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PECULIARITIES OF THE ONTOGENESIS OF BACILLI DURING DEVELOPMENT FROM A VEGETATIVE CELL TO A SPORE

Understanding the development processes of bacteria, in particular spore-forming ones, has both fundamental and applied importance, since at various stages of this process, the cells of microorganisms perform certain functions that can be regulated by influencing certain factors depending on the tasks. Literature data and the results of our research on the influence of the composition of the nutrient medium, pH, temperature, and aeration on sporulation are analyzed in the article. It isshown that the direction of bacterial cells' development in certain ways is determined by signals that come from the surrounding environment, affect their genome, and determine the ways of cell development — growth or sporulation. Sporogenesis can also be induced by metabolites formed during microorganism development. It is emphasized that the environmental factors that influence the sporulation of bacteria have been studied in sufficient detail. However, the mechanisms of their action remain debatable. Morphological, genetic, and biochemical changes of spore-forming bacteria under the conditions of macrocyclic and microcyclic ways of their development are also highlighted, which makes it possible to correctly understand the functioning of regulatory mechanisms in the ontogenesis of microbial cells. In particular, the data of our research on the dynamics of morphological changes in the ontogenesis of a specific individual bacterial cell are presented. In addition, factors, including specific terminal products of cell metabolism, such as antibiotics, and genetic mechanisms of sporogenesis regulation of various genera and species of bacteria are described in detail. The nature of the vast majority of «sporogenes» has not been clarified, and there are only a few hypotheses regarding the mechanism of their action. However, most of the biological regulators of sporogenesis were found in the culture liquid, which indicates the cellular nature of their action. Therefore, to obtain more convincing data on the regulation of sporogenesis, studies at the cellular level are needed.

Keywords: *spore formation, factors of environment, growth, macrocycle and microcycle of bacterial development, sporogenesis regulation.*

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Bacterial spores were discovered by Kohn F. and Koch R. in 1876 (Drews, 1999; Gould, 2006). Though148 years have passed since this discovery, the question of spore importance in the life of bacteria, the specific conditions, and mechanisms of their formation, is still not finally resolved (Gould, 1969; Galperin et al., 2012; Donnelly et al., 2016; Meeske et al., 2016; Zheng et al., 2016; Morlot & Rodrigues, 2018). In general, the important role of environmental factors in spore formation has been clarified (Tocheva et al., 2016; Clauwers et al., 2017; Davidson et al., 2018; Secaira-Morocho et al., 2020; Luo et al., 2021; Sun et al., 2021). Among the known factors that influence sporulation, the most important are the level and nature of nutrients, mineral composition of the medium, pH values, temperature, and aeration.

1. Sporulation depending on environmental factors. Environmental factors significantly affect the ability of vegetative cells to form spores, their properties, and the rate of spore formation. Previously, it was considered that sporulation proceeds under unfavorable conditions for vegetative growth. However, spore formation also requires favorable conditions with some peculairities. It is known that the starting signal for the process of sporulation is starvation, which is caused by a decrease in the level of growth substrates in the environment (Szulmajster, 1973). It should be noted that the term «starvation» meant a lack of factors necessary for optimal growth and reproduction of bacteria and had no relation to sporogenesis. Among the factors, some are necessary for sporulation, that is, inducers of sporogenesis and others that only contribute to this process or affect the properties of spores (Cho & Chung, 2020).

It was established that spores are formed only by healthy cells during starvation, i.e., formed in optimal conditions of the vegetative growth of the culture. First of all, this concerns the composition of the nutrient medium, based on the individual requirements of microorganisms of certain species or strains. The absolute inducers of bacterial sporulation are the level and nature of nutrients, mineral composition [magnesium cations], pH values, temperature, and aeration of the medium (Romanovskaya et al., 2016; Koopman et al., 2022).

