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NEW PERSPECTIVES FOR THE TREATMENT AND PREVENTION OF COVID-19 INFECTION. THE ROLE OF POLYAMINE-DEPENDENT MECHANISMS IN THE LIFE CYCLE OF RNA AND DNA VIRUSES IN MAMMALS

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Abstract

In the classification of pathogenic viruses proposed by Baltimore in 1971, the leading role is given to the presence of RNA and DNA of genetic material in them, which provided new opportunities in the study of infectious diseases.

In recent years, many virologists, bacteriologists and infectious disease specialists around the world have focused their attention on the newly discovered facts of coexistence and interaction of viruses, mammalian cells and positively charged aliphatic polyamines.

In addition to numerous functions in the mammalian organism, polyamines also play an important role in stabilizing the negative charges of DNA and RNA, RNA transcription, and viral protein synthesis. According to the new data of many advanced specialists in various fields of modern medicine and biology, the significance and role of polyamines in the vital activity of pathogenic viruses in mammals are involved in the processes of penetration of viruses into host cells, where they perform transcription, replication and packing of their own genetic material.

The presence of polyamines is also found in a number of viruses: enteroviruses, flaviviruses, bunyaviruses, etc. The specific role of polyamines in them is still controversial and largely incomprehensible. There is a point of view that the presence of polyamines in viral capsids is due to the processes of packing the genetic material. For many viruses, including coronaviruses, there is no information about the presence of polyamines in virions.

Among the new functions of polyamines, namely, facilitating the attachment of the virus to virus-sensitive cells, as well as the penetration of the virus into target cells, are polyamine-dependent.

The fact that the binding of RNA viruses to virus-sensitive cells is regulated by polyamines indicates that the binding of RNA viruses to virus-sensitive cells is suppressed by the ornithine decarboxylase inhibitor (synthesizes putrescine from ornithine) (ODC) - difluoromethylornithine (DFMO). It has been established that human viruses, including the pandemic SARS-CoV-2, are sensitive to polyamine depletion and require polyamines primarily for effective cellular attachment.

Thus, depletion of polyamines is a strategy by which mammalian cells can partially suppress viral infection. On the other hand, since the temporary depletion of polyamine reserves is relatively "painless" tolerated by most host cells, it becomes necessary to develop a qualitatively new strategy, by using effective therapeutic agents and/or by including polyamine-deficient products in the diet of patients, to block the level of polyamines in body, which can be the reason for the limitation of the development of a viral infection.

Keywords: *Coronavirus, RNA virus, aliphatic polyamines, difluoromethylornithine, depletion, facilitating, penetration.*

Introduction

The role of polyamines (Put, Spd, Spm, Cad, Agm), as well as their acylated derivatives in mammals, microorganisms and plants is reflected in a number of monographs and publications [*Tabor C, Tabor H, 1984; Alm K et al., 2000; Schipper R et al., 2000; Oredsson, 2003*]. It should be especially noted that, in addition to studies reflecting the functions of polyamines at the molecular, cellular and systemic levels of the mammalian organism, they simultaneously provide many physiological functions of a macroorganism, such as stages of mental development [*Fiori L et al., 2008*], behavioral reactions [*Gupta N et al., 2009*], the aging process [*Nishimura*

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K et al., 2006; Minois N et al., 2011], memory regulation [*McDonald W et al., 2001; Guerra P et al., 2011; Peg A, 2016*], act as pathogenetic and symptomatic factors in a number of neurodegenerative disorders [*Seidl R et al., 1996; Takano K et al., 2005; Inoue K et al., 2013; Avagyan S, Zilfyan A, 2020*], diseases of the gastrointestinal tract [*Edwards L et al., 1992; Cersosimo M et al., 2012*], a group of cardiomyopathic diseases [*Han L et al., 2009; Giordano E et al., 2010; Meana C et al., 2016*].

The role of polyamines in mammals is very multifaceted and is realized at all levels of integration: molecular, cellular, organ and systemic [*Tabor C, Tabor H, 1984; Schipper R et al., 2000*]. It is reported about the relationship between cell growth and polyamines [*Löser C et al., 1999*], regulation of the cell cycle [*Alm K et al., 2000; Oredsson S, 2003*] and gene expression [*Kamińska B. et al., 1992*]. So, at the molecular level, polyamines have a direct effect on RNA structural changes, stimulation of 3S-ribosomal subunits and the formation of Ile-tRNA [*Igarashi K, Kashiwagi K, 2000; 2010*]. Polyamines also play an important role in the stabilization of negative charges of DNA and RNA, RNA transcription, protein synthesis, regulation of ion channels [*Eliassen K et al., 2002; Gugliucci A, 2004; Moinard C et al., 2005; Larqué E et al., 2007; Ruíz C et al., 2012; Atiya A et al., 2013; Kalac P, 2014; Gómez G et al., 2017; Muñoz-Esparza N et al., 2019*].

Due to the optimal level of polyamines in mammals, the following integrative cellular functions are provided: transcription, translation, metabolism and structure of nucleic acids, packing of nuclear chromatin [*Basu H et al., 1992; Miller-Fleming L, 2015*]. Polyamines also participate in Z-DNA conformation, stabilizing the conformation of the DNA quadruplex together with c-myc, leading the latter to overexpression [*Thomas T et al., 1995; Kumar N et al., 2009*].

