ISSN 0006-3509, Biophysics, 2021, Vol. 66, No. 4, pp. 589–595. © Pleiades Publishing, Inc., 2021.
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CELL BIOPHYSICS

Radiation Inactivation of Coronavirus Infection Pathogen by the Example of Transmissible Gastroenteritis Virus

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Received December 21, 2020; revised January 25, 2021; accepted January 26, 2021

Abstract—In recent years, members of the *Coronaviridae* family have caused outbreaks of respiratory diseases (MERS, SARS, and COVID-19). At the same time, the potential of radiation-induced inactivation of this group of viruses have been little studied, although radiation technologies can be widely used both in the processing of personal protective equipment and in the sterilization of vaccines. In the present work, the effect of 10 MeV electron beams and 7.6 MeV bremsstrahlung on the coronavirus infection pathogen (transmissible gastroenteritis virus) has been studied in vitro. In the given experimental conditions, irradiation with photons turned out to be more effective. The virus-containing suspension frozen at –86°C was the most resistant to radiation: the dose required for complete inactivation of the virus in this case was from 15 kGy, while for the liquid suspension and lyophilized form the sterilizing dose was from 10 kGy. At lower radiation doses for all samples during passaging in cell culture, residual infectious activity of the virus was observed. These differences in the efficiency of inactivation of liquid and frozen virus-containing samples indicate a significant contribution of the direct effect of radiation.

Keywords: coronavirus, radiation sterilization, radiation processing, virus inactivation, transmissible gastroenteritis virus, ionizing radiation

DOI: 10.1134/S000635092104014X

INTRODUCTION

The SARS-CoV-2 coronavirus pandemic [1–3] has demonstrated the importance of promptly organizing a system of measures to decontaminate used personal protective equipment for medical personnel. On the one hand, this can help to improve the safety of medical waste, and on the other hand, it can provide an opportunity to reuse some types of personal protective equipment in case of their acute shortage [4].

Approaches to sterilizing medical devices from microbiological contamination include various chemical and physical methods [5]: the use of disinfectants, gas sterilization, heat, and radiation treatment. In the latter case, ultraviolet (210–400 nm) and ionizing radiation (photons, electrons, deuterons, etc.) can be used to destroy infectious agents. If the use of ultraviolet radiation, due to the small depth of penetration, is mainly limited to surface treatment, then the use of sources of ionizing radiation (for example, gamma-ray devices based on Co-60 and Cs-137 or electron accelerators) provides more opportunities.

Ionizing radiation has found application in the radiation processing of food [6], disinfection of laboratory and medical devices [7], transplants [8], sterilization of pharmaceuticals and drugs [9, 10], as well as vaccines [11]. Radiation treatment allows one to fight bacteria and endospores, fungi, protozoa, and viruses [5]. Radiation sterilization is a high-performance, noninvasive and low-cost method that does not require consumables, and existing technologies make it possible to ensure the safety of the process for personnel and the environment.

Despite the fact that the possibility of inactivation of viruses under the influence of ionizing radiation is well known [12–16], this area of radiation biology seems to be insufficiently studied and unsystematized. Currently, more than 6500 different types of viruses are known, included in 168 families. Representatives of these families differ in the structure and organization of the capsid, the presence of an envelope, and their genome can be represented by various forms of nucleic acids and contain from ≈2000 to ≈2 million

Abbreviations: TGEV, transmissible gastroenteritis virus, ELISA, enzyme-linked immunosorbent assay.

bases [17, 18]. The data on their radiosensitivity also differ [14, 19].

One of the families of viruses, whose radiation resistance is poorly understood, are coronaviruses. The *Coronaviridae* family includes four genera (*Alpha-*, *Beta-*, *Gamma-*, and *Deltacoronavirus*) [20], containing more than 40 species of viruses [21]. Virions of coronaviruses have a spherical shape and are covered with a lipid envelope with clavate peplomers consisting of S-protein, and the nucleocapsid has a helical symmetry shape and contains a single-stranded +RNA with a length of about 30000 bases. In infectious diseases of humans and animals, the main role is played by representatives of the genera *Alpha-* and *Betacoronavirus*, which cause damage to the respiratory and digestive systems [20]. In recent years, members of the *Coronaviridae* family have caused several outbreaks of disease: 2002–2003 (severe acute respiratory syndrome, SARS), 2004–present (Middle East respiratory syndrome, MERS) and 2019–present (coronavirus disease 2019, COVID-19) [22]. At the same time, only a few works on radiation inactivation of coronaviruses are known. Thus, it has been shown that in vitro inactivation of the SARS-CoV virus is achieved at doses above 1 Mrad (≈10 kGy) [19], and for the disinfection of feed contaminated with the porcine epidemic diarrhea virus (PEDV), irradiation at a dose of ≈50 kGy was required [23]. Recent studies have also been devoted to the study of radiation inactivation of the SARS-CoV-2 virus [24].