In our previous studies of the role of the nutrient medium in sporulation by the method of bacterial microcultivation, it was also established that the complete sporulation occurs in a medium with a low content of nutrient substrates (Voitsekhovsky, 1982). It was shown that when *Bacillus cereus* 24 is cultivated in standard meat-peptone broth (MPB) or Hottinger's hydrolyzate, which are usually used in laboratory practice (amino nitrogen content in the range of 33—150 mg%), sporulation almost does not occur, and the culture development ends with the lysis of most cells. In the «starved» medium, when the culture develops in MPB diluted 100 times (amino nitrogen content 0.33— 1.5 mg%), the cycle of its development ends with 100% spore formation (Fig. 1).

Also, aerobic and anaerobic bacteria sporulated when sources of carbon, nitrogen, growth factors, and inorganic components were limited (Chuiko et al., 2021). Under excess of certain medium components, sporulation was also possible. Spores were formed when the level of one or more factors influencing the induction of sporogenesis was reduced. In sporulation, the ratio between the amount of carbon and nitrogen and the correspondence of the concentration of glucose and the conditions of cultivation are also important (Berthold-Pluta et al., 2015; Mocho et al., 2021; Chiu et al., 2021; Boix et al., 2021; Augustyn et al., 2022; Toukabri et al., 2023; Pahalagedara et al., 2023).

A method for inducing sporulation by changing the composition of the nutrient medium is known. This is possible only when the cycle of DNA replication has not yet finished, and the maximum of sporulation, for example, in the temperature-sensitive mutant of *Bacillus subtilis*, clashed at the moment when replication took place near 1/3 of the chromosome (Dawes et al., 1971; Mandelstam et al., 1971; Mandelstam &