Polyamines also modulate the mechanisms of intracellular localization responsible for the processes of differentiation, proliferation, regeneration and apoptosis [*Tabor C, Tabor H, 1984; Kaminska B et al., 1992; Löser C et al., 1999; Alm K et al., 2000; Schipper R et al., 2000; Oredsson S, 2003*]. There is an opinion that hypusination, realized through the activation of eIF5A (eukaryotic translation initiation factor 5A), is carried out through the direct participation of one of the polyamines – spermidine, which in this particular case acts as its precursor [*Nishimura K et al., 2005; Olsen M et al., 2016; Mounc B, 2017; Olsen M, Connor J, 2017; Puleston D et al., 2019; Zhang H et al., 2019*].

It is established that the so-called "polyamine-sensitive module" suggests the effect of polyamines on the cellular levels of many proteins by activating the processes of transcription and translation [*Igarashi K, 2006*].

Considering the huge role of polyamines in mammals, a number of authors consider it to be a prerequisite to maintain the normal content of polyamines in mammals, due to which a wide range of basic cellular functions is realized [*Yoshida M et al., 2004; Higashi K et al., 2006; Pegg A, 2009; Pegg A, 2016*].

A somewhat detailed presentation of the material concerning the role of aliphatic polyamines in mammalian cells was presented by us for one single purpose: many of the functions that are inherent in intracellular polyamines are also possessed by a number of viruses pathogenic for humans [*Firpo M, Mounce B, 2020*].

Role of polyamines in viruses of various biolocalization

Formed (evolutionarily developed ones are also not excluded) virus-host relationships, rather earlier, before mammals began to act as a host, have a much ancient history, since viruses were found in various representatives of the plant world. It is quite remarkable that the nature of the pathogenic potencies and the functional activity of viruses, regardless of the object of their colonization (be it a human or a plant), are very similar in most general terms, which, in our opinion, once again indicates the enormous adaptive abilities of various ecological systems.

With regard to specific representatives of viruses, their localization and functional activity in various plants, there are very few literary data.

Separate but relatively informative data in this aspect are given in the review article [*Firpo M, Mounce B, 2020*].

Polyamines in bacteriophages: Historically, noteworthy is the fact that the study of the polyamine function in viruses of some plants followed early studies aimed at studying various structural and functional characteristics of bacteriophages [*Fukuma I, Cohen S, 1973; 1975; Pererva T, 2008*]. As noted by Firpo M.R. and Mounce B.C. (2020), in fact, bacteriophages were critical systems that first established the role of polyamines in viral infection. Some information on the biological

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

significance of bacteriophages is given in our previous article published in this issue of the journal [*Zilfyan A et al., 2020*].

Apparently, the role of polyamines in the functional activity of bacteriophages is very significant. Thus, the virions of DNA and RNA subsets of bacteriophages contain polyamines. A number of authors found that putrescine and spermidine were found in the virions of R-17 bacteriophage, which were bound to viral RNA [Ames *B et al., 1958; Fukuma I, Cohen S, 1975; Cohen S, McCormick F, 1979*]. There are data according to which putrescine and spermidine localized in virions, at their optimal level, are able to neutralize about 50% of the negative charge of the genome [*Firpo M, Mounce B, 2020*]. There is an opinion that polyamines localized in bacteriophages are actively involved in the "stabilization" of the phage itself by binding and enhancing the compaction of nucleic acids [*Riemer S et al., 1978*]. There are also very informative data according to which intraphageal polyamines are involved in viral DNA replication and phage translation [*Young D, Srinivasan P, 1974*].

At the same time, it should be noted that in cases of the formation of bacteriophage phenomenon, in individual bacteria, in which the phage is localized, there is a cumulation of specific representatives of aliphatic polyamines. Thus, spermidine accumulates in a bacterial cell E. Coli infected with R-17 phage, which, according to some authors, enhances the functions of the phages themselves [*Fukuma I, Cohen S.S., 1973; Fukuma I, 1975*]. Such a process could not be found in other bacteriophages, for example, in the T4 bacteriophage [*Dion A, Cohen S, 1972a; 1972b*]. Apparently, the process of introducing viruses into bacteria should not be considered as a mandatory cumulation in the latter aliphatic polyamines, which makes it possible to make an assumption according to which the main effects that bacteriophages are endowed with are precisely due to polyamines localized in their virions.

Polyamines in plant viruses: After the detection of polyamines in bacteriophages, the next chronological stage was the research, which studied the potential role of polyamines in plant viruses. Some plants, in which viruses are found, contain polyamines. In some plant viruses, the content of polyamines is much higher than that found in mammalian cells.

Thus, in the purified turnip yellow mosaic virus (TYMV), the level of spermidine and spermine is twice as high as in animal cells [*Johnson M et al., 1962; Beer S et al., 1970; Virudachalam R et al., 1983; Balint R et al., 1985*]. In other plant viruses, for example in the Bean dwarf mosaic virus (BDMV), very low levels of putrescine and spermine are determined, aimed only at maintaining the stability of the virion [*Virudachalam R et al., 1983; Savithri H et al., 1987*].

Algal virus – *Paramecium bursaria chlorella virus-1*, which is a DNA virus, apparently in the process of evolutionary development, has acquired the ability to encode various metabolic pathways, including the pathway responsible for the synthesis of polyamines. Thus, algal viruses began to clone a number of key enzymes responsible for the synthesis of polyamines — ornithine decarboxylase and polyamine acetyltransferase [*Morehead T et al., 2002; Baumann S et al., 2007; Charlop-Powers Z et al., 2012*]. This virus, in addition to spermidine synthase, also has the ability to encode homospermine synthase [*Kaiser A et al., 1999*].

The literary sources of this article are presented in the same sequence as those set out in the review article of Firpo M.R., Mounce B.C. (2020) and are characterized by a strictly consistent style of presentation of the very scanty material in the literature concerning the aspects of the presence and metabolism of polyamines in plants.

