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CONFERENCE PROCEEDINGS

Adaptogenic Functions of Extracellular Autoregulators of Microorganisms

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Abstract—Information about the functions of extracellular autoregulators, which adapt microorganisms to the stresses "scheduled" in the development cycle of microbial cultures (stresses of new medium, starvation, or space exhaustion (high cell density)) is summarized in the review. In a number of bacteria and yeasts, derivatives of alkylhydroxybenzenes (AHB), particularly of the class of alkyl resorcinols, act as autoregulators with adaptogenic functions. The chemical structure of AHB determines their amphiphility; capacity for physical and chemical interaction with membrane lipids, proteins, and DNA; properties as natural modifiers of biological membranes and enzymes; and the expression of antioxidant activity. Increase of AHB concentration up to the critical level (10^{-5}–10^{-4} M) results in cessation of cell division and in transition of the microbial culture to the stationary phase; further increase to10^{-4}–10^{-3} M induces a transition of some of the cells of a post-stationary culture to the anabiotic state with the formation of cystlike resting cells (CRC), even in non-spore-forming bacteria. AHB participate in the regulation of the phenotypic variability of bacteria. The dynamics of extra- and intracellular concentrations of AHB in growing microbial cultures and the polymodality of their effect determine the adaptogenic functions of AHB as autoinhibitors of culture growth, autoinducers of anabiosis, and autoinhibitors of germination of resting forms. Manifestation of any given function depends on the concentration of AHB, the physiological state of the recipient cells, and on environmental factors. The species nonspecificity of AHB effects points to their significant role in the regulation of the development and functioning of microbial communities.

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At the present time, there is a great body of evidence indicating that microorganisms, like other living organisms, possess specialized autoregulatory systems which enable intercellular communication and help control the behavior of the microbial population as a whole under constantly changing environmental conditions, i.e., under the influence of stressful loads. For many types of extracellular autoregulators, their chemical structure and phenomenological and physiological effects are known; for several, their functional activity in the genetic mechanisms of adaptive cell response has been demonstrated and their role in the regulation of the stages of culture development, differentiation, and secondary synthesis has been established [1-6]. The main function of extracellular autoregulators is to provide for intercellular interactions and the interactions of cells with the medium, with the aim of ensuring successful microbial growth or preserving the species under the conditions that do not support growth. From this point of view, all autoregulatory metabolites are adaptogens, but the types of interaction that they control are different; this can be confirmed by special biological testing. Changing biotests often reveal new functions of bioregulators; many of them therefore have a pleiotropic type of activity. The autoregulators adapting microorganisms to the "planned stresses" that occur during the ontogenesis of microbial cultures are better known [7]. Among these stresses are the *stress of new medium*, occurring as the result of the transfer of old or resting cells to a new growth medium, and *stress caused by exhaustion of nutrition* (starvation) or *space* (critically high cell density), i.e. by conditions in which a culture finishes its development cycle and which are often collectively termed "starvation stress." The important properties of autoregulators are as follows: they are

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metabolized slowly and can therefore accumulate in the necessary concentrations; their effect is dose-dependent; recipient cells are sensitive to them; and their extracellular concentrations depend on the number of cells that synthesize them, i.e., on the density of the cell population. Note that both the synthetic capability and the competence (sensitivity) of cells to reception of the extracellular signal depend on the phenotypic characteristics of cells and on their physiological age (stage of growth and growth phase of culture) and reflect the heterogeneity of the population.

Recently, great attention has been paid to one of the types of cell-density-dependent regulation of microbial culture growth, namely "quorum-sensing" (QS). This autoregulatory system is based on the "sensing of a minimum quantity of cells, or quorum," and the activation of a set of molecular mechanisms of bacterial genes which function only at a certain high population density, "quorum" ([8], see also the reviews [9 and 10]). Compounds of different chemical nature can act as signal metabolites in QS systems; among these, acylated homoserine lactones (aHSL) are the most widely investigated [see the review by I.A. Khmel in the present issue]. The aHSL and other signal metabolites of QS-system "estimate" the minimal population density sufficient for the activation of their synthesis (autoinduction) with subsequent expression of several genes associated with the stationary phase. Another type of autoregulator monitors the population density and causes the proliferating culture to enter the stationary phase when it reaches a certain maximum cell number under given conditions. Factors d_1 (fd_1) belong to this type of autoregulators. Increase of their extracellular concentration to the critical level causes the stopping of cell division and the transition of the culture to the stationary phase [11]. The further increase of fd_1 concentration induces a transition of some cells of the population (those responsive to fd_1 influence) to an anabiotic state with the development of resting forms [11–14]. According to their function, these autoregulators have been named autoinducers of anabiosis [11]. They form, together with factors d_2 (autoinducers of autolysis), a cooperative system of autoregulation of development of microbial cultures [14]. This system has been revealed in representatives of different taxonomic groups of pro- and eukaryotes (genera. *Bacillus*, *Clostridium*, *Micrococcus*, *Arthrobacter*, *Mycobacterium*, *Streptomyces*, *Labrys*, *Pseudomonas*, *Methylococcus*, *Thioalkalivibrio*, *Thioalkalimicrobium*, *Saccharomyces*, *Rhodosporidium* etc.) [2, 6]. The functioning of this autoregulatory system in the adaptation of microorganisms to the stresses "scheduled" in the ontogenesis of their cultures will be considered below with a focus on the functional activity of autoinducers of anabiosis, fd_1.

