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LUMPY SKIN DISEASE VIRUS: APPROACHES TO ATTENUATION FOR VACCINE DEVELOPMENT

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ABSTRACT

Lumpy skin disease (LSD) is a disease caused by the lumpy skin disease virus (LSDV) of the genus capripoxvirus. The disease is responsible for serious losses to the cattle industry globally. Vaccination is the most effective way of controlling LSDV. The currently available live attenuated vaccines are used in many countries and provide stable immunity. However, use of these vaccines can sometimes cause postvaccinal complications in animals. Attenuation of viruses by the classical method is associated with random mutations in the genome, and some vaccines can contain a mixture of viruses of different genotypes and virulence. Hence, there is a need to develop a safe immunogenic vaccine that will provide improved protection against LSDV. The most promising approach is gene modification to develop an attenuated capripoxvirus strain with high immunogenicity and protectivity. Sequencing and analysis of capripoxvirus DNA genomes has resulted in the identification of a number of genes whose protein products effectively stimulate antibody production in the host organism. These proteins are able to function both inside and outside the cell, neutralizing the complement factors, inhibiting apoptosis and synthesis of interferons, and reducing counter-inflammatory cytokines and chemokines. Here, we review the literature for instances of genetic manipulation of genes encoding the above proteins, resulting in capripoxvirus attenuation.

Key words: Lumpy skin disease virus, attenuation, vaccine, capripoxvirus, virulence genes, gene knockout

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INTRODUCTION

Capripoxvirus of the *Poxviridae* family unites viruses of sheep pox and goat pox as well as lumpy skin disease virus that cause economically important diseases of domestic ruminant animals.

While sheep pox and goat pox are common in a number of Asian and African countries and their outbreaks are occasionally recorded in Kazakhstan and adjacent countries, the lumpy skin disease has been reported till the end of the last century only in the countries of the Central and Southern Africa. Currently the disease is endemic in Africa and Near East. Conflicts in the Near Eastern countries (Syria, Iraq) that continue from 2011 have caused mass migration of people and of farm animals without appropriate veterinary control. As a consequence, during years 2013-2015 the lumpy skin disease spread through the Turkey (ProMed 20130831.1915595). Subsequently the infection was reported in Iraq (ProMed 20130718.1831781) [1] and along the western

borders of Iran (ProMed 20140623.2561202). Unauthorized migration of cattle might happen to be a probable cause of introducing the infection into Azerbaijan (ProMed 20140719.2621294) and Cyprus (ProMed 20141205.3012426) [1]. In 2015 the lumpy skin disease was for the first time recorded on the territory of the European Union, namely in Greece (OIE Wahid, ProMed 20150821.3594203) and then in the North Caucasus region of Russia, in Dagestan and in Chechnya (OIE Wahid, ProMed 20150904.3622855 и 20150921.3659823). In 2016 the list of the countries infected with the lumpy skin disease was supplemented by Armenia (ProMed 20160119.3948943), Bulgaria (ProMed 20160415.4160177), Macedonia (ProMed 20160423.4177438), Serbia (ProMed 20160609.4273545), Kosovo (ProMed 20160701.4321118), Albania (ProMed 20160711.4337862), Montenegro (ProMed 20160722.4360549), and Kazakhstan (ProMed 20160722.4363497). Rapid spread of the infection increases the risk of its penetration into the infection-free regions and requires quick response for prevention of its dissemination.

Prophylactic measures against sheep pox and goat pox outbreaks consist of vaccination with live attenuated and inactivated vaccines [2], whereas only live attenuated vaccines are available for the prevention of the lumpy skin disease, and permission of the local authorities for their use on cattle is required [3].

The inactivated lumpy skin disease vaccines provide just temporary short-term protection because they contain only intracellular mature virions. The extracellular enveloped virions are also needed to form the valid immune response [4]. However, the inactivated vaccines may be used in the capripoxvirus-free countries to prevent penetration of the infection and in case of livestock export [2].

