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REVIEW ARTICLE

Fermentation trip: amazing microbes, amazing metabolisms

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Abstract

Fermentation has been applied to many areas of human life, including industrial production, sewage treatment, and environment management. By understanding the process and mechanism of fermentation, more comprehensive and profound cognition of the fermentation may be established to lay a foundation for our further research. In this review, we present a brief summary of recent research about fermentation and microorganisms in different territories, including foods, environment, and human health. According to the growth characteristics of different stages of microorganisms, we introduced a series of metabolic changes, fermentation mechanism, and regulation methods and how the enzymes were transported out of the cell. With further understanding and utilization of microorganisms, food can produce better flavor, nutrition, and functional metabolites through fermentation. Fermentation is also used in other industries, such as wastewater and garbage disposal, environment, and soil management. The human gut flora, in particular, has begun to receive more attention. The profound influence of microorganism on human health cannot to be underestimated. It has become a hot research area in recent years. We can get the metabolites we want by controlling the rate of fermentation and regulate the direction of fermentation. As one of the important components of modern biotechnology, fermentation engineering has been widely used in areas including food, pharmaceutical, energy, chemical industries, and environmental protection. The development of genetic engineering has brought new vitality to fermentation engineering. The application of modernization, automation and artificial intelligence technology also opens up new space for fermentation engineering. In addition, research on the understanding and regulation of metabolic mechanism has further developed the fermentation function of microorganisms.

Keywords Fermentation · Microbes · Metabolisms · Regulatory mechanisms · Enzyme transport

Introduction

Fermentation is an ancient production method used since the development of human civilization. The fermentation of meats, wines, and milks has been described for thousands of years, with the earliest records dating to 6000 BC (Fox 1993). However, at that time, people knew neither the relationship between fermentation and microbes nor the reason for fermentation; the principles of fermentation were simply passed down through oral tradition and applied in practice. For example, anaerobic fermentation is used to ferment alcohols, while aerobic fermentation is used to make vinegar and Daqu, which is a characteristic raw material in traditional fermentation. This period is called the natural fermentation period.

In 1667, Antonie van Leeuwenhoek invented the microscope, revealing the secrets of the microbial world. With the discovery of microorganisms, Louis Pasteur of France discovered the principle of fermentation via experiments in 1850–1880, realizing that fermentation was caused by microbial activity. Improvements in pure culture technology have ushered in a new era of artificial microbial control. Sterilization and the invention of simple closed fermentation tanks as well as other technical equipment have greatly reduced fermentation failure (such as contamination); the artificial control of environmental conditions rapidly increases fermentation efficiency. Anaerobic fermentation, used for the production of

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alcohol, acetone, butanol, etc., was developed gradually. Therefore, the establishment of pure culture technology was the first turning point in the development of microbial engineering fermentation technology.

With the discovery of penicillin and the success of large-scale production, the laboratory adopted the highly efficient culture flask ventilation and air fiber filtration sterilization technologies. The rise of the antibiotic industry has not only allowed microbial technology to be applied to the pharmaceutical industry but has also promoted the development of the aerobic industrial microbial fermentation industry. The focus of microbial engineering has changed from decomposing metabolisms to biosynthetic metabolisms. Microbial synthesis can be used to accumulate useful metabolic products, such as organic acids, enzyme preparations, vitamins, and hormones, outside the normal metabolic range of microorganisms. Therefore, the establishment of aerobic fermentation engineering technology for aerated stirring cultures was the second turning point in the development of microbial engineering fermentation technology.

Fermentation has currently evolved into a very important branch of bioengineering and has been a multidisciplinary focus in fields, such as microbiology, chemical engineering, genetic engineering, cellular engineering, mechanical engineering, and computer software and hardware engineering. With the development of modern biotechnology, fermentation has been applied to all aspects of life; microbes and metabolites are important in the production of fermented foods, in industry, and in human health (Fig. 1).

Fermentation is generally defined as the production of foods, beverages, or other useful metabolites by aerobic or anaerobic microorganisms via enzymatic conversions of substrates and controlled microbial growth. Fermentation operates via the natural activities of microorganisms; metabolism, which ensures the growth and reproduction of microorganisms, is one of the basic characteristics of natural microbial activities. Metabolism involves the degradation of substrates and the growth, reproduction, aging, and death of microbes, and it is accompanied by the production and alteration of different metabolites. First, by sensing the environment, microbes typically produce signals in order to induce the synthesis of proteins (enzymes), which are exported from the cell via a series of transport mechanisms. Then, substrates are converted by enzymes to produce the nutrients, including amino acids, nucleotides, sugar, fatty acids, and vitamins, required for the growth of the microorganism. As the number of microorganisms increases and metabolic products accumulate, new metabolic pathways are initiated, and secondary metabolites, such as pigments, antibiotics, toxins, and hormones, are produced. Finally, as the environment changes beyond the ability of the microorganisms to adapt, they begin to die. In the laboratory, we typically measure microbial growth curves, which represent the dynamic population changes as microbes grow and divide in new and appropriate environments until their eventual death. Fermentation is a complex process; microbes have very strong regulatory mechanisms, and marginal changes in the environment may lead to the production of different products. We can obtain the desired products by controlling fermentation conditions, such as the strain filtration and transformation conditions, and by optimizing process conditions via fermentation modeling in order to generate products with the lowest cost, highest output, and best quality.

