# TRANSGENIC MICE FOR STUDY OF THE CDK8/19 CYCLIN-DEPENDENT KINASE KINASE-INDEPENDENT MECHANISMS OF ACTION

Stavskaya NI[1], Ilchuk LA[2] ✉, Okulova YuD[2], Kubekina MV[2], Varlamova EA[2], Silaeva YuYu[1], Bruter AV[2]

[1] Institute of Gene Biology, Russian Academy of Sciences, Moscow, Russia

[2] Center for Precision Genome Editing and Genetic Technologies for Biomedicine, Institute of Gene Biology, Russian Academy of Sciences, Moscow, Russia

The CDK8 cyclin-dependent transcription-associated kinase and its less studied paralog, CDK19, regulate the expression of the dependant genes via several mechanisms. CDK8/19 can directly phosphorylate some transcription factors (ICN, STAT1), but at the same time these kinases being a component of the mediator complex regulate transcrition via interaction with chromatin in the promoter and enhancer regions of appropriate genes. Recently the papers have appeared showing that CDK8/19 has kinase-independent mechanisms of action through comparison of the effects of the kinase activity genetic inactivation and chemical inhibition. The study was aimed to generate transgenic mice capable of the induced and tissue-specific expression of the kinase-negative (showing no phosphorylation activity) form of CDK8, CDK8 (D173A), which could be later used to study the CDK8 kinase-independent mechanisms of action *in vivo*. We obtained four $F_0$ transgenic animals by microinjection of linear DNA into the pronucleus, two of these animals became the ancestors of two distinct lines. The copy number of the integrated construct was measured for all $F_0$ and the lines generated. This model may be used to study the kinase-independent properties of the CDK8/19 proteins.

**Keywords:** transgenesis, transcription regulation, Cdk8, mediator kinase, kinase-independent functions

**Funding:** RSF grant, project № 22-15-00227.

**Author contribution:** Stavskaya NI — experimental procedure, working with animals; Ilchuk LA — manuscript writing, design of genotyping systems, data analysis; Okulova YuD — working with embryos; Kubekina MV — preparation of genetically engineered construct, experimental procedure; Varlamova EA — experimental procedure; Silaeva YuYu — literature analysis, study planning; Bruter AV — literature analysis, study planning, data analysis and interpretation, manuscript editing.

**Compliance with ethical standards:** the study was approved by the Ethics Commitee of the Institute of Gene Biology RAS (protocol № 1 of 10 November 2021) and conducted in full compliance with the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

✉ **Correspondence should be addressed:** Leonid A. Ilchuk
Prospekt Mira, 124, Moscow, 129164, Russia; lechuk12@gmail.com

**Received:** 22.11.2022 **Accepted:** 19.12.2022 **Published online:** 28.12.2022

**DOI:** 10.24075/brsmu.2022.066

# ТРАНСГЕННЫЕ МЫШИ ДЛЯ ИЗУЧЕНИЯ КИНАЗА-НЕЗАВИСИМЫХ МЕХАНИЗМОВ ДЕЙСТВИЯ ЦИКЛИН-ЗАВИСИМЫХ КИНАЗ CDK8/19

Н. И. Ставская[1], Л. А. Ильчук[2] ✉, Ю. Д. Окулова[2], М. В. Кубекина[2], Е. А. Варламова[2], Ю. Ю. Силаева[1], А. В. Брутер[2]

[1] Институт биологии гена Российской академии наук, Москва, Россия

[2] Центр высокоточного редактирования и генетических технологий для биомедицины, Институт биологии гена Российской академии наук, Москва, Россия

Циклин-зависимая транскрипционная киназа CDK8 и ее менее изученный паралог CDK19 регулируют экспрессию зависимых генов посредством нескольких механизмов. CDK8/19 могут напрямую фосфорилировать некоторые транскрипционные факторы (ICN, STAT1), но в то же время в составе медиаторного комплекса эти киназы регулируют транскрипцию за счет взаимодействия с хроматином в области промоторов и энхансеров соответствующих генов. В последнее время появляются работы, демонстрирующие путем сравнения эффектов генетической инактивации и химического ингибирования киназной активности наличие у CDK8/19 киназа-независимых механизмов действия. Целью работы было получить трансгенных мышей, способных к индуцируемой и тканеспецифичной экспрессии киназнонегативной (лишенной фосфорилирующей активности) формы CDK8 — CDK8 (D173A), которых впоследствии можно будет использовать для изучения киназа-независимых механизмов действия CDK8 *in vivo*. Методом случайного трансгенеза в результате микроинъекций линейной ДНК в пронуклеус нами получены четыре трансгенных особи $F_0$, две из которых стали родоначальниками отдельных линий. Для всех $F_0$ и полученных линий измерена копийность интегрировавшейся конструкции. Данная модель может быть использована для изучения киназа-независимых свойств белков CDK8/19.