Capripoxviruses are of high genetic homology [5, 6] and theoretically one attenuated capripoxvirus strain can be used to protect against infection both with sheep and goat pox and with the lumpy skin disease [7]. However, field practice evidences that some strains are highly specific for a host animal and can be used just on sheep against sheep pox (strain RM-65) and on goats against goat pox (strains Mysore and Gorgan) [8]. The data of the last outbreaks of lumpy skin disease in the Near East evidence that the use of heterologous strains provides just partial protection against the infection [9, 10, 11, 12, 13]. It should also be noted that almost all attenuated vaccines against lumpy skin disease are weakly reactogenic and cause post-vaccination complications. Therefore there is an necessity to develop a safe immunogenic vaccine against lumpy skin disease on the basis of recent achievements in science.

Currently used attenuated capripoxviruses were obtained as the result of multiple passages in cell cultures and/or chicken embryos [14]. In this case attenuation was caused by spontaneous mutations in the virus genome affecting not only virulence genes, but the genes whose functions define replicative properties of the virus and the range of sensitive hosts [15]. The progress in methods of molecular biology makes possible to modify the virus genome and thereby significantly change pathogenic and immunogenic properties of viruses [16]. Construction of attenuated capripoxvirus strains with immunogenicity and protective ability by gene-engineering methods is the most perspective line of this research.

The aim of the review is to study the modern methods and approaches that are used in attenuation of the poxviruses and to determine the most perspective of them for development of safe and effective vaccines against the lumpy skin disease.

Since capripoxviruses as well as orthopoxviruses belong to one and the same family (Poxviridae), the results of preliminary studies on the poxvirus gene functions with use of the vaccinia virus may serve a basis in the research with the lumpy skin disease virus.

Approaches used in virus attenuation

Attenuation or virulence weakening of pathogenic microorganisms is widely used in development of live vaccines. The key problem in obtaining attenuated vaccines is the effect of virulence reduction onto immunogenicity. Serial passages in non-permissive host or in cell culture of non-permissive or permissive host are a classical approach to virus attenuation. In the course of multiple passages a great number of spot mutations leading to virulence loss is accumulated in the genome of the original strain. There at the molecular basis of virus attenuation stays unidentified. Method of serial passages was used to attenuate human, animal and avian viruses [17, 18]. In spite of many rather valuable practical results attenuation of viruses via passages in the system of unnatural host is an uncontrolled process in whole, and its results are unpredictable [19]. Moreover, this approach is very slow and labor-consuming, that is fails to quickly response to the necessity of a new vaccine.

Modern methods of molecular biology allow identifying viral virulence genes and "switch them off" (knockout), thus achieving reduced or lost virulence. Gene knockout can be carried out via their complete or partial removal or else via disruption of the open reading frame by inserting a foreign sequence [20]. A fragment of the poxvirus genome containing the gene to be disrupted and flanking sequences of varying lengths is cloned and used as a template for subsequent manipulations. Two subfragments are amplified by PCR using primers designed to selectively delete a portion of the targeted ORF while introducing restriction sites (RE) for subcloning the fragments. Each fragment is cloned in series into a transfer vector containing a selection marker under a poxvirus promoter (green fluorescence protein shown), such that the marker sequences further disrupt the target ORF. The vector encoding the poxvirus sequences is transfected into permissive cells that are infected at low multiplicity with wild-type virus. Within infected-transfected cells, homologous recombination occurs between the transfected sequences and wild-type virus genomes. Knockout viruses are isolated from wild-type virus and serially purified according to the selection criteria conferred by the selection marker (fig. 1) [20].

