TRANSCRIPTIONAL KINASE CDK8, BUT NOT CDK19, PROMOTES THE DEVELOPMENT OF ATHEROSCLEROTIC LESIONS IN MICE

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Atherosclerosis, being the main cause of myocardial infarction and stroke, remains a global medical and social problem. Despite the fact that it is recognized as a chronic inflammatory disorder, the intracellular molecular mechanisms that drive the disease progression are poorly understood. The CDK8 and CDK19 cyclin-dependent kinases being the key regulators of transcription and inflammation can potentially play an important role in the atherosclerosis pathogenesis. The study aimed to assess the impact of the *Cdk8* and *Cdk19* gene knockout on the development of atherosclerotic lesions in apolipoprotein E-deficient mice (ApoE$^{-/-}$). It has been shown that both endothelium-specific and systemic *Cdk8* knockout significantly reduce the area of atherosclerotic aortic lesions, and the total knockout has a more prominent anti-atherogenic effect. This suggests a pleiotropic role of CDK8 in the atherosclerosis pathogenesis mediated by its function not only in endothelial cells, but probably also in macrophages. In contrast to *Cdk8*, the systemic *Cdk19* knockout had no significant effect on the development of atherosclerosis. Thus, CDK8, but not CDK19, has been identified as a pro-atherogenic regulator, which makes it a promising target for the development of novel therapeutic strategies.

Keywords: atherosclerosis, genetically modified animals, transcriptional kinases CDK8 and CDK19, atherosclerotic lesions, apolipoprotein E

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ТРАНСКРИПЦИОННАЯ КИНАЗА CDK8, НО НЕ CDK19 СПОСОБСТВУЕТ РАЗВИТИЮ АТЕРОСКЛЕРОТИЧЕСКИХ ПОРАЖЕНИЙ У МЫШЕЙ

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Атеросклероз, являющийся основной причиной инфаркта миокарда и инсульта, остается глобальной медико-социальной проблемой. Несмотря на его признание в качестве хронического воспалительного заболевания, внутриклеточные молекулярные механизмы, управляющие прогрессированием болезни, изучены недостаточно. Циклин-зависимые киназы CDK8 и CDK19, являющиеся ключевыми регуляторами транскрипции и воспаления, потенциально могут играть значительную роль в патогенезе атеросклероза. Целью исследования было изучить влияние нокаута генов *Cdk8* и *Cdk19* на развитие атеросклеротических поражений у мышей с дефицитом аполипопротеина Е (ApoE$^{-/-}$). Показано, что как эндотелиоспецифичный, так и системный нокаут *Cdk8* достоверно снижает площадь атеросклеротических поражений аорты, причем тотальный нокаут оказывает более выраженный антиатерогенный эффект. Это свидетельствует о плейотропной роли CDK8 в патогенезе атеросклероза, опосредованной его функцией не только в эндотелиальных клетках, но и, вероятно, в макрофагах. В отличие от *Cdk8*, системный нокаут *Cdk19* не оказал значимого влияния на развитие атеросклероза. Таким образом, CDK8, но не CDK19, идентифицирован в качестве проатерогенного регулятора, что делает его перспективной мишенью для разработки новых терапевтических стратегий.

Ключевые слова: атеросклероз, генетически модифицированные животные, транскрипционные киназы CDK8 и CDK19, атеросклеротические поражения, аполипопротеин Е

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According to the World Health Organization, myocardial infarction and stroke, being the main complications of atherosclerosis, remain the leading causes of death worldwide. In 2019 in Russia, circulatory system diseases accounted for 46.8% of all fatal cases. The high mortality rate results largely from the long asymptomatic course of atherosclerosis, which at the later (diagnosed) stages often requires surgery and responds weakly to conservative therapy [1]. Despite the existing treatment methods aimed at decreasing low-density lipoprotein (LDL) cholesterol levels and restoring blood flow, atherosclerosis remains a global medical and social problem. It is generally accepted that atherosclerosis is a chronic inflammatory disease of the arteries [2], but intracellular molecular mechanisms that control such inflammation and disease progression are poorly understood [3]. The atherosclerotic plaque formation is the key event in its pathogenesis characterized by chronic inflammation, endothelial dysfunction, lipid accumulation, and proliferation of smooth muscle cells in the wall [4, 5].

