DOI: https://doi.org/10.17816/brmma121327

Review

# ROLE OF VIRUSES IN CELL TRANSFORMATION AND ONCOGENESIS

A.V. Moskalev[1], B.Yu. Gumilevskiy[1], V.Ya. Apchel[1, 2], V.N. Tsygan[1]

[1] Kirov Military Medical Academy, Saint Petersburg, Russia

[2] Herzen State Pedagogical University of Russia, Saint Petersburg, Russia

***ABSTRACT.*** The data of modern scientific literature characterizing individual mechanisms of transformation of normal cells and various stages of oncogenesis associated with viruses were analyzed. The data of sequencing of tumor genomes and amino acid sequences indicate that most tumors are a consequence of the accumulation of sequential mutations, a significant contribution to the formation of which was made by oncogenic viruses. Processes that alter or impair the functioning of signaling pathways can contribute to transformation and oncogenesis. The phosphorylation of the ribosomal protein S6 by protein kinase B, which increases the speed, and prolongs the translation time, is critical in oncogenesis. Protein kinase B inhibits the processes of apoptosis, participates in the regulation of the cell cycle, and regulates tissue growth; an increased level of this protein is found in various tumors. Transformation and tumor-associated processes are the result of a combination of dominant mutations with increased function of proto-oncogenes and recessive mutations with a loss of function of tumor suppressor genes encoding proteins that block cell cycle progression. The function of any gene product can be altered by oncogenic viruses. Transforming proteins alter cell proliferation with a limited set of molecular mechanisms. The integration of proviral deoxyribonucleic acid in a specific region of the cellular genome contributes to the induction of tumor-associated processes by non-transductive viruses. Cellular oncogenes induce signaling at various stages of the cell cycle, which ultimately leads to its dysregulation and progression. In cell transformation, the interaction of E1A viral proteins with tumor suppressors RB, histone acetyltransferase p300/CVR, and inhibitors of cyclin-dependent kinases p27 and p21 is crucial. Virus-transforming proteins have various properties, from changing the sequences of primary amino acids to inducing various variants of biochemical activity. Most tumors induced by non-transductive retroviruses result from increased transcription of cellular genes (myc) located in close proximity to integrated proviruses. Latent membrane protein 1 is an integral protein of the plasma membrane and functions as a constitutively active receptor and facilitates the transition from a latent course of infection to a lytic one. In the absence of a ligand, this protein oligomerizes, and activates proteins that control cell proliferation and survival.

**Keywords:** apoptosis; genes; suppressor genes; sequential mutations; oncogenic viruses; nontransducing viruses; oncogenesis; signaling pathways; nucleic acids; transformation.

**To cite this article:**
Moskalev AV, Gumilevskiy BYu, Apchel VYa, Tsygan VN. Role of viruses in cell transformation and oncogenesis. *Bulletin of the Russian Military Medical Academy.* 2023;25(1):133–144. DOI: https://doi.org/10.17816/brmma121327

**Received:** 14.12.2022 **Accepted:** 16.02.2023 **Published:** 29.03.2023

УДК: 576.8.097.31

DOI: https://doi.org/10.17816/brmma121327

Обзорная статья

# РОЛЬ ВИРУСОВ В ТРАНСФОРМАЦИИ КЛЕТОК И ОНКОГЕНЕЗЕ

А.В. Москалев[1], Б.Ю. Гумилевский[1], В.Я. Апчел[1, 2], В.Н. Цыган[1]

[1] Военно-медицинская академия имени С.М. Кирова, Санкт-Петербург, Россия

[2] Российский государственный педагогический университет имени А.И. Герцена, Санкт-Петербург, Россия

**Резюме.** Анализируются данные современной научной литературы, характеризующие отдельные механизмы трансформации нормальных клеток и различные этапы онкогенеза, связанного с вирусами. Данные секвенирования геномов опухолей, аминокислотных последовательностей свидетельствуют, что большинство опухолей — это следствие накопления последовательных мутаций, значимый вклад в формирование которых внесли онкогенные вирусы. Процессы, которые изменяют или ухудшают функционирование сигнальных путей, могут способствовать трансформации и онкогенезу. Большое значение в процессах онкогенеза играет фосфорилирование рибосомального белка S6 протеинкиназой B, увеличивающее скорость и удлиняющее время трансляции. Протеинкиназа B ингибирует процессы апоптоза, принимает участие в регуляции клеточного цикла, регулирует рост тканей, повышенный уровень этого белка обнаруживается во многих опухолях. Трансформация и опухолеассоциированные процессы являются результатом комбинации доминантных мутаций с усилением функции протоонкогенов и рецессивных мутаций с потерей функций генов-супрессоров опухолей, кодирующих белки, блокирующие прогрессирование клеточного цикла. Функции любого генного продукта могут изменяться онкогенными вирусами. Трансформирующие белки изменяют пролиферацию клеток ограниченным набором молекулярных механизмов. Интеграция провирусной дезоксирибонуклеиновой кислоты в определенном участке клеточного генома способствует индукции опухолеассоциированных процессов нетрансдуцирующими вирусами. Клеточные онкогены индуцируют передачу сигналов на различных стадиях клеточного цикла, что, в конечном итоге, приводит к его дисрегуляции и прогрессированию. Для процессов трансформации клеток необходимо взаимодействие вирусных белков E1A с супрессорами опухолей RB, гистонацетилтрансферазой p300/CBP и ингибиторами циклин-зависимой киназы p27 и p21. Вирус-трансформирующие белки обладают разнообразными свойствами от изменения последовательностей первичных аминокислот до индукции различных вариантов биохимической активности. Большинство опухолей, индуцированных нетрансдуцирующими ретровирусами, возникают в результате повышенной транскрипции клеточных генов (*myc*), расположенных в непосредственной близости от интегрированных провирусов. Латентный мембранный белок 1 является интегральным белком плазматической мембраны, функционирует как конститутивно активный рецептор и облегчает переход от латентного течения инфекции к литическому. При отсутствии лиганда этот белок олигомеризуется и активирует белки, контролирующие пролиферацию и выживание клеток.

**Ключевые слова:** апоптоз; гены; гены-супрессоры; последовательные мутации; онкогенные вирусы; нетрансдуцирующие вирусы; онкогенез; сигнальные пути; нуклеиновые кислоты; трансформация.

**Как цитировать:**
Москалев А.В., Гумилевский Б.Ю., Апчел В.Я., Цыган В.Н. Роль вирусов в трансформации клеток и онкогенезе // Вестник Российской военно-медицинской академии. 2023. Т. 25, № 1. С. 133–144. DOI: https://doi.org/10.17816/brmma121327

**Рукопись получена:** 14.12.2022 **Рукопись одобрена:** 16.02.2023 **Опубликована:** 29.03.2023

## INTRODUCTION

The viral theory of cancer etiology is now widely accepted. Understanding the molecular mechanisms of oncogenesis has been made possible by the study of oncogenic viruses. These mechanisms are based on the accumulation of mutations in cell populations and epigenetic alterations to genes and nucleosomes. These changes have an impact on the stages of signaling pathways that regulate intercellular communication. Endogenous or exogenous deoxyribonucleic acid (DNA) damage can result in the inheritance of one or more genetic changes. An important finding was that the induction of malignant processes is not required for oncogenic virus reproduction. Moreover, when normal cells are cultured with certain viruses, their growth pattern and morphology can be changed. These cells can be transformed. The study of cell culture systems enabled the identification of carcinogenic potential in virus-infected cells. As a result, viral and cellular oncogenes, or circuits that control cell proliferation, emerged. The increase in the life of transformed cells, the transformation itself, and oncogenesis are distinct phenomena that are intimately linked. Transformed cells have a longer half-life, reduced inhibition of intercellular contacts, and produce their own growth factors. Retroviruses can thus either encode oncogenes or integrate into the host cell genome and alter the expression of cellular proto-oncogenes. Transforming DNA viruses encode proteins that bind to specific cellular tumor suppressor proteins, such as RB and p53, shortening the cell cycle. Proteins encoded by transforming viruses can prevent cell apoptosis, inhibit immune recognition, and promote angiogenesis. Chronic immune response induction over time causes cell and tissue damage and the emergence of cells with altered functions, which is the basis of virus-induced oncogenesis. All of this is not a discovery, but modern methods have revealed many "intimate" mechanisms of tumor-associated processes.