POLYAMINES IN MAMMALIAN VIRUSES.

Presence of polyamines in viruses pathogenic for humans: Polyamines were detected in human viruses much later than in bacteriophages. In bacteriophages, as we indicated earlier, polyamines were found by the end of the 1950s [*Kay D, 1959*], and in human viruses since 1971. The presence of individual representatives from the groups of aliphatic polyamines or all of them were simultaneously detected in a very wide range of human viruses, with a very different structure of organization, functional activity, both in vitro and their persistence in the human body Among these viruses are: Influenza virus (PR8 strain) [*Robinson W, Duesberg P, I968; Bachrach U et al., 1974*], Newcastle disease virus (NDV-strain SP) [*Bachrach U et al., 1974*], Encephalomyocarditis virus [*Sheppard S et al., 1980*], HCMV virions (AD169 ,, HCMV 751, HCMV-1) [*Gibson W et al., 1984, Tyms A et al., 1988*], herpes simplex virus (HSV-1), nucleocapsid and in the viral envelope [*Gibson W, Roizman B, 1971*], Vaccine virus (VACV) [*Gibson W, Roizman B, 1971; Lanzer W, Holowczak J, 1975*], poliovirus Coxsackievirus contain small amounts of polyamines [*Fout G et al., 1984*].

A group of aliphatic polyamines are found in enterovirus, alphavirus, flavivirus, rhabdovirus, coronavirus, bunyavirus [*Mounce B et al., 2016a*].

It should be especially noted that intraviral polyamines play a very significant role in the packaging of the genome into virions.

Particularly noteworthy are those studies in which the viral genome packaging in virions is, to a certain extent, related to the presence and amount of polyamines in capsids. We are talking about the character and degree of packing, and the high packing density, in which an important role is played by the balancing of negative DNA and RNA charges with the positively charged domain of capsid RNA (ssRNA)/DNA-binding protein, is largely due to the high content of capsid polyamines [*Sun S et al., 2010; Mounce B et al., 2017*]. As an illustrative example, we can cite molecular processes at the gene level, which were found in herpes simplex virus (HSV) and poxvirus, in which high concentrations of polyamines neutralize more than 40% of the negative DNA charge. At the same time, many mechanisms affecting aspects of the influence of polyamines localized in capsids on the viral genome packaging in terms of additional supply of polyamines into capsids, according to a number of authors, have not been sufficiently studied [*Gibson W, Roizman B, 1971; Bachrach U et al., 1974; Lanzer W, Holowczak J, 1975; Sheppard SL et al., 1980; Raina A et al., 1981; Fout G et al., 1984*].

In addition to its significant role in the viral genome packaging, polyamine is given a certain role in stimulating the activity of viral proteins. There is an opinion that some polyamines are involved in direct stimulation of viral HSV DNA polymerase [*Ostrander M, Cheng Y, 1980; Wallace H et al., 1980; 1981*], and also activate cellular DNA-polymerase [*Yoshida S et al., 1976; Osland A, Kleppe K, 1978*], kinase of varicella zoster virus (VZV), beta herpesvirus, and others [*Kenyon T et al., 2001*].

In light of the discussion, some researchers, with a high degree of probability, also note the important role of polyamines in packaging of genetic material in coronavirus virions [*Kicmal T et al., 2019*].

T*he role of polyamines in the attachment of viruses to mammalian host cells:* The initial stage of contact of the virus with target cells occurs due to its attachment to the cytoplasmic membrane. In this regard, several local factors of a nonspecific and, to a certain extent, receptor nature are discussed, which provide the earliest stage of penetration of the virus into the target cell. Electrostatic interactions between the virus and the structural components of target cells act as a non-specific factor [*Jolly C, Sattentau Q, 2013*]. The involved receptor factor is S-glycoprotein localized on the surface of the virus through the cellular receptor of the angiotensin-converting enzyme 2 (ACE2). Glycoprotein S contains two subunits, S1 and S2. The S1 fragment determines the specificity to the hosts (host range) and cellular tropism, as well as facilitates the attachment of the virus to target cells [*Hoffmann M et al., 2020*]. It should be especially noted that a similar receptor mechanism is involved when SARS-CoV-2 appears as a virus pathogenic for humans. S-glycoprotein localized on the surface of target cells determines "cellular tropism" and also promotes the attachment of the virus to target cells [*Hoffmann M et al., 2020*]. Numerous studies have established the binding of RNA viruses to ACE2 (Fig. 3-1) [*Lebeau G et al., 2020; Wang K et al., 2020*].

It is known that ACE2 was widely recognized as an important receptor in viral invasion, and viral replication was specifically inhibited by antibodies against ACE2 [*Li W et al., 2003*]. However, ACE2 is widely distributed in various tissues, especially in the heart, kidneys and testes [*Tipnis S et al., 2000*], which plays an important role in blood pressure control, prevention of heart failure and kidney damage [*Wong D et al., 2007; Der Sarkissian S et al., 2008; Rentzsch B et al., 2008*]. In lung diseases, loss of ACE2 increases vascular permeability and pulmonary edema, activates the renin-angiotensin system, and contributes to the pathogenesis of severe lung injury [*Kuba K et al., 2010; Wang K, 2020*]. Therefore, treatment with ACE2 as a target may negatively affect its protective role.