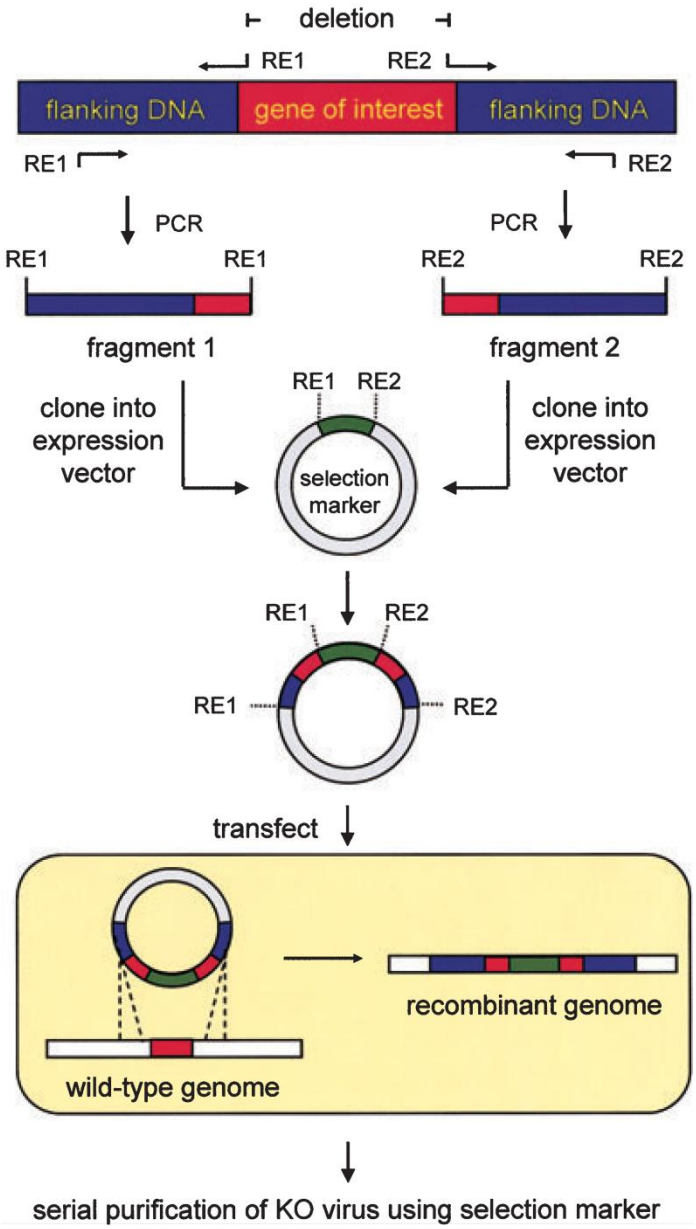

Fig. 1. General strategy for constructing knockout poxviruses [20].

Thus, for instance, recombinant viruses of Rift Valley fever obtained by deletion of two known virulence factors (NSs and NSm genes) using reverse genetics, provide protection of animals against infection without clinical manifestation of the disease and can serve as the candidates in development of safe and effective vaccines [21].

Another way of knocking gene out is codon-pairs deoptimization: introduction of multiple synonymous replacements in codons at invariable amino acid sequence of protein. Recent studies in other viruses have shown that recoding certain viral genes to employ synonymous but rarely used codon pairs resulted in viral attenuation. This method was used in development of live attenuated vaccines against flaviviruses. Novel live attenuated Zika virus vaccine candidates were designed using a codon pair deoptimization strategy. Three codon pair-deoptimized Zika viruses (Min E, Min NS1, and Min E+NS1) were de novo synthesized and recovered by reverse genetics and contained large amounts of underrepresented codon pairs in the E gene and/or NS1 gene. The amino acid sequence was 100% unchanged. The codon pair-deoptimized variants had decreased replication fitness in Vero cells (Min NS1 $\gg$ Min E > Min E+NS1), replicated more efficiently in insect cells than in mammalian cells, and

demonstrated diminished virulence in a mouse model [22]. Thus, for instance, codon-pairs deoptimization in proteins UL54/ICP27 and UL49/VP22 of Marek's disease virus resulted in reduced virulence of the virus to mice [23, 24].