The CDK8 and CDK19 cyclin-dependent kinases, being part of the mediator complex, represent the key regulators of the RNA polymerase II-mediated transcription. Despite the fact that their exact mechanisms of action are still poorly understood, it is well known that CDK8/19 play a central role in transcriptional reprogramming, which underlies cell differentiation and pathogenesis of various diseases [6]. CDK8/19 are modulators of the signaling pathways of transcription factors STAT1 and NF-kB which play a critical role in inflammatory processes [7, 8].

Recently, the data linking CDK8 to cardiovascular disorders has been accumulating. In particular, CDK8 is a co-regulator of the HIF-1α (hypoxia-inducible factor 1-alpha) transcription factor, the key mediator of the cellular response to hypoxia contributing greatly to the atherosclerosis development [9]. HIF-1α triggers expression of a broad range of genes contributing directly to the development of atherosclerosis, such as TNF, CD36, VEGF, ICAM-1, VCAM-1 [10–12]. Thus, HIF-1α mediates pro-atherogenic processes, such as lipid metabolism disturbances in macrophages, endothelial dysfunction, and enhanced inflammation [13]. Furthermore, CDK8 is a negative lipid biosynthesis regulator. CDK8 induces increased ubiquitination and degradation of SREBP through phosphorylation of this protein. The SREBP family includes the key transcription factors that regulate lipid metabolism, including transcription of the genes responsible for cholesterol synthesis and lipogenesis [14]. Since CDK8 regulates the expression of many genes associated with atherogenesis, it has been hypothesized than the CDK8 and/or CDK19 deletion may result in the slower progression of atherosclerosis due to the decrease in lipoprotein infiltration of the aortic intima.

Despite the well known CDK8/19 involvement in carcinogenesis and immune response [15, 16], their role in atherogenesis is poorly understood. In this regard, it seems promising to study the role of the CDK8/19 transcription kinases, being the well- known regulators of inflammation and contributors to cardiovascular disorders, in the development of atherosclerosis. Thus, the study aimed to assess the impact of the systemic and endothelium-specific *Cdk8* knockout, as well as systemic *Cdk19* knockout on the formation of atherosclerotic lesions in the mouse aorta against the background of the *ApoE* knockout, the well-known mouse model of atherosclerosis [17].

METHODS

Keeping mice

The study involved the use of mice of the Rosa26/Cre-ERT2 (B6.129-Gt(ROSA)26Sortm1(cre/ERT2)Tyj/J, Jackson Laboratory) and Tie2-Cre (B6.Cg-Tg(Tek-cre)1Ywa/J, Jackson Laboratory) activator lineages. Mice of these lineages were crossed with Cdk8fl/fl (Jax:008463, Jackson Laboratory) with exon 2 in the *Cdk8* gene flanked by loxP sites to obtain Rosa26/Cre-ERT2/Cdk8fl/fl (systemic knockout) and Tie2-Cre/Cdk8fl/fl (endothelium-specific knockout). Furthermore, the C57BL/6N-Cdk19 mice (RRID:MMRRC 047035-UCD, MMRRC) with the constitutive *Cdk19* knockout were used. Genotyping of the Cdk8fl/fl, C57BL/6N-Cdk19, Rosa26/Cre-ERT2 offspring was conducted as reported earlier [18]. The experiments involved mice of the above lineages against the background of the ApoE-/- status (apolipoprotein E knockout). The mice were a gift from Yury Kotelevtsev [19]. For genotyping of the ApoE-/- and Tie2-Cre mice, the P1, P2, P3 and P4, P5, P6 oligonucleotide primers, respectively, were used (Table). All primers were synthesized by Evrogen (Russia).