Autoregulatory factors d_1 (factors of cell differentiation) of microorganisms, according to their chemical nature, belong to derivatives of alkylhydroxybenzenes (AHB); they are present in microbial cultures as a mixture of isomers and homologues with different position and number of substitutes in the aromatic ring and configurations of the alkyl radical. They are represented by homologues of 5-*n*-nonadecyl- and 5-*n*-heneicosylresorcinols in *Pseudomonas carboxydoflava* [15]; by a mixture of isomers and homologues of phenyl-methanol (3,5-dimethoxy)- 2-methylpropyl in *Bacillus cereus*; by a mixture of isomers and homologues of alkylresorcinols with the substitutes in the second and fourth positions in the aromatic ring in *Micrococcus luteus* [16]; and by 2-(4-hydroxyphenyl)-ethan-1-ol in yeasts *Saccharomyces cerevisiae* [17]. Derivatives of AHB of the alkylresorcinol group are widespread in nature and have been revealed not only in microorganisms [18–20], but also in plants, predominantly in seeds. This knowledge points to an analogy between the functions of AHB in the regulation of stress response and control of the resting state both in microorganisms and plants.

Properties of AHB as adaptogens. The chemical structure of fd_1, alkylhydroxybenzenes (particularly, homologues and isomers of alkylresorcinols), determines their properties, important for their functioning as adaptogens [21–27]. These properties include the following: (1) the capability to form complexes with membrane lipids and cellular biopolymers (by means of weak physicochemical interactions—hydrogen bonds, hydrophobic, and electrostatic interactions); this capability determines changes of the structural organization and therefore of the functional activity of the membrane and macromolecules; (2) differences in degrees of polarity and hydrophobicity that influence the AHB properties as ligands in the course their interactions with subcellular structures; (3) their amphiphility, determining the capability of AHB to move in lipid–water systems and to penetrate into the cell independently of acyl-transporting proteins; (4) the capacity for multistage oxidation and, particularly, antiradical activity, which determines the important role of AHB in the nonenzymatic system of antioxidant protection of cells.

Depending on the degree of hydrophobicity of isomers and homologues and on the proton content of the medium, AHB predominantly either translocate to the lipophilic phase and form bonds with membrane lipids or cellular biopolymers at $pH < 7.0$ or pass to the water phase (medium) at $pH > 7.0$ [14]. Accumulation of AHB in cells leads to the following effects: increased membrane microviscosity [24]; changes in ionic transport and water balance of the cell, its dehydration [24, 28]; decreased functional activity of membranes including the enzymes of an electron-transport chain [24, 25]; and increased level of intracellular calcium ions which participate in the stabilization of subcellular structures and the system of intracellular effectors [29–31]. AHB form complexes with enzymes (and other proteins) and change the conformation of macromolecules; this results in their increased stability (functions of chemical chaperons) and change of their functional