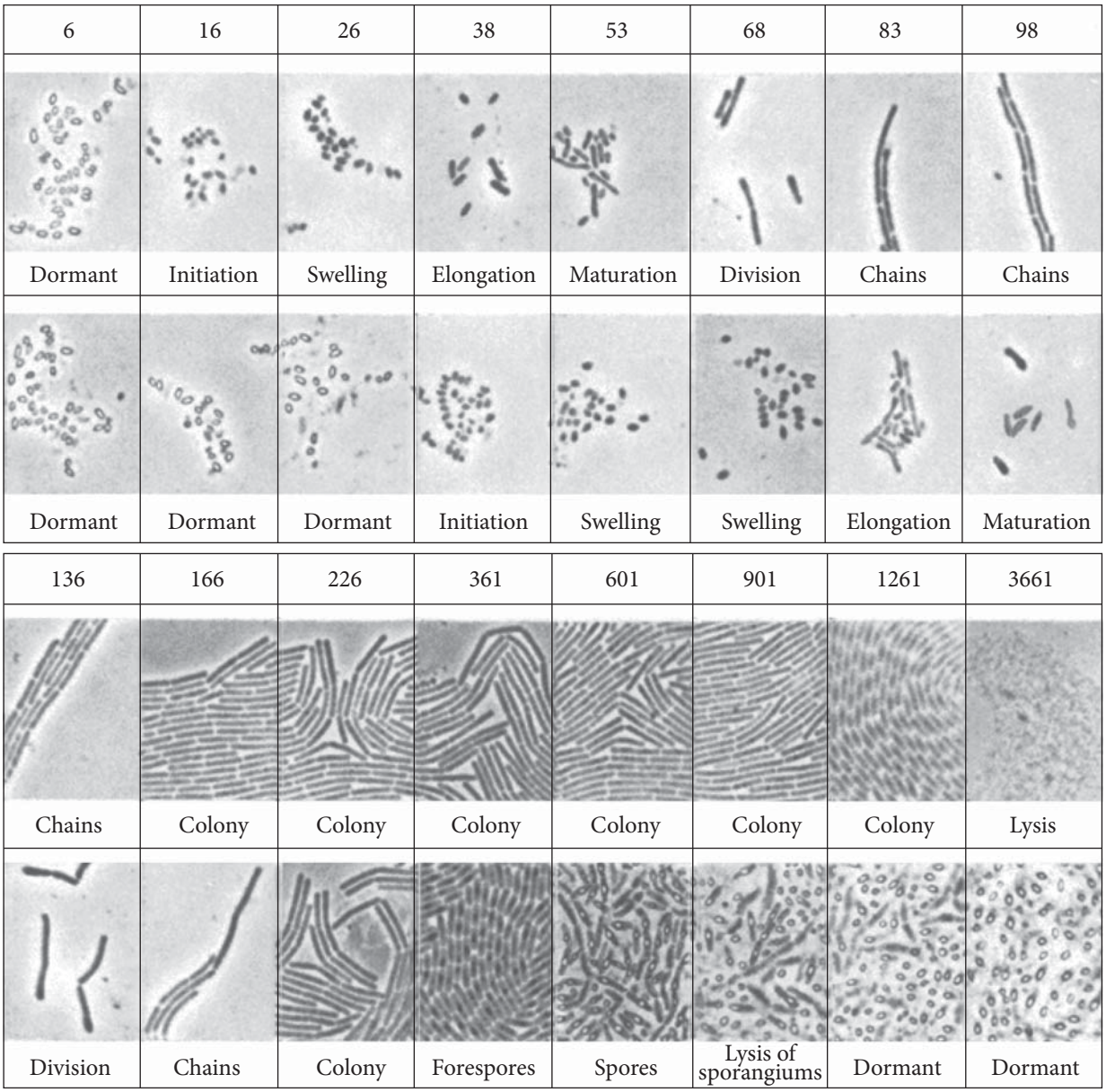

Fig. 1. Comparison of the development cycles of *Bacillus cereus* 24 microculture when cultivated in MPB and MPB diluted 100 times with physiological solution (Voitsekhovsky, 1982). Numbers mean minutes from the start of the development. The upper row is the development in standard MPB, and the bottom row — the development in MPB diluted 100 times (amino nitrogen content 1 mg%). The experiment was carried out with cells for microcultivation of bacteria. Phase-contrast microscopy, ×900

Higgs, 1974; Lopez & Thoms, 1976; Stephens, 1998). The induction of sporulation at this moment is associated with the passage of the replicative fork in the region of the operon with the gene of the «O» stage of spore formation.

One of the important inducers that determine the process of spore formation and their properties is the ionic composition of the medium. It is known that magnesium cations are necessary for sporulation, especially at the beginning of this

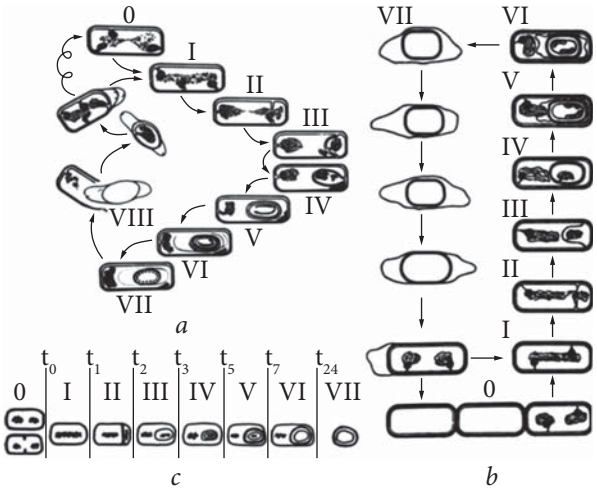

Fig. 2. Schematic image of spore formation in bacillus by different authors: A— Fitz-James P., Young E. (Fitz-Jams & Young, 1969), B — Vanek Z., Winter V. (Vanek & Winter, 1977a; Vanek & Winter, 1977b), C — Hurst A. (Hurst, 1969). t0-t24 — time, hours

process. It was supposed that cations play an important role in the activation of enzymes involved in the formation of spores. In particular, calcium cations are necessary for the formation of temperature resistance and other properties of spores (Vanek & Winter, 1977a; Vanek & Winter, 1977b). However, the need for cations is extremely individual for different species of microorganisms.