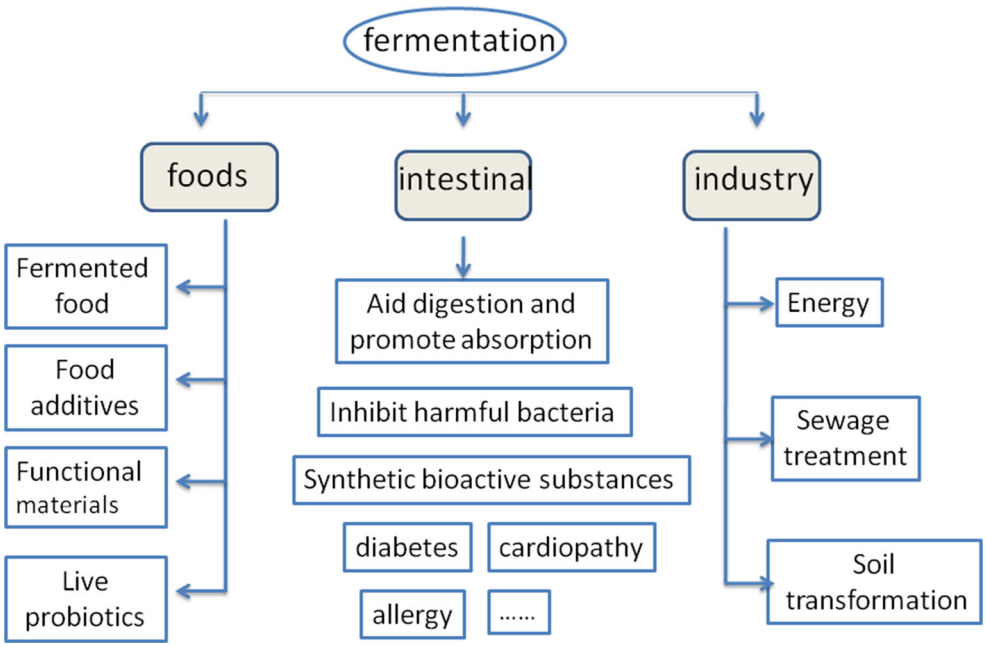

Fig. 1 The relationship between fermentation and human life

In this review, we summarize the powerful role of fermentation in food, industry, the environment, and the human body. Through examining the characteristics of different microbial growth stages, we introduce a series of metabolic alterations, mechanisms, and regulatory methods underlying fermentation, and we discuss the mechanisms by which enzymes are typically exported from the cell. By studying and understanding these processes and the mechanism of fermentation, we gain a more comprehensive and profound recognition of the fermentation process, which lays a foundation for our future studies.

Fermentation and foods

Fermented foods and beverages were the first microbial products used by humans. Fermented foods, such as cheese, beer, wine, and vinegar, were originally valued because of their safety and improved shelf life. The fermentation process is increasingly understood to potentially improve flavor and enhance nutritional and functional properties. Food fermentation can be categorized by the primary metabolites and microorganisms involved: alcohol and carbon dioxide (yeast), acetic acid (*Acetobacter*), lactic acid (lactic acid bacteria), propionic acid (*Propionibacterium freudenreichii*), and ammonia and fatty acid (*Bacillus* and molds) (Marco et al. 2017). Most fermentation, especially the fermentation of traditional fermented foods, results from the interaction of multiple microbes. Wine and Chinese spirits are the products of complex interactions among bacteria, yeasts, and fungi; these interactions encompass yeast-bacteria, yeast-yeast, and yeast-filamentous fungi interactions. In addition to producing alcohol, these microbes, especially yeasts, also influence the individuality and subtlety of flavor responses (Fleet 2003; Liu et al. 2015; Xu et al. 2017). Many wine flavor compounds are released or produced during wine production and are derived from microbial activity (Belda et al. 2017). During food fermentation, proteolysis or autolysis generates taste-active peptides and amino acids, which impart particularly bitter (e.g., hydrophobic peptides containing proline) or umami (e.g., α-glutamyl peptides) tastes (Zhao et al. 2016). More importantly, fermented foods contain many edible bacteria (probiotics) and functional substances. Increasing evidence has shown that many fermentation filtrates or extracts can benefit health via their high nutrient content, antioxidant properties, ability to balance the gut microbiota, and immune-strengthening properties, among other features (Table 1). In recent years, genomics, metabolomics, transcriptomics, and proteomics have been used to analyze fermented foods to discern their palatability and insalubrity. These methods allow us to gain a deeper understanding of fermentation (Kim BJ et al. 2016; Chen et al. 2017; Ponomarova et al. 2017; Singh et al. 2017).