**Ключевые слова:** трансгенез, регуляция транскрипции, Cdk8, киназа медиатора, киназа-независимые функции

**Финансирование:** грант РНФ#22-15-00227.

**Вклад авторов:** Н. И. Ставская — проведение экспериментов, работа с животными; Л. А. Ильчук — написание рукописи, разработка систем генотипирования, анализ результатов; Ю. Д. Окулова — с эмбрионами; М. В. Кубекина — подготовка генно-инженерной конструкции, проведение экспериментов; Е. А. Варламова — проведение экспериментов; Ю. Ю. Силаева — анализ литературы, планирование исследования; А. В. Брутер — анализ литературы, планирование исследования, анализ и интерпретация результатов, редактирование рукописи.

**Соблюдение этических стандартов:** исследование одобрено этическим комитетом ИБГ РАН (протокол № 1 от 10 ноября 2021 г.) и проведено в строгом соответствии с положениями Директивы 2010/63/EU Европейского Парламента и Совета Европейского союза от 22 сентября 2010 г. по охране животных, используемых в научных целях.

✉ **Для корреспонденции:** Леонид Альбертович Ильчук
проспект Мира, д. 124, г. Москва, 129164, Россия; lechuk12@gmail.com

**Статья получена:** 22.11.2022 **Статья принята к печати:** 19.12.2022 **Опубликована онлайн:** 28.12.2022

**DOI:** 10.24075/vrgmu.2022.066

The CDK8 cyclin-dependent kinase and its paralog, CDK19, are not directly involved in regulation of the cell cycle phase transitions and belong to the so-called transcription-associated kinases that regulate gene transcription [1]. However, the mechanisms underlying such regulation are diverse. On the one hand CDK8/19 as part of a complex with cyclin C, MED12, and MED13 directly phosphorylate some transcription factors, such as intracellular domain NOTCH [2] or STAT1 [3]. On the other

hand, together these four proteins form the kinase module of the Mediator complex that regulates gene expression via binding to the promoter and enhancer regions [1]. Despite the fact that in vitro studies have shown that, just like the CDK7 and CDK9 transcription-associated kinases, CDK8/19 can phosphorylate the RNA polymerase II C-terminal region, which represents an important event during transition to the elongation stage. This mechanism is likely to play no significant role in the cell [4]. At the same time it has been shown that CDK8/19 play an important role in expression of certain genes, especially in activation of expression of the earlier inactivated genes [5–7] and the major oncogenes, such as c-Myc [8, 9] and genes of the Wnt/β-catenin signaling pathway [10]. In some cases the expression levels correlate with the presence of CDK8/19 in the enhancers and super-enhancers of the corresponding genes [11]. However, despite the important fundamental role played by CDK8/19 and their potential as therapeutic targets, specific molecular mechanism underlying the relationship between the expression of certain genes and CDK8/19 are unknown.

Recently there are papers reporting the comparison of chemical inhibition and genetic inactivation that show that genetic inactivation provides much larger effects in some models [7, 12, 13]. It must follow from this fact that CDK8/19 has some kinase-independent mechanisms of action. However, such comparison is not always precise, even in *in vitro* studies, due to limited selectivity and efficiency of inhibitors and is almost impossible in *in vivo* studies due to the features of biodistibution and metabolism of chemical inhibitors and the difficulties associated with crossing the blood-brain and blood–testis barriers by the substances.

The study was aimed to generate transgenic mice capable of tissue-specific induced expression of the CDK8 (D173A) mutant kinase-negative form for further identification of possible CDK8/19 kinase-independent mechanisms of action.