**This study** aims to assess data from modern literature that describes the "intimate" mechanisms of normal cell transformation and the stages of oncogenesis.

## MATERIALS AND METHODS

Modern scientific literature on the characterization of tumor-associated processes has been studied.

## RESULTS AND DISCUSSION

Modern high-throughput tumor genome sequencing methods have demonstrated that most tumors are the result of the accumulation of consecutive mutations over a long period of time. The number and nature of genetic changes vary according to cancer type, patient age, mutagen contribution to oncogenesis, and other factors, including diet. Smokers with small cell lung cancer, for example, have 10 times more mutational changes in their genome than nonsmokers with the same condition. Hundreds of genetic changes, including substitutions, insertions, deletions, translocations, and copy number changes, accumulate in the later stages of cancer, particularly after gene mutations during DNA repair. However, most of these changes are secondary mutations. The number of mutations that cause cancer is minimal, ranging from 5 to 10. The nature of the first mutation is critical because it decides whether submutations provide tumor development a selective advantage. Mutations can also alter the functions of signal transduction pathways that control cell proliferation, apoptosis, and genome integrity. Such mutations are most commonly seen in genes encoding components of the mitogen-activated protein kinase (MAPK), WNT/APC signaling pathways, and the p53 protein. MAPK influences gene expression, differentiation, cell survival, and apoptosis. As a result, phosphorylation processes develop in cells, resulting in the activation, and possibly suppression, of transcription factors and regulatory proteins, which eventually leads to changes in gene expression levels [1-3].

Transformed cells are distinguished by their independence from the signals or conditions that control DNA replication and cell division. Transformed cells grow larger and can divide indefinitely. This process requires the secretion of telomerase, which maintains telomeric DNA at the ends of chromosomes and so provides intrinsic regulation. Transformed cells require fewer growth factors. Additionally, they can secrete their own growth factors, providing autocrine growth stimulation. However, it is important to understand that transformed cells are not always oncogenic. Many transformed cell lines lack the properties necessary for tumor formation. Telomerase activity is known to not disrupt cell growth regulatory mechanisms while also contributing to genome stability and preventing chromosomal rearrangements. However, telomerase activity is present in most human tumor cells. Therefore, telomerase activity can be considered a universal marker of cancer, and telomerase reactivation can play a role in oncogenesis [4].

Cell proliferation in the body is closely regulated by signals that stimulate or inhibit cell growth to maintain organ and tissue integrity. These signals cause a variety of physiological reactions, such as the activation or inhibition of metabolic pathways and cell proliferation when organs or tissues are damaged. Signal transduction begins with the secretion of growth factors by certain cell types, which bind to specific receptors on the cell surface or extracellular matrix components. The binding of the ligand to a specific receptor results in the oligomerization of receptor molecules transported to the cytoplasmic domain of the receptor. The cytoplasmic domain of the receptor contains a protein tyrosine kinase activity, and the interaction of the growth factor with the ligand causes autophosphorylation. This mutation triggers a signal transduction cascade, followed by a series of physical interactions between membrane and cytoplasmic proteins, as well as biochemical changes. Finally, the functioning of the cell is altered. Many signaling

cascades result in changes to transcriptional activators or repressors, which influence the expression of specific cellular genes. Depending on whether method is appropriate for the particular situation, the products of these genes either allow the cell to go through another cycle of cell division or cause the cell to stop developing or cause apoptosis. Errors in the mechanisms of the signaling pathways can lead to transformation. Because formative molecular features of information transmission are short-lived and easily changed, signal transduction pathways can be blocked as soon as the initiating signal fades. These alterations in signal transduction can also lead to transformation and oncogenesis (Fig. 1) [5, 6].

Ligand binding to receptor protein tyrosine kinase (RPTK) initiates activation. Signal transduction via RAS (protein proto-oncogenic products involved in cell division stimulation, associated with plasma cell membranes) and the MAP cascade activate MAPK signal-interacting kinases 1 and 2 (MNK 1 and 2), which phosphorylate and activate translation initiation of the eIF4E protein. The activity of this initiating protein is also increased when signaling from RPTK via phosphatidylinositol 3-kinase (PI3K) and 3-phosphoinositide-dependent protein kinase (PDK1), which stimulates protein kinase B (inhibits apoptosis processes, is involved in cell cycle regulation, induces protein synthesis, and is thus a key protein regulating tissue growth, responsible for muscle hypertrophy development). Because the product of the *Akt1* gene inhibits apoptosis, elevated levels of *Akt1* expression have been found in many tumors. *Akt1 was* initially identified as an oncogene. The products of the *Akt1* gene are now known to inhibit apoptosis, and higher levels have been reported in a variety of tumors. This kinase inactivates the tuberous sclerosis complex (TSC1/2) and activates the small G-protein, Ras homology enriched in brain and mammalian target of rapamycin (mTOR). mTOR phosphorylates the inhibitory eIF4E-binding protein (4EBP), suppressing it from inactivating eIF4E. Transcription of genes encoding eIF4E and other translation initiation proteins is stimulated by phosphorylation of glycogen synthase kinase β (GSK3β) by activated AKT (V-akt murine thymoma viral oncogene homolog 1 [named after the source of isolation from cells from mice inoculated with thymoma], i.e., thymoma lymphoma, a serine-threonine kinase) and inhibits the transcriptional activator MYC (a family of regulatory genes and proto-oncogenes encoding transcription factors). The Myc family of human genes includes three related genes: *c-myc (MYC), l-myc (MYCL)*, and *n-myc (MYCN)*. AKT-dependent phosphorylation of ribosomal protein S6 kinase (S6K) increases the rate and lengthens the translation time. These mechanisms increase the availability and activity of proteins that are important in selecting the appropriate rate required for cell growth. AKT regulates metabolism via GSK3β phosphorylation and inactivation and the effect of active mTOR on lipid metabolism [7, 8].

The duration of the cell cycle phases is common for many mammalian cells that are actively growing in QC. Nevertheless, there are significant differences in cell cycle duration, mainly due to differences in the G1 and G2 phases. Early embryonic animal cells, for example, bypass G1 and G2, instead proceeding directly from DNA synthesis (S) to mitosis (M) and then back to S. Consequently, their cycles range from 10 to 60 min. Other cells that have ceased growth and division are in a specialized resting state known as G0. This explains the significant differences in cell reproduction rates in multicellular organisms. It has been found that viruses can successfully reproduce in cells that spend all or most of their lives in G0, that is, in “cell cycle sleep.” In many cases, viral protein synthesis in such cells causes them to enter the cell cycle, grow, and divide rapidly, resulting in abnormal activity [9].

Kinase activation can be followed by phosphorylation of certain sites and removal of phosphate groups, in addition to binding to the corresponding cyclin. Thus, WEE1 and MYT kinases phosphorylation of Thr and Tyr residues inhibits the activity of several cyclin-dependent kinases (CDKs) and prevents cell cycle progression until the residues are dephosphorylated by CDC25 phosphatases. Kinase activity is also controlled by members of two CDK-inhibitory protein families: INK4 proteins control G1 activation alone, and CIP/KIP proteins control all other CDKs. Both types of inhibitors are important in cell cycle control. Thus, resting cells have a high concentration of p27kip1, whereas the transition of cells into G1 phase is accompanied by a decrease in the concentration of this protein; inhibition of its synthesis prevents the transition of cells into the resting phase (Fig. 2) [10].