The mice were kept in the vivarium of the Institute of Gene Biology RAS with permanent access to water and food. The light/dark cycle was 12/12 h, air temperature — 23 ± 1 °C, humidity — 42 ± 5%.

Cdk8 knockout induction

To induce *Cdk8* knockout in the Rosa26/Cre-ERT2/Cdk8fl/fl mice, intraperitoneal injections of tamoxifen (Sigma-Aldrich, USA) dissolved in corn oil (Sigma-Aldrich, USA) were used as previously reported [20]: males aged 2 months were administered 0.15 mL of tamoxifen at a concentration of 20 mg/mL daily throughout 7 days. These mice were put on the atherogenic diet (Western type diet, WTD) a month after the knockout induction.

Experimental groups

The following experimental groups were formed of male mice of the specified lineages aged 3 months (Fig. 1), a total of 46 animals:

1. ApoE — apolipoprotein E-deficient mice fed with standard feed (negative control), $n = 4$;
2. ApoE WTD — ApoE-/- mice on the WTD (positive control of atherosclerosis model for the Cdk19-/-/ApoE-/- и Tie2-Cre/Cdk8fl/fl/ApoE-/- mice), $n = 8$;
3. ApoE + Oil WTD — ApoE-/- mice treated with corn oil throughout 7 days (150 μL a day), which were on the WTD (positive control of atherosclerosis model for the tamoxifen-treated mice Rosa26/Cre-ERT2/Cdk8fl/fl), $n = 5$;
4. Rosa WTD — Rosa26/Cre-ERT2 mice on the WTD (negative control of atherosclerosis model for the Rosa26/Cre-ERT2/Cdk8fl/fl mice), $n = 4$;
5. Tie WTD — Tie2-Cre mice on the WTD (negative control of atherosclerosis model for the Tie2-Cre/Cdk8fl/fl/ApoE-/- mice), $n = 4$;
6. Cdk19/ApoE WTD — mice with the *Cdk19* knockout against the background of the *ApoE* knockout, which were on the WTD, $n = 8$;
7. Cdk8/Rosa/ApoE WTD — Rosa26/Cre-ERT2/Cdk8fl/fl mice with the inducible *Cdk8* knockout against the background of the *ApoE* knockout, which were on the WTD, $n = 6$;
8. Cdk8/Tie/ApoE WTD — mice with the constitutive endothelium-specific *Cdk8* knockout against the background of the *ApoE* knockout, which were on the WTD, $n = 7$.

Exclusion criteria

The experiment involved males only. Animals were excluded from the experiment due to clinical status deterioration