## METHODS

### The construct

Transgenesis involved the pKB2 vector that, in contrast to the previously used vector pKB1 [14, 15], was characterized by the absence of the reporter gene. The open reading frame was amplified using the KapaHiFi polymerase (Kapa Biosystems; USA) and primers P1 and P2 (hereinafter all olygonucleotides, the sequences of which are provided in Table 1, have been synthesized by Evrogen, Russia) with cDNA. cDNAs were obtained by reverse transcription using the RevertAid reverse transcriptase (Thermo Scientific; USA) based on the RNA extracted from the murine brain using the ExtractRNA reagent (Evrogen; Russia). When performing amplification, the AgeI and MluI restriction sites were added to the 5' and 3' ends of the reading frame for further transfer to the final vector, along with the Kozak consensus sequence. The amplified reading frame was cloned into the CloneJet vector (Thermo Scientific; USA) and sequenced. The c.A518C mutation was created by site-directed mutagenesis during the polymerase chain reaction with the previously phosphorylated primers P3 and P4. The presence of target mutation and the absence of additional mutations were confirmed by sequencing. Then the ORF of the obtained *mCdk8kd* gene variant (kinase-dead) was re-cloned by the AgeI and MluI sites (all the restriction endonucleases were manufactured by Thermo Scientific, USA) into the pKB2 vector. The construct was linearized by sites SalI and NotI, separated by electrophoresis, extracted from the gel with the Cleanup Mini kit (Evrogen; Russia), further purified using the spin column with the Corning Costar Spin-X 0.22 μm nylon filter (Corning; USA), and diluted in the microinjection buffer (10 mmol Tris, 1 mmol EDTA) to the DNA concentration of 2 ng/μL.

### Mice housing conditions

Embryos were obtained from 30 immature (weight 12–13 g) females (F1 hybrids CBA × C57BL/6) and similar males aged 6–8 weeks (Stolbovaya breeding station; Russia). The CD1 outbred mice (Stolbovaya breeding station; Russia) were used as recipients and foster mothers. The mice that were kept in the vivarium of the Institute of Gene Biology RAS had free access to water and food. The 22–24 °C ambient temperature was maintained, and the light/dark cycle (day/night) was 14/10 h.

### Microinjections and embryo transfer

Microinjections and embryo transfer were performed as described previously [16]. On day 19 after the embryo transfer, recipients underwent caesarean section, and the newborn mouse pups were housed together with foster mothers.

### Genotyping and copy number measurement

Animal genotyping was performed in accordance with the previously used protocol [14]. A STOP cassette (primers P5 and P6) and a terminator (primers P7 and P8) being parts of the pKB2 vector were simultaneously detected in transgenic animals by multiplex polymerase chain reaction (PCR). The copy number of the inserted construct was defined by comparison with genes with the known varying copy numbers (HPRT, HbA, H3C7) based on the results of the real-time PCR [14].

## RESULTS

To generate transgenic mice capable of induced and tissue-specific expression of the kinase-negative CDK8 variant, we created a genetic construct containing the open reading frame of the *mCdk8* gene with the c.A518C substitution in the DNA

**Table 1.** Olygonucleotide sequences

| | Sequence | Designation |
|---|---|---|
| P1 | attaaccggtGCACCATGGACTATGACTTTAAAGTGAAG | Amplification of the CDK8kd ORF |
| P2 | taatacgcgtTCAGTACCGATGTGTCT | Amplification of the CDK8kd ORF |
| P3 | CCATGGGCTTTGCCCGATTAT | Creation of the A518C mutation |
| P4 | CAGCAATTTTTACTCTTCCTCG | Creation of the A518C mutation |
| P5 | GTTAGATCTGCTGCCACCGT | Genotyping (STOP cassette) |
| P6 | AGGTGGCAAGTGGTATTCCG | Genotyping (STOP cassette) |
| P7 | GCGAGTCCATGTCACTCAGG | Genotyping (terminator) |
| P8 | GTGTTGCCCTTTGGAGCTTG | Genotyping (terminator) |

**Table 2.** Results of activities on generating primary transgenic animals

| Recipients used | Cells transferred | Number of mice that gave birth | Number of newborn mouse pups | Number of newborn transgenic animals |
|---|---|---|---|---|
| 41 | 487 | 7 | 14 | 6 |