Having analyzed the literature data, it should be noted that environmental factors that affect the sporulation of some bacteria have been studied in detail. However, the mechanisms of their action remain almost unknown. Many sporulation enzymes in representatives of *Bacillus* family were suppressed by the products of glucose and nitrogen-containing substrate decay, and a decrease in their concentration is a precondition for the completion of such impact. There is even a hypothesis that explains the mechanism of environmental components' influence on sporogenesis by catabolic repression. In particular, a decrease in the level of glucose in the environment stops the growth of microorganisms and cancels catabolic repression with subsequent activation of sporulation. The mechanisms of physiological regulation include such phenomena as induction, repression, and suppression according to the principle of feedback (Dawes et al., 1971; Mandelstam et al., 1971; Mandelstam & Higgs, 1974; Lopez & Thoms, 1976; Stephens, 1998, Guliy et al., 2014;).

Thus, the development and differentiation of a cell in a certain direction depends on the environmental conditions (Rybalchenko et al., 2019; Balko et al., 2018). The possibility of bacterial cells for development in certain ways is determined by a signal that comes from the environment (Balko et al., 2020). The components of the nutrient medium affect the packaging and arrangement of chromosomes, which determines the path of cell development — growth or sporulation. The signal for spore formation is not only qualitative and quantitative changes in the nutrient medium. Sporogenesis can also induce metabolites that are formed during the development of microorganisms. Therefore, it is necessary to dwell in more detail on the nature of such inductors and mechanisms of their action.

2. Morphological characteristics of sporulation stages. In the process of sporulation, morphological changes in cells occur, which researchers use as criteria for further biochemical and genetic manifestations of bacterial sporogenesis. In turn, this makes it possible to correctly understand the functioning of regulatory mechanisms in the ontogenesis of microbial cells. There are two basic ways of development of spore-forming microorganisms — macrocyclic and microcyclic. The development according to the macrocycle involves sporulation immediately after the end of the exponential phase of bacterial cell growth. Herein, previous cell division is not a necessary condition for sporulation. The development of microorganisms according to the microcycle is when the primary vegetative cell, formed from a spore without division, is capable of turning into a spore again. In the sporulation process of bacteria from the *Bacillus* and *Clostridium* genera, most researchers (Fitz-Jams & Young, 1969; Hurst, 1969; Vanek & Winter, 1977a; Vanek &

Winter, 1977b) distinguish 7 consecutive morphological stages (Fig. 2, Table 1).

The transition cell (stage 0) after division contains two (or more) compact nucleoids, which are associated with two poles with mesosomes, which, due to the close relationship with the cytoplasmic membrane, affect the division and location of chromatin bodies.

At Stage 1 of spore formation, nucleoids change shape, lengthen, and form an axial chromatin fiber. In this case, the nucleoid remains attached to the mesosome at the poles of the cell. Chromatin fiber is not a specific sign of sporogenesis, its formation was observed in the aging of cells, the effects of antibiotics, high concentration of salts, changes in pH, decrease in temperature, and exposure to other factors (Jaiaue et al., 2021; Anumudu et al., 2021; Galperin et al., 2022; Scepankova et al., 2022; Dikec et al., 2022; Black & Shaevitz, 2023; Corona Ramírez et al., 2023). The formation of axial fiber is considered a result of rapid divergence of nucleoids after the last DNA replication, with stretching DNA filaments (Mandelstam et al., 1971; Errington, 2003; Morlot & Rodrigues, 2018; Brown et al., 2019; Willis et al., 2020) or mesosomal attachments (Fitz-Jams & Young, 1969).

Following the chromatin fiber, new mesosomes are formed at the cell poles, which play a role in the subsequent formation of the cytoplasmic septum (Barák et al., 1998; King et al., 1999; Pogliano et al., 1999). In the process of spore formation, axial fiber under conditions of nutrient medium adding can turn into a nucleoid, and the cell returns to vegetative development.