Fermentation and the environment

Fermentation is used in other industries, including wastewater and garbage disposal and environmental and soil management. Wastewater from butanol fermentation can be used by *Trichosporon coremiiforme* to produce a biodiesel feedstock. This production method could produce lipids at a low cost and, thus, solves the environmental resource problem (Li et al. 2017). In addition, a co-immobilized microalgal-bacterial system may be an option for treating municipal wastewater (Shen et al. 2017). Solid-state fermentation can be a novel paradigm for organic waste valorization; this process leads to reduced operational and production costs, contributes to solid waste management, and decreases environmental pollution. Organic solid waste can be easily used and converted into valuable bioproducts, such as organic acids, biosurfactants, biopesticides, and bioethanol (Yazid et al. 2017). Furthermore, agroindustrial waste (e.g., wheat bran, cotton meal, soybean meal, and orange peel), animal carcasses, and sawdust waste can be broken down and used to produce enzymes and other metabolites or industrial products, such as feed (Castro et al. 2015; Daâssi et al. 2016; Liu et al. 2016; Mohapatra et al. 2017). Lignocellulosic biomasses are rich sources of carbohydrates, but degradation is a serious problem. Thus, fermentation techniques are a popular research topic (Müller et al. 2016; Amin et al. 2017; Althuri et al. 2018). In addition, microorganisms play an important role in soil. As industrialization accelerates, land pollution becomes increasingly problematic. Bioelectrochemical treatment systems can facilitate the bioremediation of oil spill-contaminated soil (Cheng et al. 2017). However, one of the most important biotechnological challenges is the development of environmentally friendly technologies for producing energy from new sources. Microbial production of biohydrogen via dark fermentation, by the conversion of residual biomass, is an attractive solution for the short-term development of biohydrogen-producing processes (Cabrol et al. 2017).

Fermentation and the human body

Variety of microbial communities and their genes (the microbiome) exist throughout the human body, from skin to intestinal tract, with fundamental roles in human health and disease (Consortium 2012). Immediately after birth, many microbes from the surrounding environment scramble to occupy our body, colonizing our mouth, digestive tract, respiratory tract, urinary tract, and skin. These microbes then become indivisible parts from normal bacteria or symbiotic microorganisms (Bassis et al. 2015; Thomas-White et al. 2016). However, whether we are colonized by microorganisms in utero is unclear. Though studies have linked microbes in the

Table 1 Effects and mechanism of fermented foods

Substrates	Strains	Mechanism	Effects	References
Wheat bran	Yeast and lactic acid bacteria	Change the material structure	Saving energy in dry process, water-extractable arabinoxylans, total dietary fiber, soluble dietary fiber, and hydration properties increased	Zhao et al. (2017)
Pineapple, papaya, mango, tea	*Weissella cibaria* 64, *Leuconostoc mesenteroides* 12b	Increase DPPH radical scavenging activity	Increase antioxidant activity and total phenolic content	Fessard et al. (2017)
Vegetables, cereals, sea foods, etc.		Produce functional metabolites	Decrease the prevalence of atopic dermatitis	Park et al. (2016)
Grain food		Suppress the lipid oxidation induced by peroxynitrite, peroxyl radical, singlet oxygen, and hypochlorite	Antioxidant action	Morita et al. (2017)
Sugar, fruits, vegetable, mushrooms, seaweed, etc.	*Lactobacillus brevis*, *Lactobacillus casei*, *Lactobacillus curvatus*, etc.	With higher total phenolic content, citric acid, total flavonoid content, etc.	Strengthen immunity and antioxidant	Zulkawi et al. (2017)
Ice cream	*Streptococcus thermophilus*	The presence of carboxyl, hydroxyl and amide groups with additional α-glycosidic linkage	High viscous and pseudoplastic non-Newtonian fluid behavior, increase the physicochemical, rheological, molecular, and sensory properties	Enes et al. (2016)
Milk	*Lactobacillus delbrueckiis* sp. *bulgaricus* OLL1073R-1	Augment natural killer cell activity and induce IFN-γproduction	Increase immunity	Makino et al. (2016)
Bovine skim milk	*Lactobacillus helveticus* ASCC953, *L. helveticus* ASCC474, *L. helveticus* ASCC1188, and *L. helveticus* ASCC1315	Antioxidant activity of peptides	Anti-colon cancer and antioxidant activities	Elfahri et al. (2016)
Skim milk	*Lactobacillus plantarum* MTCC 5690	Modulate the regulatory receptors Toll-like receptor 2 and Toll-like receptor 4	Reduce the infection of human intestines	Rokana et al. (2016)
Malt, molasses	*Kefir*	Via the regulation of prostaglandin	Anti-inflammatory and anti-ulcerogenic activities	Rodrigues et al. (2016)
Fresh milk, fructooligosaccharide	*Bifidobacterium breve* (KCTC 3419), *Streptococcus thermophilus* (YF-L812), *Lactobacillus sakei* subsp. LJ011	Conjugated linoleic acid	Decrease body weight, leptin, serum insulin, and levels of fasting blood glucose	Song et al. (2016)
Soluble fiber	Gut microbiota	Butyrate and propionate generated by fermentation activate intestinal gluconeogenesis,	Butyrate and propionate influence the host metabolism positively	Devadder et al. (2014)