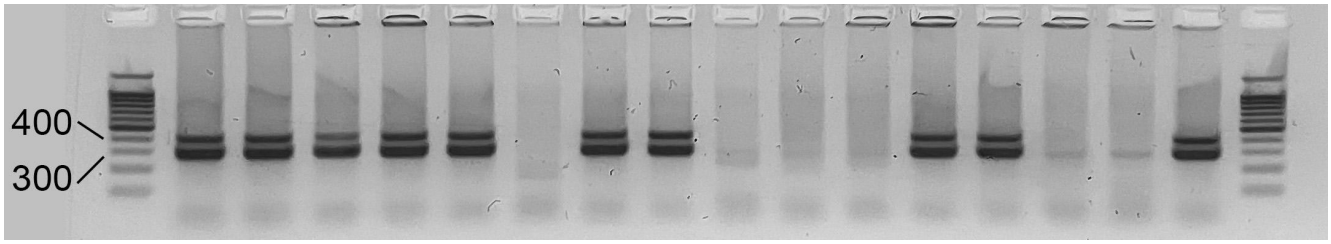


**Fig. 1.** $F_1$ mouse genotyping by gel electrophoresis. The lanes with the bands of PCR products with the size of about 300 bp (fragment of STOP cassette) and about 400 bp (fragment of terminator) correspond to transgenic mice. The lanes with no bands correspond to the wild type mice. The first and the last lanes contain the size markers

(and, consequently, with the D173A substitution in the protein) based on the pKB2 vector [17]. Along with the insulator and terminators which are protection against the position effect during insertion, the vector used contains the CAG promoter and the STOP cassette flanked by LoxP sites that separates promoter from the ORF. The STOP cassette inserted in such a way significantly reduces thetransgene transcription and makes further translation of the transcript impossible [14].

The linearized construct was microinjected into the zygotes, among which 487 zygotes survived and were transferred to recipients. As a results, 14 mouse pups were born, among which six pups were transgenic. The presence of the transgene was confirmed by PCR in all newborn animals (Fig. 1). A numerical representation of the results of activities on generating transgenic animals is provided in Table 2.

Among six primary transgenic animals, two died before puberty and four produced offspring when bred with the C57BL/6J mice. To date, four independent substrains have been generated: 369, 372, 375, 376. When random integration takes place in the genome, multimers of the construct can be formed and then inserted in chromosomes. In turn, the expression levels can be a fuction of the number of monomers. Furthermore, since insertion in distinct blastomeres may occur independently, $F_0$ animals may be mosaic due to the varying copy numbers of the construct in various cells. We have defined the average copy number of insertion for $F_0$ and the copy number for the substrains obtained (Fig. 2). The resulting values can be non-integers because of using exponential approximation when assessing the copy numbers and averaging the values of various cells. However, in fact this is due to the measurement error. Starting from the $F_1$ generation, the copy numbers are constant integer values. Two substrains of $F_1$ hybrids with the copy numbers of about 2, which correspond to the copy numbers of the majority of genes in diploid genomes, were selected for further breeding.

## DISCUSSION

We have generated the mice line capable of the induced and tissue-specific expression of the kinase-negative mCDK8 form: six $F_0$ animals, among which four animals have produced offspring and two have become the founders of substrains by now. Furthermore, the efficiency of obtaining transgenes was 50% (6 out of 12), and further segregation compared to $F_1$ that was associated with mosaicism in $F_0$ together with the wide range of copy numbers of the inserted construct (1–17) was found in the animals generated. This allowed us to select the lines with the copy numbers most close to natural for further studies.

A series of studies consider the consequences of the CDK8 and/or CDK19 genetic knockout [18–20], however, the models used in these studies make it impossible to to draw a final conclusion about the role played by the lack of CDK8/19 proteins and impossibility of the Mediator complex kinase module assembly in the observed phenotypes, and about the role of appropriate phosphorylation. Moreover, the use of the CDK8/19 inhibitors in animals has resulted in the effects that are different from that reported in knockout animals [21]. The animal line we have generated is a right tool for distinguishing between kinase-dependent and kinase independent CDK8/19 functions.

## CONCLUSIONS

During the study transgenic mice were generated providing the possibility of the tissue-specific and induced expression of the kinase-negative form of the CDK8 cyclin-dependent kinase.