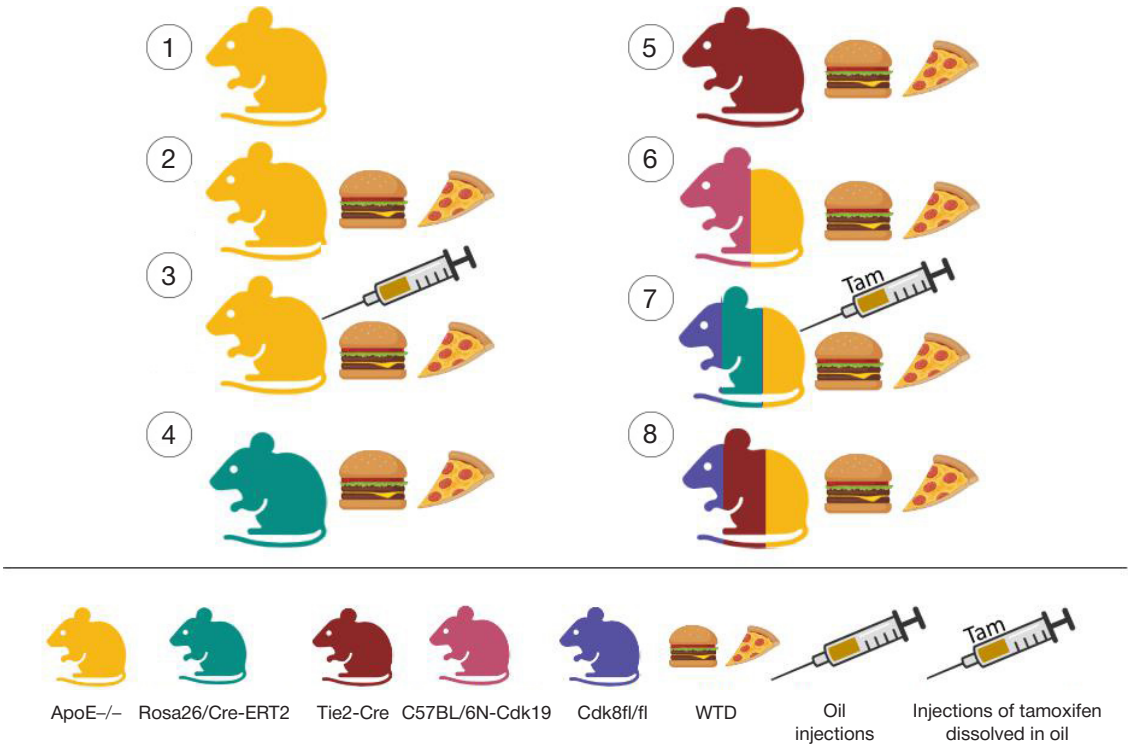

Fig. 1. Schematic representation of the experimental groups of mice used in the experiment

manifested by fatigue, apathy, refusal to eat, as well as in cases of the animal's spontaneous death before scheduled euthanasia. A total of five animals were excluded based on the latter criterion: two from group 1, one from groups 4, 5, and 7.

Atherogenic diet

Adult mice in different experimental groups aged 3 months were kept on the atherogenic diet. The diet composition was as follows: 21.2% dairy fat (Parmalat, Russia), 34% sucrose (Solarbio, China), and 0.2% cholesterol (Macklin, China) [21]. To induce the development of atherogenic lesions, mice were kept on the diet for 2 months.

Aortic examination

The mouse aorta separation and staining, as well as image processing were conducted as previously reported [22]. The mice were intraperitoneally anesthetized with the solution of 0.6 mL Zoletil (Virbac, France) + 0.3 mL Xylazine (Interchemie Werken "de Adelaar" BV, Netherlands) + 9 mL saline (PanEco, Russia) at the dose of 100 μL per 10 g of the animal's body weight, then the cardiovascular system was perfused through a puncture of the apex of the left ventricle with 10 mL of PBS (BioinnLabs, Russia) to flush out blood. The Zeiss Stemi DV4 stereo microscope (Carl Zeiss, Germany) was used to accurately separate the entire aorta, from the arch to the iliac arteries; perivascular adipose and connective tissues around the aorta were removed, avoiding damage to these. To immobilize tissues, perfusion with 10 mL of 4% paraformaldehyde solution (Medix, Russia) was performed. Then the aorta was put in 1 mL of the freshly prepared 0% Oil Red O solution (Sigma-Aldrich, USA) and incubated for 60 min at room temperature. After staining, the specimen was washed with the 60% isopropanol (Panreac AppliChem, Germany) for 20 min, then triple washed with the distilled water for 5 min. The microscope was used to completely clear the aorta of the remaining stained perivascular adipose tissue, put it onto the slide, and acquire high-resolution digital micrographs. The images obtained were processed using the ImageJ software tool. The percentage of atherosclerotic lesions was calculated as the ratio of the area of lesions to the total area of the ascending aorta and aortic arch.

