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EXPERIMENTAL ARTICLES

Effect of the Reactivating Factor of *Luteococcus japonicus* subsp. *casei* on the Expression of SOS Response Genes

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Abstract—The effect of the extracellular peptide reactivating factor (RF) synthesized by *Luteococcus casei* on stress response of *Escherichia coli* cells subjected to UV irradiation was studied. For these studies, we constructed a test strain carrying the *umuD–lacZ* operon. The expression rate of this operon reflects the rate of SOS response. Protective effect of RF, defined as the number of cells retaining the colony-forming activity (CFU) after UV irradiation (49–1166 J/m^2), was dose-dependent, species-nonspecific, and increasing with increase of the stress load. RF was demonstrated to possess the properties of a direct adaptogen: 15 min of preincubation with RF caused a 1.5–6-fold decrease in expression of the *umuD* SOS response gene in UV-treated cells, concurrently with a 1.2–7.5 times increase in the number of viable cells (those having retained their colony-forming activity). The probable mechanisms of the protective effect of RF are being discussed.

Keywords: reactivating factor (RF), *Luteococcus japonicus* subsp. *casei,* stress, protection, UV irradiation, *E. coli,* SOS response, *umuD–lacZ* hybrid operon

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Considerable changes in any of the significant environmental parameters are known to lead to the emergence of stress response in microorganisms, which is diagnosed by a slowdown of their metabolic activity and a decrease in growth rate, or even complete cessation of division [1, 2]. The mechanisms recruited to adapt to the new conditions and aimed at the maintenance of cell viability and population survival include changes in the metabolic activity of the cells, expression of the stress genes, increase in the rate of adaptive mutations, phase variations, dissociate transitions, etc. [3–6]. Intracellular events of adaptive compensatory reactions developing under stress induced by hunger, heat shock, and γ- or UV radiation, accompanied by activation of the mechanisms of DNA reparation and stabilization, and expression of stress regulon genes *rpoS, oxyR*, and SOS response genes, have been extensively studied [5–9]. The SOS response system comprising an expression of over 40 genes—including those responsible for DNA recombination reparation and division control—is induced in response to the factors causing single-strand DNA breaks or interfering with its replication, such as UV radiation [10]. In *E. coli* recombination, reparation is performed by special DNA polymerases Pol IV, a product of the *dinP* gene, and Pol V, that of the RecA-dependent gene *umuD*. These polymerases are characterized by low accuracy, which results in a 100-fold increase of erroneous reparation acts and causes the effect of hypermutability for increased population survival [11].

At the level of population, extracellular low molecular-weight communicative autoregulators are engaged in stress response formation to ensure coordinated response of the whole population to various stress effects [12]. Adaptogenic regulators of varying chemical nature are known [13–16]. They include peptides, SH-containing metabolites, alkylhydroxybenzenes, as well as the reactivating factor (RF) initially isolated from the culture of *Luteococcus japonicus* subsp. *casei* [17, 18]. It was subsequently demonstrated that RF was also synthesized by *Saccharomyces cerevisiae* and representatives of other yeast species; it accumulated in the medium at concentrations sufficient to produce its effect, acts at low concentrations, and exhibits thermal and storage stability [17–20]. RF effect was found to be nonspecific toward gram-positive and gram-negative bacteria and yeast and was manifested through both protection and reactivation of the cells subjected to various stress factors, including heat shock and UV irradiation [19–21]. For example, preincubation (10 min) of bacteria with RF prior to heating increased the number of viable cells (CFU) 5.5-fold [20]. Introduction of RF of *L. casei* to a UV-treated suspension of *S. cerevisiae* cells increased yeast survival 2.7 times [21]. In the work [21] it was hypothesized that the reactivating effect of RF was associated

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with the triggering of the common reparation mechanisms providing for both DNA damage reparation and restoration of integrity of the cytoplasm membrane. The mechanisms of the protective effects remained unclear. It is reasonable to study the protective effects of compounds in models of SOS system regulation [16], because its operation is well studied [10, 11].

The goal of the present work was to study the effects of RF as an extracellular regulator controlling the expression rates of the SOS system stress genesin a model *E. coli* strain containing a hybrid *umuD–lacZ* operon under normal growth conditions and upon UV treatment.

MATERIALS AND METHODS

Subject of the study. Strain um250 constructed genetically on the basis of *E. coli* C600 *thi, thr, leu* Δ*(pro-lac)* bacteria [16] was used in the work. Since *E. coli* um250 cells contain a hybrid *umuD-lacZ* operon, it is a model to study the regulation of expression of the SOS response genes.

