1 Introduction

1.1 Historical Aspects

In everyday language, yeast is synonymous for *Saccharomyces cerevisiae* – a name given to a yeast strain discovered in malt in 1837 (Meyen) – in connection with making beer. This notion immediately calls to mind that yeast probably is the oldest domesticated organism – it was used for beer brewing already in Sumeria and Babylonia around 6000 BC. In parallel, *S. cerevisiae* strains were employed in wine production in Georgia and for dough leavening in old Egypt. In Egypt, beer was a common refreshment, and gifts of beer were awarded to civil servants and workers for extraordinary services. The scientific name "*Saccharomyces*" is derived from a word meaning "sugar fungus" in Greek, while the root for *cerevisiae* stems from Ceres, the Roman God of the crops.

The French word for yeast, *levure*, goes back to Latin *levare*, and so is *leaven*, simultaneously used for dough and yeast as an organism able to anaerobically release carbon dioxide during the baking process. The English word *yeast*, like Dutch *guist*, or even the German *Hefe*, is derived from a west-Germanic expression, *haf-jon*, meaning the potential to leaven. The provenance of the words used for beer in western European languages (French "bière," German "Bier," and Italian "birra") is not known, but in Roman languages, the expressions used for beer are directly related to the organism (*cerevisiae*), most obvious in the Spanish "cerveza" or in the Portuguese "cerveja." The Greek *zymi* (ζυμι) is used simultaneously for yeast and dough, and occurs as a root in words related to beer or fermentation. Thus, the modern expression "enzymes" (*en zymi* = in yeast), originally coined by Kühne in 1877, designates the compounds derived from yeast that are able to ferment sugar.

We owe the description of the microscopic appearance of yeasts in 1680 to Antoni van Leeuwenhoek in Leiden, who also observed bacteria and other small organisms for the first time. The observation that yeast budding is associated with alcoholic fermentation dates back to Cagnaird-Latour in 1835. In his work carried out during his tenure at Strasbourg University, Louis Pasteur correlated fermentation with yeast metabolism (1857). Pasteur's famous "*Études sur la bière*" appeared in 1876. Sometime later, two technical applications were based on this notion. In the late 1880s, E. Buchner and H. Buchner used cell-free fermentation to produce alcohol and carbon dioxide, and in 1915, Karl Neuberg used "steered" yeast fermentations to produce glycerol (unfortunately as a convenient source to convert it into trinitroglycerol). The knowledge of yeast physiology, sexuality, and phylogeny was later reviewed in a book by A. Guilliermond (Guilliermond, 1920).

In the 1950s, when yeast research entered a novel era of biochemistry, researchers became aware that many useful compounds could be isolated from yeast cells. Among the first companies to produce biochemicals from yeast (nonengineered at that time and obtained from a local Bavarian brewery) for the biochemical and clinical laboratory was Boehringer Mannheim GmbH in Tutzing (Germany). In a "semi"-industrial procedure, a variety of compounds were manufactured and commercialized, dominated by the coenzyme nicotinamide adenine dinucleotide (NAD). In many enzymatic tests (also called optical tests), NAD was an obligatory ingredient, because the increase of NADH generated from NAD by an appropriate enzymatic reaction (or coupled reaction) could be used to follow the timecourse of that reaction by spectrophotometry. This was, for the time being, also a helpful technique to determine enzyme levels or metabolites in the clinical laboratory. The methodology had been collected by Hans Ulrich Bergmeyer, a representative of Boehringer Company, who edited a famous compendium (16 volumes) of *Methods in Enzymatic Analysis* (Wiley & Sons).

1.2 Yeast as a Eukaryotic Model System

The unique properties of the yeast, *S. cerevisiae*, among some 1500 yeast species (a subgroup from 700 000 different fungi, which still may expand to over 3000 different yeast species) and its enormous "hidden potential" that has been exploited for many thousands of years made it a suitable organism for research. In fact, yeast was introduced as an experimental organism in the mid-1930s by Hershel Roman (Roman, 1981) and has since received increasing attention. Many researchers realized that yeast is an ideal system in which cell architecture and fundamental cellular mechanisms can be successfully investigated.

Among all eukaryotic model organisms, *S. cerevisiae* combines several advantages. It is a unicellular organism that,

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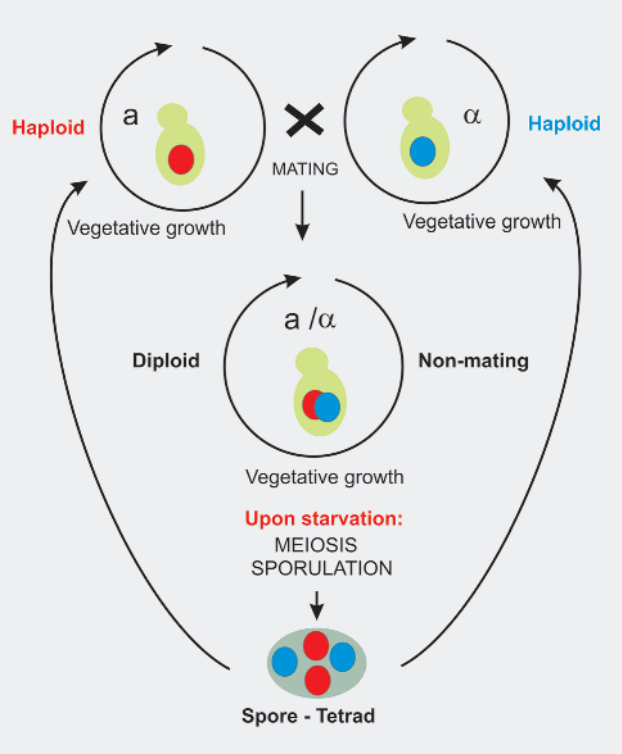

Fig. 1.1 Life cycle of *S. cerevisiae*. Vegetative growth is indicated by the circles.

unlike more complex eukaryotes, can be grown on defined media, giving the investigator complete control over environmental parameters. Yeast is tractable to classical genetic techniques. Both meiotic and mitotic approaches have been developed to map yeast genes (e.g., Mortimer and Schild, 1991). The first genetic map of *S. cerevisiae* was published by Lindegren in 1949 (Lindegren, 1949).

