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Generation of Mature Esophageal Epithelium using Human Pluripotent Stem Cells

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Description du projet

During embryonic development, esophagus and trachea develop from the anterior foregut (AF) tube. Disruption in the separation into two distinct tubes results in foregut malformations such as esophageal atresia and trachea-esophageal fistula (EA/TEF) affecting 1 in 3500 births. The only treatment available for children born with these malformations involves surgically connecting the deformed esophagus with the stomach with life-long complications. Moreover, the mechanisms underlying the embryonic and fetal development of EA/TEF are poorly understood. Much work has focused on understanding the differentiation of the respiratory and digestive system from the AF tube but many questions about the process of compartmentalization remain unanswered. Most of our knowledge on foregut bifurcation, and subsequent esophagus development is based on genetic mouse models, which revealed key genes, molecular pathways and signaling molecules that regulate foregut separation and continue to play key roles in esophagus development and homeostasis. Although mice models have contributed immensely to our understanding on esophagus development and diseases, key structural differences between human and mouse esophageal epithelium necessitate the need to develop a reliable model of the human esophageal epithelium. Human pluripotent stem cells

(hPSCs) provide an efficient system to model and understand human organ development based on mimicking embryonic developmental stages to generate cell and tissue types originating from all 3 germ layers.

Recently, two groups Zhang et al.(2018), and Trisno et al.(2018) proposed methods to differentiate hPSCs into mature human esophageal organoids (HEOs). This was achieved by manipulating key signaling pathway like wingless related integration site (Wnt),and introducing growth factors such as transforming growth factor (TGFß), bone morphogenetic proteins (BMPs), retinoic acid (RA) and fibroblast growth factors (FGFs). The mature HEOs generated through these methods were confirmed by the expression of key mature esophageal epithelium markers such as p63, SOX2 and KRT4 and KRT13. Though these groups achieved differentiation of hPSCs to mature esophageal epithelium, the study did neither focus in depth on the critical time point nor on factors or pathways that would determine whether the cellular progression from AF will be either trachea or esophagus. It is crucial to understand foregut compartmentalization to either esophagus or trachea and investigate mechanisms leading to esophageal malformations and associated disorders.

Therefore, our work will concentrate on developing methods to successfully generate mature esophageal epithelium using hPSCs, focusing specifically on foregut compartmentalization to esophageal development.

Mots clés
Esophageal Atresia, Human Pluripotent Stem Cells, Mesenchymal Stem Cells, Mature Esophageal Epithelium