Activation and inactivation of specific kinases underlie cell cycle regulation. Thus, the synthesis of E-cyclin decreases the rate of mammalian cell transition from G1 phase to S-phase, and E-CDK2 cyclin accumulates during the late Gr phase. E-cyclin rapidly disappears from the cell during S-phase. DNA replication, chromosome segregation, and cell division are not so much related to changes in CDK concentration as to the CDK cycle itself, which ensures the integration of numerous exosignals and endosignals from the cell into appropriate responses. Various gene products can influence the rate of the cell cycle (both positive and negative). Transformation and tumor-associated processes are caused by a combination of dominant mutations with increased function of proto-oncogenes and recessive mutations with loss of function of tumor suppressor genes that encode proteins that inhibit cell cycle progression. Oncogenic viruses can alter the functionality of any gene product [11].

Oncogenic viruses have several traits. A single viral particle, for example, is sufficient to infect and alter a susceptible cell. The whole or part of the viral genome can remain in the transformed cell. Most often, cell transformation is accompanied by continuous expression of

DOI: https://doi.org/10.17816/brmma121327

specific viral genes. Transformed cells (with the exception of some retroviruses) do not secrete infectious viral particles, and transforming proteins alter cell proliferation through a limited number of molecular mechanisms [12].

Cells transformed with oncogenic viruses retain viral DNA in their nuclei. These DNA sequences correspond to all or part of the infected genome or to proviral DNA synthesized in retrovirus-infected cells. Viral DNA sequences can be integrated into the cellular genome or maintained autonomously as replicating episomes. The enzyme integrase is essential for viral DNA integration and the subsequent viral reproductive cycle. Integration occurs at different sites of cellular DNA, but it does not disrupt the fixed order of viral genes and provirus sequences. The integration of proviral DNA in a certain region of the cellular genome contributes to the induction of tumor-associated processes

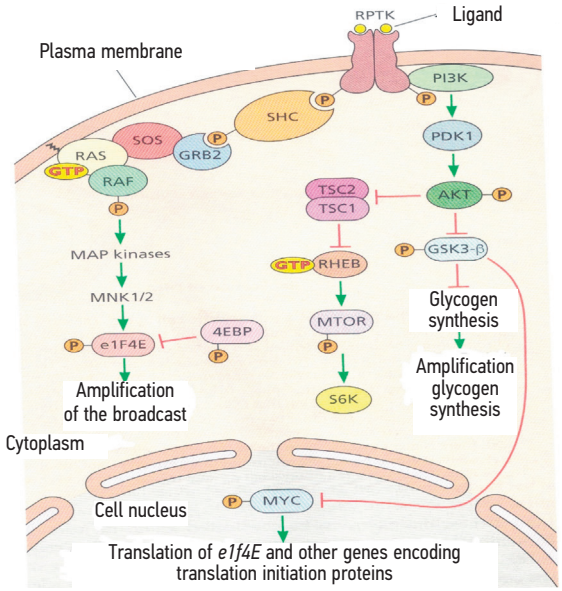


**Fig. 1.** Signaling pathways contributing to an increase in cell size and mass (according to J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)
**Рис. 1.** Сигнальные пути, способствующие увеличению размера и массы клеток (по J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)

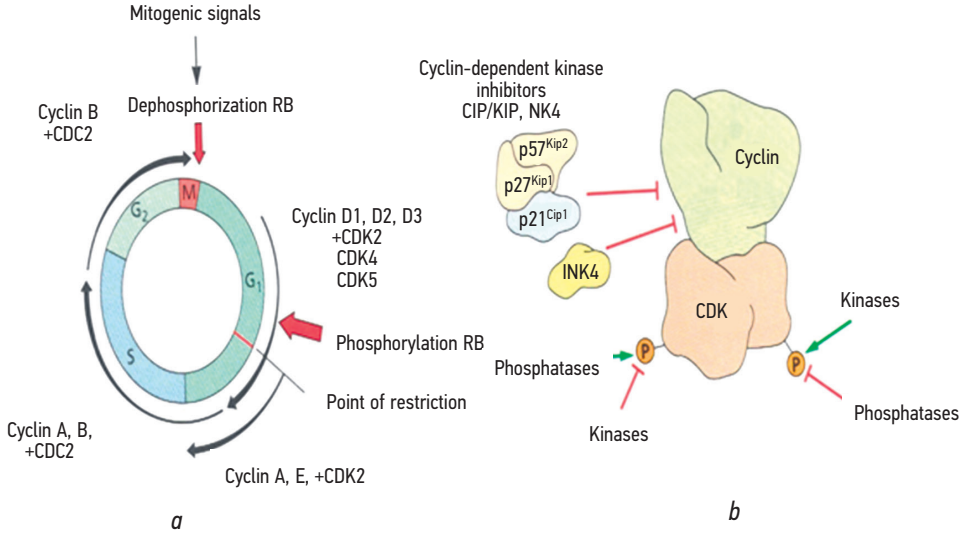


**Fig. 2.** The mammalian cyclin-CDK cell cycle engine: *a* — phases of the cell cycle are indicated on a circle. The progressive accumulation of specific cyclins and cyclin-dependent kinases (CDKs) is represented by expanding arrows that mark the time of abrupt disappearance; *b* — secretion, accumulation, and biological effects of both cyclins and CDKs are regulated by numerous mechanisms. Green arrows and red bars indicate activating and inhibitory effects, interactions, or post-translational modifications (according to J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)
**Рис. 2.** Клеточный цикл циклической CDK млекопитающих: *a* — фазы клеточного цикла обозначены на окружности. Прогрессирующее накопление специфических циклинов и циклин-зависимых киназ (CDK) представлено расширяющими стрелками, которые отмечают время резкого исчезновения; *b* — секреция, накопление и биологические эффекты как циклинов, так и CDK регулируются многочисленными механизмами. Зеленые стрелки и красные полосы указывают на активирующие и тормозящие эффекты, взаимодействия или посттрансляционные модификации (по J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)

by non-transmissible viruses. Proviral sequences are found in the same chromosomal region in each tumor cell. Provirus integration activates the transcription of cellular oncogenes. Although integration is not required for the spread of any oncogenic DNA virus, it is required for adenovirus or polyomavirus cell transformation. The transformation is dependent on viral proteins that are required for viral episome persistence, which directly modulates cell growth and proliferation [13].

The mouse polyomavirus (Polyomavirus muris or Mus musculus polyomavirus 1) and monkeypox virus SV40 have become ideal models for studies of oncogenesis and transformation. Human polyomaviruses 1 and 2 (VC and JC, respectively) were discovered in 1971 and cause persistent infections in immunosuppressed individuals. Then, from the tumor tissue of patients with Merkel cell carcinoma, eight types of other polyomaviruses were identified, whose genomes are similar to the organization of the primate polyomavirus genome. The Merkel cell polyomavirus genome is found in most Merkel cell carcinomas but not in tissues or other tumor types. It is clear that viral DNA integration came before cell proliferation. In addition, the T-antigen(s) are produced by tumor cells. This indicates that the polyomavirus gene products of Merkel cells are required to maintain the oncogenic phenotype of the transformed cells. Thus, a pronounced causal relationship between viral infection and the development of Merkel cell carcinoma has been established. Although Merkel cell carcinoma is rare, Merkel cell polyomavirus infection is widespread. Approximately 80% of people have the virus on their skin. In this case, the low frequency of tumor-associated process induction is associated with the formation of immunosuppression due to a variety of causes. Furthermore, transformation and oncogenesis depend on rare integration reactions that support the coding sequences of viral transforming proteins, LT, and sT [14, 15].