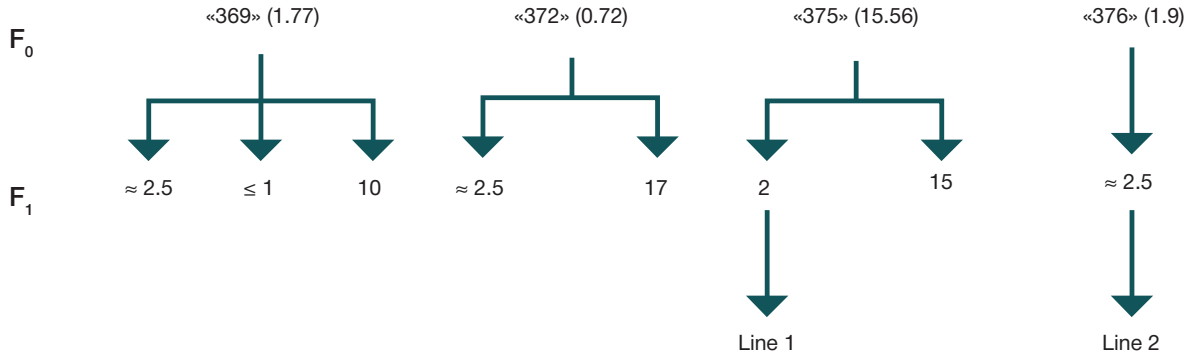


**Fig. 2.** Scheme of the substrains obtained and copy numbers of the substrain members. The names of substrains are put in quotes. The average copy numbers of ansectors ($F_0$) are put in parentheses. Only the copy numbers are provided for $F_1$

In the future, after breeding with the CDK19$^{-/-}$, CDK8$^{fl/fl}$ mice and various activators, animals will be generated, in which the wild type CDK8 and CDK19 could be replaced by the kinase-negative variant in the ubiquitous or tissue-specific manner. The experiments involving such animals can possibly reveal the CDK8/19 kinase-independent mechanisms of action.