Western blot

The CDK8 and CDK19 levels were assessed in the aortas of mice in all of the studied groups. To detect CDK8 and CDK19, the CDK8 (D6M3J) Rabbit 17395 antibody (Cell Signaling, USA) and CDK19 antibody from the paper [18], respectively, diluted 1 : 1000 were used. The β-actin protein levels were determined as a load control. For that the mouse monoclonal

Table. Oligonucleotides used in the study

	Sequence 5' → 3'
P1	GCC TAG CCG AGG GAG AGC CG
P2	TGT GAC TTG GGA GCT CTG CAG C
P3	GCC GCC CCG ACT GCA TCT
P4	CTG TGA CCT GAG TGC CCA GT
P5	GCG TTT AAG TAA TGG GAT GGT C
P6	CCA CAC ACG TGC ACA TAT AGA

anti-β-actin antibody (A2228, Sigma-Aldrich, USA) diluted 1 : 1000 was used. Detection involved the use of the secondary antibodies conjugated with horseradish peroxidase (HRP): anti-rabbit IgG (catalogue number 7074, Cell Signaling, USA) and anti-mouse IgG (catalogue number 7076, Cell Signaling, USA) diluted 1 : 2000. Visualization of the Western blot assay results was accomplished using the iBright FL1500 system (Invitrogen, USA).

Statistical data processing

Significance of differences was assessed using one-way ANOVA in GraphPad Prism 8.0.1 (GraphPad Software, USA). The data are presented as the mean ± standard error of the mean.

RESULTS

In this study, the genetically modified mice with the systemic and endothelium-specific knockout of the *Cdk8* gene, as well as with the systemic knockout of the *Cdk19* gene were the research objects. In the first phase of the study, the CDK8 and CDK19 protein levels in the aortas of mice of different experimental groups were validated (Fig. 2).

It has been found out, that in the aortas of the ApoE, Tie, and Rosa control mice, the CDK8 and CDK19 proteins are detected, while in mice with the systemic *Cdk8* knockout (group Cdk8/Rosa/ApoE) there is no CDK8, and in mice with the systemic *Cdk19* knockout (group Cdk19/ApoE) there is no CDK19. However, the CDK8 protein is detected in mice with the endothelium-specific *Cdk8* knockout (group Cdk8/Tie/ApoE). The reported presence of protein is consistent with the histological structure of the aorta consisting of three layers: tunica adventitia, media, and intima, which is constituted mainly by the endothelium [23]. Thus, in this group the *Cdk8* knockout affects mainly endothelial cells of the intima, which explains detection of the CDK8 protein in the homogenate of the entire aorta.

Then aortas were assessed in mice of all experimental groups after being kept on the atherogenic diet throughout 2 months. The values reported for the mice of the experimental groups Cdk19/ApoE WTD and Cdk8/Tie/ApoE WTD were compared to the values of the group ApoE WTD representing a positive control in the experiment and to the values of groups Tie WTD and ApoE kept on the standard diet representing a negative control (Fig. 3).

It has been found out that in the group of mice with the endothelium-specific *Cdk8* knockout there is a significant (p = 0.0295) reduction of the aortic lesion compared to the ApoE positive control. Furthermore, in the group with the systemic *Cdk19* knockout the lesion area does not differ from that in control groups.

When inducing the *Cdk8* knockout in the Cdk8/Rosa/ApoE group, the mice received injections of tamoxifen dissolved in corn oil daily. To create positive controls for this group, the ApoE mice treated with corn oil in accordance with the same scheme were used. After keeping on the atherogenic diet, atherosclerotic lesions of the aorta were assessed in the Cdk8/Rosa/ApoE WTD, ApoE + Oil WTD mice as a positive control; Rosa WTD, as well as ApoE on the standard diet as a negative control (Fig. 4).

It has been found out, that the values obtained in mice with the systemic *Cdk8* knockout are significantly (p = 0.0024) lower compared to the positive control values and do not differ from the negative control values.