Recently, a new pathway for viruses to enter the cell through the receptor CD147 (Basigin) was found. Zhou Y. and co-authors (2020), while studying porcine reproductive and respiratory syndrome virus (PRRSV), identified CD147 as a novel receptor. CD147-spike protein (SP), and the CD147-SP interaction facilitated viral invasion for host cells. As mentioned earlier, CD147 is highly expressed in tumor tissues, inflamed tissues and cells infected with various pathogens, which leads to low cross-reaction with normal cells [*Kosugi T et al., 2015; Su H et al., 2018*]. Meanwhile, mepolizumab, a humanized anti-CD147 antibody, can effectively prevent viruses from entering host cells by blocking CD147. All previous researches and development of original antibody-based drugs such as metuximab, metuzumab, mepolizumab demonstrate high safety in preclinical studies and in clinical use. Therefore, a drug that targets CD147 is safe and reliable in its use, and is a drug that inhibits the receptors that block the entry of the virus into host cells without being influenced by the variations of the virus (Fig. 3-1) [*Lebeau G et al., 2020; Ulrich H, Pillat M, 2020; Wang K et al., 2020*].

However, a number of authors hold the opposite opinion regarding Basigin-CD147 as a receptor for SARS-CoV-2. Shilts J. and co-authors (2021) investigated human Basigin-CD147 as an alternative receptor for interaction with the SARS-CoV-2 virus.

Their previous works on the role of Basigin-CD147 as a host receptor in Plasmodium virus allowed the authors to study Basigin-CD147 as a SARS-CoV-2 receptor. The authors were unable to detect any binding in biochemical or cellular assays, neither for the common Basigin-CD147 isoform, nor for the configuration, nor for the allele of the SARS-CoV-2 spike protein. In addition, in tests for viral infection with authentic SARS-CoV-2 in lung cell lines, it was not possible to establish the role of Basigin-CD147 in infection [*Shilts J et al., 2021*].

It is for this reason that the hypotheses based on the binding of Basigin-CD147 to explain viral tropism need a more thorough revision [*Leonardi A et al., 2020*].

Heparin sulfates act as another known factor, involved, as is commonly believed, by the receptor mechanism. SARS-CoV-2 infection depends on the interaction of cellular heparan sulfate and ACE2. In particular, heparin sulfate is a selective factor of the virus attachment (avian coronavirus) in infectious bronchitis Beaudette [Madu I et al., 2007; Clausen T et al., 2020; Kim S et al., 2020; Thachil J, 2020]

In the past decade, many researches have been conducted to find endogenous factors that facilitate the attachment of viruses to target cells. In these studies, a "new function of polyamines" was revealed due to which this process is noticeably facilitated [*Matrosovich M et al., 2004; Shinya K et al., 2006; Van Riel D et al., 2006; Nishimura Y et al., 2009; Belser J et al., 2013; de Graaf M, Fouchier R, 2014; Dalrymple N, Mackow E, 2014; Shi Y et al., 2014; O'Hara S et al., 2014; Kicmal T, 2019*]. According to Kicmal T.M. (2019), a number of viruses pathogenic for humans – enteroviruses, flaviviruses and bunyaviruses, use polyamines in the process of their attachment to target cells.

The possible mechanisms by which polyamines perform their specific function in mammals – to facilitate the attachment of viruses to the surface of target cells, are a subject of special discussion.

1. Polyamines, due to their cationic nature, enhance the binding of the virus to target cells [*Nakamura A et al., 2019*].

2. Strengthening of the binding of the virus with target cells occurs by a mechanism similar to the action of diethylaminoethyl (DEAE) – dextran and polybrene [*Nguyen T et al., 1987; Conti C et al., 1991; Guibinga G et al., 2002*].

3. In the process of facilitating attachment, heparin sulfates are involved, which have part in the absorption of polyamines [*Belting M et al., 1999; Zautner A et al., 2003; Jolly C, Sattentau Q, 2013*].

Thus, at present, a new function of polyamines in mammals has been established – to facilitate the attachment of a number of viruses pathogenic for humans to the surface of virus-sensitive target cells.

Viruses pathogenic for humans – coronaviruses, carry out their realizing effect – facilitating the attachment of the virus to the target cell, under the conditions of the participation of polyamines. The significant role of polyamines in this process is supported by the fact that the induction of such a polyamine-dependent mechanism is blocked under the conditions of using DFMO. In particular, the process of binding of RNA viruses to target cells is mainly regulated by a specific representative of the group of aliphatic polyamines – putrescine, while the putrescine-dependent process of binding of the virus to the target cell is suppressed by DFMO, by inhibiting the ODC enzyme (Fig. 1). U.S. Food and Drug Administration (FDA) approved drug - DFMO, according to a number of authors, exhibits pronounced antiviral activity against a number of RNA viruses pathogenic for humans [*Mounce B et al., 2016a*], while having low toxicity and causing only mild, transient side effects [*Milord F et al., 1992*].

Concluding this section of our article, we consider it appropriate to cite the opinion of a number of advanced authors [*Firpo M, Mounce B, 2020; Wang K, 2020*], which are presented with the maximum expression of the text of the article by the authors themselves – "Depletion of polyamines is a strategy by which mammalian cells can reduce viral infection".

