” *Acta Biomater*, vol. 49, pp. 1–15, 2017.
[2] H. Xing, et al., “Extracellular matrix-derived biomaterials in engineering cell function,” *Biotechnol Adv*, vol. 42, p. 107421, 2020.
[3] Sun, Kai, et al., "Extracellular matrix and fibrosis in adipose tissue: overview and perspectives." *Compr. Physiol* 13, no.1, 2023.