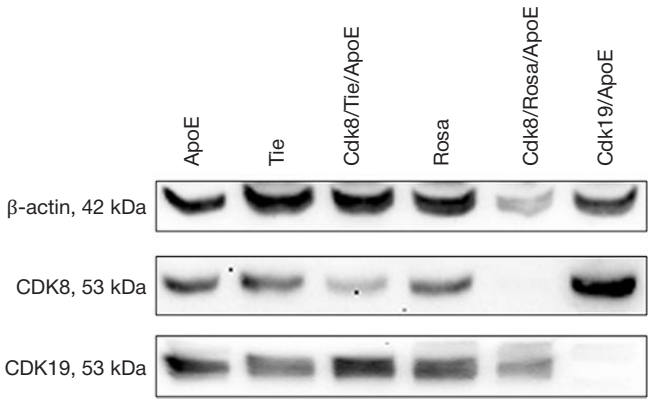

Fig. 2. Representative Western blot image showing the content of CDK8 and CDK19 in the aortas of mice of different experimental groups

DISCUSSION

Genetically modified animals represent a common tool for modeling and further investigation of pathogenesis of human disorders, as well as for the development of therapy methods [24]. This determines their important role in the study of such socially significant disorders, as atherosclerosis. Atherosclerosis, as a chronic progressive disorder, underlies most cases of cardiovascular disorders, which determines high mortality and disability rates in the population [25].

It is well known that the CDK8 transcription kinase and its paralogue CDK19 modulate signaling pathways of the STAT1 and NF-kB transcription factors, thereby regulating the inflammatory response. In a number of studies, it has been shown that the low molecular weight CDK8/19 inhibitors, such as SenexinA/B, Cmpd3/4, Cpd32, Cortistatin A, effectively suppress activation of the key pro-inflammatory transcription factors STAT1 and NF-kB *in vitro* and *in vivo* [7, 8, 26, 27]. Furthermore, the role of CDK8 in the pathogenesis of cardiovascular disorders has been shown, since this kinase is a co-regulator of HIF-1α involved in pro-atherogenic processes [9, 10, 28].

This research was focused on studying the role of the CDK8 and CDK19 transcription kinases in the atherosclerotic lesion formation using the genetically modified mice with the systemic and endothelium-specific *Cdk8* knockout, as well as with the systemic *Cdk19* knockout. To model accumulation of lipoproteins in the aortic wall, these mice were put against the *ApoE* knockout background. The *ApoE* gene encodes the apolipoprotein E protein playing a central role in lipoprotein metabolism. One of its main functions is to serve as a ligand for the hepatic receptors that remove chylomicron and LDL remnants from the bloodstream. The ApoE-/- mice have no key mechanism for blood plasma purification from cholesterol-rich lipoproteins, which results in the dramatic increase in plasma cholesterol levels, LDL accumulation in blood, and subsequent development of atherosclerotic lesions [17].

The *Cdk8* and *Cdk19* knockout in the aortas of the mice assessed was confirmed by Western blot assay (Fig. 2). It was shown that there were no CDK19 in the group of the CDK19/ApoE mice with the systemic *Cdk19* knockout, no CDK8 in the group of the CDK8/Rosa/ApoE mice with the systemic *Cdk8* knockout, and incomplete CDK8 removal in the CDK8/Tie/ApoE group with the endothelium-specific *Cdk8* knockout. Thus, we have shown that these models are relevant.

The study of the lipid inclusion accumulation in the aortas of experimental mice has shown that both endothelium-specific (Fig. 3) and systemic (Fig. 4) *Cdk8* knockout results in significant