At present, genetic methods have been used to identify the transforming genes of oncogenic viruses, characterize viral genes present and expressed by transformed cell lines, and analyze the transforming activity of viral DNA fragments introduced into cells. This allowed the detection of spontaneous deletion of the viral genome. Such mutants could not transform infected cells but retained the ability to reproduce. These characteristics of the mutants showed that cell transformation and virus reproduction are different processes [16].

Because of the deletions detected in the mutants, a nucleic acid sample specific to the v-oncogene, v-src, was obtained. It was found that v-src hybridizes with cellular DNA, confirming that v-oncogenes are of cellular origin rather than viral. This crucial discovery showed that such cellular genes can become oncogenes, although such changes are very rare. Most transducing retroviruses contain a single v-oncogene in their genomes, but some, particularly the avian erythroblastosis virus *ES4,* have two oncogenes, erbA and erbB. In such cases, one oncogene induces the transformation, and the other accelerates it. Cellular oncogenes can interfere with signal transduction pathways at various stages, ultimately leading to cell cycle progression dysregulation [17].

Cell transformation requires the interaction of viral E1A proteins with tumor suppressors, such as RB, histone acetyltransferase p300/CP, and cyclin-dependent kinase inhibitors p27 and p21. E1A protein substitutions that impair these interactions reduce or terminate transforming activity. The E6 protein of human papillomaviruses type 16 or 18 also interacts with p300/CP and the tumor suppressor protein p53, as well as with proteins containing the PDZ domain (a common structural domain found in signaling proteins of bacteria, yeast, plants, viruses, and animals). The name is a combination of the first letters of three proteins: postsynaptic density protein (PSD95), Drosophila large disc tumor suppressor (Dlg1), and zonula occludens-1 (zo-1) protein). The PDZ domain is involved in the activation of signal transduction pathways that promote cell growth and inhibit apoptosis. In addition, the E6 protein binds to the transcriptional regulators c-MYC and NFX1-91 to stimulate transcription of the gene encoding the telomerase protein component. These interactions have been linked to an increase in telomerase secretion by cells synthesizing the E6 protein. The cellular E6-AP ubiquitin ligase, as well as other cellular proteins targeting proteasomal degradation, were also involved in the activation processes, in addition to p53 and NFX1-91. Degradation of PDZ-domain-containing proteins is also induced by the viral protein E6 [18].

Viral transforming proteins contain a variety of features that contribute to changes in the primary amino acid sequences and the development of various biochemical activity variants. They vary in the number and nature of signaling pathways they modify. Despite these differences, these viral proteins induce continuous cell proliferation and contribute to the formation of the final transformation variant. They result in the continuous activation of cell signal transduction cascades that induce cell cycle proliferation or disrupt pathways that regulate or inhibit this process. The v-src protein was the first to be identified as a transforming protein with protein tyrosine kinase function. The study of the protein's properties led to the identification of a large number of other proteins with similar enzymatic activity and a special role in cell signaling [19].

The SH4 domain of various viral transforming proteins has a myristic acid binding site, which allows the protein to be anchored in the cell membrane. The SH2 and SH3 domains mediate protein–protein interactions by binding phosphotyrosine-containing and proline-rich sequences, thus participating in signal transduction pathways and phosphorylating the Y527 protein. Transduced oncogenes that are homologs of cellular genes encode signal transduction components. The human herpes virus type 8 genome, for example, contains homologs of various cellular genes. The viral genome encodes proteins required for viral particle

reproduction and assembly. The cellular gene homologs are located between the major gene blocks. Some are associated with cellular chemokines (v-IL-6, v-IL-17, CCL-3, and CCL-4), chemokine receptors (v-GPCR), and signaling molecules (interferon-responsive protein [v-IRF], an N-CAM family transmembrane protein involved in v-OX2 intercellular signaling). Interferon is inhibited by v-IL-6 and v-IRF. Viral genes associated with cellular genes encode proteins (v-cyclin, v-BCL-2) that regulate cell proliferation and apoptosis. Infected HPV type 8 cells secrete v-GPCR and v-IL-6. The production of v-FLIP by infected cells promotes their survival and the latent course of the infection, whereas the secretion of v-ciclin promotes proliferation. Because the lytic course of infection is accompanied by cytotoxic effects, a paracrine model of oncogenesis has been proposed (Fig. 3).

In this model, v-GPCR secreted by infected cells triggers signal transduction via RAS (β and γ subunits of the trimeric G-protein [Gβγ]) via MAPK, PI3K, and N-terminal kinase. This stimulates the expression of cellular genes encoding interleukins (IL-6 and IL-8), vascular endothelial growth factor, and platelet growth factor (PDGF). Signal transduction via the small G-protein RAC play an important regulatory role in cell motility and growth. Rac1 is expressed by various tissues and stimulates cell motility. Disruption of cell motility regulation is one of the major complications of cancer cell invasion and metastasis. Rac1 V12 overexpression in mice causes a tumor phenotypically similar to human Kaposi sarcoma and promotes the secretion of reactive oxygen species, which activate the AKT/mTOR pathway and thereby promote protein synthesis. v-IL-6, like other viroquins that also secrete lytically infected cells, acts on neighboring cells (paracrine regulation) to maintain the proliferation of latently infected cells and induce angiogenesis. This pattern is found in individuals with Kaposi's sarcoma [20, 21].

Most tumors induced by non-transmissible retroviruses result from increased transcription of cellular genes (*myc*) located in close proximity to integrated proviruses. This mechanism of oncogenesis is known as "insertional activation of proto-oncogenes" (potential oncogenes) or "insertional carcinogenesis", a type of chromosome rearrangement in which a gene can be inserted into the cell genome and enhance the activity of neighboring proto-oncogenes. Insertion genes are also called enhancer genes. They are transmitted by ribonucleic acid (RNA) retroviruses, whereas DNA viruses can cause cell transformation mainly by blocking suppressor genes [22].

The study of avian viruses isolated from Rose's sarcoma allowed us to evaluate the basic mechanisms of the processes of insertion activation. As a rule, these viruses do not carry an oncogene, but in young chickens, they can induce B-cell lymphomas in the Fabricius pouch. Analysis of the integration sites of proviral DNA and gene products produced in these tumors allowed us to identify two types of insertion activation: promoter insertion and enhancer (enhancer) insertion. Promoter insertion leads to the formation of chimeric RNA. Viral and cellular transcripts do not merge during enhancer insertion. Cellular gene activation is mediated by viral enhancers, which enhance cellular promoter transcription [23].