Attenuation and immunogenicity of poxviruses

Currently live attenuated vaccines obtained by classical method of serial passages in non-permissive host or in cell culture are used for prophylaxis of poxvirus infections.

It was found that a great number of viral proteins that effectively change multiple protective responses of an organism regulates manifestation of poxvirus pathogenicity [25]. In the process of evolution, poxviruses elaborated the greatest number of molecular mechanisms for overcoming immune system barriers of a host. They are apoptosis inhibition, blocking of inflammatory processes, interferon-blocking system, and some other processes that ensure replication and spread of the virus in a host organism. Interaction of the virus with the host immune system is described in details in reviews [26, 27, 28]. Identification of poxvirus virulence factors allows to modify purposefully the virus genome and to evaluate the effect of individual proteins on virulence, immunogenicity and replicative activity.

Attenuated recombinant strains were obtained via deletion both of separate and of several genes. For instance, nine deletion mutants of the virulent strain NYCBH of the vaccinia virus with wide range of attenuated phenotypes were obtained by Lee et al. [29] via deletion of single genes. Intracerebral 50% lethal dose varied within 2-7 lg. Three mutants (J2R –thymidine kinase, A56R -hemagglutinin, and F4L- small subunit of ribonucleotide reductase) demonstrated reduced replication in lungs, brain, liver and spleen of mice after intranasal infection. One mutant (F4L- a small subunit of ribonucleotide reductase) showed decreased transmission from mice infected by tail scarification to naïve animals. Analysis of mutants NYCBH has shown that RR-deletion mutant has a number of favorable characteristics thus making itself a potential candidate for future development of a vaccine. Immunogenicity of the mutants at low immunization doses markedly decreased versus the wild-type virus while at high immunization doses most mutants induced immune response similar to that of the wild-type virus. In most cases stimulation of the immune response by vaccinia virus mutants at the level of parental viruses is achieved by application of high immunizing doses [30, 31, 32, 33].

At the same time it was shown that the attenuated mutant of the vaccinia virus strain Tian Tan obtained via deletion of a large subunit of ribonucleotide reductase gene (I4L) sustained immunogenicity at the level of the parental strain [34]. Virulence of the mutant was 100 times lower (changes in a body weight) and 3200 times lower (intracranial 50% lethal dose) versus the original virus.

Lynn et al. [35] in their studies have shown that deletion of gene A36R of ectromelia virus results in reduced number of formed extracellular viruses and smaller size of plaques. Virulence of the ectromelia virus mutant ECTV-ΔA36R for the normally susceptible BALB/c mice was reduced. Despite the attenuation of the mutant virus, its injection nonetheless induced protective immunity in mice

Also decreased pathogenicity of the vaccinia virus to mice resulted from mutation of gene B8R that encodes INF-gamma receptor-like protein [36]. Deletion of gene B8R failed to effect the replication of vaccinia virus strain Western Reserve *in vitro*, but provided reduction of the virus virulence for mice [37, 38]. In addition, deletion of gene B8R fails to significantly affect the humoral immune responses [37].

Bartlett et al. [39] have found out in their studies that the mutant virus with deleted gene N1L replicated in cell culture but is less virulent to mice versus control wild-type virus at intranasal and intradermal administration. The secreted virulence

factor, Bcl-2-like apoptosis inhibitor, is a protein product of gene N1L. Deletion of gene N1L from vector vaccinia virus strains enhanced CD8(+) T-cellular immunity and simultaneously decreased virulence [40].

On the ground of homology of extracellular domain of the protein encoded by gene B5R with the complement control proteins its possible implication in the evasion of poxviruses from the immune response was predicted [41], but experimentally only its participation in generation of virus-neutralizing antibodies was confirmed [42]. At the same time gene B5R deletion resulted in attenuation of the virus *in vivo*, plaque size decrease, and 10-fold reduction of EEV formation level in cell culture [43].