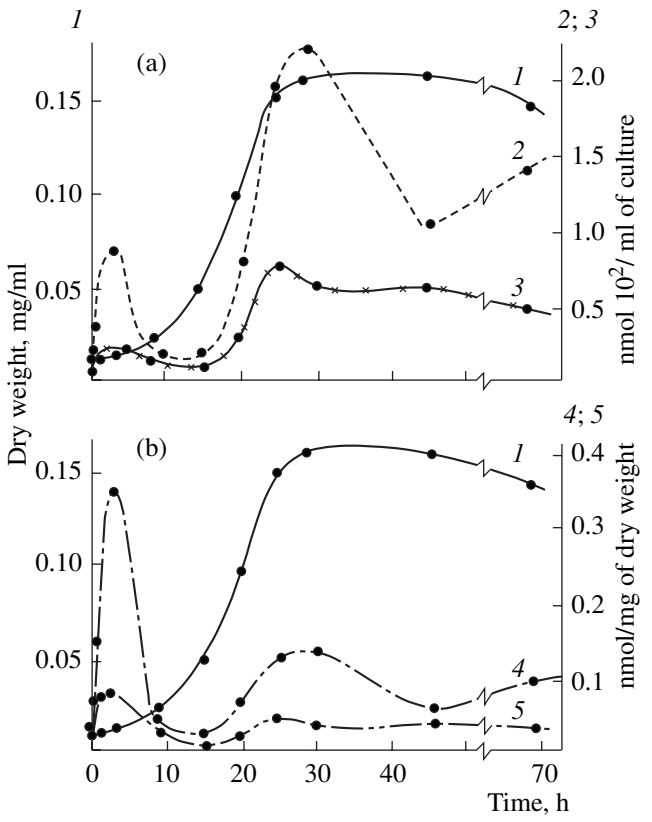

Fig. 1. Change of AHB content in an autotrophically growing culture of *P. carboxydoflava* (a) and AHB productivity (b): *1*, growth curve, mg dry cell weight/ml; *2*, AHB content in cells, nmol × 10^2/ml; *3*, AHB content in culture liquid, nmol × 10^2/ml; *4*, AHB quantity in cells, nmol × 10^2/mg dry weight; *5*, AHB quantity in culture liquid, nmol/mg dry weight.

activity [21–23, 32, 33]. The vector of change of their activity depends on the degree of hydrophobicity of different AHB homologues and on their concentrations (see review of Yu.A. Nikolaev et al. in the present issue). Thus, both the level of AHB in a growing culture and the changes in the qualitative composition of isomers and homologues are important for the regulatory effects of AHB. The tests of induction of the SOS response in *B. subtilis* revealed that during interaction with DNA, AHB stabilize its structure [34, 35] and influence the structural organization of DNA supramolecular complexes [36] and transcription activity [37]. Owing to these properties, when AHB (fd_1) are accumulated in the cells, they induce the development of stress response and the development of hypometabolic states at 10^{-5}–10^{-4} M, and of anabiotic states under high concentrations (10^{-4}–10^{-3} M).When they are released into the medium, the metabolic block in the cells is removed [6, 14, 38–40]. At high density of inoculum cells (stationary or resting), however, the concentration of releasing fd_1 (AHB) is also high; growth is therefore inhibited by the critically high level of AHB at overthreshold densities of inoculum, as was demonstrated by an investigation of spore germination of *B. cereus* [unpublished data]. According to this function, AHB can be placed among the autoinhibitors of spore germination, well-investigated for phytopathogenic fungi [41]. Thus, cell density "corrects" not only the growth limitations of microbial cultures, but also their capacity to commence growth in the lag phase.

Adaptogenic functions of AHB in "unscheduled" stress situations are achieved via appropriate changes in their extra- and intracellular concentrations in growing microbial cultures. The typical dynamics of AHB content during the development of an autotrophic culture of *P. carboxydoflava* (growth on $^{14}CO_2$) inoculated with stationary-phase cells (according to [14]) is shown in Fig. 1. Two maximums of AHB concentrations were revealed: the first, in the lag phase, is related to the stress of new medium and caused by the inoculation of stationary cells; the second, during transition to the stationary phase, is related to space exhaustion and caused by the critical increase in cell numbers. A regular increase of AHB concentration first in the medium and then in the cells is essential; it indicates AHB redistribution between the cells of a population via an extracellular pool of autoregulators. The inducing effect of stress on the stimulation of AHB biosynthesis was confirmed in the model of *M. luteus* subjected to heat shock [42, see the review of Yu. A. Nikolaev et al. in present number]. Increase of AHB concentration in microbial cultures induces, in turn, an SOS response in the cells [37].

The main directions of adaptation during the lag phase (stress of new medium) mediated by AHB: (1) maintenance of the optimal structural organization of cellular membranes under increasing content of unsaturated fatty acids; (2) conformational changes of cell proteins which increase their stability (against elevated concentrations of reactive oxygen species ROS under stress conditions) and modulate their activity; (3) antioxidant protection (supplementary to the enzymatic antioxidant system) of cell structures, especially of the unsaturated fatty acids of membrane lipids, the level of which increases at the beginning of culture development, from ROS accumulation.

The main directions of adaptation at the transition to the stationary phase (starvation stress) mediated by AHB: (1) increase of microviscosity of cellular membranes and stabilization of their structure; (2) change of conformation of cellular biopolymers to increase their stability against biogenic (depolymerases) and abiogenic (ROS) agents; (3) induction of a hypometabolic state (retardation of biosynthetic processes, dehydration of the cell, accumulation of intracellular Ca^{2+}) and of the stationary phase; (4) induction of an SOS response.