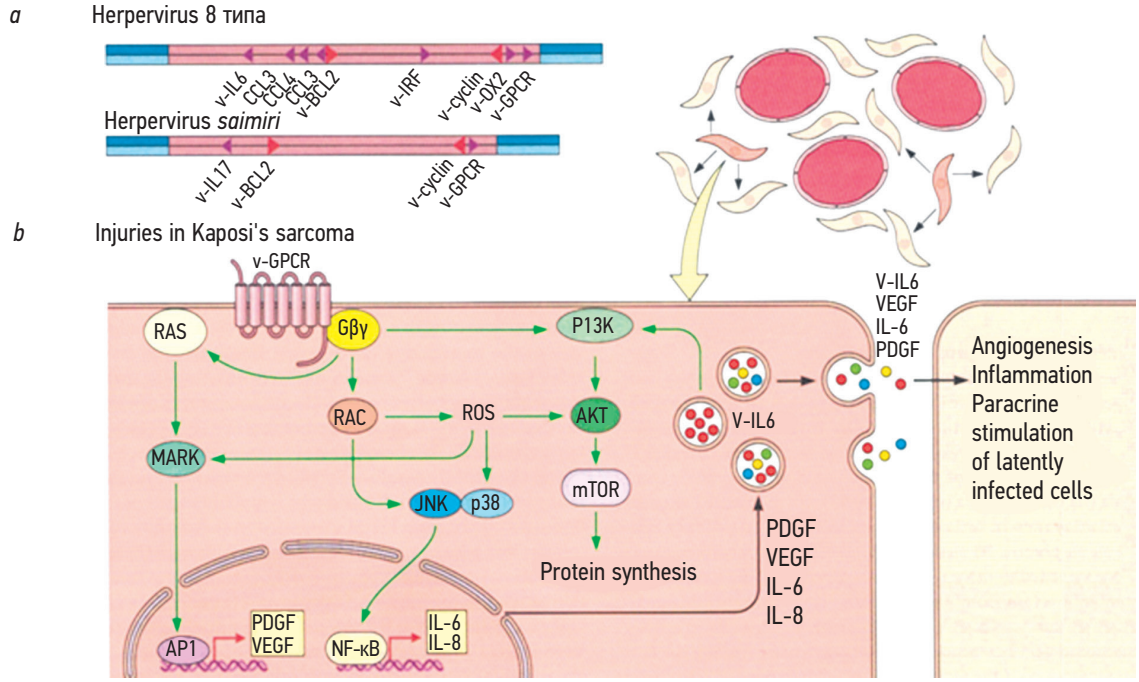


**Fig. 3.** A model of paracrine oncogenesis caused by products of type 8 HCV gene (according to J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)

**Рис. 3.** Модель паракринного онкогенеза, вызванного продуктами гена ВГЧ 8-го типа (по J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)

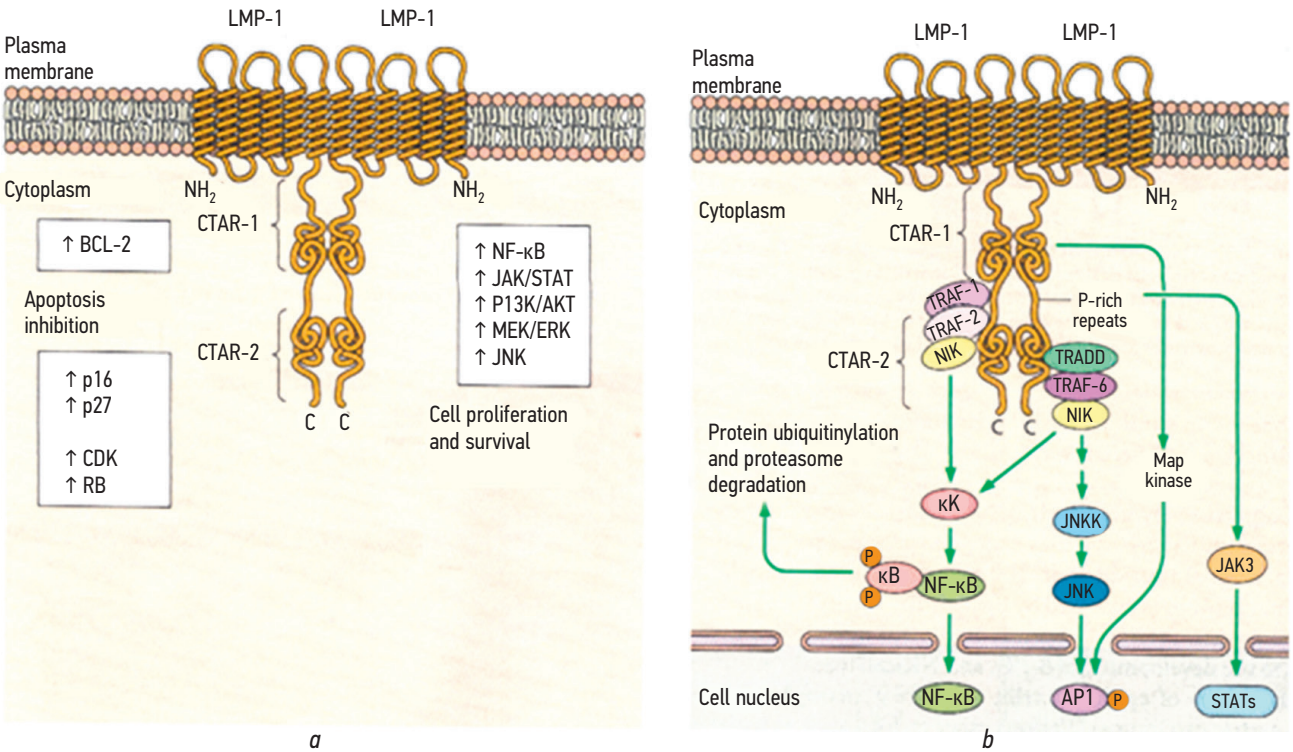


**Fig. 4.** Constitutive activation of the cell membrane by Epstein–Barr virus protein 1: *a* — Summary of transcriptional and other regulators that are stimulated or repressed by signaling from LMP-1; *b* — LMP-1, which possesses six membrane-spanning segments but no large extracellular domain, oligomerizes in the absence of ligand, a property represented by the LMP-1 dimer depicted. When localized to the plasma membrane, the C-terminal segment of LMP-1 to which cellular proteins bind is sufficient for both activation of cellular transcriptional regulators and immortalization of B cells. The long cytoplasmic C-terminal domain of the viral protein contains three segments implicated in the activation of signaling, designated C-terminal activation regions (CTARs) 1 and 2, and the intervening proline-rich repeats. As shown, multiple members of the tumor necrosis factor receptor-associated protein family (TRAFs) bind to CTAR-1, leading to activation of the protein kinase NIK (NF-KB-inducing kinase) and IkK (Ik-kinase), and ultimately of NF-kB. The CTAR-2 domain of LMP-1 further induced activation of NF-kB via association with TRADD and TRAF-6. Moreover, it is responsible for the activation of AP-1 via the JUN N-terminal kinase pathway. Additionally, the TRAF-binding domain of CTAR-1 induces the activation of the MAP kinase cascade, whereas the proline-rich repeat region is crucial for the activation of JAK3 and STATs. These responses to LMP-1 are required for the transformation of rat fibroblasts. (according to J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)

**Рис. 4.** Конститутивная активация клеточной мембраны белком 1 вируса Эпштейна — Барр: *a* — краткое описание транскрипционных и других регуляторов, которые стимулируются или подавляются передачей сигналов от LMP-1; *b* — LMP-1 олигомеризуется в отсутствие лиганда. При локализации на плазматической мембране С-концевой сегмент LMP-1, с которым связываются клеточные белки, активирует клеточные транскрипционные регуляторы и увеличивает продолжительность жизни В-клеток. Длинный цитоплазматический С-концевой домен вирусного белка участвует в активации сигнализации (CTAR) 1 и 2. Как показано, несколько членов семейства белков, ассоциированных с рецепторами фактора некроза опухоли (TRAF), связываются с CTAR-1, что приводит к активации протеинкиназы NIK (NF-KB-индуцирующая киназа) и IkK (Ik-киназа) и, в конечном счете, NF-kB. Домен CTAR-2 LMP-1 также индуцирует активацию NF-kB через ассоциацию с TRADD и TRAF-6. Он также отвечает за активацию AP-1 через путь JUN N-концевой киназы (JNK). Кроме того, TRAF-связывающий домен CTAR-1 индуцирует активацию каскада киназы MAP, в то время как богатая пролином область необходима для активации JAK3 и STATs. Эти реакции на LMP-1 необходимы для трансформации фибробластов крыс (по J. Flint, Vincent R. Racaniello, G. Rall, Th. Hatzoocannon, 2020)

Viruses affect the growth and proliferation of infected cells through signal transduction proteins. They carry out these processes by different mechanisms (Fig. 4).