At Stage II of spore formation, the so-called sporangium cell is formed. This stage is specific in terms of the dynamics of sporogenesis. Part of chromatin moves in the place of localization of future spores to the pole of a cell (Wu & Errington, 1997; Wu & Errington, 1998; Khvorova et al., 1998). Due to the invagination of the cytoplasmic membrane, chromatin is separated by a double, asymmetrically located septum. Thus, foresporas in *Bacillus megaterium* was formed in the proximal position to the «old» cell pole; in *B. Cereus,* spores were arranged in an adjacent position, and in *B. Subtilis,* their position depended on growth conditions (Dunn & Mandelstam, 1977; Lopez-Garrido et al., 2018).

Forespora septum as a double membrane is formed not by moving it but due to synthesis *de novo* (Ju et al., 1997; Cervin et al., 1998; Levin et al., 1998; Arigoni et al., 1999). Confirmation of

Table 1. **Stages of spore formation according to different authors**

Stage	Authors		
	Fitz-James P., Young E. (Fitz-Jams & Young, 1969)	Vanek Z., Winter V (Vanek & Winter, 1977a; Vanek & Winter, 1977b)	Hurst A. (Hurst, 1969)
0	Transition from replicated cells to an axial stage	Growth	Growth
I		Formation of axial chromatin fiber	Axial fiber
II	Formation of a septum	Formation of a septum	The sporulation septum
III	The occurrence of forespora	The occurrence of forespora	Forespora
IV	Synthesis of the cortex layer	Synthesis of the cortex layer	Formation of cortex
V	Development of cortex	Spore maturation	Fully formed spore in bacteria
VI	Formation of coats proteins	Sporangia lysis and spore release	Spore release
VII	Dehydration of spore protoplast, accumulation of DPA and Ca^{2+} in spore	Free spore	Free spore
VIII	Spore release	—	—

this fact is the appearance of new mesosomes in the area of forespora septum formation. In addition, the peak of phospholipid activity coincided with the synthesis of the septum. When the forespora septum was forming, traces of murein were determined in the zone of connection with the cell membrane. Penicillin and other substances that are able to inhibit cell division also delay the formation of sections.

At Stage III of spore formation, a double membrane of the septum surrounds the replicated chromosome of forespora and cytoplasm. It was established that two or more chromosomes could get into the spore. The double membrane that surrounds the cytoplasm and DNA with other structures forms a closed ring near the cell pole. Mesosomes of forespora and mother cells are involved in the completion of double membrane formation (Decker & Maier, 1975).

It is also shown that forespora septum grows toward the pole of the cell. Perhaps, the mother cell pushes the growing septum into the zone of least resistance. Such growth is also due to the similarity of the membrane with some forespora complexes or the molecular properties of an unknown substance between the double membranes. The cell wall ensures further development of the spore. Mucopeptides, which form the germ of the cell wall, penetrate from the core of forespora into the layer between the two membranes. The layer between the forespora membranes is considered equivalent to the periplasmic space of vegetative cells (Freese, 1972; Serrano et al., 1999; Jaiaue et al., 2021).

At Stage IV of sporulation, a cortex is formed in the space between the inner and outer membranes, the main structural component of which is peptidoglycan. Peptidoglycan enters the spore from the cytoplasm of the mother cell (Freese, 1972; Sadoff, 1973; Charlton et al., 1999). Its composition is slightly different from the peptidoglycan of the cell wall of the sporangium. The formation of the cortex occurs through the widening of the internal membrane space with the appearance of cell wall germ in the form of several layers. Vesicles appeared on the inner membrane of the spores, which later form an exosporium, dipicolinic acid (DPA), and Ca^{2+} accumulate in the cytoplasm (Freese, 1972: Charlton et al., 1999). It has been shown that after the end of Stage IV, the mother cells of *B. megaterium ATCC 19213* and *B.subtilis* 60015 lost their viability (Freese & Freese, 1977; Stragier & Losick, 1996; Stephens, 1998; Cho & Chung, 2020; Khanna et al., 2020; Bremer et al., 2023).