The entry and fusion process of viruses with a cell: The main pathway of the virus entry into the target cell is now generally accepted. This pathway is activated by a receptor mechanism with included re-

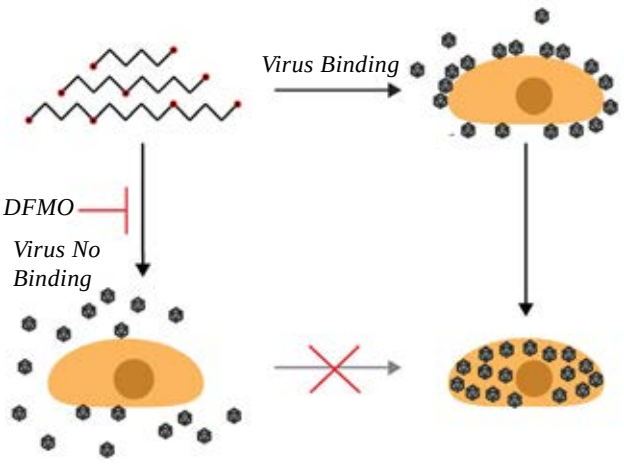

FIGURE 1. Polyamines promote binding virus to cell surfaces and initiate infection, while polyamine depletion via DFMO decreases binding [*Kicmal T, 2019*]

ceptors localized on the cell surface. This pathway is via ACE 2 receptor (Fig. 3-1) due to the RDB-S1 (receptor-binding domain) S viral protein [*Hoffmann M, 2020; Letko M, 2020; Ou X et al., 2020*]. The fusion of the viral and cell membranes occurs due to the S-2 subunits of S glycoprotein.

It is quite remarkable that this mechanism is more clearly represented in the study of SARS-CoV-2 adhesive function. So, after the binding of SARS-CoV-2 virion to ACE-2 receptor, the S-2 subunit of glycoprotein S is activated, as a result of which the viral membrane fusion with the cellular membrane, the subsequent penetration of the virus into the target cell occurs by endocytosis (Fig. 3-1) [*Hoffmann M, 2020*]. After endocytosis, invagination (protrusion) of the cell membrane occurs, with the formation of endosomes (vacuoles) and their subsequent fusion with lysosomes. This sequential stage of virus entry into the cell is characteristic only for RNA positive viruses, including SARS-CoV-2. Subsequently, the "naked" viral genome is released from endosomes into the cytoplasm of the host cell.

As the viral membranes are removed, deproteinization (release) of viral RNA occurs due to lysosomal proteases and lipases. At this stage, cores, nucleocapsids and nucleic acids begin to act as the end product of deproteinization (Fig. 3-1) [*Litusov N, Ustyuzhanin A, 2012; Fipro M, Mounce C, 2020*]. This stage of the virus interaction with the macroorganism cells is referred to as shadow phase. During this period, the virus stops to exist as a formalized virion. In the process of releasing the contents of the virion – "naked nucleocapsid" – the genome, the latter contains from 3 to 100 or more genes, which are subdivided into structural and regulatory. Structural genes encode the synthesis of proteins that make up the virion, regulatory genes significantly change the metabolism of the target cell, and subsequently regulate the rate of viral reproduction. The stages of penetration and deproteinization of viruses are combined into the stage of internalization [*Litusov N, Ustyuzhanin A, 2012*]. Viruses of positive RNA are released into the cytoplasm of the target cell and then translated by ribosomes (Fig. 3-2). Replication of (+) RNA viruses occurs in the cell itself, while (which is typical for (+) RNA viruses) the function of the informative RNA of the cell begins to be performed by the viral genome itself.

The role of viruses and polyamines in infected cells: Viruses depend on host resources to produce progeny viruses and usually alter cellular metabolism to provide the metabolites necessary for successful infection. Polyamines are numerous multifunctional biomolecules that have close relationships with viruses (such as facilitating viral entry and maintaining transcription, translation, packaging and synthesis of the viral genome, binding of the virus to host cells, and regulating the activity of viral proteins). Therefore, it is not surprising that polyamines also support the multiplication of viruses, including DNA viruses and RNA viruses belonging to different families [*Wallace H et al., 1981; Moussatche N, 1985; Sun S et al., 2010; Kenyon T et al., 2001; Mounce B et al., 2016b; Zhou Y et al., 2020*]. It is interesting that viruses (i.e. Coronaviridae (MERS-CoV), and Arteriviridae (PRRSV)), which are classified within the order Nidovirales, are characterized by the fact that each of them have a 3-co-terminal nested set of subgenomic mRNAs, suggesting the possibility that viruses belonging to other families of Nidovirales, such as the families Roniviridae and Mesoniviridae, infect host cells in a polyamine-dependent manner. Notably, several other viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV), MERS-CoV and novel coronavirus (SARS-CoV-2), are members of the Coronaviridae family in the order Nidovirales, highlighting the potential positive role of polyamines in functional activity of these viruses.

Conversely, the level and activity of polyamines are modulated by viruses (Fig. 2): Epstein-Barr herpes virus (EBV), herpes simplex virus (HSV), bovine herpes virus (BoHV), and human cytomegalovirus (HCMV) induce polyamine levels via ODC1 and SAMDC. Hepatitis C virus (HCV) proteins induce both SAT1 and ODC1, and cells carrying HCV replicons exhibit decreased polyamine levels. Paramecium bursaria chlorella virus 1 (PBCV-1) encodes a biosynthetic pathway for polyamines. Not fully studied mechanisms are represented by dashed lines [*McCormick F, Newton A, 1975; Clarke J, Tyms A, 1991; Firpo M, Mounce B, 2020; Zhou Y et al., 2020*].

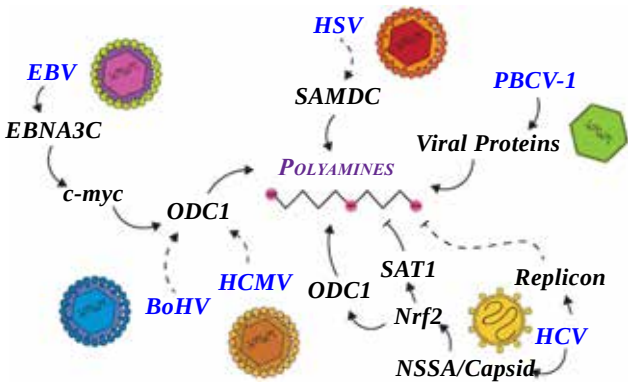

Figure 2. *Viral manipulation of polyamines in infected cells [Fipro M, Mounce C, 2020]*

Viruses use different approaches to control the metabolism of polyamines. Most viruses regulate the levels of polyamines, interfering with the expression and activity of metabolic enzymes of polyamines [*Zhou Y et al., 2020*].