**References**


1. Dannappel MV, Sooraj D, Loh JJ, Firestein R. Molecular and in vivo Functions of the CDK8 and CDK19 Kinase Modules. Frontiers in Cell and Developmental Biology. 2019; 6. DOI: 10.3389/fcell.2018.00171.
2. Li N, Fassl A, Chick J, Inuzuka H, Li X, Mansour MR, et al. Cyclin C is a haploinsufficient tumour suppressor. Nature cell biology. 2014; 16 (11): 1080–91. Epub 2014/10/27. DOI: 10.1038/ncb3046. PubMed PMID: 25344755; PubMed Central PMCID: PMCPMC4235773.
3. Bancerek J, Poss ZC, Steinparzer I, Sedlyarov V, Pfaffenwimmer T, Mikulic I, et al. CDK8 kinase phosphorylates transcription factor STAT1 to selectively regulate the interferon response. Immunity. 2013; 38 (2): 250–62. Epub 2013/01/29. DOI: 10.1016/j.immuni.2012.10.017. PubMed PMID: 23352233; PubMed Central PMCID: PMCPMC3580287.
4. Galbraith MD, Donner AJ, Espinosa JM. CDK8: a positive regulator of transcription. Transcription. 2010; 1 (1): 4–12. Epub 2011/02/18. DOI: 10.4161/trns.1.1.12373. PubMed PMID: 21327159; PubMed Central PMCID: PMCPMC3035184.
5. Chen M, Liang J, Ji H, Yang Z, Altilia S, Hu B, et al. CDK8/19 Mediator kinases potentiate induction of transcription by NFκB. Proceedings of the National Academy of Sciences. 2017; 114 (38): 10208–13. DOI: 10.1073/pnas.1710467114.
6. Galbraith Matthew D, Allen Mary A, Bensard Claire L, Wang X, Schwinn Marie K, Qin B, et al. HIF1A Employs CDK8-Mediator to Stimulate RNAPII Elongation in Response to Hypoxia. Cell. 2013; 153 (6): 1327–39. DOI: https://doi.org/10.1016/j.cell.2013.04.048.
7. Steinparzer I, Sedlyarov V, Rubin JD, Eislmayr K, Galbraith MD, Levandowski CB, et al. Transcriptional Responses to IFN-γ Require Mediator Kinase-Dependent Pause Release and Mechanistically Distinct CDK8 and CDK19 Functions. Molecular Cell. 2019; 76 (3): 485–99. Available from: https://doi.org/10.1016/j.molcel.2019.07.034.
8. Adler AS, McCleland ML, Truong T, Lau S, Modrusan Z, Soukup TM, et al. CDK8 Maintains Tumor Dedifferentiation and Embryonic Stem Cell Pluripotency. Cancer Research. 2012; 72 (8): 2129–39. DOI: 10.1158/0008-5472.CAN-11-3886.
9. Fukasawa K, Kadota T, Horie T, Tokumura K, Terada R, Kitaguchi Y, et al. CDK8 maintains stemness and tumorigenicity of glioma stem cells by regulating the c-MYC pathway. Oncogene. 2021; 40 (15): 2803–15. DOI: 10.1038/s41388-021-01745-1.
10. Firestein R, Bass AJ, Kim SY, Dunn IF, Silver SJ, Guney I, et al. CDK8 is a colorectal cancer oncogene that regulates beta-catenin activity. Nature. 2008; 455 (7212): 547–51. Epub 2008/09/17. DOI: 10.1038/nature07179. PubMed PMID: 18794900; PubMed Central PMCID: PMCPMC2587138.
11. Bruter AV, Rodionova MD, Varlamova EA, Shtil AA. Super-Enhancers in the Regulation of Gene Transcription: General Aspects and Antitumor Targets. Acta naturae. 2021; 13 (1): 4–15. Epub 2021/05/08. DOI: 10.32607/actanaturae.11067. PubMed PMID: 33959383; PubMed Central PMCID: PMCPMC8084300.
12. Audetat KA, Galbraith Matthew D, Odell Aaron T, Lee T, Pandey A, Espinosa Joaquin M, et al. A Kinase-Independent Role for Cyclin-Dependent Kinase 19 in p53 Response. Molecular and Cellular Biology. 2017; 37 (13): e00626–16. DOI: 10.1128/MCB.00626-16.
13. Menzl I, Zhang T, Berger-Becvar A, Grausenburger R, Heller G, Prchal-Murphy M, et al. A kinase-independent role for CDK8 in BCR-ABL1(+) leukemia. Nature communications. 2019; 10 (1): 4741. Epub 2019/10/20. DOI: 10.1038/s41467-019-12656-x. PubMed PMID: 31628323.
14. Bruter AV, Korshunova DS, Kubekina MV, Sergiev PV, Kalinina AA, Ilchuk LA, et al. Novel transgenic mice with Cre-dependent co-expression of GFP and human ACE2: a safe tool for study of COVID-19 pathogenesis. Transgenic research. 2021; 30 (3): 289–301. Epub 2021/04/16. DOI: 10.1007/s11248-021-00249-8. PubMed PMID: 33855640; PubMed Central PMCID: PMCPMC8045570.
15. Kubekina MV, Silaeva YY, Bruter AV, Korshunova DS, Ilchuk LA, Okulova YD, et al. Transgenic mice Cre-dependently expressing mutant polymerase-gamma: novel test-system for pharmacological study of mitoprotective drugs. Research Results in Pharmacology. 2021; 7 (3): 33–9.
16. Silaeva YY, Kirikovich YK, Skuratovskaya LN, Deikin AV. Optimal Number of Embryos for Transplantation in Obtaining Genetic-Modified Mice and Goats. Russian Journal of Developmental Biology. 2018; 49 (6): 356–61. DOI: 10.1134/S106236041806005X.
17. Akoulitchev S, Chuikov S, Reinberg D. TFIIH is negatively regulated by cdk8-containing mediator complexes. Nature. 2000; 407 (6800): 102–6. DOI: 10.1038/35024111. PMID: 10993082.
18. McCleland ML, Soukup TM, Liu SD, Esensten JH, de Sousa e Melo F, Yaylaoglu M, et al. Cdk8 deletion in the Apc(Min) murine tumour model represses EZH2 activity and accelerates tumourigenesis. The Journal of pathology. 2015; 237 (4): 508–19. Epub 2015/08/04. DOI: 10.1002/path.4596. PubMed PMID: 26235356.
19. Dannappel MV, Zhu D, Sun X, Chua HK, Poppelaars M, Suehiro M, et al. CDK8 and CDK19 regulate intestinal differentiation and homeostasis via the chromatin remodeling complex SWI/SNF. The Journal of clinical investigation. 2022; 132 (20). Epub 2022/08/26. DOI: 10.1172/jci158593. PubMed PMID: 36006697; PubMed Central PMCID: PMCPMC9566890.
20. Prieto S, Dubra G, Camasses A, Aznar AB, Begon-Pescia C, Simboeck E, et al. CDK8 and CDK19 act redundantly to control the CFTR pathway in the intestinal epithelium. EMBO reports. n/a (n/a): e54261. DOI: https://doi.org/10.15252/embr.202154261.
21. Clarke PA, Ortiz-Ruiz MJ, TePoele R, Adeniji-Popoola O, Box G, Court W, et al. Assessing the mechanism and therapeutic potential of modulators of the human Mediator complex-associated protein kinases. eLife. 2016; 5. Epub 2016/12/10. DOI: 10.7554/eLife.20722. PubMed PMID: 27935476; PubMed Central PMCID: PMCPMC5224920.