placenta or the amniotic fluid to preterm birth (Aagaard et al. 2014), the initial findings have not been widely reproduced. Healthy fetuses are currently believed to host no bacteria, although, as with everything in science, this hypothesis may be subject to revision as new data accumulate (Knight and Rob 2015). The intestinal flora, which is closely related to our health, is a popular research topic for many investigators due its strong link to human health. The human intestine harbors a dense microbial ecosystem which is different between individuals, dynamic over time, and critical for aspects of health and disease (Fig. 2). A mutualistic role of gut microbes is to digest dietary complex carbohydrates, liberating host-absorbable energy via fermentation products (Porter and Martens 2017). Undernourished children exhibit impaired gut microbiota development because of factors such as the lack of human milk oligosaccharides. Therefore, gut microbes could be potential therapeutic targets and agents (Blanton et al. 2016; Charbonneau et al. 2016). Moreover, the intestinal microbiota can regulate the body composition through the circadian transcription factor NFIL3. Certain microbes can produce flagellin and lipopolysaccharide to tune the oscillation amplitude of NFIL3 expression through ILC3 (type 3 innate lymphoid cell) signaling, the epithelial cell clock, and STAT3. This mechanism probably explains why circadian clock disruptions arising from shift work are associated with diabetes, obesity, and cardiovascular disease (Ash 2017; Wang et al. 2017). Interactions with microorganisms are commonplace for nearly all animals and plants. Although the gastrointestinal tract, which is exposed to microorganisms from the external environment, is home to a dense community of resident bacteria, it has an immune defense mechanism. The epithelial surface of the intestine plays a critical role in protecting the host; it can produce diverse antimicrobial proteins in order to kill or inactivate adversarial microorganisms. However, such bacterial molecules may enhance immunity in humans. For example, microorganisms colonizing pregnant mice were found to improve innate immune system priming in newborn offspring. These offspring were thus prepared for life in association with microbes. The levels of ILCs and F4/80(+)CD11c(+) mononuclear cells in the pups increased during the gestational period. Maternal colonization then reprograms intestinal transcriptional profiles in the offspring, including profiles related to the metabolism of microbial molecules and the expression of genes encoding epithelial antibacterial peptides (Mukherjee and Hooper 2015; Gomez et al. 2016; Pendse and Hooper 2016).

However, the problem of "deficiency heat" arises in the study of the microbiota. Currently, most research focuses on correlation studies, with many differences between the health and disease models, but very few studies on causality and molecular mechanisms have been performed (Meijnikman et al. 2018). "Causality" is the most important scientific question in the study of the relationship between the microbiota and disease. Specifically, we need to determine whether the disease changed the flora, changes in the flora led to the disease, or a process acted in which the body first appears to have a disease but subsequent changes in the microbiota structure aggravate the disease or induce a new disease. In this way, we can use the microbiota structure to diagnose disease and predict disease progression, and it can be a target for disease treatment and prevention. Therefore, confirming whether the relationship between bacteria and disease is one of correlation or one of causality is the direction for future research breakthroughs; only in this way can research on the microbiome trigger revolutionary

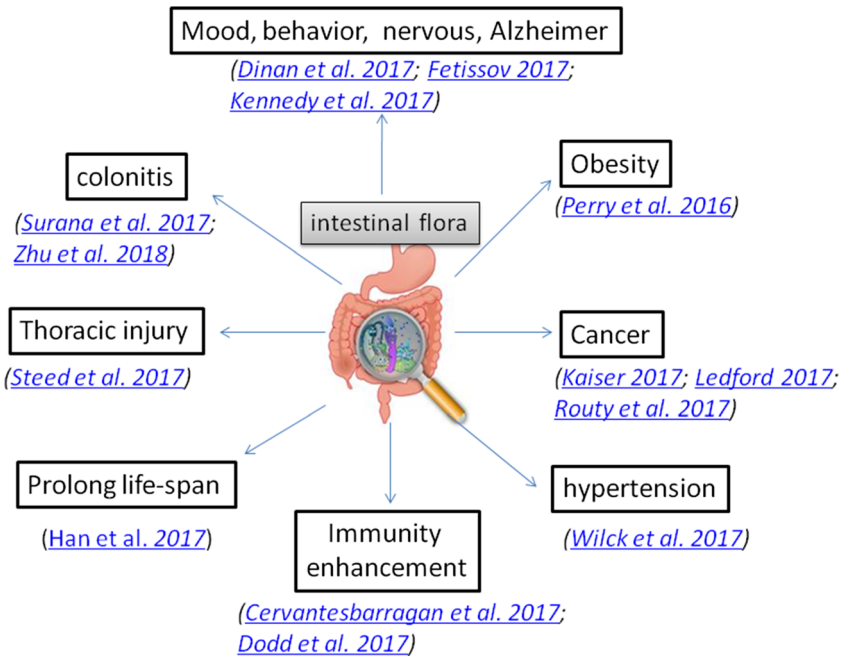

Fig. 2 Intestinal flora and human health

changes in biological medicine (Zhao 2013). Excitingly, a recent study was the first to demonstrate causality between the gut microbiota (*Akkermansia* and *Parabacteroides*) and susceptibility to seizure (Olson et al. 2018).