Adaptive advantages of resting nonproliferating stationary cells consist in the following: (1) minimization of energy costs for the maintenance of metabolic cell activity; (2) increased stability against environment

influences; (3) elimination of space expansion simultaneously with the fulfillment of the ecological function in a microbial community.

If the pressure from starvation stress continues, the microbial culture will pass to the debilitation stage, which is coupled by autolysis of those cells in the population which are sensitive to the influence of the extracellular autoinducer of autolysis fd_2. Factors d_2 are represented among bacteria and yeasts by free unsaturated fatty acids (FUFA) [14, 43–45]; like fd_1 (AHB), they have a membranotropic effect, but of the opposite character. Their binding to the membranes decreases membrane microviscosity; therefore, at low concentrations they accelerate germination of the inoculum, while at critically high concentrations, they destabilize membranes and induce autolysis. The concentration of AHB increases due to their release from the autolysed cells (Fig. 1). They induce processes of forming of resting forms and development of the anabiotic state in the cells which remain intact [40, 46, 47]. The coupling of autolysis and cell differentiation in bacteria was first revealed during investigations of the development cycles of myxobacteria [48]; it is controlled by a number of extracellular autoregulators [49–51], and turns out to be universal for microorganisms of different taxa of pro- and eukaryotes. It is noteworthy that distinct variants (R and S types) of bacteria or anamorphs A and α of yeasts differ in the degree of productivity of $f\ d_1$ and $f\ d_2$ and in the sensitivity of cells to their influence [43, 52, 53]. This explains the different responses of various cells of stationary cultures to maximal concentrations of fd_1 and fd_2. Some cells metamorphose to resting forms under such conditions due to the "altruism" of other cells which die off and liberate their intracellular factors fd_1 (AHB) for completion of the extracellular pool of these autoregulators.

Adaptogenic functions of AHB in the formation of resting forms of microorganisms. The transition of microbial cells to a resting state is universally believed to be an extreme form of their adaptation to conditions unfavorable for growth. The intrigue of the situation is that reproductive resting forms are known only for a few microorganisms, and the overwhelming majority of bacterial species are non-spore-forming. In the 1950s, Bisset postulated that all bacteria have the capacity to form resting cells of the "microcyst" type during the development cycles of their cultures [54, 55]; experimental proofs of this hypothesis were obtained in later investigations [6, 38–40]. Cystlike resting cells (CRC) are formed in the post-stationary phase of culture growth, and their quantity increases sharply under conditions of essential increase of AHB concentrations in the culture. In order to promote CRC formation, the following methods to increase the level of extracellular AHB have been developed: (1) modification of cultivation conditions, directed to the intensification of AHB biosynthesis with limitation by nitrogen, phosphorus, or oxygen, or with C > N imbalance (model of starvation stress) [6, 38–40]; (2) spontaneous or induced (by unsaturated fatty acids) autolysis of a part of the cell population, when AHB concentration increases due to their release from the autolysed cells (model of starvation stress or damaging actions) [14, 40, 46, 47]; (3) increase of AHB concentration by their exogenous introduction (model of desiccation of soils or drainage from the upper layers) [12, 13, 36, 45, 56]. Under such conditions, the titer of CRC increases up to 10–30% of the number of cells in the stationary phase. The capacity for CRC formation under these conditions has been demonstrated for bacteria of the genera *Bacillus, Micrococcus, Arthrobacter, Pseudomonas, Escherichia, Methylococcus, Thioalkalivibro*, and *Thioalkalimicrobium*; for archaea *Natrinema* spp.; for yeasts of the genera *Saccharomyces* and *Rhodosporidium*, etc. [6, 11–13, 36, 38–40, 46, 47, 56, 57]. The formed CRC possess all the attributes of resting forms of microorganisms according to the accepted criteria of sporology [58]: (1) they all demonstrate long-term preservation of viability and are intended for reproduction (according to CFU numbers); (2) they have a sharply decreased and not experimentally revealed level of metabolism, characteristic of the anabiotic state; (3) they exhibit heightened stability to unfavorable or damaging actions; (4) they have distinctive features of ultrastructural organization; (5) they are formed in microbial cultures as necessary stages in their ontogenesis. "Portraits" of several bacterial CRC are shown in Fig. 2–5 and illustrate the peculiarities of their ultrathin structure, different from that of vegetative cells. These differences include the following: essential thickening of the cell wall (in *N. pallidum*); often, a multi-layer cell wall (in *M. luteus*); formation of a capsular layer (in *M. luteus, P. aurantiaca*); compacting of the nucleoid; fine-grained texture of cytoplasm and aggregation of polyribosomes; and inclusions of poly-β-hydroxybutyric acid (in *B. cereus*, *N. pallidum*) [13, 38, 56, 57]. It is noteworthy that the intraspecific polymorphism of resting forms of bacteria is one more adaptive property of microbial species; this feature is particularly strongly expressed in *B. cereus* (formation of endospore or CRC) and *M. luteus* (formation of CRC of different morphological types).

