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FeLV-induced feline leukemia as a natural model for leukemia pathophysiology study (review)

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SUMMARY

Leukemia is a large group of diseases different in etiopathogenetic mechanisms and common in almost all mammalian species. The review focuses on feline leukemia, a common disease of domestic and wild felids (*Carnivora*, *Felidae*), being one of the main causes of their deaths. Feline leukemia pathogenesis and etiology are described; possible methods for the infection treatment and prevention, as well as possibility of using cats as a model for feline leukemia study are assessed. Feline leukemia etiological agent is a feline leukemia virus (FeLV), having single-stranded RNA genome surrounded with icosahedral capsid formed by p27 capsid protein monomers. Leukemia clinical manifestations in felids depend on high virulence of the virus and the disease is characterized with pronounced clinical picture and multiple organ dysfunction. Treatment of leukemia in cats is ineffective and is mainly aimed at maintaining the functions of the body organs and systems. Immunomodulators and chemotherapy are also used. Vaccination is used as a preventive measure, but commercially available adjuvanted and non-adjuvanted vaccines do not confer effective protection from the infection. The leukemia virus is reported in wild felids including rare and endangered feline species that is undoubtedly affects their population sizes. Despite very few data on leukemia, the reported cases show that leukemia in large cats is also severe and fatal. Feline leukemia, despite the accumulated of data, remains an ongoing serious and unresolved problem not only for veterinarians, but also for ecologists, zoologists and virologists involved in the research related to the feline family, study of retroviruses and biodiversity conservation on the planet. Further applied and fundamental research and verification thereof in the field of feline leukemia virus study, leukemia treatment and prevention are required.

Keywords: review, feline leukemia, retroviruses, feline leukemia virus, experimental models

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FeLV-индуцированный лейкоз кошачьих как естественная модель для изучения патофизиологии лейкозов (обзор)

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РЕЗЮМЕ

Лейкозы – большая группа различных по этиопатогенетическим механизмам заболеваний, распространенных практически у всех видов млекопитающих. В обзоре внимание уделено лейкозу кошек, или лейкемии кошачьих, – часто встречающемуся заболеванию домашних и диких представителей

семейства кошачьих (*Carnivora*, *Felidae*), которое является одной из основных причин их смертности. Дана характеристика этиологии и патогенеза лейкемии кошачьих, оцениваются возможные способы лечения и профилактики инфекции, а также возможность использования домашней кошки как модели для изучения лейкозов семейства кошачьих. Этиологический агент лейкемии кошачьих – вирус лейкемии кошачьих (FeLV – Feline leukemia virus), геном которого представлен одноцепочечной РНК, упакованной в капсид икосаэдрической симметрии, формируемый мономерами капсидного белка p27. Клинические проявления лейкемии у кошачьих связаны с высокой вирулентностью вируса и характеризуются ярко выраженной клинической картиной и развитием полиорганной недостаточности. Лечение лейкемии у кошек малоэффективно и направлено в основном на поддержание функционирования органов и систем. Также применяются иммуномодуляторы и химиотерапия. В качестве превентивной меры используется вакцинопрофилактика, однако существующие на рынке адъювантные и безадъювантные вакцины не обеспечивают надежной защиты от инфекции. Вирус лейкемии встречается у диких кошачьих, в том числе у редких и исчезающих видов, что, несомненно, влияет на численность их популяций. Несмотря на то что данных по лейкемии у диких кошачьих крайне мало, отдельные зарегистрированные случаи свидетельствуют о том, что заболевание у крупных кошек также имеет тяжелое течение и приводит к летальному исходу. Лейкемия кошачьих, несмотря на накопленный массив данных, и по сей день остается серьезной, нерешенной проблемой не только для специалистов ветеринарной практики, но также для экологов, зоологов и вирусологов, чья область исследования так или иначе связана с семейством кошачьих, изучением ретровирусов и сохранением биоразнообразия на планете. Необходимы дальнейшие прикладные и фундаментальные исследования и их верификация в области изучения вируса лейкемии кошачьих, лечения и профилактики лейкоза.