However, not always deletion of the gene whose protein product interacts with the immune system of an organism results in the virus attenuation. Thus, Estep et al. [44] have shown that the protein product of gene D14L (an inhibitor of the complement system enzymes of the monkey pox virus) modulates an immune response to the monkey pox virus. Knockout of gene D14L leads to enhanced virus replication *in vivo* and to weakened adaptive immune response to the monkey pox virus as compared to the original strain.

Attenuation of a number of vaccinia virus strains was achieved by deletion of two and more genes. Legrand et al. [45] have found out that reduction of the vaccinia virus virulence (measured by decrease in mice weight loss level and limited dissemination of the virus) at retention of high immunogenicity level can be achieved by deletion of genes B13R and B22R. B13R (SPI-2) and B22R (SPI-1) are two immune modulating genes of the vaccinia virus whose sequences are homologous to the inhibitors of serine proteases (serpins) and have anti-apoptotic and anti-inflammatory characteristics. Vaccinia virus Tian Tan was attenuated via deletion of four genes (M1L, M2L, K1L and K2L) with simultaneous insertion of gene GFP [46]. Modified vaccinia virus Tian Tan MVTT2-GFP lost its ability to replicate in cell lines RK13 и HeLa. MVTT2-GFP was less virulent for mice at intranasal inoculation. Vaccinia virus strain Tian Tan was also attenuated in the result of deletion of five segments of the virus genome associated with immune modulating and virulence functions [47]. Knockout of segments TC7L-TK2L, TE3L, TA35R, TB13R and TA66R failed to affect the replicative ability of the virus, markedly weakened virulence, but at the same time retained high immunogenicity.

Disruption of five virulence genes encoding hemagglutinin (A56R), γ-interferon-binding protein (B8R), thymidine kinase (J2R), complement-binding protein (C3L) и Bcl-2-like apoptosis inhibitor (N1L) in genome of vaccinia virus LIVP resulted in obtaining recombinant strain 1421ABJCN that was characterized by lower reactogenicity and neurovirulence versus the original strain [48]. The authors have found out that subcutaneous injection of the recombinant 1421ABJCN induces formation of virus-neutralizing antibodies at the level of the parental strain LIVP and provides complete protection of mice against lethal dose of highly pathogenic for them ectromelia virus.

Highly attenuated strain NYVAC (vP866) was obtained by deletion of 18 genes from the genome of the vaccinia virus Kopenhagen [49]. These were two genes implicated in nucleotide metabolism: thymidine kinase (J2R) and the large subunit of ribonucleotide reductase (I4L); gene encoding viral hemagglutinin (A56R); a remnant of highly expressed gene (A26L) responsible for formation of A-type inclusion bodies, the disrupted gene (B13R/B14R), normally encoding serine protease inhibitor; and a block of 12 genes bounded by two known viral host range regulatory functions (C7L through K1L). Within this block a secretory protein (N1L) implicated in viral virulence and a functional complement 4b binding protein (C3L) are encoded. In spite of these highly attenuated characteristics, strain NYVAC as a vector retains its ability to induce strong immune responses to foreign antigens.

Deletion/insertion of host range genes results not only in the virus attenuation, but affects its replicative activity *in vitro* [50]. After multiple deletions NYVAC lost its ability to replicate in human cells but reinsertion of gene C7L led to recovery of its replicative ability in human and murine cells without enhancement of its virulence to BALB/c mice at nasal inoculation [51]. Moreover, insertion of genes C7L and K1L increased immunogenic properties of NYVAC virus [52, 53]. In the experiments with the modified vaccinia virus Ankara, Wyatt et al. [54] have found that reinsertion of gene K1L correlates with the ability of recombinant viruses to spread in cells RK-13 (rabbit kidney), but fails to improve replication in human or simian cell lines. Deletion of genes C7L and K1L from vaccinia virus TianTan modified as a vector vaccine against AIDS resulted in significant attenuation without reducing immunogenicity [55].