The role of polyamines in host cells: As we indicated earlier, the role of aliphatic polyamines in mammals is very multifaceted and is aimed at the formation and implementation of the ultrastructural organization of exclusively all cellular functions that are realized at the initial stages at the level of their ultrastructural organization. Among the most important polyamine-dependent functions, in particular, appear: growth, differentiation, proliferation, mobility and stabilization of ion channel activity, apoptosis, etc. [*Raina A et al., 1966; Russell D, Snyder S, 1968; Pegg A et al., 1970; Pegg A, 2016*].

The structure and stability of nucleic acids are largely provided by polyamines [*Iacomino G, 2012*]. Thus, many intracellular polyamines are associated with RNA, and many of the effects are due to their binding to ribosomes, tRNA and mRNA, and the effect on protein synthesis [*Igarashi K, 2010*]. This interaction of polyamines with RNA on the content of specific proteins occurs in multiple ways, including structural transformations in ribosomes, facilitating the formation of initiating complexes and the ability to считывания ineffective initiating complexes and enhancing frameshifting [*Igarashi K, 2010; Ivanov I et al., 2010; Yamashita T et al., 2013; Sakamoto A et al., 2015*].

Moreover, intracellular polyamines, by acting with proteins, provide the assembly and structure of their microtubules [*Ojeda-Lopez M, 2014*].

The interaction of polyamines with protein receptors localized on the cell membrane largely determines their functional activity [*Williams K et al., 1991; Bowie D et al., 1998; Hesterberg R et al., 2018*].

AUTHORS' HYPOTHESIS

POSSIBLE MECHANISMS FOR THE INCLUSION OF POLYAMINES INTO RNA-ПОSITIVE VIRUSES.

During the replication period, daughter nucleocapsids of the virus are produced in the infected host cell (Fig. 3-6), which need to be tightly packed. In this process, polyamines play an important role, which has been established in numerous studies.

As a result, in our opinion, in the process of packing the daughter nucleocapsid in the host cell, polyamines are involved as its structural component. After that, a daughter virion is formed, with the presence of polyamines in it.

Free polyamines of the host cell can also appear as sources of polyamines entering the virion.

Separate and/or combinations of several polyamines can be involved in the packaging of daughter nucleocapsids. The biochemical properties of the nucleocapsid may largely depend on this circumstance, which, in our opinion, determines different functional properties of the same virus.