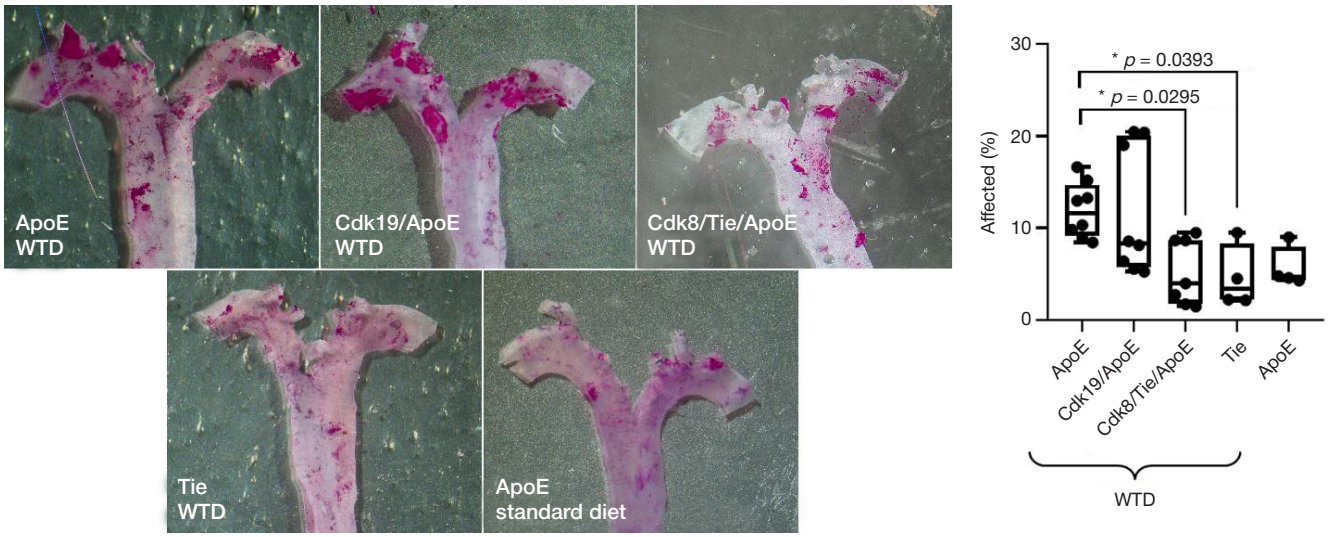

Fig. 3. Aorta assessment in mice of experimental groups ApoE WTD, Cdk19/ApoE WTD, Cdk8/Tie/ApoE WTD, Tie WTD, as well as ApoE fed with standard feed. Representative image of the studied aortas (on the left), diagram of the affected area calculation (on the right). The aortic lesions are marked with white dotted lines (*— $p < 0.05$)

reduction of the vascular lesion area. Furthermore, the total *Cdk8* knockout has a stronger anti-atherogenic effect compared to the endothelium-specific one. The data obtained suggest that the CDK8 contribution to the atherosclerosis pathogenesis is not limited to endothelial cells; it is also mediated by its function in the key cell types for this disorder, such as macrophages and possibly vascular smooth muscle cells. These findings are consistent with the literature data showing the decrease in the anti-inflammatory response upon CDK8/19 inhibition in monocytes/macrophages [29]. According to the results obtained, CDK8 is involved in the atherosclerotic phenotype enhancement, possibly through regulation of the transcription programs associated with the inflammatory response and lipid metabolism.

In contrast to *Cdk8*, the systemic *Cdk19* inactivation had no significant effect on the area of the aortic atherosclerotic lesions, which demonstrates the values comparable to that of both negative and positive control groups (Fig. 3). It should be noted, that in the Cdk19/ApoE group, a significant inter-individual variability was observed, including specimens with both large and minimal lesion areas. Such a distribution, along with the lack of the general effect, suggests that CDK19, in contrast to its paralogue CDK8, does not determine the atherosclerosis progression.

Chronic inflammation is a cornerstone of the atherosclerosis pathogenesis [2], and our results clearly indicate the CDK8 pro-atherogenic role. Considering the fact that CDK8 is an inflammatory response regulator [6–8], it can be assumed that pharmacological inhibition of this kinase will reproduce the reported anti-atherogenic effect by suppressing pro-inflammatory signaling pathways. Thus, the use of the well-known CDK8 inhibitors in experimental atherosclerosis models seems to be a promising area for the development of novel therapeutic approaches.