The um250 test strain was grown in Luria–Bertani medium (LB, 20 g/L, Sigma, United States) with ampicillin (50 μg/mL) in 250-mL flasks (50 mL medium) at 30°C on a shaker (160 rpm). The stationary phase culture was inoculated in the amount sufficient to provide initial optical density (OD) of 0.2 (Specord, Germany; $\lambda = 450$ nm, $l = 10$ mm).

Number of viable cells was determined from the number of colony-forming units (CFU) upon plating the relevant dilutions of cell suspensions onto agarized LB medium.

Reactivating factor (RF) is synthesized by *L. japonicus* subsp. *casei* [17, 18]. These bacteria were grown under static conditions at 30°C on a glucose–mineral medium of the following composition (%): glucose, 1.5; $(NH_4)_2SO_4$, 0.3; KH_2PO_4, 0.2; $CaCl_2$, 0.002; $MgSO_4$, 0.002; NaCl, 0.002; $CoCl_2 \cdot 6H_2O$, 0.001; tryptone (Difco, United States), 0.1; yeast extract (Difco), 0.05; pH 6.8–7.0. The exponential phase culture was centrifuged (10000 *g*, 5 min), the separated culture liquid (1 L) was filtered through a filter with pore size of 0.22 mm (Nucleopore Corp., United States), and the adsorbed extracellular proteins were eluted with 3% NaCl. Protein saline solution was centrifuged (10000 *g*, 5 min) for the guaranteed removal of bacterial cells, which was controlled by plating of the solution onto petri dishes with agarized medium of the above-stated composition. The supernatant, containing extracellular proteins possessing a reactivating effect (RF), was lyophilized.

A lyophilized sample of the reactivating factor was dissolved in 1 mL of Z buffer and used in the initial concentration or upon 10-fold dilution (RF/10).

Effect of RF on expression of the SOS response genes was studied upon introduction of RF or RF/10 solutions (0.1 mL) into aliquots (0.9 mL) of the um250 test strain cultures in the exponential growth phase (OD 2.7). The suspensions were incubated under static conditions for 15 min. Then, β-galactosidase activity was determined in the cells washed twice with Z buffer. In the control, Z buffer (0.1 mL) was added to the samples (0.9 mL).

β-Galactosidase activity in the cells was determined spectrophotometrically by that of the substrate (*o*-nitrophenyl-β-galactopyranoside) and formation of the colored product [22]. The activity unit was defined as the amount of the enzyme isolated by the standard procedure from 1 mL of the cell suspension, which would cause a 1-unit increase in OD_{420} nm per 1 min (A, U/(min mL)).

Specific activity of the enzyme (counted per one CFU) was calculated according to the formula: sp. A = A/B (U/(min cell)), where A is gross β-galactosidase activity in the sample,U/(min mL) and B is the amount of viable cells (CFU) in a sample, cells/mL.

Protective properties of RF were studied by subjecting the cells of the test strain pre-incubated for 15 min with RF or RF/10 and the control ones (not treated with RF) to various doses of UV radiation and then determining β-galactosidase activity.

UV irradiation of the cells was performed in three setups using a BUV 30 RDN-100 mercury high pressure lamp ($\lambda = 251$ nm, distance from the radiation source, 25–100 cm, energetic illumination intensity of the sample from 0.405 to 1.62 W/m^2).

(1) Cells of the control and experimental samples were irradiated in the culture medium in closed plastic Eppendorf tubes, which provided for additional protection from UV radiation. Energetic illumination intensity was 0.405 W/m^2, and doses of radiation depending on irradiation time (5, 10, and 20 min) were 121.5, 243, and 486 J/m^2, respectively.

(2) Cells of the control and experimental samples were irradiated in the culture medium in open petri dishes. Doses of radiation depending on irradiation time (2, 6, and 12 min) were 194.4, 583.2, and 1166.4 J/m^2, respectively.

(3) Cells of the control and experimental samples were irradiated upon washing off the incubation medium and resuspending in Z buffer in open petri dishes. Doses of radiation depending on irradiation time (25, 50, and 75 s) were 48.6, 81.0, and 121.5 J/m^2, respectively.

Three independent series of experiments were repeated in triplicate each. The data presented in this work reflect averaged values; standard deviation values were calculated for the probability $P > 0.95$. Student's test was used for statistical data processing.