Many microorganisms that benefit our health are probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Pot et al. 2014). According the October 2013 conclusion of the International Scientific Association for Probiotics and Prebiotics, evidence of a health benefit is required for a microorganism to be classified as a probiotic at either a group- or strain-specific level, depending on the nature of the benefit. Many well-studied microbial species delivered in food or supplements at a functional dose, such as *Bifidobacterium* (*adolescentis*, *bifidum*, *longum*, *breve*, and *animalis*) and *Lactobacillus* (*acidophilus*, *fermentum*, *casei*, *gasseri*, *paracasei*, *johnsonii*, *plantarum*, *rhamnosus*, and *salivarius*), are probiotics (Canada 2009). A core claim of these probiotics is the general benefit of supporting a healthy gut microbiota. The EFSA (European Food Safety Authority) has also approved *Streptococcus salivarius* subsp. *thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* as probiotics for aiding lactose digestion (Agostoni 2010). For other human gut microbes, such as *Faecalibacterium prausnitzii* (Miquel et al. 2013) and *Akkermansia muciniphila* (Joyce and Gahan 2014), along with other butyrateproducing bacteria, such as *Eubacterium hallii* (Vrieze et al. 2012) and *Roseburia* spp. (Louis et al. 2007), more evidence of their safety and efficacy is needed to determine whether they can be used in food and medicine.

Moreover, the panel of experts categorized probiotics as follows: probiotic in food or supplement form without a health claim, probiotic in food or supplement form with a specific health claim, and probiotic drugs (Pot et al. 2014). A randomized controlled trial evaluated clinical outcomes associated with probiotic therapy alone or in combination with prebiotic fiber. Thirty trials comprising 2972 patients were identified for analysis; the result indicated that probiotics showed promise in reducing infections, including ventilator-associated pneumonia (Manzanares et al. 2016). In addition, another clinical trial reported that probiotics can prevent infections in newborns (Tancredi 2017). Moreover, probiotics may be beneficial for osteoporosis, gingival health, and many other aspects (Eren et al. 2017; Jafarnejad et al. 2017). However, although most published studies have focused on populations with specific health pathologies, the exact role of probiotics is still unclear in many therapeutic settings, and safety issues in some populations (e.g., immunosuppressed individuals, pregnant women, and individuals with severe underlying diseases) are of primary concern (Doron and Snydman 2015; Khalesi et al. 2018). Additional high-quality research is needed to improve our understanding of the benefits and risks of these complex microbial therapies, and more accurate information is needed to support clinicians' decisions.

Microorganism growth

Lag phase

When microorganisms enter a new environment, the number of cells does not increase until the metabolic system adapts to the new environment. During this period, cells grow, and many bacilli can form filaments. The cells are sensitive to external adverse conditions, such as inhospitable temperatures and antibiotics. In cells, anabolism is active, and the RNA content is increased. Spores must undergo germination, including activation, budding, and growth. Under favorable conditions, the cysteine-rich proteins in the spore coat undergo a three-dimensional structural change, which increases the permeability of the spore and promotes germination-related protease activity. Then, the proteins in the spore coat are progressively degraded, and cations continuously flow into the spore core; thus, the core expands, many cell wall synthesis enzymes are activated, and spore outgrowth and metabolism are initiated (Setlow 2003; Francis and Sorg 2016; Mares et al. 2017). The microbial population in the lag phase is generally related to the heterogeneity in the behavior of individual cells. Therefore, to understand cell adaptation and growth mechanisms in new environments, many mathematical models, such as individual-based modeling, individual discrete simulation, and one-step kinetic analysis, allow us to more deeply probe the behavior of individual cells (Prats et al. 2006; Huang 2016). During the lag phase, the metabolites synthesized are very active and readily induce the production of various enzymes (Table 2). In the lag phase, 28 highly expressed proteins were identified in *Lactococcus lactis* subsp. *lactis* CNRZ 157. These proteins were implicated in nucleotide metabolism, stress response, translation, cell division, amino acid metabolism, glycolysis, and coenzyme synthesis (Larsen et al. 2006). Many factors may influence the duration of the lag phase, including the physiochemical environment of the new growth medium, the physiological history of the cells, and the inoculum size (Robinson et al. 2001; Swinnen et al. 2004; Shibata et al. 2018). To improve growth efficiency, we can regulate the length of the lag phase. Microorganisms can be activated during the lag phase and rapidly respond to the newly available resources. For example, the catalytic capacity of adenylate kinase may affect the length of the lag phase of wild-type *Escherichia coli* (Adkar et al. 2017).