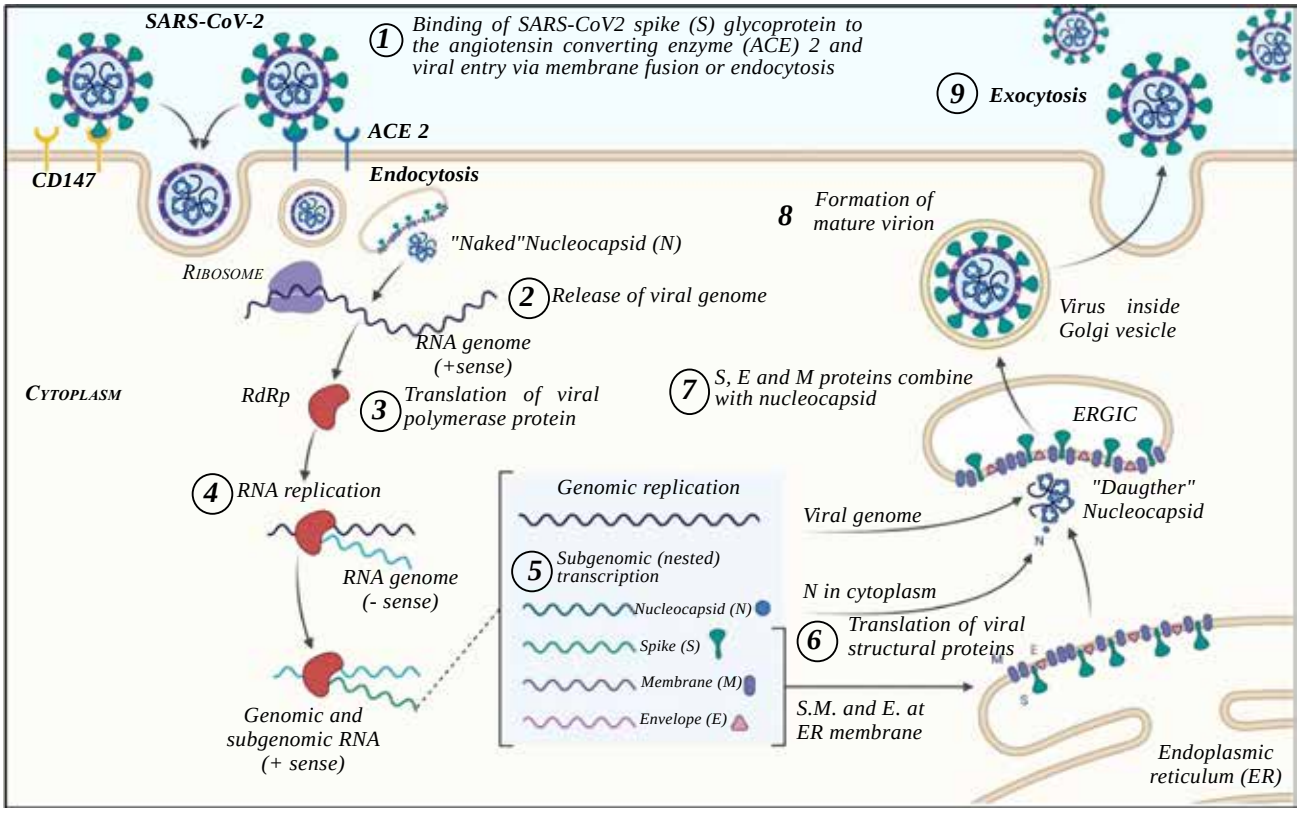

FIGURE 3. *SARS-CoV-2 supposed life cycle [Fipro M, Mounce C, 2020]*

In order to influence the content and various functions of the protein, polyamines include mechanisms such as post-translational modification of the protein [*Tolbert W et al., 2003; Pegg A, 2009*] and causing protein degradation [*Mitchell J et al., 1996; Pegg A, 2006; 2009*].

Molecular genetic polyamine-dependent mechanisms of intracellular protein synthesis, apparently, are universal exclusively for all cells of different origin and functional purpose of mammals. So, polyamines indirectly – through protein synthesis, are actively involved in the implementation of a number of integrative functions of the body: osteogenesis [*Lee M et al., 2013; Yeon J et al., 2014*], muscle development [*Luchessi A et al., 2009*], stem cell differentiation [*Ishii I et al., 2012; Brenner S et al., 2015*]. It is established that polyamines, by activating key regulatory proteins, are actively involved in cell migration, activation of reparative-proliferative processes during wound healing, tissue remodeling, through a balanced interaction of proliferation and apoptosis processes [*Firpo M, Mounce B, 2020*], in the reparation processes of mucous cells of the gastrointestinal tract [*Ray R et al., 2007; Rao J et al., 2012; Gao J et al., 2013*].

Role of polyamines for viruses within host cells: After the fusion of the viral virion with the cell, in the latter, with the participation of ultrastructural components of the cell, all the necessary conditions are created, exclusively for the implementation of the main functions of viruses pathogenic for humans, the individual defining stages of which are identical to those involved in the processes of self-reproduction of mammalian cells.

The entry of SARS-CoV-2 into the target cell is mediated by the expression of ACE2 or the proposed new CD147 receptor. After penetration into the host cells, the viral "naked nucleocapsid" undergoes RNA replication (Fig. 3-4), after which the process of gene replication and subgenomic transcription is activated (Fig. 3-5), in order to form new subunits for the formation of future daughter viruses. After that, new nucleocapsids are formed in the cytoplasm of the host cell (Fig. 3-7), with the formation of a mature virion, which is packed inside the Golgi vesicle (Fig. 3-8), with subsequent release from the host cell.

Under these conditions, viruses have developed fundamental mechanisms for maintaining, amplifying, or directing the replication of new viruses.

From the standpoint of the role of polyamines in the processes associated with the genetic material of both cells and the virus, including changes in the structure of ribosomes, the formation of initiating complexes and the enhancement of frameshifting are facilitated [*Igarashi K, 2010; Ivanov I et al., 2010; Yamashita T et al., 2013; Sakamoto A et al., 2015*].

It was shown that polyamines are involved in the transcription process by stimulating RNA-dependent RNA polymerases [*Wallace H et al., 1980; Korovina A et al., 2012; Mounce B et al., 2016*]. However, viral titers do not increase, which indicates that, despite the increased transcription, the downstream bottleneck limits the packaging or production of virions. This result indicates a significant role of polyamines in the stimulation of DNA-dependent RNA polymerases [*Iwata M et al., 2000*] to RNA-dependent RNA polymerases of these two viral families.

As is known, for RNA-positive viruses, translation is considered as the initial stage of the life cycle of pathogenic viruses in mammals. There is very informative data, which established the important role of polyamines in the induction and regulation of the translation process, under conditions of persistence in the macroorganism of RNA-positive viruses. Thus, polyamines are actively involved in the induction and activation of the translation process through the hypusinization of the eukaryotic translation initiation factor 5A (eIF5A) [*Landau G et al., 2010*]. It is this receptor mechanism, according to the authors, that functions in the context of viral RNA.

Additional, but no less important, polyamine-dependent mechanisms underlying translation regulation, including structural changes and transport frame shifts, are also considered [*Lightfoot H, Hall J, 2014; Igarashi K, Kashiwagi K, 2015; Yordanova M et al., 2015*].

Fundamental studies by Mounce B.C. and co-authors (2016b) found that under conditions of depletion of polyamines, the initial stage of the life cycle of pathogenic viruses in a macroorganism – translation, is significantly disrupted. In this regard, the authors put forward a very important conclusion, according to which the deficiency of polyamines in mammals "limits this important stage necessary for the expression of non-structural proteins (including viral polymerase), due to which the viral replication is limited".

According to the authors, additional confirmation of this conclusion is provided by their own studies, which established the correspondence of the restored transfected RNA obtained from the siCHECK2 plasmid encoding luciferase – a non-viral exogenous translation control that is at the stage of replication, is also sensitive to the depletion of polyamines, which allows the authors suggest - "that exogenous RNA molecules, including viruses, need polyamines for translation".