Sporulation at Stage V is characterized by the formation of protein layers of spores, which are located between the outer membrane and the exosporium. Proteins are different in their composition, but the high content of cysteine is common to them. The formation of spore coats is accompanied by enlightenment, which increases with the accumulation of DPA and Ca^{2+} and can be determined by a phase contrast microscopy (Henriques et al., 1998; Gao et al., 2021; Mortier et al., 2023).

At Stage VI, maturation of spore occurs, it acquires maximum refractivity, and the metabolic processes necessary for synthesis of individual structures decrease (Henriques et al., 1998; Setlow, 2006; Gao et al., 2021; Chan et al., 2022).

Subsequently, the parasporal part of the sporangium is destroyed by lytic enzymes, and mature spore is released (Stage VII). Under optimal conditions, spore formation comes to the end in *Bacillus* within 6—8 hours, a little longer-in *Clostridium*. It should be noted that some differences in the presentation of morphological signs of sporogenesis may be related to the various methodological approaches of the authors studying this problem. The vast majority of researchers have studied periodic macroculture by monitoring the development of various bacterial cells at different stages of sporulation in periodic culture.

Accordingly, we decided to study not cells taken selectively from periodic culture, but the dynamics of morphological changes in the ontogeny of an individual bacterial cell.

3. Regulation of sporogenesis in bacteria. The regulation of sporogenesis in bacteria is one of the important problems that researchers study and implement new ideas, theories, and hypotheses when solving issues of the development of microorganisms (Gudzenko et al., 2022; Kruť et al., 2014). It is known that the basis of both normal and, apparently, pathological cell development is the phenomenon of differential activity of genes. The essence of such a phenomenon lies in the interaction of information flows arriving at genes and leaving them in the form of corresponding signals (Wu et al., 1998; Dworkin & Losick, 2001; Berendsen et al., 2016a; Wahia et al., 2022; Pedreira et al., 2022).

A large number of genes — from several dozen to 200 — are involved in the regulation of sporogenesis. Spore-specific genes are combined in more than 40 operons, located on the entire surface of the bacterial chromosome, each of them contains no more than three genes (Wu et al., 1998; Dworkin & Losick, 2001; Berendsen et al., 2016a; Berendsen et al., 2016b; Pedreira et al., 2022).

Genes are activated under the action of various inducers, including substances synthesized by microorganisms (Lazarenko et al., 2023; Balko et al., 2013). Bioregulators (cytodifferentiation factors, stress proteins, pheromones, signaling proteins, *etc.*) discovered in bacterial cultures are able to specifically stimulate sporogenesis, which became one of the most important successes achieved as a result of the experimental study of sporulation (Chary & Piggot, 2003; Paredes-Sabja et al., 2008; Fimlaid et al., 2015; Qin et al., 2022; Norris et al., 2023; Butala & Dragoš, 2023).

Under the study of sporogenesis in *Clostridium spp.* RA 3679 ATCC 7955, a substance able to enhance spore formation of both homologous strains, *Clostridium aerofoetidum* ATCC 4894 and *Clostridium botulinum* 62A, was found in the culture medium. A similar substance was also isolated from the supernatant of the *C. botulinum* strain (Miyata et al., 1995). It was heat-resistant and slowed down the growth of the exponential culture.

