Примечательно, что и мутации комплексов конденсинов приводят к многочисленным нарушениям развития организма, в том числе микроцефалии (Perche et al., 2013; Martin et al., 2016; Khan et al., 2019). Этот спектр заболеваний был назван отдельным термином – конденсинопатии. Показано, что в случае дефектов комплексов конденсинов также происходит нарушение декатенации и сегрегации сестринских хроматид, что негативно сказывается на пролиферации и выживаемости нейральных предшественников (Nishide, Hirano, 2014). Таким образом, нарушение длительности митоза и расхождения сестринских хроматид в *MCPH1*-дефицитных клетках также может играть важную роль в нарушении нейрогенеза, приводящего к микроцефалии.

Животные модели *MCPH1*-опосредованной микроцефалии позволили исследователям получить целый ряд важной информации о молекулярных основах патогенеза этой патологии развития. Согласно им можно полагать, что основной причиной микроцефалии является нарушение регуляции клеточного деления в нейральных предшественниках, вызванное подавлением активности сигнального пути киназы клеточного цикла Chk1 (Gruber et al., 2011; Journiac et al., 2020; Liu et al., 2021). Одновременно с этим были выявлены видоспецифические различия, которые не позволяют должным образом оценить вклад других аспектов функциональной активности MCPH1 при данном типе нарушения нейрогенеза. Так, например, действие MCPH1 как транскрипционного фактора и его участие в поддержании целостности теломер показано только на линиях клеток человека, но не мыши. Исследований по изучению роли MCPH1 на приматах очень ограниченное количество (Shi et al., 2013; Ke et al., 2016). Однако даже эти немногие показали существование важных функций MCPH1 в нейрогенезе, отсутствующих у мышей.

Видоспецифические особенности в формировании мозга человека ограничивают изучение различных его патологий на модельных животных. В течение долгого времени исследователям не удавалось преодолеть эти ограничения, однако с развитием технологий репрограммирования и редактирования генома был сделан большой прорыв в этой области (Takahashi, Yamanaka, 2006). Получение пациент-специфичных индуцированных плюрипотентных стволовых клеток и возможность их дифференцировки в нейральные стволовые клетки и нейроны, а также создание любых направленных модификаций генома позволили не только изучать последствия мутаций, но также тестировать лекарственные препараты и проводить скрининги химических соединений (Rowe, Daley, 2019). В 2013 году была опубликована ключевая работа (Lancaster et al., 2013), где впервые было описано получение трехмерных структур, названных церебральными органоидами. Церебральные органоиды точно воспроизводят процессы, происходящие при развитии коры головного мозга аналогично первым трем месяцам эмбрионального развития человека. Измерение различных морфометрических параметров органоидов исключительно удобно и информативно в случае микроцефалии (Lancaster et al., 2013; Cugola et al., 2016; Fair et al., 2023). Удивительно, но *MCPH1* – исторически первый описанный ген, ассоциированный с микроцефалией, еще не был изучен на модели церебральных органоидов. Мы полагаем, что использование такой модели также может принести важные результаты и пролить свет на роль MCPH1 в развитии и эволюции головного мозга человека.

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В работе не участвовали животные или люди в качестве объектов исследования.

КОНФЛИКТ ИНТЕРЕСОВ

Авторы заявляют об отсутствии конфликта интересов

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FUNCTIONS OF MICROCEPHALIN IN NEUROGENESIS AND HUMAN BRAIN EVOLUTION

A. M. Yunusova[1, *], T. A. Shnaider[1]

[1] Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia

** E-mail: anastasiajunusova@gmail.com*

Primary microcephaly is a brain growth disorder of which the main phenotypic hallmarks is a reduction of brain size with varying degrees of intellectual disability. *MCPH1* is the first gene reported to cause primary microcephaly. Microcephalin (MCPH1), the encoded protein product, has been implicated in various cellular processes deregulation of which can negatively affects neurogenesis. In our review we will discuss the clinical cases of MCPH1 primary microcephaly and summarize the knowledge about the functions of MCPH1 employing animal models with mutations in various domains of *MCPH1*. We also pay special attention to the role of MCPH1 in in the evolution of the human brain.

Keywords: primary microcephaly, microcephalin (*MCPH1*), animal models of *MCPH1* primary microcephaly, human brain evolution