RESULTS AND DISCUSSION

Involvement of RF in regulation of expression of the SOS response genes was studied using a genetic construction, test strain *E. coli* um250 [16] with the

Table 1. Effect of RF on the cell number of test strain *E. coli* um250 and activity of the *umuD–lacZ* galatose operon

Sample	Measured parameter	Variant		
		Control	RF	RF/10
Culture	CFU × 10^8	6.3	6.5	6.4
Suspension in *Z* buffer		3.8	4.3	4.5
Culture	β-galactosidase activity, U/(min mL)	39.9	49.4	46.7
Suspension in *Z* buffer		22.4	29.7	31.0
Culture	β-galactosidase specific activity,	6.3	7.6	7.3
Suspension in *Z* buffer	U/(min cell)	5.9	6.9	6.9

cells containing a hybrid *umuD–lacZ* operon. The *umuD* gene codes for a low-accuracy polymerase PolV and is a component of the SOS response regulon. Under UV radiation, doses leading to formation of single-strand DNA breaks, and β-galactosidase synthesis is activated in *E. coli* um250 cells; an increase in the enzyme level indicates initiation of the SOS response.

Effect of RF on the number of cells of the test strain and activity of the *umuD–lacZ* operon. Incubation of the exponential-phase cells of the test strain (OD_{450} = 2.7, 3 h growth)—either in culture or in the form of suspension washed from the growing medium and resuspended in Z buffer—with RF and RF/10 for 15 min did not affect the optical density of the samples or cause reliable changes in the number of viable bacteria (according to the number of CFU) (Table 1). Changes in the level of expression of the hybrid operon upon introduction of exogenous RF into the samples were monitored by changes in the activity of the marker enzyme, β-galactosidase. β-Galactosidase activity in the samples after 15 min exposure to RF and RF/10 increased somewhat (Table 1). Comparison of β-galactosidase specific activity in the cells of the test strain in growth medium or in Z buffer before and after incubation with RF or RF/10 showed that the regulatory peptide, on average, increased the level of expression of the SOS response genes by 20%, while the effect of RF on their expression depended little on its concentration (Table 1). Although the level of the *umuD* gene expression in experimental samples in the presence of RF was reliably higher than in the control ones, the activation value (~20%) was low, which does not agree with the conclusion that RF functions as a signaling metabolite recognizing stress conditions. RF probably affects other signal systems of the cell, which in turn indirectly influence the level of SOS response gene expression.

Earlier, it was demonstrated that one of the effects of preincubaiton of the cells with RF was decreased damage produced by various stress factors, including UV irradiation, which was determined as a reliable increase in the number of surviving cells [20, 21]. Therefore, at the next stage of the work we studied the correlation between the protective properties of RF and changes in expression of the SOS response genes in the exponential-phase cells of the *E. coli* um250 test strain upon UV irradiation.

Effect of RF on the test strain cell survival upon UV irradiation. Studies were carried out under various modes of cell exposure to UV radiation, differing not only by dose, but also by irradiation conditions. Under first mode (the milder one), the cells (culture aliquots) were suspended in growth medium, which contained bacterial metabolites with a probable adaptogenic effect. The samples were put in plastic Eppendorf tubes, which provided additional protection. Moreover, the intensity of the radiation was lowered by means of increased distance from the lamp to the subject of irradiation. Under the second mode, the bacteria were also suspended in culture growth medium, but in open petri dishes, where they were directly subjected to UV radiation. Under the third mode, the most severe one, UV radiation was applied to the cells washed from the growth medium, resuspended in Z buffer, and irradiated in open petri dishes. Under all conditions the cells were treated with three doses of UV radiation with varying irradiation time. The degree of the effect produced by UV radiation on the cells was determined by assessing the cell viability upon irradiation which was determined from the number of CFU upon plating onto agarized medium (Table 2).

In the first series of experiments, the titer of viable cells decreased insignificantly after irradiation (by 13–36%). Protective effect of RF could hardly be detected; only under the highest UV radiation dose (486 J/m^2), preincubation with RF or RF/10 prior to irradiation resulted in an insignificant (by 10%) increase in the number of CFU.