Moreover, genes encoding proteins homologous to *Drosophila* kelch proteins were found in genomes of *Orthopoxvirus* genus members [56]. Proteins encoded by these genes are implicated in various processes of cell life activity [57, 58]. In orthopoxvirus genomes, kelch-like genes are located in terminal variable regions and show species-specific differences in organization of the proteins they potentially encode [59]. Functions of these proteins are not studied completely. It has been shown that kelch-like genes of vaccinia virus are inessential for its replication in cell culture [60], but vaccinia virus mutant deprived of gene C2L has a different plaque morphology due to the altered cytopathic effect to the infected cells [61]. Kochneva et al. [62] have demonstrated that deletion of four kelch-like genes D11L, C18L, G3L and A57R from the vaccinia virus results in reduced virulence for intranasally infected BALB/c mice (body weight loss and 50% lethal dose).

Expression of cytokines is another approach to attenuation of recombinant viruses suitable for use as live vaccines. Cytokines are effective adjuvants [63]. Interferon-γ (IFNγ) is one of the key cytokines with antivirus activity. It is experimentally confirmed that only expression of cytokines inducing the IFNγ secretion causes a decrease in the virulence of the recombinant vaccinia virus, while the expression of IFNγ fails to affect the virus virulence and immunogenicity. It has been shown that expression of interleukin-2 (IL-2) by the recombinant vaccinia virus significantly reduced the virus virulence for rodents without decrease of its immunogenicity [64]. The skin lesions caused by recombinant vaccinia viruses expressing IL-2 were less pronounced, thus confirming their attenuation while maintaining immunogenicity [65]. The recombinant vaccinia viruses expressing human or murine gene IL-2 are rapidly eliminated in non-immunocompetent mice while the control viruses induce lethal infections. Role of IL-2 in virus attenuation is associated with activation of NC cells and induction of IFNγ secretion [65].

NK-cell increase in spleen, enhanced IL-12 and IFNγ expression as well as induction of chemokines were obvious in mice inoculated with vaccinia virus expressing IL-15. Gene IL-15 insertion into vaccinia virus genome led to reduced virulence for mice but attenuation of the virus in the result of IL-15 co-expression was far less than in the result of IL-2 co-expression [66].

Another cytokine inserted into the vaccinia virus genome is IL-18 known also as a factor inducing IFNγ by activation of T and NK-cells. The recombinant vaccinia virus expressing IL-18 was considerably attenuated for mice and induced more strong cellular and humoral immune responses versus the control virus [67].

Current strategies of capripoxvirus attenuation

Scant data in available publications show that capripoxvirus attenuation occurs during serial passages (up to 90 passages) in cell culture and chicken embryos [68]. So, LSDV vaccine strains: OBP Neethling-LSD (61 passages in lamb kidney cell culture,

20 passages on chorioallantoic membrane (CAM) of chicken embryos, 2 passages in lamb kidney cells and 5 passages in bovine embryonic kidney cells); Neethling-Herbivac (61 passages in primary lamb kidney cells, 20 passages on CAM of chicken embryos, 5 passages in primary ovine embryonic kidney cells and 3 passages in primary lamb testicle cells); SIS-Lumpyvax (78 passages in calf testicle cell lines (BTRD)) were obtained. The attenuated sheep pox virus RM 65 (Yugoslavian SPPV RM-65) resulted from 30 passages in ovine kidney cell culture. All above strains are used as commercial vaccines for LSD prevention and demonstrate high immunogenic efficacy. However, the studies have shown that up to 10% of animals vaccinated with any of these vaccines demonstrate postvaccinal complications with clinical manifestation of the disease. The complications included formation of infiltrations of different size at the injection site (over the whole body in some cases), short-term fever, lower milk yields and reduced weight increments.

