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CRITICISM

A Review of the Book *Mikrobiologicheskii sintez* (Microbiological Synthesis) by A.M. Bezborodov and G.I. Kvesitadze (St. Petersburg: Prospekt Nauki, 2011)

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This concise book consists of a short introduction and six chapters: (1) "A General Overview of the Nature of Biochemical Processes during Fermentation," (2) "Initial Stages of Biosynthesis of Biological Structures," (3) "Fermentation and Techniques of Process Regulation," (4) "Microbial Enzymes As Biocatalysts," (5) "The Metabolic Pool of Microorganisms," and (6) "Metabolic Engineering." At the end of each chapter, a list of references is provided.

Chapter 1 gives a general idea of the processes occurring in the cells during their growth on different media. Specific examples illustrate the processes of transport of different compounds depending on their structure, as well as the functioning of the anabolic and catabolic pathways. In particular, the processes of assimilation of nitrogen-containing components of the medium, including the effect of nitrogen sources on the biosynthesis of secondary metabolites (antibiotics, alkaloids and mycotoxins), are discussed in detail.

Chapter 2 presents a thorough analysis of the amphibolic functions of the tricarboxylic acid cycle (Krebs cycle), which, together with the oxidation of acetyl-CoA to CO_2, is a source of initial components for the reactions of biosynthesis of organic acid. Reductive amination or transamination of α-ketoglutarate into glutamic acid initiates biosynthesis of proline, hydroxyproline, arginine, and citrulline. The authors thoroughly consider reactions with the involvement of acetyl-CoA as a precursor, exemplified by lipid synthesis and synthesis of cyclic compounds. The characteristics of the hexose monophosphate pathway of carbohydrate assimilation (which, finally, via shikimate and chorismate, leads to synthesis of anthranilic, *p*-aminobenzoic, and *o*- and *p*-hydroxybenzoic acids, as well as such aromatic amino acids as phenylalanine, tyrosine, and tryptophan) are also discussed in detail. Furthermore, the data are presented concerning different biosynthetic pathways of isoprenoids, the precursors of which may be C_5 units (isopentenyl diphosphate and dimethylallyl diphosphate). The mevalonate pathway of biosynthesis of C_5 units from acetyl-CoA via mevalonic acid is the most widespread. This is the pathway of isoprenoid synthesis in microorganisms, plants, and animals. The alternative pathway, via 2-C-methyl-D-erithrytol-4-phosphate, functions in eubacteria and cyanobacteria. Isoprenoids form a large group of structurally and functionally diverse compounds participating in various processes of metabolism, growth, and development. Many compounds of this class are classed as secondary metabolites, such as steroids, vitamins, and the anticancer agent Taxol. The chapter ends with a section devoted to biosynthesis of porphyrin structures, which are among the most widespread vital metabolites.

Techniques for regulation of the fermentation process are logically presented. The authors clearly formulate the general requirements for industrial production strains: good growth rate, stability of physiological characteristics, maximum utilization of nutrient sources from the medium, changes in the genome structure providing high yields of the end products without adding an inducer (for the biosynthesis of inducible enzymes), minimum synthesis of other metabolites, the absence of cyto- and genotoxic metabolites among the products, and high yield and rapid accumulation of target products. One of the methods for enhancing the process efficiency is introduction of an unmetabolized inducer analog structurally close to the true inducer into the cultivation medium. The classical examples are thiomethyl and isopropyl galactosides providing high yields of β-galactosidase.

Catabolite repression and its causes and consequences, as well as the techniques for elimination or drastic reduction of its negative effect on technological processes, are considered with specific examples. The problems of the regulation of enzyme activity are discussed—in particular, the most frequent type of negative feedback inhibition, when excessive accumulation of the end product results in "switching off" of the respective enzymes. In this case, the activity of the first enzyme holding the key position in the biosynthetic chain is usually suppressed. Industrially significant metabolites, synthesis of which is regulated by the principle of feedback, include amino acids, vitamins, and nucleotides.

The authors place special emphasis on obtaining practically valuable products during the growth retardation phase of producer cultures. Differentiation into the trophophase, or growth phase, and the synthesis phase was originally formulated by V.N. Shaposhni-

kov, and the terms tropho- and idiophase were proposed by J.D. Bullock. Two-phase processes were described most completely for fermentation and biosynthesis of antibiotics and alkaloids. The regulatory mechanism is probably accounted for by the fact that, before the idiophase, the genes of enzymes for the synthesis of secondary metabolites are in a state of repression, while, by the moment of transition to the phase of synthesis of the target product, the repressor (e.g., phosphate) has been completely consumed by the culture.

The concluding part of Chapter 3 is devoted to the synthesis of secondary metabolites and their possible precursors, as well as to the influence of various factors, e.g., the ratio of carbon and nitrogen concentrations in the medium, on their synthesis. Very useful information on the types of the biological activity of microbial metabolites and their distribution by activities and producers is summarized in the tables. Moreover, examples of secondary metabolites are given: from antibiotics, flavonoids, and terpenoids to Taxol or Paclitaxel (Taxane, a dosage form), which is the most commercially effective antitumor agent.

Application of microbial enzymes for obtaining commercial optically active products, chemical and enzymatic methods of polyacrylamide production, and other processes are described in Chapter 4.

The sense and meaning of such popular terms as metabolome, metabolone, proteome, and proteomics are explained in Chapter 5. For example, a metabolome is a set of low molecular weight molecules, which is part of a cell and a gene expression product. There are extracellular (exometabolome) and intracellular (endometabolome) metabolites. The metabolites comprising a metabolome are identified by physicochemical methods. A metabolone is a supramolecular enzyme complex catalyzing the steps of a metabolic pathway, which is formed on biological membranes. The assembly of a metabolone results in formation of a microcompartment, where the metabolic process can be isolated, without release of reaction products into the fermentor.

The final chapter is devoted to a novel and challenging scientific trend: metabolic engineering. Its primary objectives are production of homo- and heterologous proteins for biomedicine, including hormones, antibodies, vaccines, and enzymes; broadening of the spectrum of initial substrates; selection of conditions for metabolic pathways yielding new products; metabolic engineering in association with the biochemical mechanism of xenobiotics degradation and its application for improvement of the physical processes in the cell; removal or decrease in the quantity of the side products; and, finally, increase in the productivity level.

The book is written at a high professional level. The authors have given a concise account of the theoretical foundations of microbiological synthesis in a conceptual and popular form. The usefulness of this book for students and scientific workers in biotechnology is unquestionable.

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