In the second series of experiments, the number of bacteria surviving varied doses of UV irradiation decreased 2 to 200 times in the control samples (without preincubation with RF), while in the experimental samples, preincubated with RF, it decreased only 1.4 to 100 times, that is, the number of colony-forming

Table 2. Effect of UV radiation on the number of viable *E. coli* um250 cells (CFU)

Series of experiments	Parameters of UV treatment			Number of viable cells, CFU/mL (% to the number of cells prior to UV treatment)		
	Time, min	Dose, J/m^2	Conditions	Control	RF	RF/10
1	0	0	Plastic Eppendorf tubes, growth medium	6.9×10^8 (100)	7.0×10^8 (100)	6.9×10^8 (100)
	5	121.5		6.0×10^8 (87.0)	6.2×10^8 (88.6)	6.2×10^8 (89.9)
	10	243.0		5.2×10^8 (75.4)	5.6×10^8 (80.0)	5.5×10^8 (79.7)
	20	486.0		4.4×10^8 (63.8)	4.9×10^8 (70.0)	4.8×10^8 (69.6)
2	0	0	Petri dishes, growth medium	6.3×10^8 (100)	6.5×10^8 (100)	6.4×10^8 (100)
	2	194.4		3.3×10^8 (52.4)	4.0×10^8 (61.5)	3.6×10^8 (56.3)
	6	583.2		5.8×10^7 (9.2)	7.8×10^7 (12.0)	7.1×10^7 (11.1)
	12	1166.4		3.3×10^6 (0.52)	6.4×10^6 (0.98)	4.7×10^6 (0.78)
3	0	0	Petri dishes, Z buffer	3.8×10^8 (100)	4.3×10^8 (100)	4.5×10^8 (100)
	0.5	48.6		2.9×10^6 (0.76)	6.0×10^6 (1.4)	4.9×10^6 (1.1)
	1	81.0		3.7×10^5 (0.097)	1.0×10^6 (0.23)	7.1×10^5 (0.16)
	1.5	121.5		4.6×10^4 (0.012)	3.9×10^5 (0.091)	2.4×10^5 (0.053)

Table 3. Effect of UV radiation on β-galactosidase activity in the exponential-phase *E. coli* um250 cells. First series of experiments: plastic Eppendorf tubes, growth medium

β-Galactosidase activity (change in the background (prior to UV irradiation) activity level, times))	UV dose, J/m^2	Variant		
		Control	RF	RF/10
A, U/(min mL)	0	43.2	53.4	50.8
	121.5	50.8 (1.18)	52.5 (0.98)	51.5 (1.01)
	243.0	57.2 (1.32)	57.8 (1.08)	55.8 (1.10)
	486.0	58.7 (1.40)	61.8 (1.16)	59.4 (1.17)
Specific A $\times 10^{-8}$, U/(min cell)	0	6.3	7.6	7.4
	121.5	8.5 (1.4)	8.5 (1.1)	8.3 (1.1)
	243.0	11.0 (1.8)	10.3 (1.4)	10.1 (1.4)
	486.0	13.3 (2.1)	12.6 (1.7)	12.4 (1.7)

cells was twice higher than that in the control sample (Table 2). The tenfold diluted RF solution was also effective, although to a lesser extent.

In the third series of experiments, when UV irradiation was applied to the cells washed from the culture medium, considerably lower doses of radiation caused death of all cells: 0.76–0.012% of bacteria survived. In the case of preincubation of the bacteria with RF, the number of surviving cells was reliably higher than that in the control samples: 2 and 8.5 times higher at UV doses of 48.6 J/m^2 and 121.5 J/m^2, respectively. Protective effect of tenfold diluted RF was also reliable, providing for a 1.4–5-fold increase in viable cell numbers compared to the control. In the third series of experiments, protective effect of RF was especially distinct. Therefore, the stronger the stress factor action, the more pronounced was the protective effect of the regulatory peptide was. These results agree with the previously reported observations [17, 20] and may probably be explained by the fact that upon lethal action of the stress factor only a sub-population of cells most sensitive to the protective effect of RF survives. It may be assumed that this subpopulation is represented by persisters, non-dividing cells resistant to antibiotics [23]. Another explanation may be that the dying cells excrete metabolites functioning as anabiosis autoinducers into the incubation medium; the larger is the number of dying bacteria, the higher is the concentration of these metabolites [12]. Their effect promotes transition of surviving cells to a quiescent or,

Table 4. Effect of UV radiation on β-galactosidase activity in the exponential-phase *E. coli* um250 cells. Second series of experiments: petri dishes, growth medium