Sequencing and annotation of the complete genomes of several LSDV, SPPV and GTPV isolates allowed the determination of a number of suspected virulence factors [5, 6]. However, the studies aimed at obtaining attenuated capripoxviruses via gene knockout are not numerous.

Balinsky et al. [69] have experimentally proved that the kelch-like gene SPPV019 renders considerable influence on the sheep pox virus virulence. The recombinant virus ΔKLP resulted from deletion of gene SPPV019 in the genome of the virulent sheep pox virus strain A demonstrated significant attenuation for lambs. All lambs infected with the virus ΔKLP survived while the original sheep pox virus caused almost 100% mortality. Thereat the lambs infected with ΔKLP virus demonstrated marked decrease or delay of clinical manifestation of the infection (fever response, gross lesions, viremia, and virus shedding**)**.

Gene knockout was used to attenuate the lumpy skin disease virus [70, 71]. Two predicted immunomodulating genes ORF005 and ORF008 encoding respectively an interleukin 10-like and interferon-gamma receptor-like homologs were separately deleted from the genome of the virulent LSDV. In the course of assessing safety, immunogenicity and protectivity of the obtained recombinant strains for cattle severe post-vaccinal reactions and febrile responses were observed. In spite of incomplete attenuation of the viruses, cellular and humoral responses were higher as compared to commercial vaccines. The results showed that the attenuation of LSDV by knockout of one of the genes was insufficient for further use as a vaccine because of the observed adverse reactions.

CONCLUSION

Deletion of individual virulence genes not affecting virus replication in cell culture and not influencing the virus host range is a perspective approach to the poxvirus attenuation. There at a combination of several deletions in one virus genome makes unlikely the virus reversion to the virulent phenotype and allows obtaining potentially more safe but effective vaccine. In this review, we described the experimentally proved functions of some virulence genes of the vaccinia virus. Potential genes of virulence for capripoxviruses were identified based on comparative analysis of nucleotide sequences [5, 6].

We suppose that for protection of cattle against lumpy skin disease a vaccine based on a recombinant virus with deletions of several virulence genes should be elaborated. In future, the recombinant virus can be used as a vector containing immunogenic proteins of the agents causing infectious diseases of ruminants (brucellosis, rabies, peste des petits ruminants, bluetongue, etc.). To perform this study grant AP05131892 was awarded by the Science Committee of the RK Ministry of

Education and Science. On the first stage of the vaccine development integration plasmids will be constructed for insertion or deletion knockout of virulence genes. Among them there will be genes implicated in nucleotide metabolism: thymidine kinase (LSDV066) and small subunit of ribonucleotide reductase (LSDV020); genes LSDV005 and LSDV008, encoding respectively interleukin 10-like and interferon-gamma receptor-like homologs; as well as LSDV142 ortholog of gene N1L, a secretory virulence factor, Bcl-2-like apoptosis inhibitor. Safety and immunogenicity of the obtained constructions with single and multiple gene deletions will be assessed on target animals. After testing the most perspective candidate will be selected for introduction of genes encoding glycoproteins of the rabies virus or of the virus of peste des petits ruminants (or some other). Genes will be inserted into thymidine kinase or ribohucleotide reductase gene under control of the synthetic early/late poxvirus promoter [72]. Efficacy of expression of inserted genes will be assessed *in vitro* and *in vivo*.

Development of an effective vaccine against the lumpy skin disease, as well as perspectives of using it as a vector for polyvalent vaccines will contribute to the maintenance of veterinary safety and will serve a basis of a new strategy in controlling infectious diseases of ruminants.