Ключевые слова: обзор, лейкоз кошачьих, ретровирусы, вирус лейкемии кошачьих, экспериментальная модель

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INTRODUCTION

Leukemia is a large group of diseases that differ in etiology and pathogenesis, being a type of hemoblastoses (from ancient Greek *αἷμα* – blood and *βλαστός* – growth), i.e. malignant hematopoietic and lymphatic diseases. Hemoblastoses can be systemic diseases (leucosis/leukemia) as well as regional nodular tumor neoplasms (lymphoma and hematosarcoma). All hematoblastoses of this group have a clonal nature [1, 2]. Moreover, a malignantly transformed clone can originate both from immature hematopoietic cells of the bone marrow, and from maturing and mature blood cells.

Malignant blood and lymph cell clones can be of two main origins-myeloid and lymphoid. The myelogenesis products are erythrocytes, granulocytes, platelets, monocytes, dendritic cells, macrophages and mast cells, and the lymphopoiesis products are B-lymphocytes and plasmacytes, T-lymphocytes, NK cells. The particular cell line undergoing malignant transformation gives rise to particular variant of hemoblastosis, and there can obviously be a lot of such variants. Variable leukemia morphological forms and clinical courses are also accounted for rather broad spectrum of malignantly transformed blood cell maturity – from slightly-differentiated cells to cells that have practically lost normal phenotype signs (blast crisis is typical for this leukemia stage).

Leukemias and lymphomas differ not only in presence and absence of systemic lesions. It is known that lymphoma in its terminal stage can spread with extensive metastases in various tissues and organs, including the bone marrow [3], i.e. the disease becomes systemic. However, the bone marrow is affected primarily in case of leukemia, and secondarily as a result of metastasis in case of lymphomas and hematosarcomas.

This review focuses on leukemias developing in all species of feline family (*Carnivora*, *Felidae*). This pathology is increasingly prevalent and the main cause of death in felids. The study of leukemia in domestic cats (*Felis catus*) is of importance [4–6] from the point of view of pet animal life quality improvement and biomedical ethics [7], but also as an accessible model for rare and endangered felids, limited populations of which are extremely vulnerable. The situation is the most critical in the south of Russian Far East. Forward-looking economic development of the region poses objective threats for Far Eastern leopards (*Panthera pardus orientalis*) and Amur tigers (*Panthera tigris altaica*) [8]. There are specialized animal shelters where leukemia-affected felids are kept. Our practice shows that it is possible to organize full-fledged and well-randomized studies of both the fundamental mechanisms of the feline leukemia development and effectiveness of certain experimental treatment methods in case of cooperation with such shelters.