The objective of this study was to investigate the possibility of inactivating the causative agent of coronavirus infection pathogen using high-energy electron and photon beams using the example of the transmissible gastroenteritis virus (TGEV) and to study the effect of exposure conditions on the effectiveness of radiation treatment. This virus was chosen because, on the one hand, it is a well-studied member of the *Coronaviridae* family, and on the other hand, it does not pose a threat to humans and does not require specific safety conditions.

MATERIALS AND METHODS

In this work, we used TGEV strain PUR46-MAD (family *Coronaviridae*, genus *Alphacoronavirus*; subgenus *Tegacovirus*) from the collection of the University of Madrid (Department of Molecular and Cell Biology, CNB-CSIC, Spain). The virus was cultured in a pig embryonic kidney cells line (SPEV). The cultivation was carried out in roller bottles using DMEM medium (Sigma, United States) supplemented with 5% fetal bovine serum (Gibco, United States). Titration of the cytopathic activity of the virus was carried out by the micromethod in cell culture. The virus titer was calculated by the Reed–Muench method and expressed in $TCID_{50}/cm^3$.

Liquid and frozen samples were prepared from a virus-containing suspension with an infectious activity of $10^{5.66}$ $TCID_{50}/cm^3$ based on DMEM medium. Radiation treatment was carried out in sealed polypropylene tubes with a volume of 15 mL (Greiner Bio-One, Germany). To prepare lyophilized samples, a virus-containing suspension with an infectious activity of $10^{7.33}$ $TCID_{50}/cm^3$ was mixed with a stabilizer, packed by 1 cm^3 in 3 cm^3 glass vials (Schott, Germany) and sublimated on a VirTis AdVantage Pro device (SP Scientific, United States). The TGEV titer in lyophilized samples was $10^{6.66}$ $TCID_{50}/cm^3$ at a residual moisture content of 3%.

The samples were irradiated on an ILU-14 industrial linear electron accelerator manufactured by the Budker Institute of Nuclear Physics (Novosibirsk, Russia) [25]. Radiation treatment was carried out in the modes of electron and photon irradiation at doses up to 25 kGy. The maximum energy of particles in the spectrum at electron irradiation was 10 MeV, and at bremsstrahlung irradiation it was 7.6 MeV. The dose rate in both cases was 1.0–1.2 kGy/min. Irradiation of liquid and lyophilized forms of TGEV was carried out at a temperature of 6–8°C, and frozen samples were irradiated in dry ice at a temperature of –86°C. Four independent samples were prepared for each radiation dose. Dose control under photon and electron irradiation was carried out using dosimetric films SO PD(F) R-5/50 and SO PD(F) R-1/10 (VNIIFTRI, Russia). The optical density of the irradiated films was measured at a wavelength of 512 nm using a Specord M40 spectrophotometer (Analytik Jena, Germany). The error in determining the absorbed dose was no more than 20%.

In 1–2 h after radiation treatment of the samples, the efficiency of TGEV inactivation was assessed by titration of the cytopathic activity of the virus in the SPEV cells line with confirmation of the presence of antigens by enzyme-linked immunosorbent assay (ELISA). The ELISA sensitivity limit was 10^2 $TCID_{50}/cm^3$. Unirradiated samples were used as a control. To identify the residual cytopathic activity of the virus, three consecutive passages in the culture were performed for each irradiated sample with an interval of 96 h. The presence of antigens was determined using an appropriate kit produced by the LLC Vetbiohim (Russia) according to the manufacturer's recommendations.

RESULTS AND DISCUSSION

The figure shows the results of research on the cytopathic activity of TGEV irradiated with bremsstrahlung in a liquid suspension. In logarithmic scale, the dose inactivation curve (inset in the Fig. 1) had a pronounced linear character and satisfied the value of $D_{10} < 2$ kGy established for TGEV [26]. The initial cytopathic activity of the virus in suspension was