Logarithmic phase

Microorganisms in the logarithmic phase exhibit characteristics such as growth at the maximum rate, balanced cell growth, active enzyme systems, and active metabolisms. As the logarithmic phase of microbial growth begins with its increased nutrient demand, more extracellular enzymes are produced and transported in vivo to degrade substrates into more

Table 2 Change of microbial metabolites at different growing phases

Growing phase	Microbes	Metabolisms	Metabolites
Lag phase	Individual growth	Anabolic metabolism dominates in cell, extracellular enzyme synthesis and transshipment, substrate begin to degrade	Enzymes
Logarithmic phase	Individual reproduction, population growth increasing geometrically	All kinds of metabolism are very high	Enzymes, functional polysaccharide, polypeptides, etc. Primary metabolites, such as alcohol, amino acid, pyruvate, and citric acid
Stationary phase	Population growth and the rate equal to the death	Accumulation of metabolites begins the secondary metabolism	Secondary metabolites, such as antibiotics, hormones, toxins, and pigments
Decline phase	Growth is inhibited by substrate, and the cells begin to autophagy	Old cell degradation, and new microbe population begins the new metabolism	Nucleotide, spore, sulfide, amino, monosaccharide, secondary metabolites

absorbable nutrients and functional molecules, such as monosaccharides, amino acids, and polypeptides (Table 2). These primary metabolites are directly involved in the growth, development, or reproduction of the producing organism. During fermentation, the metabolic activity of microorganisms and the enzymatic activity on substrates can change the bioactive and nutritive properties of the matrices. Many functional molecules, including peptides, polysaccharides, and enzymes, are widely used in industry and may benefit animals, plants, and human health. Feeding *Saccharomyces cerevisiae* fermentation products to calves can improve the gastrointestinal morphology, change the abundance of different intestinal flora, and reduce diarrhea (Xiao et al. 2016; Alugongo et al. 2017). Fermentation liquid containing microbially solubilized phosphate improved plant growth and phosphate uptake in both soil and soilless conditions with equal effectiveness (Mendes et al. 2017). Milk and dairy contain a large percentage of lactose. The absorption of lactose requires the hydrolysis of this disaccharide in the mucosa of the small intestine. However, many individuals are lactose-intolerant due to insufficient activity of intestinal β-galactosidase, but this problem can be solved by fermentation. For example, *kefir* (a fermented milk), most cheeses, and yogurt are typically well-tolerated by lactose-intolerant persons. β-Galactosidase is released in vivo during fermentation and reduces lactose content, which renders the final product suitable for individuals with lactose intolerance. The release of lactase appears to require cell membrane disruption (Savaiano 2014; Marco et al. 2017; Rosa et al. 2017). The proteolytic activity of *koji* (rice fermented with *koji* molds, such as *Aspergillus*) in meat sauce can produce the bioactive Gln-Tyr-Pro peptide, which showed extremely high antioxidant activity against the OH radical (Ohata et al. 2016). Additionally, a novel LVYPFP peptide was produced by *Bifidobacterium bifidum* MF 20/5 (isolated from fermented milk); this peptide strongly inhibits angiotensin-converting enzyme (Gonzalez-Gonzalez et al. 2013). Lactic acid bacteria have very efficient proteolytic systems to release bioactive peptides that are able to control nutrition, metabolism, cardiovascular function, the gut-brain axis, and infection (Pessione and Cirrincione 2016).

Stationary phase

When entering the stationary phase, cells begin to accumulate glycogen, transfection granules, and fat (Table 2). During this phase, the cell growth rate is zero; the number of newly reproducing cells is equal to the number of dying cells. Bacilli usually begin to form spores during stationary phase. The regular growth pattern in stationary phase has important guiding significance for production. For fermentation products (lactic acid, etc.) whose production depends on increasing bacterial growth or for other metabolic products whose production parallels bacterial growth, the stationary phase is the best time for harvest. To avoid the adverse effects of accumulating certain metabolic products during growth, some microbes begin using a type of metabolism conducive to survival; they start to synthesize secondary metabolites via complex secondary metabolic pathways. Secondary metabolites, such as antibiotics, hormones, pigments, and toxins, are low molecular mass, structurally complex organic compounds with diverse biological activities. Secondary metabolites are not directly involved in growth, development, or reproduction (Deutsch 2000).

However, secondary metabolites play a key role in microbial communication. Communication is a physiological trigger to activate silent gene clusters and leads to the production of novel secondary metabolites. Genomic sequence data have revealed many putatively silent biosynthetic gene clusters. The high abundance of different species of microorganisms forming diverse multispecies communities results in specific interspecies communication (Marmann et al. 2014; Netzker et al. 2015). Thus, many biological or chemical elicitation studies have revealed strategies to activate cryptic genes, and

coculture or mixed fermentation efficiently improves the production of secondary metabolites by microorganisms (Abdelmohsen et al. 2015; Reen et al. 2015; Zhang 2016). In addition, genome editing techniques may have potential application for the metabolic engineering of biologically active secondary metabolites (Leitão et al. 2017).