Thus, the genomes of some viruses encode membrane proteins that initiate signal transduction. The most well-known is the latent membrane protein 1 of the Epstein-Barr virus (latent membrane protein 1 [LMP-1]). LMP-1 is one of the main gene products required for B-lymphocyte survival and is synthesized by most tumor cells with viral etiology. LMP-1 is a plasma membrane protein that functions as a constitutively active receptor and facilitates the transition from latent to lytic infection. In the absence of a ligand, LMP-1 oligomerizes and activates proteins that control cell proliferation and survival. The cytoplasmic C-terminal domain of LMP-1 contains three segments involved in C-terminal activation signaling regions (CTARs) 1 and 2 and intermediate proline-rich repeats. Several tumor necrosis factor receptor-associated protein family (TRAFs) proteins bind to CTAR-1, leading to NF-kB-inducing kinase and IkK (Ik-kinase) and ultimately NF-kB. The CTAR-2 LMP-1 domain also induces NF-kB activation through association with tumor necrosis factor receptor type 1-associated death domain protein (TRADD) and TNF receptor-associated factor 6 (TRAF-6). It is also responsible for AP-1 activation via the JUN N-terminal

kinase pathway. Furthermore, the TRAF-binding domain of CTAR-1 induces cascade activation of MAP kinase, whereas the proline-rich repeat region is required for JAK3 and STAT activation. These responses to LMP-1 are required for rat fibroblast transformation. Thus, LMP-1 induces the release of NF-kB from its association with cytoplasmic inhibitors via several mechanisms and the activation of the second transcriptional regulator AP-1 and signal transduction via phosphorinositide 3-kinases (PI3Ks) and AKT protein kinase. Increased expression of most cellular genes present in cells secreting LMP-1 and changes in the properties of these cells are associated with activation of these pathways. Increased secretion of adhesion molecules and activation of cell proliferation are associated with these changes. It is important to remember that LMP-1 is not synthesized in all Epstein-Barr virus-associated tumor cells. However, these cells will be influenced by LMP-1 secreted in exosomes that are formed in the endosomal compartment of most eukaryotic cells [24–26].

Viruses of the families *Polyomaviridae* and *Herpesviridae* encode proteins that permanently activate signal transduction pathways by binding to SRC family tyrosine kinases. This mechanism was first identified in a study on the polyomavirus protein mT, which has the ability to transform rodent cell lines and induce endothelioma formation in transgenic animals. The N-terminal mT sequence in sT binds to protein phosphatase 2A (PP2A) in the cytoplasm, which is required for subsequent association with c-SRC in the endoplasmic reticulum. When this kinase is associated with mT, its catalytic activity is reduced. Despite the activation of c-SRC family kinases, phosphotyrosine levels in mT-transformed cells are unchanged. The phosphorylation of specific mT tyrosine residues by activated c-SRC provides some cellular proteins with recognition domains with the ability to bind to mT, causing the signaling proteins to trigger transduction by activating RAS and MAP kinase. Consequently, mT bypasses the normal mechanism that regulates c-SRC kinase activity and also functions as a virus-specific adapter that integrates proteins that are not normally involved in cellular signal transduction. In all cases, substitutions that disrupt cellular protein binding to mT impair the transforming activity of the viral protein [27, 28].

The Epstein-Barr virus promotes several types of B-lymphocyte and epithelial cell cancers. All the viral genome is present in all monoclonal tumors, the expression of the gene encoding the transforming protein LMP-1 is variable and rarely detected in tumor samples. LMP-1 is secreted by extracellular vesicles called exosomes. Exosomes are unique structures that are involved in antigen presentation, IO suppression, neuronal communication, transformation, and tumorigenesis. Exosomes can transfer not only soluble and membrane proteins but also matrix and small interfering RNA from one cell to another. All of these indicates that exosomes are involved in tumor-associated processes [29, 30].

## CONCLUSION

The study of viral immunopathogenesis has greatly contributed to the understanding of the specific molecular mechanisms of oncogenesis. Various protein molecules and signaling pathways involved in cell activation and transformation are involved in oncogenesis. Thus, telomeres and telomerase contribute significantly to the preservation of physiological properties in cells. The properties and morphology of transformed cells differ markedly from normal cells, which may indicate critical changes. Transformation begins with the secretion of growth factors. Mitogenic and growth-promoting signals induce cell proliferation, which results in metabolic changes required to stimulate and maintain cell growth. The outcome of transformation largely depends on the regulation of the cell cycle, which is provided by complex regulatory mechanisms. The identification of oncogenes allowed researchers to determine their role in the inactivation of tumor suppressor gene products. Oncogenic viruses share common characteristics, allowing us to identify the molecular features of immunopathogenesis of tumor-associated processes. First, it is related to the peculiarities of viral genetic information location in transformed cells. Thus, viral sequences can be integrated into the genome or stored independently. Therefore, the identification of changes and cellular properties after viral gene transformation that result from recombination between viral and cellular nucleic acids is important. The activity of transformation processes induced by oncogenic viruses correlates with binding to specific cellular proteins. The finding that the transforming v-SRC protein, as well as a large number of related proteins, exhibit protein tyrosine kinase activity has shown that cellular protein phosphorylation is important in oncogenesis. Non-transmissible viruses can also induce tumor-associated processes through insertion activation mechanisms, which result in increased transcription of cellular genes located in close proximity to integrated proviruses. Some viruses can influence the growth and proliferation of infected cells via viral signal transduction proteins that have been shown to be unrelated to cellular proteins.

Thus, two major mechanisms controlling cell proliferation can be distinguished among the numerous others. Viral transformation can occur as a result of constitutive activation of signal transduction cascades or disruption of pathways that negatively regulate cell cycle progression. In both cases, there is a disruption of finely tuned mechanisms that are associated with an increase in cell size, mass, survival, DNA duplication, and cell division only when external and internal conditions are favorable.

Unfortunately, our understanding of viral oncogenesis is still limited. Therefore, a more in-depth evaluation of additional parameters related to host responses to transformed cells is required to understand the complex process of oncogenesis..

DOI: https://doi.org/10.17816/brmma121327

## REFERENCES


**1.** Griffin DE. The Immune Response in Measles: Virus Control, Clearance and Protective Immunity. *Viruses*. 2016;10(8):282–291. DOI: 10.3390/v8100282

**2.** Katze MG, Korth MJ, Law GL, et al. *Viral Pathogenesis: From Basics to Systems Biology*. San Diego, CA: Academic Press; 2016. 422 p.

**3.** Stecca B, Rovida E. Impact of ERK5 on the Hallmarks of Cancer. *Int J Mol Sci*. 2019;20(6):1426. DOI: 10.3390/ijms20061426

**4.** Guo Y-J, Pan W-W, Liu S-B, et al. ERK/MAPK signaling pathway and tumorigenesis. *Exp Ther Med*. 2020;19(3):1997–2007. DOI: 10.3892/etm.2020.8454

**5.** Lee H-J, Kim M-Y, Park H-S. Phosphorylation-dependent regulation of Notch1 signaling: the fulcrum of Notch1 signaling. *BMB Rep*. 2015;48(8):431–437. DOI: 10.5483/bmbrep.2015.48.8.107

**6.** Luoa LY, Hahnb WC. Oncogenic Signaling Adaptor Proteins. *J Genet Genomics*. 2015;42(10):521–529. DOI: 10.1016/j.jgg.2015.09.001

**7.** Gong B-L, Mao R-Q, Xiao Y, et al. Improvement of enzyme activity and soluble expression of an alkaline protease isolated from oil-polluted mud flat metagenome by random mutagenesis. *Enzyme Microb Technol*. 2017;106:97–105. DOI: 10.1016/j.enzmictec.2017.06.015

**8.** MacDonald BT, He X. Frizzled and LRP5/6 Receptors for Wnt/β-Catenin Signaling. *Cold Spring Harb Perspect Biol*. 2012;12(4):1–23. DOI: 10.1101/cshperspect.a007880

**9.** Burrell C, Howard C, Murphy F. *Fenner and White's Medical Virology, 5th ed*. San Diego, CA: Academic Press, 2016. 454 p.