**Литература**


1. Dannappel MV, Sooraj D, Loh JJ, Firestein R. Molecular and in vivo Functions of the CDK8 and CDK19 Kinase Modules. Frontiers in Cell and Developmental Biology. 2019; 6. DOI: 10.3389/fcell.2018.00171.
2. Li N, Fassl A, Chick J, Inuzuka H, Li X, Mansour MR, et al. Cyclin C is a haploinsufficient tumour suppressor. Nature cell biology. 2014; 16 (11): 1080–91. Epub 2014/10/27. DOI: 10.1038/ncb3046. PubMed PMID: 25344755; PubMed Central PMCID: PMCPMC4235773.
3. Bancerek J, Poss ZC, Steinparzer I, Sedlyarov V, Pfaffenwimmer T, Mikulic I, et al. CDK8 kinase phosphorylates transcription factor STAT1 to selectively regulate the interferon response. Immunity. 2013; 38 (2): 250–62. Epub 2013/01/29. DOI: 10.1016/j.immuni.2012.10.017. PubMed PMID: 23352233; PubMed Central PMCID: PMCPMC3580287.
4. Galbraith MD, Donner AJ, Espinosa JM. CDK8: a positive regulator of transcription. Transcription. 2010; 1 (1): 4–12.

Epub 2011/02/18. DOI: 10.4161/trns.1.1.12373. PubMed PMID: 21327159; PubMed Central PMCID: PMCPMC3035184.
5. Chen M, Liang J, Ji H, Yang Z, Altilia S, Hu B, et al. CDK8/19 Mediator kinases potentiate induction of transcription by NFκB. Proceedings of the National Academy of Sciences. 2017; 114 (38): 10208–13. DOI: 10.1073/pnas.1710467114.
6. Galbraith Matthew D, Allen Mary A, Bensard Claire L, Wang X, Schwinn Marie K, Qin B, et al. HIF1A Employs CDK8-Mediator to Stimulate RNAPII Elongation in Response to Hypoxia. Cell. 2013; 153 (6): 1327–39. DOI: https://doi.org/10.1016/j.cell.2013.04.048.
7. Steinparzer I, Sedlyarov V, Rubin JD, Eislmayr K, Galbraith MD, Levandowski CB, et al. Transcriptional Responses to IFN-γ Require Mediator Kinase-Dependent Pause Release and Mechanistically Distinct CDK8 and CDK19 Functions. Molecular Cell. 2019; 76 (3): 485–99. Available from: https://doi.org/10.1016/j.molcel.2019.07.034.
8. Adler AS, McCleland ML, Truong T, Lau S, Modrusan Z, Soukup TM, et al. CDK8 Maintains Tumor Dedifferentiation and Embryonic Stem Cell Pluripotency. Cancer Research. 2012; 72 (8): 2129–39. DOI: 10.1158/0008-5472.CAN-11-3886.
9. Fukasawa K, Kadota T, Horie T, Tokumura K, Terada R, Kitaguchi Y, et al. CDK8 maintains stemness and tumorigenicity of glioma stem cells by regulating the c-MYC pathway. Oncogene. 2021; 40 (15): 2803–15. DOI: 10.1038/s41388-021-01745-1.
10. Firestein R, Bass AJ, Kim SY, Dunn IF, Silver SJ, Guney I, et al. CDK8 is a colorectal cancer oncogene that regulates beta-catenin activity. Nature. 2008; 455 (7212): 547–51. Epub 2008/09/17. DOI: 10.1038/nature07179. PubMed PMID: 18794900; PubMed Central PMCID: PMCPMC2587138.
11. Bruter AV, Rodionova MD, Varlamova EA, Shtil AA. Super-Enhancers in the Regulation of Gene Transcription: General Aspects and Antitumor Targets. Acta naturae. 2021; 13 (1): 4–15. Epub 2021/05/08. DOI: 10.32607/actanaturae.11067. PubMed PMID: 33959383; PubMed Central PMCID: PMCPMC8084300.