Antibiotics, which are important secondary metabolites, are typically regarded as microbial weapons for protecting human health (Bérdy 2005). In fact, many investigators have recently proposed that these molecules act as signaling molecules within and between species (Linares et al. 2006; Shank and Kolter 2009). Moreover, these molecules might act as chemical manipulators or cues as well as perform other functions such as regulating carbon sources and genes, contributing to nutrient scavenging, altering central metabolic pathways, or participating in developmental pathways (Linares et al. 2006; Shank and Kolter 2009; Sánchez et al. 2010; Romero et al. 2011; Beyersmann et al. 2017). Though many microorganisms use secreted compounds to impair or kill neighboring target cells, in reality, these compounds could damage the producer. Several works have revealed that these target species could have a physiologically tolerant state that coordinates the response to environmental conditions (Eran et al. 2016; Kubistova et al. 2017; Ghosh et al. 2018). How could a microbe both prevent the acquisition of tolerance and ensure the delivery of a killing dose? Quorum sensing (QS) may be one possible mechanism. Unsurprisingly, the regulation of antimicrobial functions by QS is widespread in many species (Hibbing et al. 2010). A recent study indicates that the autoinducer concentration can reliably indicate cell density, cell history, and environmental cues and allows cells to integrate antibiotic stress into their QS response (Morenogámez et al. 2016). The metabolic function and molecular regulation of the QS system in *Klebsiella pneumonia* have been investigated; the production of ethanol, acetic acid, and acetoin was lower in the mutant strain than in the wild-type strain after the disruption of QS (Sun et al. 2016). By understanding the mechanism of action underlying QS, we can intervene in and regulate fermentation via QS.

Decline phase

Finally, as fermentation proceeds, the change in substrate concentrations and the accumulation of metabolites lead to the inhibition of microbial growth. The individual death rate of microorganisms exceeds the division rate, and the whole population is in a negative growth state. The population thus enters the decline phase (Table 2). Cell morphology begins to change; for example, enlargement occurs or irregular degenerative forms are produced. Some cells begin to undergo autolysis. At the end of the decline phase, the population that can adapt to the new environment gradually becomes dominant and renews metabolism.

Fermentation mechanisms and regulation

In microorganisms, metabolic pathways are precisely selected, organized, regulated, and controlled. These precise controls are based partially on the high selectivity of biocatalytic reactions and the controlled cross-membrane transport of biomacromolecules and chemicals between the compartmentalized cells, organelles, and organs. Enzymes play a key role in these biological reactions. The mechanism of enzyme production first requires support from signal-triggered synthesis, release, secretion, conversion, and degradation processes, which occur in different compartments in organs and cells. The highly selective biocatalysis processes orchestrate a complex system of biochemical reactions. However, some enzymes cannot provide 100% selectivity. For example, proteases can promiscuously interact with numerous substrates with similar chemical structures, possibly strongly reducing the efficiency of biocatalytic process. However, the overall high specificity of biocatalytic processes is strengthened by localizing the enzymatic reactions within specific spatial compartments and environments (Zakharchenko et al. 2017).

The chemical mechanism underlying the regulation of enzyme concentration is the control of gene expression. In cells, the types and quantities of enzymes synthesized are determined by specific genetic information. DNA carries the genetic information of enzyme proteins and must be transcribed and translated to guide protein synthesis. Transcriptional regulation is dominant, so the regulation of gene expression is mainly carried out at the transcriptional level. For example, the sugar composition and content of fruits varies with species, developmental stage, and cultivar. Enhancing fruit quality by genetically controlling sugar metabolism is essential (Desnoues et al. 2016). Three most upregulated heat-shock response genes (CPR6, STI1, and FES1) were co-overexpressed in *Komagataella phaffii* (*Pichia pastoris*). They proved their positive effect on the secretion of reported enzymes (prolyl endopeptidase and PLA2) (Yu et al. 2017). During research on lignocellulosic biomass, the overexpression of the transcriptional activator MSn2 in *S. cerevisiae*, which regulates numerous genes involved in antioxidative stress responses, was found to confer furfural tolerance by reducing the intracellular levels of reactive oxygen species and to improve the initial rate of fermentation (Sasano et al. 2017). In addition, transcriptional profiling showed that the overexpression of the SFP1 gene improved ethanol productivity and that the overexpression of the ACE2 gene enhanced the fermentation rate in the presence of acetic acid and furfural (Chen et al. 2016).

During evolution, cells acquired the ability to sense and adapt to varying environmental conditions, particularly the

available nutrient supply. Metabolic alterations and differential gene expression are very important in major cell decisions and are often epigenetically driven. Recently, a new mechanistic link between metabolic flux and the regulation of gene expression was found, which operates via the moonlighting of metabolic enzymes in the nucleus. This moonlighting facilitates the nuclear delivery of unstable or membrane-impermeable metabolites, including key substrates for epigenetic processes, such as acetyl-CoA, which is used in histone acetylation (Boukouris et al. 2016). A study of the transcriptional responses of *Aspergillus flavus* to oxidative stress showed that genes differentially expressed in response to increasing oxidative stress included those encoding antioxidant enzymes, antibiosis-related proteins, primary metabolism components, and secondary metabolite biosynthetic components. The expression of fungal development-related genes, including aminobenzoate degradation genes and conidiation regulators, was regulated in response to increasing stress (Fountain et al. 2016).