An active substance that specifically stimulated sporulation was also isolated from the destroyed cells of *B. cereus* and was called «sporogen» (Kerravala et al., 1964; Srinivasan, 1965). To obtain the «sporogen», granulated cells were used, which were washed with a 0.01 M solution of potassium phosphate, destroyed by ultrasound, centrifuged, and most of the proteins were extracted from the supernatant by treating it with a 1 M solution of hydrochloric acid. In this way, an active substance was obtained in the non-protein fraction, which did not lose its properties after the action of DNAse, RNAse, and trypsin. After the addition of «sporogen» to the medium with vegetative cells, cells became granular, and after 2—3 hours they formed spores. If the active substance was not added, then after a few hours, the vegetative cells were destroyed. Later, this «sporogen» was isolated and crystalized. It had tne following composition: carbon—42.78%, oxygen—33.7%, nitrogen—18.63%, hydrogen—4.89% with a melting point of 162—1650 C and peak absorption at 249 nm (Srinivasan, 1966).

An endogenous substance that caused spore formation was also found in the *B. subtilis* strain (Vidwans et al., 1995; Seyler et al., 1997). The effect of spore formation stimulation depended on the age of producer- culture and ranged from 0.4% of spores when applying for 6 hours to 87% — for 33 hours. The peak of spore formation enhancement was observed when using a 15-hour culture. Unlike *B. cereus* (Bursík & Němec, 1999), *B. subtilis* cells formed spores even in the presence of glucose and glutamat residues in the medium. This phenomenon was well consistent with the data of other authors who observed the spore formation of a small part of *B. subtilis* and *B. megaterium* populations that were in the exponential phase of culture growth (Smith & Foster, 1995; Wu et al., 1995; Loshon et al., 1997; Barák et al., 2019).

The question of endogenous substance availability in not only spore forming cultures emerged. Therefore, extracts were obtained

from different strains of non-spore forming bacterial species in the stationary phase, with following testing of their sporogenic activity in the system of *B. cereus* T vegetative cells (Srinivasan, 1965; Lu et al., 1995; Cattoni et al., 2014; Driks & Eichenberger, 2016; Emami et al., 2017; Dembek et al., 2018). All investigated cultures of spore-forming bacteria (5 strains of *B. cereus*, 2 — *B.cereus* var. *mycoides*, *B. megaterium*, *B. subtilis*, 4 — *Bacillus popilliae*) produced an active substance that triggered sporogenesis. Among the cultures that are not capable of forming spores (*Staphylococcus aureus, Escherichia coli, Proteus vulgaris, Aerobacter aerogenes, and Pseudomonas fluorescens*), such substance could not be isolated.

An autoregulatory substance was isolated from the*B. cereus* strain. It did not cause sporulation but stimulated the transition of vegetative cells to a hypometabolic state. At the same time, the synthesis of the most important cellular biopolymers such as DNA, RNA, proteins, phospholipids, etc. was stopped in the cells. Specific terminal products of cell metabolism, such as antibiotics, also participated in the regulation of sporogenesis. Thus, after cultivation of P+ variant of *Bacillus brevis* var *GB* in medium with 20—40 μg/mL gramicidin C for 13 hours, the number of cells turning into spores and the rate of their sporulation increased (Catinean et al., 2019; Koopman et al., 2022).

During the study of thedynamics of streptomycin synthesis in *Streptomyces griseus*, a fraction called C-factor (factor of cytodifferentiation) was isolated from the culture medium of the intensively spore-forming mutant H 45. Due to this factor influence, the development and sporogenesis of mutant 52-1 was significantly accelerated. Its sporulation was delayed without the C-factor, and the growth of vegetative hyphae finished with autolysis (Biró et al., 2000). The C-factor was fermented by trypsin, but it was resistant to DNAse, RNAse, pepsin, lysozyme, papain, and diastase.

Stimulation of sporogenesis and production of antibiotics has been convincingly demonstrated among other strains of actinomycetes (Biliavska et al., 2016; Loboda et al., 2019; Todosiichuk et al., 2019). Thus, the culture filtrate of *Actinomyces streptomyces* (strain No. 1211), capable of forming spores, restored the ability of the strain of the same species No. 1439, which did not form spores, to produce deep and surface spores. An endogenous factor was identified, and some of its properties were described for *Actinomyces circulatus*. A-factor, which is a substance with low molecular weight (MM 242 D) and the general formula $C_{13}H_{22}O_4$, was isolated from the filtrate of tht *Streptomyces griseus* strain, which formed spores well. A-factor influenced not only the synthesis of streptomycin but also the processes of differentiation in actinomycetes, for example, the formation of deep and surface spores. In the absence of A-factor, mutant 1439 formed on agar media colonies devoid of spores, while the same mutants in the presence of A-factor formed colonies with signs of sporulation. The acquired ability to sporulate was not inherited, that is, the action of A-factor did not cause changes in the genome of sensitive cells (Khokhlov et al., 1973; Popham et al., 1999).