"Portrait" diagnostics of microbial cells isolated from environmental samples, (without growing) is one of the approaches to revealing their possible physiological state in environmental objects [59]. Figure 6 illustrates this approach by demonstrating the similarities between the ultrathin structures of CRC, obtained in laboratory conditions (ex situ) and of the cells isolated from samples of frozen rocks (in situ).

The adaptive advantages of CRC of microorganisms consist in (1) possibility to regulate the density of cell population; (2) preservation of the reproductive function, the capability to revert to active metabolism and active cell division; (3) acquisition of high stability against damaging actions; (4) elimination of exchange processes with environment, which enables waiting through periods of unfavorable growth conditions;

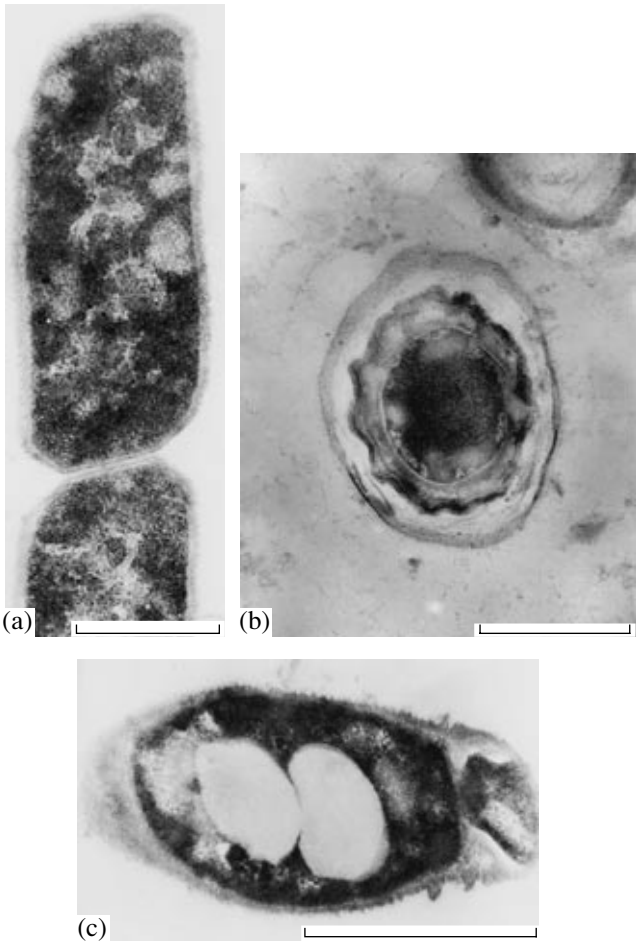

Fig. 2. Micrographs of ultrathin sections of vegetative cell of *B. cereus* (a), endospore (b), and cystlike refractive cell (c) in culture, grown on the medium with 6% of glucose and stored for 45 days. Scale bar, 1 μm.

5) providing of phenotypic variability within the population, manifested during the germination of resting forms and giving a rise to the phenotype most adaptive to new environmental conditions.

The final item in the above list of adaptive advantages concerns the instability of the genotype of CRCs formed under control of AHB; this feature enables the phenotypic dissociation of populations. Phenotypic heterogeneity of the population has been experimentally revealed in the case of CRC germination at the first passage on solid media as a sharp (up to 50%) increase in the number of colonies of the nondominant type [36, 52, 60]. Phenotypic dissociation constitutes the adaptive potential of a population, determined by the differences of dissociants (variants, clones) in terms of (1) nutritive requirement; (2) range of tolerance to physical and chemical environmental conditions; (3) characteristics of growth and physiological and biochemical characteristics; (4) resistance to damage; and (5) production of extracellular autoregulators (fd_1 - AHB and fd_2 - FUFA) and sensitivity to them [52, 53, 61]. The possibility of the regulation of dissociative transitions of bacteria with AHB follows from the last thesis and has been experimentally confirmed for *B. subtilis, B. licheniformis* [62], *P. aurantiaca* [36], *S. aureus* [60], and *S. typhimurium* [63]. Possible mechanisms of AHB effect in the regulation of phenotypic dissociation may include (1) effect of AHB as modifiers of protein structure, participating in gene expression at the level of transcript forming; and (2) direct interaction with DNA, causing modifications of genetic material. Weak mutagenic activity of several AHB homologues has been revealed in Ames test with strains of *S. typhimurium* and *B. subtilis*, auxotrophic in several amino acids [62, 63]. This fact allows us to consider AHB as endogenous mutagens that can be accumulated in resting cells and induce reversible recon-

