

В настоящее время наиболее актуальные подходы к сердечно-сосудистым исследованиям основаны на использовании кардиомиоцитов, дифференцированных из индуцированных плюрипотентных стволовых клеток (КМ-иПСК). Изучение активности ионных каналов на модели КМ-иПСК позволяют оценить биофизические свойства натриевых каналов в их нативном тканеспецифическом окружении с учетом генетического фона пациента.

КМ-иПСК активно используются для изучения ассоциированных с кардиомиопатиями изменений активности ионных каналов (Craστο, Di Pasquale, 2018; Steele-Stallard et al., 2018; Giacomelli et al., 2020; Shah et al., 2021). Однако в этих исследованиях авторы, как правило, ограничиваются изменениями плотности тока и не пытаются рассмотреть более детальные механизмы активности натриевых каналов. Так, на модели КМ-иПСК было показано уменьшение плотности тока в клетках пациентов с аритмогенной кардиомиопатией (Khudiakov et al., 2020), с дилатационной кардиомиопатией и прогрессирующим нарушением сердечной проводимости (Kamga et al., 2021) и в клетках пациентов с синдромом Бругада (El-Battrawy et al., 2019; Zhu et al., 2021), а также замедление активации при миотонической дистрофии 1 типа (Poulin et al., 2021).

Актуальность данной работы во многом определяется тем, что в настоящее время большая часть данных, полученных на модели КМ-иПСК, фокусируется на описании изменений плотности натриевого тока и уровня экспрессии *SCN5A*, в то время как изучение других электрофизиологических характеристик натриевых каналов остается вне фокуса подавляющего числа исследований.

Мы продемонстрировали, что у пациентов с генетически обусловленными кардиомиопатиями, сопровождающимися желудочковыми аритмиями, ассоциированными с генетическими вариантами в генах *DSP* и *FLNC*, наблюдается усиление стационарной медленной инактивации. Это соотносится с данными литературы об изменениях медленной инактивации, обусловленных генетическими вариантами в гене *SCN5A*, ассоциированных с развитием желудочковых нарушений ритма. Например, при мутации T512I в гене *SCN5A* обнаружено изменение кинетики активации и инактивации и усиление медленной инактивации $Na_v1.5$ (Yang et al., 2002), а генетический вариант G1712S сопровождался спектром биофизических изменений, в том числе нарушением медленной инактивации $Na_v1.5$ (Sanner et al., 2021).

Таким образом, пока информации о роли процесса медленной инактивации $Na_v1.5$ в развитии наследственных кардиомиопатий и аритмий недостаточно. Мы показали, что процесс медленной инактивации потенциал-зависимых натриевых каналов сердца может быть усилен в клетках пациентов с желудочковыми нарушениями ритма, вызванными генетическими вариантами в различных генах, регулирующих активность каналов $Na_v1.5$ (*FLNC* и *DSP*).

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ANALYSIS OF THE ROLE OF NAV1.5 SLOW INACTIVATION IN THE DEVELOPMENT OF INHERITED CARDIAC PATHOLOGY

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Voltage-gated cardiac sodium channels Na_v1.5 are responsible for the initiation and propagation of action potentials in cardiomyocytes. Dysfunction of Na_v1.5 can be caused both by pathogenic variants in the *SCN5A* gene itself, which encodes Na_v1.5, and by genetic variants in the genes of other proteins, regulating channel activity and trafficking. The change of different phases of the action potential is determined by the strict temporal organization of activation and inactivation of various ion channels. Transitions between channel functional states (for example, to slow inactivated state) can be influenced by various factors and proteins interacting with the channel. Despite the fact that the process of slow inactivation of the channel has been known for several decades, its role in the mechanism of development of hereditary heart pathology remains unclear. In this work, using the patch clamp method in whole-cell leads, we studied changes in the process of slow Nav1.5 inactivation under the influence of various mutations in structural genes (*DSP*-H1684R, *LMNA*-R249Q, *FLNC*-R1267Q, *FLNC*-V2264M) associated with a genetically determined myocardial pathology leading to dysfunction of cardiomyocytes. The study used a model of cardiomyocytes differentiated from induced pluripotent stem cells (CM-iPSCs). We have demonstrated an increase in slow inactivation in the model of CM-iPSCs obtained from patients with a phenotype of cardiomyopathy combined with ventricular arrhythmias. Thus, this work contributes to understanding the role of the slow inactivation process in the mechanism of the development of heart pathology.

Keywords: *DSP*, *FLNC*, gating, inherited arrhythmia, *LMNA*, Na_v1.5, slow inactivation