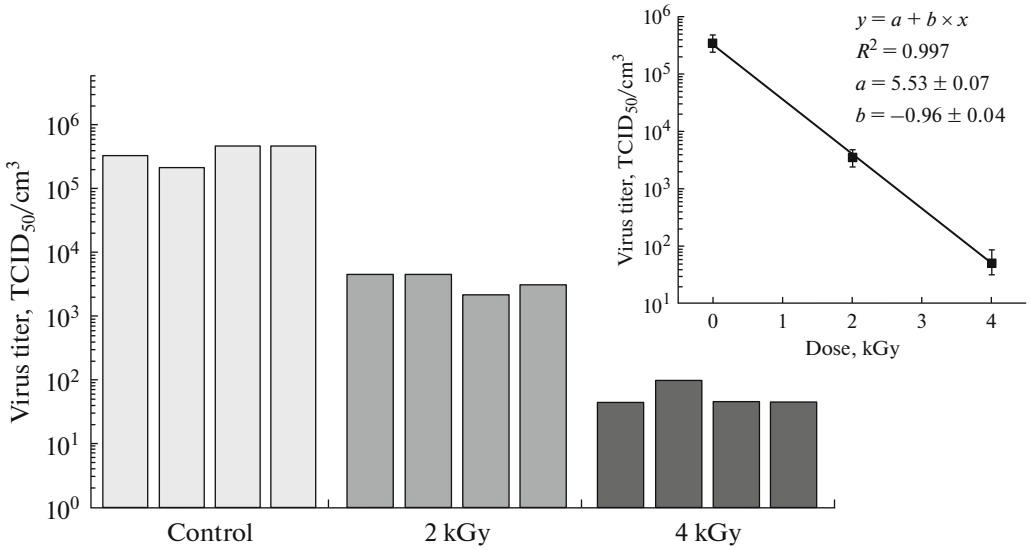

Fig. 1. The dose dependence of the cytopathic activity of TGEV in a liquid suspension in the case of bremsstrahlung irradiation. Inset: the dose curve of TGEV inactivation (errors are standard deviations from four independent measurements).

$\approx 10^{5.66}$ $TCID_{50}/cm^3$. After the radiation treatment of the samples, a noticeable decrease in cytopathic activity was observed: already at an irradiation dose of 2 kGy the virus titer decreased by ≈100 times, while at a dose of 4 kGy it decreased by more than 6000 times. At the same time, after irradiation at a dose of 4 kGy, while maintaining the cytopathic activity of the virus, in three out of four samples it was not possible to detect viral antigens using ELISA within the limits of the sensitivity of the method. At doses over 4 kGy, no cytopathic activity of the virus and viral antigens was detected immediately after irradiation.

The results of the study of the infectious activity of TGEV in three successive passages after photon irradiation are presented in Table 1. Restoration of the initial level of cytopathic activity at irradiation doses of 2 kGy and 4 kGy was observed at the first and second passages, respectively. Immediately after exposure in a dose of 6 kGy, the virus infectious activity and viral antigens was also not recorded in the samples of the liquid virus-containing suspension. At the same time, starting from the second passage, the presence of virus antigens in the culture and a fairly high level of cytopathic effect were noted. Full recovery of the infectious activity of the virus at a dose of 6 kGy was observed after the third passage. Thus, this radiation dose is insufficient for effective inactivation of TGEV under the given experimental conditions. Complete suppression of the infectious activity was observed only at radiation doses from 8 kGy.

The effectiveness of radiation treatment for samples contaminated with viral particles may differ depending on the type of ionizing radiation. As an example, in [14], a higher efficiency of Co-60 γ-radiation (≈1.25 MeV; up to ≈2.6-fold at D_{37}) compared to electron irradiation (10 MeV) was shown based on the example of herpes simplex virus (HSV) and Rauscher leukemia virus (RLV). The phenomenon of different biological effectiveness of ionizing radiation is well known; however, for photons and electrons, the values of the relative biological effectiveness are often taken equal to unity. At the same time, there are technological differences between industrial photon and electron irradiation, which are especially significant for large-scale sterilization on a conveyor line. Thus, photons are characterized by a higher accuracy of the dose coverage, and high doses of electron irradiation can lead to heating of the samples.

This work also compares the efficiency of TGEV inactivation by photons and electrons in a liquid suspension. As can be seen in Tables 1 and 2, a drop in the virus titer by three to four orders of magnitude was observed at close doses of photon and electron irradiation, 4 and 5 kGy, respectively. During irradiation of samples of a liquid virus-containing suspension with electrons at a dose of 7 kGy the residual infectious activity was manifested already at the first passage, while at irradiation doses from 10 kGy the virus infectious activity and viral antigens was not detected during passaging in cell culture.