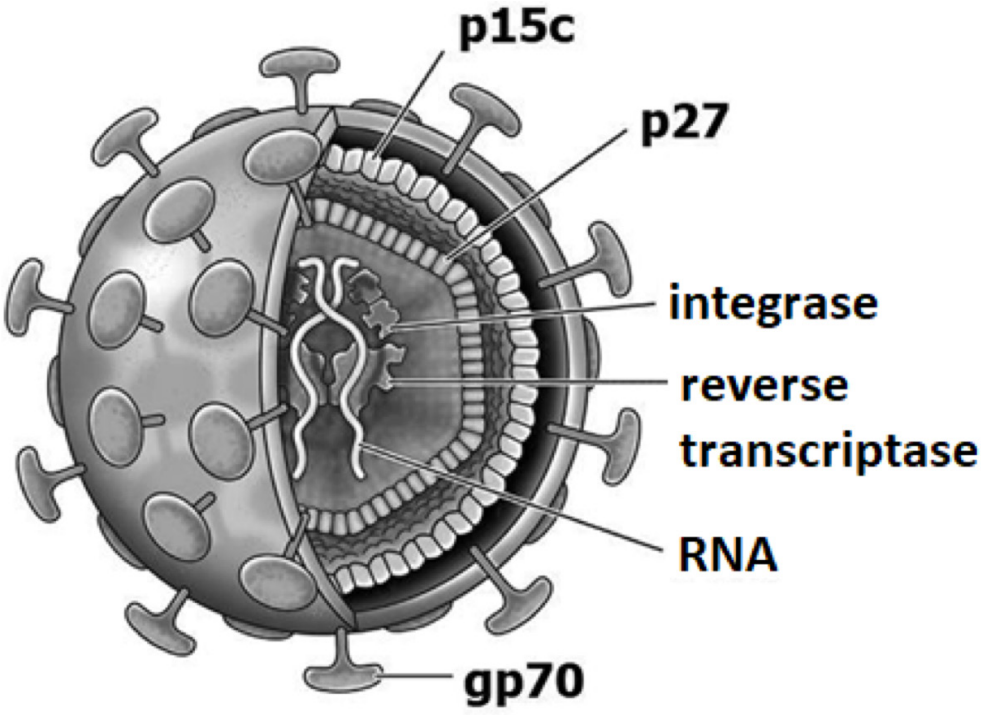

Fig. Morphology of feline leukemia virus virion

Moreover, the studies can be carried out for a long time including monitoring of the survival of animals within their natural lifespan.

Feline leukemia virus (FeLV) belongs to *Ortervirales* order, *Retroviridae* family, *Orthoretrovirinae* subfamily, *Gammaretrovirus* genus. In addition to FeLV, this genus of orthoretroviruses includes chick syncytial virus (CSV), Finkel-Biskis-Jinkins murine sarcoma virus (FBJ MuSV), Gardner-Arnstein feline sarcoma virus (GA-FeSV), gibbon ape leukemia virus (GaLV), Guinea pig type-C oncovirus (GPCOV), Hardy-Zuckerman feline sarcoma virus (HZ-FeSV), Harvey murine sarcoma virus (Ha-MuSV), Kirsten murine sarcoma virus (Ki-MuSV), koala retrovirus (KoRV), Moloney murine sarcoma virus (Mo-MSV), murine leukemia virus (MuLV), porcine type-C oncovirus (PCOV), reticuloendotheliosis virus (REV), Snyder-Theilen feline sarcoma virus (ST-FeSV), Trager duck spleen necrosis virus (TDSNV), viper retrovirus (VRV), woolly monkey sarcoma virus (WMSV)[1].

In accordance with D. Baltimore's classification, the *Retroviridae* family belongs to group VI (ssRNA-RT), i.e. to the viruses containing the enzyme called reverse transcriptase (revertase), which allows for generating a double-stranded DNA replica (cDNA) on the viral genomic RNA template. The viral genome-encoded integrase, being a part of the nucleoprotein, enables cDNA incorporation into host cell chromosome (cDNA incorporated in the chromosome is called provirus or pvDNA). In the infected cell nucleus some cDNAs become circulized (ccDNAs) and acquire cosmid functions [9, 10].

[1] Current ICTV Taxonomy Release.
Available at: https://ictv.global/taxonomy.

Virion morphology. Feline leukemia virus virion is a spherical enveloped particle 100–110 nm in diameter. The virion structure is given in figure below. The virion contains two copies of single-stranded positive-sense RNA and nucleoprotein-associated enzymes: revertase, integrase and protease. The nucleoprotein is packed in an icosahedral capsid formed by capsid protein p27 monomers. The outer lipid envelope is impregnated by p15c matrix protein on the inside and contains p15e transmembrane protein and gp70 surface glycoprotein receptor.

At the virion level, *FeLV genome* consists of two identical copies of positive-sense single-stranded RNA 9.6 kb in size. The virus contains untranslated regulatory long terminal repeats (LTR) at the 5′ and 3′ ends, flanking three viral genes: *gag* (encoding structural group-specific capsid proteins), *pol* (encoding protease, reverse transcriptase and integrase) and *env* (encoding virion surface proteins). FeLV genome has two open reading frames (ORF): 1) *gag* + *pol*; 2) *env* [11].