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НОДУЛЯРЛЫҚ ДЕРМАТИТ ВИРУСЫ: АТТЕНУАЦИЯҒА АРНАЛҒАН ЖАҢА ТӘСІЛДЕР

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ТҮЙІНДЕМЕ

Нодулярлық дерматит – бұл әлемдегі көптеген елдердің мал шаруашылығына елеулі зиян келтіретін аса қауіпті ауру. Вакцинация – аурумен күресудің ең тиімді жолы. Қазіргі уақытта барлық каприпоквирус вакциналары кездейсоқ түрде мутацияға ұшыраған, ал кейбіреулері вирус қоспасының әртүрлі генотиптері мен вируленттілігін қамтиды. Классикалық әдіспен алынған нодулярлық дерматитке қарсы қолданылатын аттенуирленген вакциналар көптеген елдерде пайдаланылады және төзімді иммунитетті қамтамасыз етеді. Алайда, осы вакциналарды пайдаланған кезде, жануарларда вакцинациядан кейінгі асқынулар пайда болуы мүмкін. Осыған байланысты, аталған вирустық инфекциядан қорғауды қамтамасыз ететін дерматитке қарсы қауіпсіз иммуногенді вакцина әзірлеу қажеттілігі туындайды. Осындай жұмыстың ең перспективалы бағыты гендік инженерия әдістерін қолдану арқылы жоғары иммуногенділік пен қорғау қасиеті бар каприпоквирустардың

аттенуирленген штаммдарын әзірлеу болып табылады. Поксвирус ДНҚ геномын жүйелеу және оларды талдау, ағза иесінің көптеген қорғаныс функцияларын тиімді өзгертетін ақуыз өнімдерінің көп гендерін анықтауға мүмкіндік берді. Бұл ақуыздар комплемент факторларын, интерферондарды, цитокиндер мен химокиндерді бейтараптандырып, интерферондардың апоптозы мен синтезін және қабынуға қарсы цитокиндер мен химокиндерді ингибирлейтін клетканың сыртында да, ішінде де қызмет етуі мүмкін. Мақалада поксвирустарды аттенуацияға әкелетін осы ақуыздарды гендермен кодтайтын манипуляциялардың мысалдары қарастырылған.

Түйінде сөздер: аттенуация, вакцина, каприпоксвирус, вируленттілік гендер, гендер нокауты

ВИРУС НОДУЛЯРНОГО ДЕРМАТИТА: СОВРЕМЕННЫЕ ПОДХОДЫ АТТЕНУАЦИИ

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АБСТРАКТ

Нодулярный дерматит особо опасное заболевание, которое наносит значительный ущерб скотоводству многих стран мира. Вакцинация наиболее эффективный способ борьбы с данным заболеванием. Все доступные в настоящее время вакцины против каприпоксвирусов мутированы случайным образом, а некоторые содержат смесь вирусов с различными генотипами и вирулентностью. Существующие аттенуированные вакцины против нодулярного дерматита получены классическим методом применяются во многих странах и обеспечивают стойкий иммунитет. Однако при применении этих вакцин у животных могут возникать поствакцинальные осложнения. В связи с этим существует необходимость в создании безопасной иммуногенной вакцины против бугорчатки, обеспечивающей защиту от данной вирусной инфекции. Наиболее перспективным направлением таких работ является создание аттенуированных штаммов каприпоксвирусов, обладающих высокой иммуногенностью и протективностью, с использованием генно-инженерных методов. Секвенирование poxvirus DNA genomes и их анализ позволило идентифицировать большое количество генов, белковые продукты которых эффективно изменяют многочисленные защитные функции организма хозяина. Данные белки могут функционировать как вне, так и внутри клетки, нейтрализуя факторы комплемента, интерфероны, цитокины и хемокины, ингибируя апоптоз и синтез интерферонов и провоспалительных цитокинов и хемокинов. В данном обзоре рассмотрены примеры манипуляции с генами, кодирующими данные белки, приводящие к аттенуации поксвирусов.

Ключевые слова: аттенуация, вакцина, каприпоксвирус, гены вирулентности, нокаут генов