Ex vivo models leading to personalised diagnostic and therapeutic approach in patients with cystic fibrosis

ABSTRACT

Cystic fibrosis (CF) is a hereditary disease caused by a biallelic mutation of the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene, resulting in a defective CFTR protein functioning as a chloride ion channel. Clinical manifestations are caused by abnormal transport of chloride ions and water across epithelial membranes. The predominant symptoms include progressive lung disease and pancreatic insufficiency. The treatment of CF is mainly symptomatic: respiratory physiotherapy, substitution of digestive enzymes and vitamins, and early and intensive treatment of respiratory infections. Since 2012, new drugs known as CFTR modulators have gained importance. CFTR modulators target the defective CFTR protein at the cellular level; the treatment is indicated based on the patient's specific *CFTR* genotype; however, it's not available for all patients, especially ones with rare *CFTR* mutations due to the inability to conduct clinical trials with a small number of patients, even though some might benefit from modulator treatment. One method to overcome this challenge is using *ex vivo* models, which allow preclinical testing of treatment responses *in vitro*. This dissertation focuses on the use of patient-derived intestinal organoids to predict individual treatment responses to CFTR modulators using the forskolin-induced swelling assay in selected patients; moreover, it focuses on differences in the morphology of intestinal organoids in CF patients and healthy controls and using these differences in CF diagnostics. Our work shows that intestinal organoids are a useful *in vitro* model for CF research. It highlights the need for developing predictive tools to evaluate individual treatment responses to CFTR modulators to personalise treatment, especially for patients with rare genotypes.

KEYWORDS

Cystic fibrosis, tissue models, intestinal organoids, CFTR modulators, personalised medicine