Like other retroviruses, FeLV genome is highly variable. This leads to the emergence of new genotypes and antigenic variants causing various clinical disease forms, and eventually hinders development of effective medicines and vaccines [12]. Lack of 3′–5′-exonuclease activity in the retrovirus reverse transcriptase is one of the most important mechanisms for the point nucleotide substitutions emergence, that prevents this enzyme from correction of its own errors during strand elongation [13, 14]. There are numerous recombinants between different FeLV variants, including those with the endogenous enFeLV virus. The pathogen genetic and antigenic variability is associated with large range of FeLV virulent properties, various pathogenetic

mechanisms giving rise to various clinical manifestations of FeLV infection [15]. The concept that RNA-containing viruses, and especially retroviruses, exist only in the form of populations representing complex topological objects in the space of their variable digital images [16] has been known since the end of the last century. In the paper of L. L. Bolin and L. S. Levy [17], this concept has been applied to FeLV infection: there is a complex of genetically heterogeneous virus populations in the body – FeLV itself, that has initiated the disease and the products generated due to its natural variability, that may increase virus aggressiveness and ability to evade the immune system.

There are several FeLV variants classified to subgroups: A, B, C, D, T and TG35 that also comprise several variants. It should be noted that each of them has own specific mechanisms of the virus attachment to target cells [18, 19].

Clinical manifestations of FeLV infection depend on the virus variant, virus burden and host immune status. FeLV is highly virulent therefore most of infected animals demonstrate apparent clinical manifestations [20]. Kittens at the age of 4 months are the most susceptible to FeLV, whereas aging cats are usually being the source of infection, in which the virus can be found in the blood and various tissues of internal organs, and excreted with urine, saliva and nasopharyngeal mucus. The virus can be transmitted both horizontally and vertically: kittens from infected cat can be infected during their prenatal development.

The infection is much more common in urban (domestic and stray) cats than in rural cats. It is believed that this is accounted for higher frequency of contacts between cats in urban settings.

The virus is characterized by low resistance to environmental factors. FeLV is inactivated outside the animal within 8 hours. Therefore, FeLV-infected cats are the main source of infection. Animals can transmit the virus among themselves through casual close contacts, and there is also evidence of possible horizontal virus transmission by cat fleas of the *Ctenocephalides felis* species [21].

FeLV circulating in domestic cat populations is also found in populations of wild felids (tigers, lions, leopards, cougars, jaguars, lynxes, cheetahs, etc.) [12, 15, 22–26]. All the species of the *Felidae* family examined so far have been found to be more or less susceptible to FeLV. However, it appeared that there are certain interspecies differences in the susceptibility and clinic courses of pathological conditions developing in infected cats. For example, T. M. Harrison et al. [15] performed an interesting study involving 11 African lions affected by malignant lymphoma. In all the examined animals, lymphomas were of T-cell genesis, unlike B-cell lymphomas characteristic of other feline species, including *Felis catus*. No FeLV was detected in any of the lions examined; although one diseased animal was found to be seropositive to this virus, i.e. it had specific antibodies to the virus antigens. The results of such study evidenced that the pathogenesis mechanisms and malignancy processes in infected animals are currently insufficiently investigated. Also, the study results have supported the opinion that the virus initiating carcinogenesis (leukogenesis) may not be detected further by current diagnostic methods. At a minimum, this is indicative of the need for a combination of immunochemical and molecular genetic analysis methods for viral feline leukemia diagnosis to detect both virus-specific seroconversion and viral genome replicative and expression activity.

The feline leukemia virus is a specific member of the *Felidae* family and does not infect other animals, in particular, it is not transmitted to humans or dogs being in frequent and prolonged contact with domestic cats [11, 20, 21].

The mechanisms of the progression of feline leukemia-associated pathological conditions are currently insufficiently investigated. Leukemias and lymphomas (or lymphosarcomas) are considered to be the final stage of feline leukemia. Moreover, disease transformation into leukemic form may not require the presence of virus-specific antigens [27]. The detection of FeLV-infected cats, seronegative to virus-specific antigens, indicates that the virus can fulfil its leukogenic potential not only through expression of FeLV provirus genetic material at the translation level, but also through variations in proviral genome integration into various sites of the host cell genome, induction of chromosomal rearrangements, activation of c-oncogenes and other genomic alterations in host cells [28].