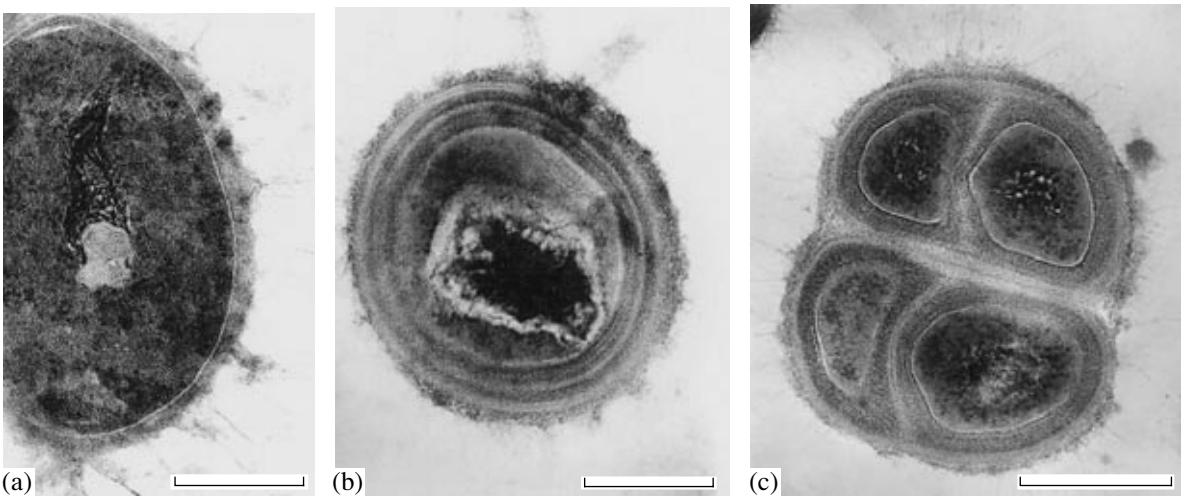

Fig. 3. Micrographs of ultrathin sections of vegetative cell of *M. luteus* (a) and cystlike cells (b, c) of two types which differ in thickness of cellular wall and quantity of layers with different electron density. Assembly from four cells (c), which are combined by common external layer of cellular wall. Scale bar, 0.5 μm.