**10.** Mok YK, Swaminathan K, Zeeshan N. Engineering of serine protease for improved thermostability and catalytic activity using rational design. *Int. J. Biol. Macromol*. 2019;(26):229–237. DOI: 10.1016/j.ijbiomac.2018.12.218

**11.** Ashraf NM, Krishnagopal A, Hussain A, et al. Engineering of serine protease for improved thermo stability and catalytic activity using rational design. *Int J Biol Macromol*. 2019;126:229–237. DOI: 10.1016/j.ijbiomac.2018.12.18

**12.** Garcia-Sastre A. Ten strategies of interferon evasion by viruses. *Cell Host Microbe*. 2017;22:176–184. DOI: 10.1016/j.chom.2017.07.012

**13.** Lee S, Liu H, Wilen CB, et al. A secreted viral nonstructural protein deters intestinal norovirus pathogenesis. *Cell Host Microbe*. 2019;25(6):845–857.E5. DOI: 10.1016/j.chom.2019.04.005845–857

**14.** Thapa RJ, Ingram JP, Ragan KB, et al. DAI Senses Influenza A Virus Genomic RNA and Activates RIPK3-Dependent Cell Death. *Cell Host Microbe*. 2016;20(5):674–681. DOI: 10.1016/j.chom.2016.09.014

**15.** Ahmad L, Mostowy S, Sancho-Shimizu S. Autophagy-Virus Interplay: From Cell Biology to Human Disease. *Front Cell Dev Biol*. 2018;6:155. DOI: 10.3389/fcell.2018.00155

**16.** Yang L, Shi P, Zhao G, et al. Targeting cancer stem cell pathways for cancer therapy. *Signal Transduct Target Ther*. 2020;5:8. DOI: 10.1038/s41392-020-0110-5

**17.** Tubita A, Lombardi Z, Tusa I, et al Beyond Kinase Activity: ERK5 Nucleo-cytoplasmic shuttling as a novel target for anticancer therapy. *Int J Mol Sci*. 2020;21(3):938. DOI: 10.3390/ijms21030938

**18.** Xu X, Zhang M, Xu F, Jiang S. Wnt signaling in breast cancer: biological mechanisms, challenges and opportunities. *Mol Cancer*. 2020;19:165. DOI: 10.1186/s12943-020-01276-5

**19.** Wang B, Li X, Liu L, Wang M. β-Catenin: oncogenic role and therapeutic target in cervical cancer. *Biol Res*. 2020;53:33. DOI: 10.1186/s40659-020-00301-7

**20.** Reizis B. Plasmacytoid Dendritic Cells: Development, Regulation, and Function. *Immunity*. 2019;50(1):37–50. DOI: 10.1016/j.immuni.2018.12.027

**21.** Takata MA, Gonçalves-Carneiro D, Zang TM, et al. CG dinucleotide suppression enables antiviral defence targeting non-self RNA. *Nature*. 2017;550(7674):124–127. DOI: 10.1038/nature24039

**22.** Nash A, Dalziel R, Fitzgerald J. *Mims' Pathogenesis of Infectious Disease, 6th ed*. San Diego, CA: Academic Press, 2015. 348 p.

**23.** Maillard PV, van der Veen AG, Poirier EZ, e Sousa C.R. Slicing and dicing viruses: antiviral RNA interference in mammals. *EMBO J*. 2019;38(8):e100941. DOI: 10.15252/embj.2018100941

**24.** Ma Z, Damania B. The cGAS-STING defense pathway and its counteraction by viruses. *Cell Host Microbe*. 2016;19(2):150–158. DOI: 10.1016/j.chom.2016.01.010

**25.** Diner BA, Lum KK, Javitt A, Cristea IM. Interactions of the Antiviral Factor Interferon Gamma-Inducible Protein 16. NIFI16 Mediate Immune Signaling and Herpes Simplex Virus-1 Immunosuppression. *Mol Cell Proteomics*. 2015;14(9):2341–2356. DOI: 10.1074/mcp.M114.047068

**26.** van Gent M, Braem SGE, de Jong A, et al. Epstein-Barr virus large tegument protein BPLF1 contributes to innate immune evasion through interference with toll-like receptor signaling. *PLoS Pathog*. 2014;10(2):e1003960. DOI: 10.1371/journal.ppat.1003960

**27.** Hemann EA, Green R, Turnbull JB, et al. Interferon-λ modulates dendritic cells to facilitate T cell immunity ion with influenza A virus. *Nat Immunol*. 2019;20:1035–1045. DOI:10.1038/s41590-019-0408-z

**28.** Hadjidj R, Badis A, Mechri S, et al. Purification, biochemical, and molecular characterization of novel protease from Bacillus licheniformis strain K7A. *Int J Biol Macromol*. 2018;114:1033–1048. DOI 10.1016/j.ijbiomac.2018.03.167

**29.** Behzadi P, García-Perdomo HA, Karpiński TM. Toll-Like Receptors: General Molecular and Structural Biology. *J Immunol Res.* 2021;2021:9914854. DOI: 10.1155/2021/9914854

**30.** Jeong YJ, Baek SC, Kim H. Cloning and characterization of a novel intracellular serine protease (IspK) from *Bacillus megaterium* with a potential additive for detergents. *Int J Biol Macromol.* 2018;108:808–816. DOI: 10.1016/j.ijbiomac.2017.10.173