There are six main stages of FeLV infection [29]:

1. The virus enters the cat's body orally or parenterally (usually by bite and other skin wounds, as well as a result of "friendly" contacts: mutual licking, shared bowl, etc.). After oronasal invasion the virus at first infects epithelial cells and leucocytes (mainly tonsil B-lymphocytes and macrophages). Infected leucocytes can recirculate, but in most cases they are retained in the nearest regional lymph nodes, where the virus actively replicates.

2. *De novo*-generated virus progeny enters to blood-lymph circulation systems, i.e. infectious agents disseminate throughout the body. Since FeLV like other retroviruses has a cytolytic potential the virus can be released from the infected cell by lysis. Pools of lymphocytes and monocytes are depleted and the host immunity becomes apparently compromised.

3. Number of infected peripheral lymphoid cells and circulating lymphocytes increases. This stage of the infectious process is characterized by the active production of anti-FeLV antibodies enabling monitoring of the disease dynamics, as well as evaluation of the therapy effectiveness.

4. Pronounced viremia develops. Total infection of hemolymphatic system is followed by the infection of intestine epithelial cells.

5. The disease takes leukemic form characterized by bone marrow cell infection and malignant transformation of bone marrow progenitor cells. At this stage, spontaneous eradication of the virus is practically

impossible and the disease becomes fatal. The virus actively replicates in all leukocytes produced in the bone marrow (in lymphocytes, neutrophils, monocytes, eosinophils). As a result, the immunity becomes largely and severely compromised. This leads to the development of various secondary infectious processes and increasingly aggravated multiple organ dysfunction.

6. Terminal stage (blast crisis). At this stage cells of almost all organs and tissues of the diseased animals are infected. Mucous membrane and glandular epithelial cells demonstrating the highest metabolic and proliferative activity are the most affected. The virus actively replicates in oral, nasal and pharyngeal epithelial tissues, salivary glands, gastric and intestinal mucosa, tracheal cells, cells of renal tubules, bladder, pancreas, sebaceous glands. The terminal stage is considered to be untreatable stage of the disease.

The virus can be vertically transmitted from a pregnant female to its kittens, in this case the kittens immediately enter the second stage of infection. The probability of a newborn kitten become infected depends on the viral load in the mother's body during pregnancy.

Feline leukemia-associated non-oncological pathologies are mediated by the effect of the virus on the immune system. In addition to systemic blood disorders (anemia and leukopenia), the infection can cause various organ lesions in cats, for example, myocarditis. The clinical manifestations of the infection developing in affected cats are very variable: loss of appetite, skin and coat disorders, prolonged and recurrent bacterial, fungal, viral infections of the skin and other tissues, eye lesions, otitis, inflammatory lesions of the bladder and respiratory tract, lymphadenopathy, fatigue, fever, weight loss, stomatitis, gingivitis, changes in behavior, diarrhea, jaundice, immunodeficiency of various types, leukemic manifestations, development of thymus lymphomas and other manifestations in the form of lymphomas and sarcomas of various localization [30–32].

In some cases, the infection can be prolonged asymptomatic and latent, i.e. animals carrying the virus do not show any signs of the disease for many years [31]. Is it associated with specific nature of the virus only, or with more effective immunological antiviral and antitumor surveillance mechanisms? The answers to these questions are of obvious fundamental and extremely practical importance.

There are some very interesting (but insufficiently verified) reports on the infected cats that can effectively fight the infection by developing strong immunity and becoming completely resistant to the diseases associated with this virus. However, the virus is not completely eradicated and such "healthy" virus carriers can infect other cats at contact, facilitating the virus spread in the population [33, 34]. Nevertheless, the above data on the clinical feline leukemia extreme polymorphism and, in particular, on the leukemic process variability indicate the importance of studying immunological mechanism features, involvement of the interferon system and other factors of antiviral and antitumor innate immunity for development of techniques and technologies enabling improvement of the effectiveness of treatment of at least these hemoblastosis forms in cats.

Treatment of feline leukemia is a difficult task: firstly, due to the retroviral nature of the infection (which implies the insertion of the provirus into the host cell chromosome), and secondly, due to nonspecific symptoms and ability to affect many organs and systems that results in multiple organ failure at later stages. For this reason, there is currently no single and effective treatment pattern for leukemia in cats. The treatment includes symptomatic therapy aimed, on the one hand, at maintaining the functioning of the cardiovascular system, kidneys, liver and other vital organs, on the other hand, at containment of the secondary infections associated with immunodeficiency.