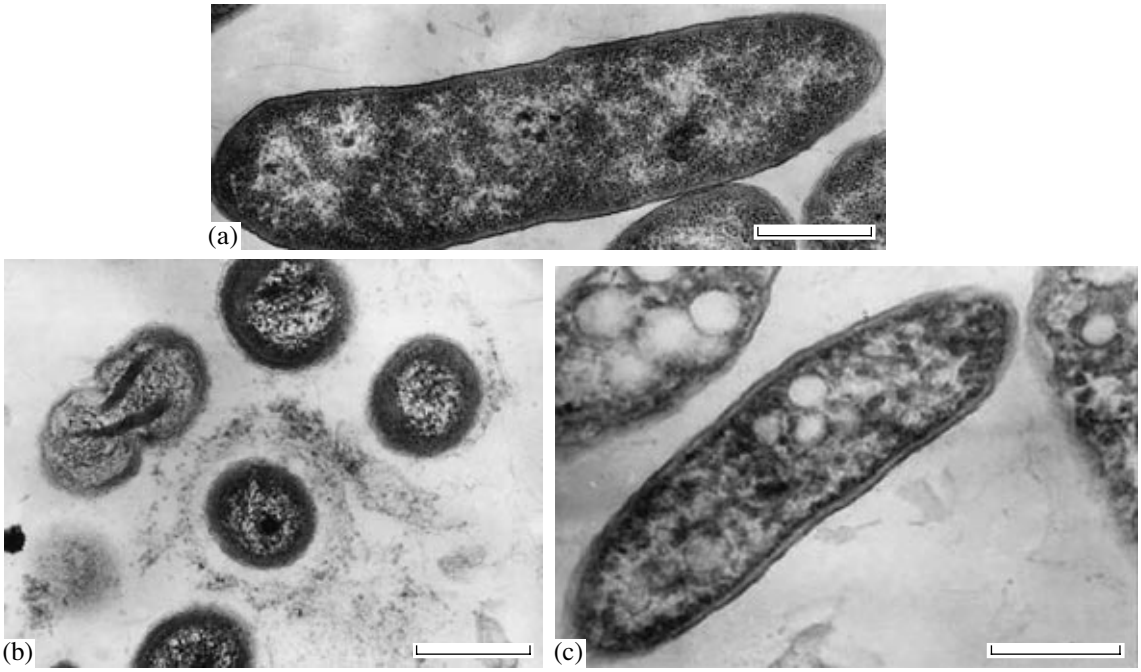

Fig. 4. Ultrathin sections of vegetative cell of *P. aurantiaca* (a) and cystlike cells that are formed in protractedly long-stored cell suspension in 0.09% solution of sodium silicate (0.9 g of SiO_2/l) (b) or after addition of AHB (10^{-4} M) (c). Scale bar, 0.5 μm.

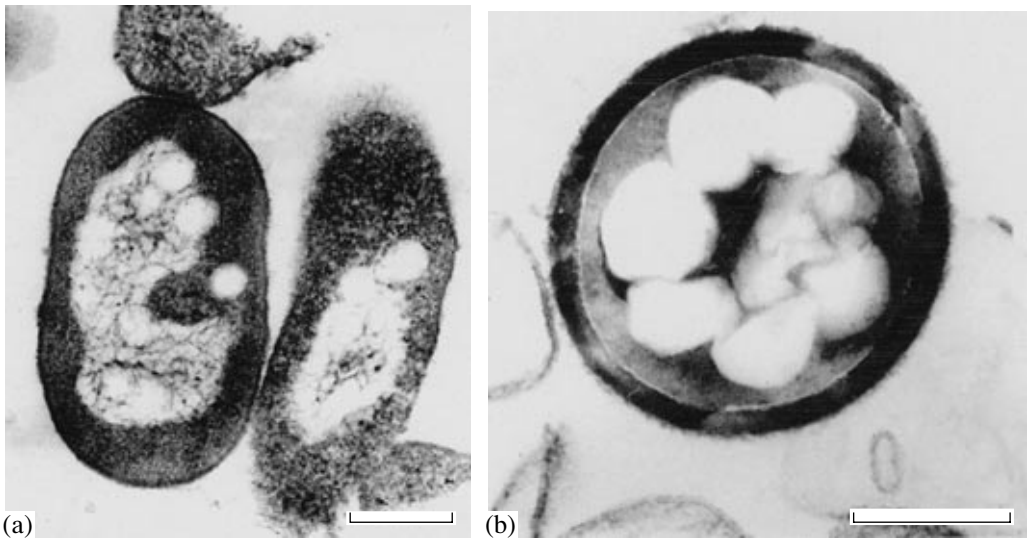

Fig. 5. Ultrathin sections of vegetative (a) and cystlike (b) cells of archae *N. pallidum*. Scale bar, 0.3 μm.

struction of genetic material, determining dissociative transitions of phenotypes [61]. Essentially, the AHB concentration that induced a reversion of auxotrophic strains to prototrophy, at the same time induced a transition of initial S variant of *S. typhimurium* to R form (the same effect was observed in a test with *B. subtilis*).

In conclusion, it is noteworthy that AHB, like fd_1 factors of other chemical structure, are species-nonspecific. They act in the system "producer–recipient," as determined by the mechanism of their effect: AHB are natural structure modifiers of biological membranes (membrane-acting properties) [24, 25] and of biopolymer macromolecules, such as enzymatic proteins (functions of chemical chaperons) and DNA (functions of stabilizers) [21, 23, 32, 34–36]. The nonspecificity of the action mechanisms of AHB is also confirmed by the results of investigations which show the influence of long-chain alkylresorcinol of plants on the permeability of liposomes loaded with dye [64] and also the effect of AHB of this type on the phage DNA [65]. It has been