To approximate the practical conditions of radiation processing, the lyophilized form of TGEV and the virus-containing suspension frozen in dry ice (–86°C) were irradiated with electrons. The results are presented in Tables 3 and 4. In both cases, immediately after irradiation at a dose of 5 kGy, the infectious activity of the virus was observed, but its level in the case of irradiation of the lyophilized form was significantly lower. As well, for the lyophilized form of TGEV, a more significant decrease in the virus titer

Table 1. The infectious activity of TGEV in liquid suspension after photon irradiation

Dose, kGy	After irradiation		First passage		Second passage		Third passage	
	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA
0	$10^{5.5}$	+	Not studied					
	$10^{5.33}$	+						
	$10^{5.66}$	+						
	$10^{5.66}$	+						
2	$10^{3.66}$	+	$10^{5.33}$	+	$10^{5.66}$	+	$10^{5.33}$	+
	$10^{3.66}$	+	$10^{5.66}$	+	$10^{5.66}$	+	$10^{5.66}$	+
	$10^{3.33}$	+	$10^{5.66}$	+	$10^{5.5}$	+	$10^{5.66}$	+
	$10^{3.5}$	+	$10^{5.66}$	+	$10^{5.33}$	+	$10^{5.66}$	+
4	$10^{1.66}$	–	$10^{4.66}$	+	$10^{5.5}$	+	$10^{5.66}$	+
	10^{2}	+	$10^{4.66}$	+	$10^{5.33}$	+	$10^{5.5}$	+
	$10^{1.66}$	–	$10^{4.5}$	+	$10^{5.66}$	+	$10^{5.33}$	+
	$10^{1.66}$	–	$10^{5.0}$	+	$10^{5.66}$	+	$10^{5.5}$	+
6	n/d	–	n/d	–	$10^{4.66}$	+	$10^{5.5}$	+
	n/d	–	n/d	–	$10^{4.66}$	+	$10^{5.66}$	+
	n/d	–	n/d	–	$10^{4.5}$	+	$10^{5.66}$	+
	n/d	–	n/d	–	$10^{4.0}$	+	$10^{5.5}$	+
8	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–

Here and below: n/d, the cytopathic effect of the virus was not detected; (+) and (–), the presence/absence of virus antigens in the cell culture.

was noted (by ≈6 orders of magnitude), given the higher titer of the virus in the samples before irradiation. Complete inactivation of the lyophilized form of TGEV, as well as of viral particles in a liquid suspension, was detected at radiation doses from 10 kGy. For frozen samples at a given dose, residual cytopathic activity of the virus and the presence of viral antigens in the cell culture were observed from the second passage. Complete inactivation of TGEV in the frozen suspension was observed only with an increase in the dose of electron irradiation to 15 kGy. When frozen samples were irradiated with photons inactivation of the virus was observed at a dose of 11 kGy (data not shown). Thus, under the given experimental conditions irradiation with photons of both liquid and frozen virus-containing samples turned out to be more effective.

These observations are important for understanding the mechanisms of radiation inactivation of viruses. Radiation-induced damage in biological systems occurs due to the direct and indirect action of radiation, i.e., as a result of ionization of biomacromolecules or their damage by the products of radiolysis of the environment [27]. In biological systems, the indirect damage is dominant (up to 80–90%) [28]. The direct and indirect action of ionizing radiation can be directed to various structural components of viral particles [29]. In the absence of the damaging effect of radiolysis products, for example, when biomolecules are irradiated in anhydrous systems, their inactivation requires doses that are several of magnitude higher than in the presence of a solvent [30, 31]. To some approximation, oxidizing particles formed during radiolysis in sufficiently hard ice (at sufficiently low temperatures) can be considered immobile; therefore, in samples of a virus-containing suspension frozen at –86°C the probability of radiation damage by an indirect mechanism is significantly reduced. The decrease in the effectiveness of radiation exposure noted in this work is in good agreement with the data of [32] (Lassa, Marburg and Ebola viruses) and [33] (porcine parvovirus (PPV), bovine viral diarrhea virus (BVDV), porcine enterovirus (PEV)): immediately after irradiation at a dose of 5 kGy, the titer of the virus

Table 2. The infectious activity of TGEV in liquid suspension after electron irradiation