With the development of material technology, new materials have been applied to biology. Many materials can efficiently release biological molecules or therapeutic chemicals on demand when exposed to remotely controlled and safe external sources of energy, for example, in a system involving magnetic fields and DNA nanostructures. In this type of system, a magnetic platform combines two different kinds of core-shell magnetic nanoparticles: one loaded with enzymes and another loaded with a substrate-bound therapeutic biochemical (Zakharchenko et al. 2017). A DNA origami device has been developed that functions as a nanoscale vault: an enzyme is loaded in an isolated cavity, and the access to free substrate molecules is controlled by a multilock mechanism. This device was shown to control the enzymatic reaction catalyzed by an encapsulated protease.

Throughout the fermentation process, many physical means are used to control the rate of fermentation and regulate the direction of fermentation, such as ultrasound technology (Incharoensakdi and Velmurugan 2016; Ojha et al. 2016, 2017), microencapsulation technology (Kim EB et al. 2016; Patrignani et al. 2017), and electrofermentation (in which an imposed electrical field influences the fermentation environment and microbial metabolism in either a reductive or an oxidative manner to more selectively produce target materials; electrofermentation enhances microbial growth, limits the need for PH control, and increases carbon efficiency) (Moscoviz et al. 2016; Schievano et al. 2016; Awate et al. 2017; Xafenias et al. 2017). Other technologies, such as the screening and mutagenesis of fungi, optimization of microbial growth conditions, and pretreatment of substrates (e.g., as noted in Murali et al. 2017), have been extensively studied.

Export of extracellular enzymes

Extracellular enzymes are proteins with catalytic properties that are secreted from cells after synthesized intracellularly, for example, amylases, lipases, and proteases. These enzymes are primarily used to degrade complex compounds into small molecules that are easy to absorb. In addition, many enzymes can detect changes in the environment (Allison and Vitousek 2005; Luo et al. 2017). These enzymes play a crucial role in the metabolism of microorganisms. In both eukaryotic and prokaryotic cells, mRNA carries the genetic information that guides the initial synthesis of proteins on cytoplasmic ribosomes. In eukaryotic cells, these precursor proteins are then translocated to the endoplasmic reticulum, where the synthesis of secreted proteins (including extracellular enzymes) is completed; proteins are then transported to the Golgi, the plasma membrane, and finally, the cell membrane, through which they are secreted into the external environment. However, proteins secreted from prokaryotic cells can be exported into the growth medium. This transport is generally controlled by the amino-terminal signal peptide in the precursor protein and is supported by various pathways and mediators, such as the Sec (secretory) pathway (types I–VIII), the Tat (twin-arginine translocation) pathway, ABC (ATP-binding cassette) transporters, the FEA (flagellar export apparatus), the WSS (WXG100 secretion system), holins (hole-formers), and FPE (fimbrillin-protein exporter) (Von Heijne 1990; Von 1998; Tjalsma et al. 2000; Desvaux et al. 2009). These preproteins are first recognized by targeting factors and are transported to the translocation machinery in the cell membrane. Next, the polypeptide chain is moved through a protein channel via a translocation motor (whose power comes from the hydrolysis of nucleotide triphosphates). Finally, the signal peptide is removed, and the mature protein is released to fold into its native conformation (Tjalsma et al. 2004). Thus, the term "secretome" was coined to describe the components of the translocation systems and their substrates, including the exoproteome and other proteins released to the membrane (Desvaux et al. 2009; Dragana et al. 2016). By the exploitation of the secretome, some components of the Sec pathway may be targets for novel antibiotics (Economou 2002).

Therefore, we can regulate protein secretion according to the pathway characteristics mentioned previously. For example, we can improve enzyme secretion efficiency by optimizing protein synthesis and secretion (Song et al. 2017). Direct pharmacological control can also stimulate the secretion of proteins accumulated in the endoplasmic reticulum (Rivera et al. 2000).

The mechanisms underlying enzyme production and transportation are very complex. Many topics, such as identifying the signaling pathways that induce the production of specific enzymes and the means by which these enzymes pass through the cell wall, require further exploration.

Summary

Fermentation seems simple, but the mechanism is complex. Microbes are small but powerful. With the current constraints on energy and resources, concerns about population, food production, and pollution are increasingly pressing. As an important component of modern biotechnology, fermentation engineering has been widely used in industries, such as the food, pharmaceutical, energy, chemical, and environmental protection industries. The development of genetic engineering has renewed fermentation engineering. Furthermore, modernization, automation, and artificial intelligence technologies have provided new opportunities in fermentation engineering. In addition, research to better understand the regulation of metabolic mechanisms has further developed the fermentation ability of microorganisms. Particularly, regarding human health, the in-depth study of human microorganisms (especially the intestinal flora) has laid a new foundation for understanding the mechanisms of disease and treatment.

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Compliance with ethical standards

This article does not contain any studies with human or animal subjects.

Conflict of interest The authors declare that they have no conflict of interest.

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