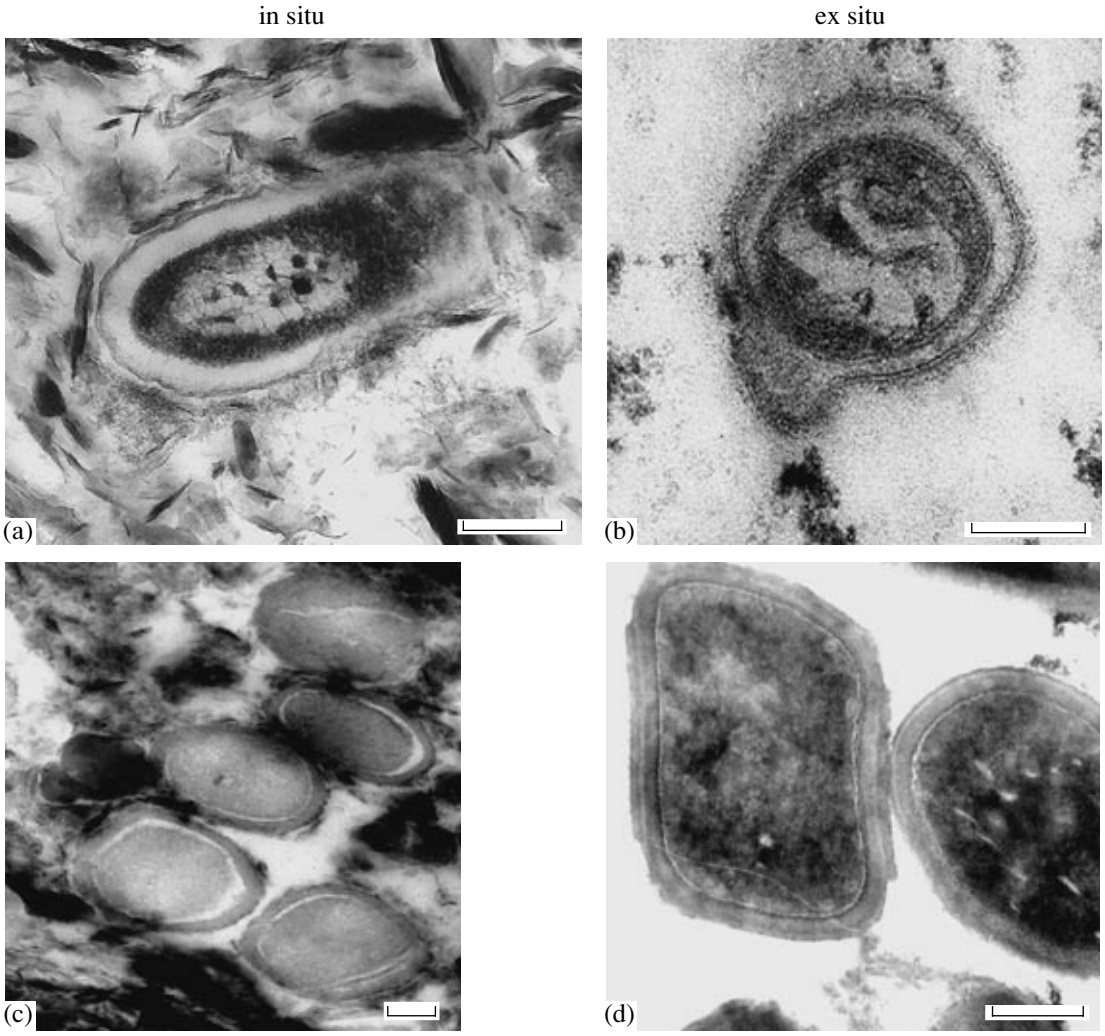

Fig. 6. Structure of bacterial cells in situ isolated from the permafrost of different age and genesis. Scale bar, 0.2 μm.

shown that resveratrol influences the increase in lifetime of yeast *S. cerevisiae* (during repeated transfers) due to the up-regulation of *Sir2* genes, and also possesses a protective effect on cultured cells HEK 293 (human embryonic kidney) exposed to radiation at doses of 2–5 Gy [66]. In our works, the AHB protector effect was shown in yeast (under conditions of γ-irradiation, photooxidation), murine fibroblasts (toxic action) and micrococci cells (heat shock) [27, 67, 68, 42].

Considering the versatility of microbial response to the AHB (and to fd_1 of other chemical structure), we emphasize that the representatives of different taxonomic groups of pro- and eukaryotes vary in their sensitivity to these factors; the range of sensitivity is very broad and varied from 2 to 12 times. Thus, a pool of low-molecular species-nonspecific extracellular autoregulators (such as fd_1, AHB, aHSL, and others) can be formed in a natural microbe community. These autoregulators control the development of microbial populations (components of the community) and the resistance of microorganisms to changing environmental conditions. Expansion of the functional activity of species-nonspecific AHB (fd_1), acting as adaptogens in mechanisms of increase of the stability of microorganisms up to control level of their phenotypic variability can be important in regulation of the succession and stability of functioning of microbial communities.

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