Factors stimulating sporulation are found not only in bacilli. They are also found in some other microorganisms, in particular, in cyanobacteria, myxobacteria, slime molds, etc (Plaga et al., 1998; Errington & Wu, 2017; Hoch, 2017). The nature of the vast majority of «sporogens» has not been clarified, and regarding the mechanism of their action, there are only a few hypotheses, including the initiation of sporogenesis by a specific substance with hormonal activity. Most of the biological regulators of sporogenesis were found in the culture liquid, which confirms the intercellular nature of their action. These factors, together with activators, antibiotics, and inhibitors of various types, belong to the class of substances called «ecological ectocrines» (Smirnova et al., 1996; Balko, 2012; Khanna et al., 2019; Khanna et al., 2021). Perhaps, the substances-

metabolites that cause sporogenesis are the «language» of communication between microorganisms. Elucidation of the mechanisms of action of sporulation factors will help advance our understanding of the control of cell development.

Thus, according to the literature data, studies of sporogenesis regulation were mainly carried out in the population of bacterial cells. To obtain more convincing data, studies at the cellular level are needed.

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ОСОБЛИВОСТІ ОНТОГЕНЕЗУ БАЦИЛ У РОЗВИТКУ ВІД ВЕГЕТАТИВНОЇ КЛІТИНИ ДО СПОРИ

Розуміння процесів розвитку бактерій, зокрема спороутворюючих, має як фундаментальне, так і прикладне значення, оскільки на різних етапах цього процесу клітини мікроорганізмів виконують певні функції, які можна регулювати, впливаючи тими чи іншими факторами в залежності від поставлених завдань. У статті проаналізовано дані літератури і власних досліджень щодо впливу на спороутворення складу поживного середовища, показників pH, температури та аерації. Напрямок розвитку бактеріальних клітин певними шляхами визначається сигналами, які потрапляють із оточуючого середовища та впливають на їхній геном і визначають шляхи розвитку клітини — ріст чи спороутворення. Спорогенез спроможний індукувати також метаболіти, які утворюються в процесі розвитку мікроорганізмів. Наголошено на тому, що фактори навколишнього середовища, які впливають на спороутворення ряду бактерій, досить детально вивчено, однак механізми їхньої дії залишаються дискутабельними. Також висвітлено морфологічні, генетичні і біохімічні зміни спороутворюючих бактерій за умов макроциклічного та мікроциклічного шляхів їх розвитку, що дає можливість вірно зрозуміти функціонування регуляторних механізмів в онтогенезі мікробних клітин. Зокрема, представлено дані власних досліджень щодо динаміки морфологічних змін в онтогенезі конкретної окремої бактеріальної клітини. Крім того, детально описано фактори, зокрема такі специфічні кінцеві продукти метаболізму клітини як антибіотики, а також генетичні механізми регуляції спорогенезу різних родів та видів бактерій. Природа переважної більшості «спорогенів» не з'ясована, а щодо механізму їх дії, то існують лише деякі гіпотези. Однак більшість біологічних регуляторів спорогенезу знаходили в культуральній рідині, що вказує на клітинний характер їхньої дії. Тому для одержання більш переконливих даних щодо регуляції спорогенезу потрібні дослідження на клітинному рівні.

Ключові слова: *спороутворення, фактори середовища, ріст, макроцикл та мікроцикл розвитку бактерій, регуляція спорогенезу.*