## СПИСОК ЛИТЕРАТУРЫ

**1.** Griffin D.E. The Immune Response in Measles: Virus Control, Clearance and Protective Immunity // Viruses. 2016. Vol. 10, No. 8. P. 282–291. DOI: 10.3390/v8100282
**2.** Katze M.G., Korth M.J., Law G.L., et al. Viral Pathogenesis: From Basics to Systems Biology. San Diego, CA: Academic Press, 2016. 422 p.
**3.** Stecca B., Rovida E. Impact of ERK5 on the Hallmarks of Cancer // Int J Mol Sci. 2019. Vol. 20, No. 6. ID 1426. DOI: 10.3390/ijms20061426
**4.** Guo Y.-J., Pan W.-W., Liu S.-B., et al. ERK/MAPK signaling pathway and tumorigenesis // Exp Ther Med. 2020. Vol. 19, No. 3. P. 1997–2007. DOI: 10.3892/etm.2020.8454
**5.** Lee H.-J., Kim M.-Y., Park H.-S. Phosphorylation-dependent regulation of Notch1 signaling: the fulcrum of Notch1 signaling // BMB Rep. 2015. Vol. 48, No. 8. P. 431–437. DOI: 10.5483/bmbrep.2015.48.8.107
**6.** Luoa L.Y., Hahnb W.C. Oncogenic Signaling Adaptor Proteins // J Genet Genomics. 2015. Vol. 42, No. 10. P. 521–529. DOI: 10.1016/j.jgg.2015.09.001
**7.** Gong B.-L., Mao R.-Q., Xiao Y., et al. Improvement of enzyme activity and soluble expression of an alkaline protease isolated from oil-polluted mud flat metagenome by random mutagenesis // Enzyme Microb Technol. 2017. Vol. 106. P. 97–105. DOI: 10.1016/j.enzmictec.2017.06.015
**8.** MacDonald B.T., He X. Frizzled and LRP5/6 Receptors for Wnt/β-Catenin Signaling // Cold Spring Harb Perspect Biol. 2012. Vol. 12, No. 4. P. 1–23. DOI: 10.1101/cshperspect.a007880
**9.** Burrell C., Howard C., Murphy F. Fenner and White's Medical Virology, 5th ed. San Diego, CA: Academic Press, 2016. 454 p.
**10.** Mok Y.K., Swaminathan K., Zeeshan N. Engineering of serine protease for improved thermostability and catalytic activity using rational design // Int. J. Biol. Macromol. 2019. Vol. 126. P. 229–237. DOI: 10.1016/j.ijbiomac.2018.12.218
**11.** Ashraf N.M., Krishnagopal A., Hussain A., et al. Engineering of serine protease for improved thermo stability and catalytic activity using rational design // Int J Biol Macromol. 2019. Vol. 126. P. 229–237. DOI: 10.1016/j.ijbiomac.2018.12.18
**12.** Garcia-Sastre A. Ten strategies of interferon evasion by viruses // Cell Host Microbe. 2017. Vol. 22. P. 176–184. DOI: 10.1016/j.chom.2017.07.012
**13.** Lee S., Liu H., Wilen C.B., et al. A secreted viral nonstructural protein deters intestinal norovirus pathogenesis // Cell Host Microbe. 2019. Vol. 25, No. 6. P. 845–857.E5. DOI: 10.1016/j.chom.2019.04.005845–857
**14.** Thapa R.J., Ingram J.P., Ragan K.B., et al. DAI Senses Influenza A Virus Genomic RNA and Activates RIPK3-Dependent Cell Death // Cell Host Microbe. 2016. Vol. 20, No. 5. P. 674–681. DOI: 10.1016/j.chom.2016.09.014
**15.** Ahmad L., Mostowy S., Sancho-Shimizu S. Autophagy-Virus Interplay: From Cell Biology to Human Disease // Front Cell Dev Biol. 2018. Vol. 6. ID 155. DOI: 10.3389/fcell.2018.00155
**16.** Yang L., Shi P., Zhao G., et al. Targeting cancer stem cell pathways for cancer therapy // Signal Transduct Target Ther. 2020. Vol. 5. ID 8. DOI: 10.1038/s41392-020-0110-5
**17.** Tubita A., Lombardi Z., Tusa I., et al Beyond Kinase Activity: ERK5 Nucleo-cytoplasmic shuttling as a novel target for anticancer therapy // Int J Mol Sci. 2020. Vol. 21, No. 3. ID 938. DOI: 10.3390/ijms21030938
**18.** Xu X., Zhang M., Xu F., Jiang S. Wnt signaling in breast cancer: biological mechanisms, challenges and opportunities // Mol Cancer. 2020. Vol. 19. ID 165. DOI: 10.1186/s12943-020-01276-5
**19.** Wang B., Li X., Liu L., Wang M. β-Catenin: oncogenic role and therapeutic target in cervical cancer // Biol Res. 2020. Vol. 53. ID 33. DOI: 10.1186/s40659-020-00301-7
**20.** Reizis B. Plasmacytoid Dendritic Cells: Development, Regulation, and Function // Immunity. 2019. Vol. 50, No. 1. P. 37–50. DOI: 10.1016/j.immuni.2018.12.027
**21.** Takata M.A., Gonçalves-Carneiro D., Zang T.M., et al. CG dinucleotide suppression enables antiviral defence targeting non-self RNA // Nature. 2017. Vol. 550, No. 7674. P. 124–127. DOI: 10.1038/nature24039
**22.** Nash A., Dalziel R., Fitzgerald J. Mims' Pathogenesis of Infectious Disease, 6th ed. San Diego, CA: Academic Press, 2015. 348 p.
**23.** Maillard P.V., van der Veen A.G., Poirier E.Z., e Sousa C.R. Slicing and dicing viruses: antiviral RNA interference in mammals // EMBO J. 2019. Vol. 38, No. 8. ID e100941. DOI: 10.15252/embj.2018100941
**24.** Ma Z., Damania B. The cGAS-STING defense pathway and its counteraction by viruses // Cell Host Microbe. 2016. Vol. 19, No. 2. P. 150–158. DOI: 10.1016/j.chom.2016.01.010
**25.** Diner B.A., Lum K.K., Javitt A., Cristea I.M. Interactions of the Antiviral Factor Interferon Gamma-Inducible Protein 16. NIFI16 Mediate Immune Signaling and Herpes Simplex Virus-1 Immunosuppression // Mol Cell Proteomics. 2015. Vol. 14, No. 9. P. 2341–2356. DOI: 10.1074/mcp.M114.047068
**26.** van Gent M., Braem S.G.E., de Jong A., et al. Epstein-Barr virus large tegument protein BPLF1 contributes to innate immune evasion through interference with toll-like receptor signaling // PLoS Pathog. 2014. Vol. 10, No. 2. ID e1003960. DOI: 10.1371/journal.ppat.1003960
**27.** Hemann E.A., Green R., Turnbull J.B., et al. Interferon-λ modulates dendritic cells to facilitate T cell immunity ion with influenza A virus // Nat Immunol. 2019. Vol. 20. P. 1035–1045. DOI:10.1038/s41590-019-0408-z
**28.** Hadjidj R., Badis A., Mechri S., et al. Purification, biochemical, and molecular characterization of novel protease from Bacillus licheniformis strain K7A // Int J Biol Macromol. 2018. Vol. 114. P. 1033–1048. DOI 10.1016/j.ijbiomac.2018.03.167
**29.** Behzadi P., García-Perdomo H.A., Karpiński T.M. Toll-Like Receptors: General Molecular and Structural Biology // J Immunol Res. 2021. Vol. 2021. ID 9914854. DOI: 10.1155/2021/9914854
**30.** Jeong Y.J., Baek S.C., Kim H. Cloning and characterization of a novel intracellular serine protease (IspK) from Bacillus megaterium with a potential additive for detergents // Int J Biol Macromol. 2018. Vol. 108. P. 808–816. DOI: 10.1016/j.ijbiomac.2017.10.173

## AUTHORS INFO

***Alexander V. Moskalev,** MD, Dr. Sci. (Med.), professor;
ORCID: https://orcid.org/0000-0002-3403-3850;
eLibrary SPIN: 8227-2647; e-mail: alexmav195223@yandex.ru

**Boris Yu. Gumilevsky,** MD, Dr. Sci. (Med.), professor;
Scopus Author ID: 6602391269; Reseacher ID: J-1841-2017;
eLibrary SPIN: 3428-7704

**Vasiliy Ya. Apchel,** MD, Dr. Sci. (Med.), professor;
ORCID: https://orcid.org/0000-0001-7658-4856;
Scopus Author ID: 6507529350; Researcher ID: E-8190-2019;
Scholar ID: g9EKlssAAAAJ&hl; eLibrary SPIN: 4978-0785

**Vasiliy N. Tsygan,** MD, Dr. Sci. (Med.), professor;
ORCID: https://orcid.org/0000-0003-1199-0911;
eLibrary SPIN: 7215-6206

## ОБ АВТОРАХ

***Александр Витальевич Москалев,** д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0002-3403-3850;
eLibrary SPIN: 8227-2647; e-mail: alexmav195223@yandex.ru

**Борис Юрьевич Гумилевский,** д-р мед. наук, профессор;
Scopus Author ID: 6602391269; Reseacher ID: J-1841-2017;
eLibrary SPIN: 3428-7704

**Василий Яковлевич Апчел,** д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0001-7658-4856;
Scopus Author ID: 6507529350; Researcher ID: E-8190-2019;
Scholar ID: g9EKlssAAAAJ&hl; eLibrary SPIN: 4978-0785

**Василий Николаевич Цыган,** д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0003-1199-0911;
eLibrary SPIN: 7215-6206

* Corresponding author / Автор, ответственный за переписку