INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Graves Eye Disease New Treatment

TECHNOLOGY NUMBER: 2018-321

Technology ID
2018-321

Category
Therapeutics and Vaccines
Life Sciences

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OVERVIEW

A novel method for production of a three-dimensional organoid model of thyroid eye disease (TED)

- A microenvironment that mimics tissue stiffness, remodeling, and inflammation in Grave's orbitopathy
- Describes how GO results from changes in hypoxia inducible factor-2 alpha and lysyl oxidase

BACKGROUND

Thyroid eye disease (TED) is a condition in which the inflammation and fibrosis of fat tissues and muscles around the orbits cause irritation, swelling, bulging eye, double vision, and eventually, blindness. TED, also called as Grave's orbitopathy (GO), is most often associated with autoimmune hyperthyroidism (Grave's disease), and its prevalence is about 0.3% in the population. The pharmacological treatment for GO has been limited, and patients with progressive TED commonly need to undergo decompression surgeries in an effort to preserve vision. While the fibrotic and inflammatory tissue remodeling in GO is triggered by autoimmune processes, the mechanisms underlying the progressive tissue changes and inflammation remain poorly defined. As such, a need exists for further research into the pathogenesis of GO to provide further opportunities for development of therapeutic agents.

INNOVATION

Researchers at the University of Michigan have developed a three dimensional (3D) organoid model of thyroid eye disease (TED) which has subsequently facilitated discovery of a novel therapeutic target for Grave's orbitopathy (GO). A GO model was created through isolation of human orbital fibroblasts recovered from GO and non-GO patients following which the cells were placed in a hanging droplet culture to generate 3D organoids which recapitulated in vivo

microenvironments that mimic the tissue stiffness, extracellular matrix remodeling, and inflammatory gene expression characteristics of GO. This 3D model exists in an architecture that more closely approximates conditions in the orbit than does a two-dimensional model, thereby allowing for results that better represent those in the in vivo state. The scientists demonstrated through the GO model that upregulation of hypoxia inducible factor-2 alpha (HIF2A) and the resulting induction of lysyl oxidase (LOX) correlate with fibrotic and inflammatory tissue damage and stiffness. Therefore, inhibition of HF2A or LOX activity should provide a means by which to develop therapeutic agents that effectively prevent and treat GO in affected patients.