β-Galactosidase activity (change in the background (prior to UV irradiation) activity level, times)	UV dose, J/m^2	Variant		
		Control	RF	RF/10
A, U/(min mL)	0	39.9	49.4	46.7
	194.4	63.4 (1.59)	67.7(1.37)	64.3 (1.38)
	583.2	54.6 (1.37)	73.1 (1.48)	66.5 (1.50)
	1166.4	49.7 (1.25)	67.7 (1.37)	61.2 (1.31)
Specific A × 10^{-8}, U/(min cell)	0	6.3	7.6	7.3
	194.4	19.2 (3.1)	16.9 (2.2)	17.9 (2.5)
	583.2	94.1 (14.9)	93.7 (12.3)	93.6 (12.8)
	1166.4	1506 (239.0)	1058 (139.2)	1302 (178.4)

Table 5. Effect of UV radiation on β-galactosidase activity in the exponential-phase *E. coli* um250 cells. Third series of experiments: petri dishes, Z buffer

β-Galactosidase activity (change in the background (prior to UV irradiation) activity level, times)	UV dose, J/m^2	Variant		
		Control	RF	RF/10
A, U/(min mL)	0	22.4	29.7	31.0
	46.8	34.9 (1.56)	35.9 (1.21)	38.2 (1.23)
	81.0	21.3 (0.95)	39.1 (1.31)	41.5 (1.34)
	121.5	25.5 (1.14)	37.6 (1.27)	37.1 (1.20)
Specific A × 10^{-8}, U/(min cell)	0	5.9	6.9	6.9
	46.8	1203 (203.9)	598 (86.7)	780 (113.0)
	81.0	5757 (975.8)	3910 (566.7)	5845 (847.1)
	121.5	55435 (9395.8)	9641 (1397.2)	15458 (2240.3)

probably, nonculturable state, which increases the difference between the numbers of CFU in the control samples and those pre-incubated with RF.

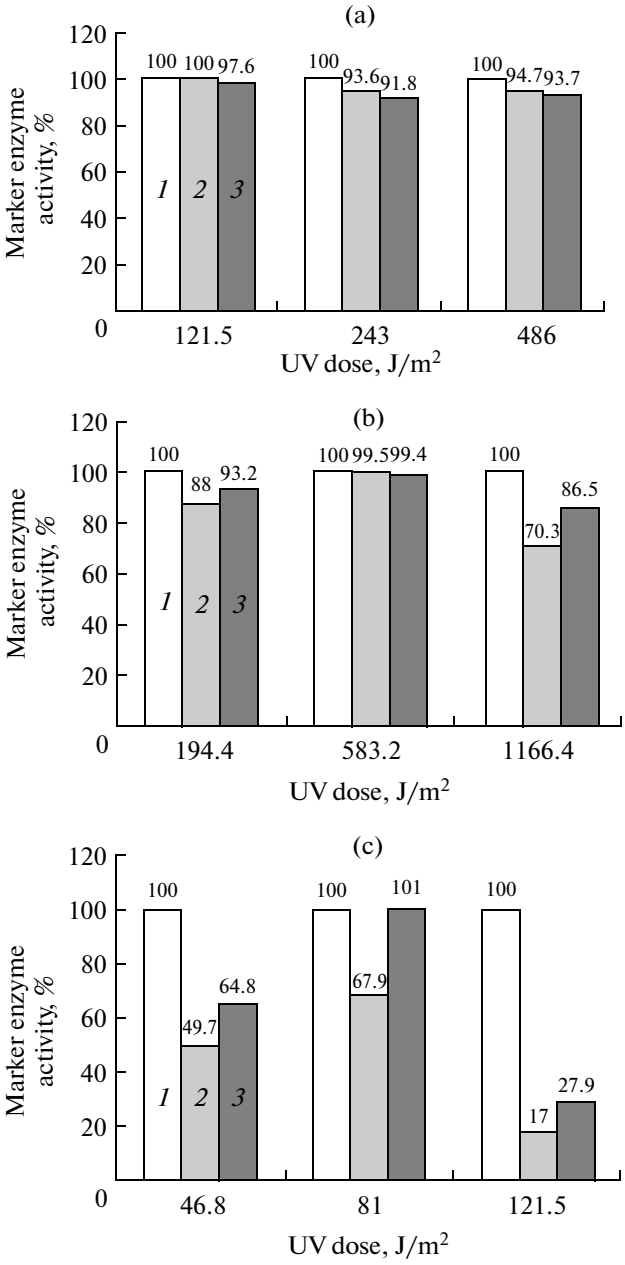
Effect of RF on expression of the SOS response genes upon UV irradiation. In parallel with determination of the death/survival rate of the um250 test strain cells upon UV irradiation, we measured β-galactosidase activity reflecting the rate of *umuD* SOS response gene expression in the cells (Tables 3, 4, and 5). In the first series of experiments (cells were in growth medium in plastic tubes), the minimum UV dose (121.5 J/m^2) applied to the control cells caused an 18% increase in β-galactosidase activity. In the cells pre-incubated with RF but not yet irradiated, the enzymatic activity increased by the same value (20%) and practically did not change upon irradiation (Table 3). That is why the absolute values of the enzyme activity in control and experimental samples did not differ considerably.