12. Audetat KA, Galbraith Matthew D, Odell Aaron T, Lee T, Pandey A, Espinosa Joaquin M, et al. A Kinase-Independent Role for Cyclin-Dependent Kinase 19 in p53 Response. Molecular and Cellular Biology. 2017; 37 (13): e00626–16. DOI: 10.1128/MCB.00626-16.
13. Menzl I, Zhang T, Berger-Becvar A, Grausenburger R, Heller G, Prchal-Murphy M, et al. A kinase-independent role for CDK8 in BCR-ABL1(+) leukemia. Nature communications. 2019; 10 (1): 4741. Epub 2019/10/20. DOI: 10.1038/s41467-019-12656-x. PubMed PMID: 31628323.
14. Bruter AV, Korshunova DS, Kubekina MV, Sergiev PV, Kalinina AA, Ilchuk LA, et al. Novel transgenic mice with Cre-dependent co-expression of GFP and human ACE2: a safe tool for study of COVID-19 pathogenesis. Transgenic research. 2021; 30 (3): 289–301. Epub 2021/04/16. DOI: 10.1007/s11248-021-00249-8. PubMed PMID: 33855640; PubMed Central PMCID: PMCPMC8045570.
15. Kubekina MV, Silaeva YY, Bruter AV, Korshunova DS, Ilchuk LA, Okulova YD, et al. Transgenic mice Cre-dependently expressing mutant polymerase-gamma: novel test-system for pharmacological study of mitoprotective drugs. Research Results in Pharmacology. 2021; 7 (3): 33–9.
16. Silaeva YY, Kirikovich YK, Skuratovskaya LN, Deikin AV. Optimal Number of Embryos for Transplantation in Obtaining Genetic-Modified Mice and Goats. Russian Journal of Developmental Biology. 2018; 49 (6): 356–61. DOI: 10.1134/S106236041806005X.
17. Akoulitchev S, Chuikov S, Reinberg D. TFIIH is negatively regulated by cdk8-containing mediator complexes. Nature. 2000; 407 (6800): 102–6. DOI: 10.1038/35024111. PMID: 10993082.
18. McCleland ML, Soukup TM, Liu SD, Esensten JH, de Sousa e Melo F, Yaylaoglu M, et al. Cdk8 deletion in the Apc(Min) murine tumour model represses EZH2 activity and accelerates tumourigenesis. The Journal of pathology. 2015; 237 (4): 508–19. Epub 2015/08/04. DOI: 10.1002/path.4596. PubMed PMID: 26235356.
19. Dannappel MV, Zhu D, Sun X, Chua HK, Poppelaars M, Suehiro M, et al. CDK8 and CDK19 regulate intestinal differentiation and homeostasis via the chromatin remodeling complex SWI/SNF. The Journal of clinical investigation. 2022; 132 (20). Epub 2022/08/26. DOI: 10.1172/jci158593. PubMed PMID: 36006697; PubMed Central PMCID: PMCPMC9566890.
20. Prieto S, Dubra G, Camasses A, Aznar AB, Begon-Pescia C, Simboeck E, et al. CDK8 and CDK19 act redundantly to control the CFTR pathway in the intestinal epithelium. EMBO reports. n/a (n/a): e54261. DOI: https://doi.org/10.15252/embr.202154261.
21. Clarke PA, Ortiz-Ruiz MJ, TePoele R, Adeniji-Popoola O, Box G, Court W, et al. Assessing the mechanism and therapeutic potential of modulators of the human Mediator complex-associated protein kinases. eLife. 2016; 5. Epub 2016/12/10. DOI: 10.7554/eLife.20722. PubMed PMID: 27935476; PubMed Central PMCID: PMCPMC5224920.