ABSTRACT

According to the latest WHO statistics, cardiovascular diseases are the leading cause of death, contributing to approximately 18.6 million deaths annually. Due to the growing problem, it is crucial to understand the causes of these diseases in order to provide new treatment methods. The development of an appropriate human model is necessary.

One of the most advanced heart models is Engineered Heart Tissue (EHT) with a structure and function similar to real cardiac tissue. It consists of cardiomyocytes, fibroblasts, and extracellular matrix, enables advanced assessment of cardiac tissue function and physiology in vitro.

In this study, we focused to achieve three aims: 1) to enhance the model by creating a chamber-specific EHT (chEHT), 2) to confirm the usefulness of the previously developed chEHT model for testing a drug (AP14145) with known clinical activity specific to the atria, and 3) to prove cardiac fibroblasts influence on the differentiation of cardiomyocytes towards atrial and ventricular, using the EHT model.

The first part of our research resulted in the development of the methodology for using a fully chamber-specific tissue model, chEHT, which represents a significant advancement over previously used tissue models. It allows for the replication of functional differences between the atria and ventricles of the heart, including contraction frequency and duration.

In the second part, we demonstrated that atrial chEHT differs from ventricular chEHT not only in gene expression and physiological parameters but also allows for the functional differentiation of both tissue types. This was achieved using the atrial-specific inhibitor of calcium-activated potassium channels – AP14145. The atrial specificity of AP14145 had not been demonstrated in some animal models, which indicates a better representation of human heart physiology by the developed model.

The mechanisms underlying the terminal differentiation of the human heart are still unclear. One hypothesis suggests that cardiac fibroblasts play a key role in this process, although this has not yet been proven. The EHT model aimed to determine whether cardiac fibroblasts direct the final stages of cardiomyocyte differentiation into atrial and ventricular subtypes. During our research, we observed that atrial fibroblasts can influence the differentiation and change the characteristics of ventricular cardiomyocytes towards an atrial cardiomyocyte phenotype.

In conclusion, the conducted experiments allowed us to develop and demonstrate the potential of the ventricular-specific chEHT model in pharmacological and in cardiac biology studies. The EHT model provides a unique platform for studying the cellular microenvironment and intercellular interactions, supporting the structural and functional maturation of cardiomyocytes. Our results suggest that cardiac fibroblasts play a significant role in terminal differentiation of cardiomyocytes, highlighting the mechanisms of cardiovascular diseases.

In conclusion, the conducted experiments allowed for the development and demonstration of the potential of the chamber-specific chEHT model in pharmacological studies and heart biology studies. The EHT model provides a unique platform for studying the cellular microenvironment and intercellular interactions, supporting the structural and functional maturation of cardiomyocytes. Our results suggest that cardiac fibroblasts play a significant role in the terminal differentiation of cardiomyocytes, highlighting the importance of the EHT model in expanding our understanding of heart development and the mechanisms of cardiovascular diseases.