Immunomodulating drugs have the greatest effectiveness and less side effects as manifested by improved general condition and reduced mortality in diseased animals [18]. However, this treatment fails to cure the disease in animal and completely eradicate the virus. Chemotherapy based on a combination of vincristine, cyclophosphamide and prednisolone or involving use of L-asparaginase and doxorubicin is another effective type of treatment. Chemotherapy achieves the remission, but it does not exceed 10 months. Moreover, this therapy is associated with various side effects that preclude its use in animals with hepatic or renal failures [35].

The vaccines were proposed for the disease prevention as early as at the beginning of the XXI century, but no highly effective vaccine has been developed so far. Currently, there are several polyvalent vaccines – both adjuvanted (for example, Nobivak® Feline 2-FeLV, Merck & Co., Inc., USA) and vector non-adjuvanted vaccines, but none of them confers strong protection against feline leukemia.

Non-adjuvanted Purevax® FeLV vaccine (also known as Eurifel FeLV) produced by Merck & Co. (France) and Biokema SA (Switzerland) is currently the most popular vaccine against FeLV infection. This is a recombinant DNA vaccine that contains Canarypox virus (*Chitovirales: Poxviridae, Avipoxvirus*) as a genetic vector carrying two FeLV genes, *gag* and *env*, incorporated in its genome. The vaccine is a living whole-virion construct that does not replicate in feline cells. This vaccine is the most preferred, as it has practically no side effects [5, 36, 37].

The leukemia has a significant impact on the populations of specially protected wild felids due to their small sizes and therefore increased susceptibility to infectious agents, especially those capable of circulating in latent form.

The conservation and reproduction of rare and endangered large predator species occupying the top of the food pyramid is an important task for maintaining biodiversity on the planet. The wild large felids are the most diverse in the Russian Far East, habitat of the Amur tigers and the Far Eastern leopards, whose populations still require comprehensive protection despite their significant increase over the past two decades owing to conservation measures. The following

ecological and biological factors have a significant impact on the large wild felid population sizes: climatic changes, anthropogenic impact, feed availability (deer and wild boars) [38–40]. Infectious diseases can significantly reduce populations, causing mass deaths in animals, and affect the survival and reproduction of animals. Even a slight decrease in survival can be critical for slow-breeding and small-numbered feline species, such as the Amur tiger and the Far Eastern leopard. However, data on infectious and parasitic diseases of these animals are scarce [8, 41–45]. Available epidemiological data do not allow full assessment of the infectious disease impact on the rare feline species population and the clinical picture described for the isolated cases does not give the understanding of the infection pathogenesis in wild large felids [41, 46].

FeLV cases in large cats kept in zoos are reported. Most often, the infection is latent, and animals do not demonstrate any clinical symptoms [47–49]. In some cases, secondary infections and organ lesions associated with FeLV infection develop in tigers. For example, fatal amyloidosis associated with feline leukemia virus was reported in a Bengal tiger in Mexico [50]. Similar to domestic cats, FeLV infection in wild cats is manifested by acute leukemia and leads to the development of immunodeficiency and secondary infections [51, 52].

At the moment, there are no uniform procedures for the leukemia diagnosis, treatment and vaccination in large felids [47]. Due to the fact that both wild and domestic cats are susceptible to FeLV infection, leukemia pathogenesis and clinical course are similar that enables use of infected domestic cats as a model for the development of anti-feline leukemia treatment and vaccination methods [6, 44, 53], as well as putting the obtained results into veterinary practice when working with large felids, at first zoo felids, and then wild felids.

CONCLUSION

Feline leukemia, despite the accumulated data, remains a serious and unresolved problem for veterinary practitioners, as well as for ecologists, zoologists and virologists involved in investigations related to the feline family, retroviruses and maintaining biodiversity on the planet. Further applied and fundamental research and verification thereof in the field of feline leukemia virus study, leukemia treatment and prevention are required.

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