Dose, kGy	After irradiation		First passage		Second passage		Third passage	
	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA
0	$10^{5.5}$	+	Not studied					
	$10^{5.33}$	+						
	$10^{5.66}$	+						
	$10^{5.66}$	+						
5	10^{2}	+	$10^{5.33}$	+	$10^{5.66}$	+	$10^{5.33}$	+
	10^{2}	+	$10^{5.66}$	+	$10^{5.5}$	+	$10^{5.5}$	+
	10^{2}	+	$10^{5.5}$	+	$10^{5.66}$	+	$10^{5.66}$	+
	10^{2}	+	$10^{5.66}$	+	$10^{5.5}$	+	$10^{5.66}$	+
7	n/d	–	$10^{4.66}$	+	$10^{5.66}$	+	$10^{5.5}$	+
	n/d	–	$10^{4.5}$	+	$10^{5.66}$	+	$10^{5.66}$	+
	n/d	–	$10^{5.0}$	+	$10^{5.5}$	+	$10^{5.33}$	+
	n/d	–	$10^{4.5}$	+	$10^{5.66}$	+	$10^{5.5}$	+
10	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–

Table 3. The infectious activity of TGEV in lyophilized form after electron irradiation

Dose, kGy	After irradiation		First passage		Second passage		Third passage	
	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA
0	$10^{6.5}$	+	Not studied					
	$10^{6.76}$	+						
	$10^{6.66}$	+						
	$10^{6.66}$	+						
5	$10^{0.66}$	–	$10^{4.33}$	+	$10^{5.66}$	+	$10^{5.5}$	+
	10^{1}	–	$10^{4.5}$	+	$10^{5.5}$	+	$10^{5.33}$	+
	$10^{0.66}$	–	$10^{5.0}$	+	$10^{5.33}$	+	$10^{5.5}$	+
	$10^{0.66}$	–	$10^{5.0}$	+	$10^{5.66}$	+	$10^{5.5}$	+
10	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–

in the liquid suspension was ≈40 times less than in the frozen form, and the dose required for complete inactivation of the virus increased during its freezing from 10 to 15 kGy. Such a decrease in the efficiency of irradiation by approximately 1.5-fold indicates a significant contribution of direct damage to the radiation-induced inactivation of TGEV. It is important to note that freezing the samples does not exclude the possibility of damage due to the action of hydrated electrons. This assumption is also supported by close val-

Table 4. The infectious activity of TGEV in frozen suspension after electron irradiation

Dose, kGy	After irradiation		First passage		Second passage		Third passage	
	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA	virus titer, $TCID_{50}/cm^3$	ELISA
0	$10^{5.5}$	+	Not studied					
	$10^{5.33}$	+						
	$10^{5.66}$	+						
	$10^{5.66}$	+						
5	$10^{3.66}$	+	$10^{5.33}$	+	$10^{5.5}$	+	$10^{5.33}$	+
	$10^{3.5}$	+	$10^{5.5}$	+	$10^{5.5}$	+	$10^{5.33}$	+
	$10^{3.66}$	+	$10^{5.5}$	+	$10^{5.33}$	+	$10^{5.5}$	+
	$10^{3.66}$	+	$10^{5.66}$	+	$10^{3.66}$	+	$10^{5.5}$	+
10	n/d	–	n/d	–	$10^{3.66}$	+	$10^{5.33}$	+
	n/d	–	n/d	–	$10^{4.0}$	+	$10^{5.66}$	+
	n/d	–	n/d	–	$10^{4.66}$	+	$10^{5.66}$	+
	n/d	–	n/d	–	$10^{3.66}$	+	$10^{5.33}$	+
15	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–
	n/d	–	n/d	–	n/d	–	n/d	–

ues of the radiation doses required for the complete inactivation of TGEV in a liquid suspension and in a lyophilized form.

The doses of TGEV inactivation established in this work are in good agreement with the data on the radiosensitivity of the MERS-CoV, SARS-CoV, and SARS-CoV-2 coronaviruses [19, 24, 34]. Since the level of contamination of personal protective equipment can be significantly less [35] than the amount of infectious viral particles studied in this work, high efficiency of their radiation treatment can be achieved at significantly lower dose loads. However, it is still important to note that polymeric materials used in clinical practice can be very sensitive to high radiation doses [36]. This is related to the possibility of significant changes in the protective properties of medical equipment treated with ionizing radiation [37]. Since the characteristics of radiation sterilization devices can vary significantly, it can be difficult to reproduce the conditions of a specific experiment in detail. Therefore, the decision to include radiation processing in the disinfection protocol must be made individually for each product based on careful selection of the irradiation conditions.

ACKNOWLEDGMENTS

The authors are grateful to V. I. Feldman for help in discussing the research results and Y. V. Morozov for his help in preparing the stand for radiation exposure.

COMPLIANCE WITH ETHICAL STANDARDS

In carrying out this work, all ethical standards were observed.

Conflict of Interest. The authors declare that they have no conflicts of interest.

This article does not contain any studies involving humans and animals as objects.

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Translated by A. Ostyak