Different viruses have developed different mechanisms to enhance or control polyamine metabolism to maintain viral infection (Fig. 3) [*Baumann S et al.,*

2007; Firpo M, Mounce B, 2020]. So the Epstein-Barr herpes virus (EBV), herpes simplex virus (HSV) [*Greco A et al., 2005; Bajaj B et al., 2008; Shi M et al., 2013*], bovine herpes virus (BoHV) and human cytomegalovirus (HCMV) induce polyamine levels via ODC1 and SAMDC [*Isom H, 1979*]. Hepatitis C virus (HCV) proteins induce polyamine levels through both SAT1 and ODC1 [*Korovina A et al., 2012; Smirnova O et al., 2014*], and cells carrying HCV replicons show decreased levels of polyamines. Paramecium bursaria chlorella virus-*1* (PBCV-1) encodes a biosynthetic pathway for polyamines [*Morehead T et al., 2002; Baumann S et al., 2007; Charlop-Powers Z et al., 2012*]. Mechanisms not fully understood are represented by dashed lines [*Firpo M, Mounce B, 2020*].

It should be especially noted that tactics aimed at depletion of the polyamine reserves in an organism infected with viruses is a very relevant direction in modern theoretical and clinical medicine, since it is directed (at least) to weaken a number of functions of pathogenic viruses persisting in mammals.

As rightly noted by Firpo M.R. and Mounce B.C. (2020), polyamine depletion is a strategy by which mammalian cells can attenuate viral infection, as the temporary depletion of polyamines is well tolerated by most cells.

In order to deplete polyamines, you can use three approaches, or a combination of them:

- therapeutic method – medicines containing natural and/or synthetic inhibitors of polyamines;
- antibacterial agents that block the synthesis of polyamines in the microbial cells themselves,
- supportive method in combination with therapeutic methods, following a diet using foods that do not contain or contain low amounts of polyamines (known “polyamine deficiency diet”).

Comprehensive information on the polyamine diet will be presented by us in the next article.

A summary of the diet role is provided at the end of this article.

Conclusion

In recent years, many virologists, bacteriologists, and infectious disease specialists have concentrated their attention on the newly discovered facts of coexistence and interaction of viruses, mammalian cells, and positively charged aliphatic polyamines.

In addition to numerous functions in mammals, polyamines also play an important role in the stabilization of negative charges of DNA and RNA, RNA transcription, and the synthesis of viral proteins. According to new data, the significance and role of polyamines in the vital activity of pathogenic viruses in mammals. according to many advanced specialists in various fields of modern medicine and biology, is due to their inclusion in the viral penetration processes into host cells, where they carry out transcription, replication and packaging of their own genetic material.

The presence of polyamines is also found in a number of viruses: enteroviruses, flaviviruses, bunyaviruses, etc. The specific role of polyamines in them is still debatable and largely incomprehensible. There is a point of view according to which the presence of polyamines in virus capsids is due to the packaging processes of genetic material.

For many viruses, including coronaviruses, there is no information about the presence of polyamines in virions.

New functions of polyamines include facilitating the attachment of the virus to virus-sensitive cells, as well as the penetration of the virus into target cells.

The fact that the binding of RNA viruses to virus-sensitive cells is regulated by polyamines indicates that the binding of RNA viruses to virus-sensitive cells is inhibited by the ornithine decarboxylase (ODC) inhibitor difluoromethylornithine (DFMO).

It has been found that human viruses, including the pandemic SARS-CoV-2, are susceptible to depletion of polyamines and require polyamines primarily for effective cellular attachment.

Polyamine depletion is a strategy by which mammalian cells can partially suppress viral infection. On the other hand, since the temporary depletion of polyamine stores is relatively “painless” tolerated by most host cells, a qualitatively new tactic arises, through the use of effective therapeutic agents and/or through the inclusion of polyamine-deficient foods in the diet of patients that block the level of polyamines in the body than may be due to the limitation of the viral infection devel

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NEW PERSPECTIVES FOR THE TREATMENT AND PREVENTION OF COVID-19 INFECTION
THE ROLE OF THE POLYAMINE-DEFICIENT DIET BEFORE AND DURING THE TREATMENT OF PATIENTS

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Abstract part 2

It is generally accepted that the level of polyamines in mammals is realized in three ways. The first is due to the metabolism of the macroorganism cells; the second one – due to the active absorption and uptake of polyamines that have entered the gastrointestinal tract with food and the third one as a result of the synthesis and absorption of polyamines by the expanded intestinal microflora.

In mammals, the amount of food polyamines is higher than that of endogenous ones, and the level of microflora polyamines depends on the biological state of the microbial flora.

It is established that in malignant degenerated cells, regardless of their origin, the level of aliphatic polyamines is very high. According to many oncologists, the control of polyamine synthesis is an important step in anti-tumor therapy. Tumor cells, in addition to numerous functions, have the ability to absorb polyamines that are ingested with food, as well as polyamines produced and/or previously adsorbed by gastrointestinal bacteria.

So, given the presence of polyamines (in high and low levels) in food products and the fact of their intensive assimilation by the cells of the macroorganism, many clinicians of various specialties, in polyamine-dependent pathological conditions, recommend to pay special attention to polyamine diet, as a preventive agent in addition to drugs, in order to correct their required level (optimal, increased, decreased) in the microorganism.

Comparing the role of polyamines in the development of malignant neoplasms and viral infections, it becomes obvious that on the basis of these diseases there is also one common tendency – an uncontrolled increased level of aliphatic polyamines. From this point of view, it seems advisable, both in the development of neoplasms and in viral infections in pandemic zones, as a preventive measure to strictly adhere to a polyamine-deficient diet, taking into account the food ration specifically in the region of residence of the urban and rural population of different countries.

In the development of a viral infection or oncological disorders, different polyamines may be of key importance. For a rational choice of the correct and necessary diet, we propose to necessarily determine the level of polyamines in biological materials.