Intensification of the stress factor (increased doses of UV radiation) resulted in increased *umuD* gene expression in the control cells (up to 140% of the initial level upon UV dose of 486 J/m^2) and, to a lesser extent, in experimental cells (up to 117%). However, it is not appropriate to assess stress gene expression by the values of absolute (gross) activity of β-galactosidase in analyzed samples (in 1 mL of culture medium), since the effect of UV radiation caused unequal death of bacteria in the control and experimental samples. Analysis of the values of specific enzymatic activity (per CFU) demonstrated that *umuD* stress response gene expression in the cells pre-incubated with RF or RF/10 was insignificantly but reliably lower than that

in the control cells and the difference increased with increase of the radiation dose (Table 3).

The noted tendencies were more pronounced in the second and third series of experiments under more rigid conditions, leading to a considerable decrease in the amount of viable cells (by the number of CFU) (Tables 4 and 5). In both series, absolute enzyme activity in the control samples (without RF) after the first dose of UV radiation increased more than 1.5-fold, which reflected the activation of the SOS response DNA reparation system. However, an increase in the radiation dose resulted in a decrease in the absolute activity, apparently due to the massive cell death shown above (Table 2). Calculation of β-galactosidase specific activity in the control samples demonstrated that the level of *umuD* gene expression increased by one, two, and three orders of magnitude; in cells preincubated with RF or RF/10, its expression level in all experimental variants was considerably lower. In the third series of experiments, upon irradiation of washed cells resuspended in the buffer, the difference was from 2 to 6 times for RF and from 1.5 to 4 times for RF/10, depending on the UV radiation dose.

Earlier [24], it was demonstrated that RF has a protective effect on UV-irradiated cells of *E. coli* reparation mutants Uvr-, RecA-, and PolA-, which was manifested as a multiple increase in their viability and agrees with the results of the current study. The authors of [24] conclude that the protective effect of RF is not connected with the activation of reparation systems in *E. coli* and is apparently due to involvement of RF in the regulation of cell division. In the present work, using *E. coli* test strain cells with a *umuD–lacZ* hybrid operon to reveal the SOS response, the previously obtained data on protective effect of RF [24], its dose dependence, and maximum protective effect upon stresses of lethal intensity were confirmed. It was also found that protective effect of RF is not associated with induction of the SOS response. Predicting the possible mechanism of the demonstrated protection, we may assume that since RF does not participate in SOS-dependent regulation of damaged DNA reparation system, it may be engaged at the stage of decrease of the amount of damages induced by UV radiation. This alternative possibility of RF effect realization is supported by the observed decrease in the expression of the SOS response genes (figure). It should be noted that a similar protective effect was discovered in the group of microbial extracellular autoregulators of a different chemical nature: (short-chain) alkylhydroxybenzenes. Their effects as of direct adaptogens were caused by a decrease in the damaging potential of UV radiation by capturing the formed reactive oxygen species and thereby decreasing the amount of damaged DNA [16]. Taking this into account, the proposed hypothetical explanation of the RF protective effects seems possible and needs further experimental confirmation.



β-Galactosidase specific activity in the exponential-phase *E. coli* um250 cells preincubated with RF and subjected to UV radiation, % of the activity of the control cells after irradiation: first series of experiments: aliquots of culture in plastic eppendorf tubes (a); second series of experiments: aliquots of culture in open petri dishes (b); and third series of experiments: cells washed off culture medium and resuspended in Z buffer in open petri dishes (c). Designations: *1*, control, without pre-incubation with RF; *2*, pre-incubation with RF; and *3*, pre-incubation with RF/10.

Thus, based on our results we may state that the extracellular peptide reactivating factor synthesized by *Luteococcus casei* has a protective effect on *E. coli* cells functioning as a direct adaptogen and diminishing, to a great extent, the SOS-dependent regulation of DNA

damages characteristic for UV radiation and is not an inducer of SOS response.

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