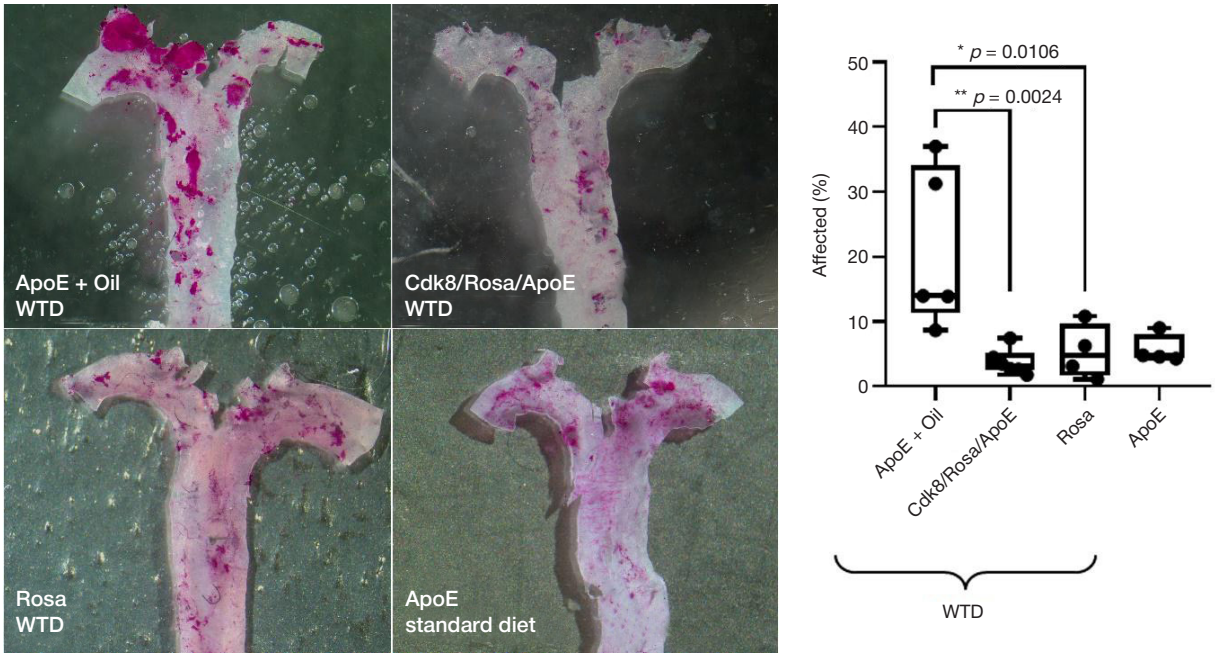

Fig. 4. Aorta assessment in mice of experimental groups ApoE + Oil WTD, Cdk8/Rosa/ApoE WTD, Rosa WTD, as well as ApoE fed with standard feed. Representative image of the studied aortas (on the left), diagram of the affected area calculation (on the right). The aortic lesion is marked with the white dotted line (*— $p < 0.05$, ** — $p < 0.01$)

CONCLUSIONS

The study conducted discloses the fundamental atherogenesis regulation aspects related to the function of the CDK8 and CDK19 transcription kinases. The use of genetic models in the ApoE$^{-/-}$ mice with the knockout of the above genes has shown that CDK8 functions as a pro-atherogenic regulator, which is confirmed by significant reduction of the atherosclerotic lesion area in knockout mice. The stronger anti-atherogenic effect of the systemic knockout compared to the endothelium-specific one suggests the pleiotropic nature of the CDK8 impact on the disease pathogenesis, including its role in not only endothelial cells, but also other cell populations, specifically in macrophages. The CDK8 pro-atherogenic effect molecular mechanisms are likely to be related to its capability of regulating the key transcription programs, including the HIF-1α, STAT1, and NF-κB pathways, which modulate the inflammatory response and lipid metabolism in the vascular wall. CDK19 has no significant effect on the development of atherosclerotic lesions, which emphasizes functional divergence between the structurally homologous kinases CDK8 and CDK19 in the context of atherosclerosis pathogenesis. The findings not only expand the knowledge about the atherosclerosis molecular basis, but also open up new opportunities for target therapy development. The CDK8 inhibition is a promising strategy for suppression of the atherosclerotic lesion progression. Further research should be focused on clarifying the cell-specific CDK8 mechanisms of actions in various populations of vascular wall cells and assessment of the CDK8 selective inhibitor efficacy in pre-clinical trials.

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