The life cycle of *S. cerevisiae* (Figure 1.1) normally alternates between diplophase and haplophase. Both ploidies can exist as stable cultures. In heterothallic strains, haploid cells are of two mating-types, **a** and α. Mating of **a** and α cells results iin **a**/α diploids that are unable to mate, but can undergo meiosis. The four haploid products derived from meiosis of a diploid cell are contained within the wall of the mother cell (the ascus). Digestion of the ascus and separation of the spores by micromanipulation yields the four haploid meiotic products. Analysis of the segregation patterns of different heterozygous markers among the four spores constitutes the "tetrad analysis" and reveals the linkage between two genes (or between a gene and its centromere). It was mainly Mortimer and his colleagues who undertook the considerable task of collecting and editing all of the genetic data accumulating in diverse laboratories (Mortimer and Hawthorne, 1966), up to the point when genetic maps could be replaced by physical maps. Prior to the start of the Yeast Genome Sequencing Project in 1989 (*cf.* Chapter 12), some 1200 genes had been mapped to the 16 yeast chromosomes, most of them attributable to particular gene functions and others to particular phenotypes only.

During molecular biology's infancy, around the late 1950s, yeast became a convenient organism to be used for the mass preparation of biological material in sufficient quantity or the mass production of other biological compounds. Yeast has a generation time of around 80 min and mass production of cells is easy. Simple procedures for the isolation of high-molecular-weight DNA, ribosomal DNA, mRNA, and tRNA were at hand. It was possible to isolate intact nuclei or cell organelles such as intact mitochondria (maintaining respiratory competence). Eventually, yeast also gained a leading position in basic molecular research. The possibility to apply genetics and molecular methods to an organism at the same time made yeast such a successful a model system. It was the technical breakthrough of yeast transformation (Beggs, 1978; Hinnen, Hicks, and Fink, 1978) that could be used in reverse genetics and for the characterization of many yeast genes that essentially fostered the enormous growth of yeast molecular biology.

The elegance of yeast genetics and the ease of manipulation of yeast substantially contributed to the fact that functions in yeast were studied in great detail using biochemical approaches. A large variety of protocols for genetic manipulation in yeast became available (e.g., Campbell and Duffus, 1988; Guthrie and Fink, 1991; Johnston, 1994). High-efficiency transformation of yeast cells was achieved, for example, by the lithium acetate procedure (Ito *et al.*, 1983) or by electroporation. A large variety of vectors have been designed to introduce and to maintain or express recombinant DNA in yeast cells (e.g., Guthrie and Fink, 1991; Johnston, 1994). The ease of gene disruptions and single-step gene replacements is unique in *S. cerevisiae*, and offered an outstanding advantage for experimentation. Further, a large number of yeast strains carrying auxotrophic markers, drug resistance markers, or defined mutations became available. Culture collections are maintained, for example, at the Yeast Genetic Stock Center (YGSC) and the American Type Culture Collection (ATCC).

The wealth of information on metabolic pathways and the characterization of the enzymes involved in biochemical processes, such as carbon, nitrogen, or fatty acid metabolism, as well as the underlying regulatory circuits and signal transduction mechanisms (e.g., roles of cAMP, inositol phosphates, and protein kinases), has been gathered by numerous yeast researchers. For cytology, studies on yeast contributed to the knowledge of mechanisms in mitosis and meiosis, biogenesis of organelles (such as endosomes, Golgi apparatus, vacuoles, mitochondria, peroxisomes, or nuclear structures), as well as cytoskeletal structure and function. Major contributions came from investigations into nucleic acid and genome structure, protein traffic and secretory pathways, mating-type switching phenomena, mechanisms of recombination, control of the cell cycle, control of gene expression and the involvement of chromatin structure, functions of oncogenes, or stress phenomena. There is too little space here to describe all the achievements made through "classical" approaches and the reader is referred to

detailed collections of articles in standard books (Strathern, Hicks, and Herskowitz, 1981; Broach, Pringle, and Jones, 1991; Guthrie and Fink, 1991).

The success of yeast as a model organism is also due to the fact, which was not fully anticipated earlier than some 20 years ago (Figure 1.2), that many basic biological structures and processes have been conserved from yeast to mammals and that corresponding genes can often complement each other. In fact, a large variety of examples provide evidence that substantial cellular functions are also highly conserved from yeast to mammals.

It is not surprising, therefore, that in those years yeast had again reached the forefront in experimental molecular biology. When the sequence of the entire yeast genome became amenable to thorough analysis, the wealth of information obtained in this project (Goffeau *et al.*, 1996; Goffeau *et al.*, 1997) turned out to be useful as a reference against which sequences of human, animal, or plant genes and those of a multitude of unicellular organisms under study could be compared. Moreover, the ease of genetic manipulation in yeast still opens the possibility to functionally dissect gene products from other eukaryotes in this system.

As it is extremely difficult to follow the contributions of yeast to molecular biology in a strictly chronological sequence *in toto*, I prefer to select particular fields of interest in which the yeast system has served to arrive at fundamental observations valid for molecular and cell biology in general.

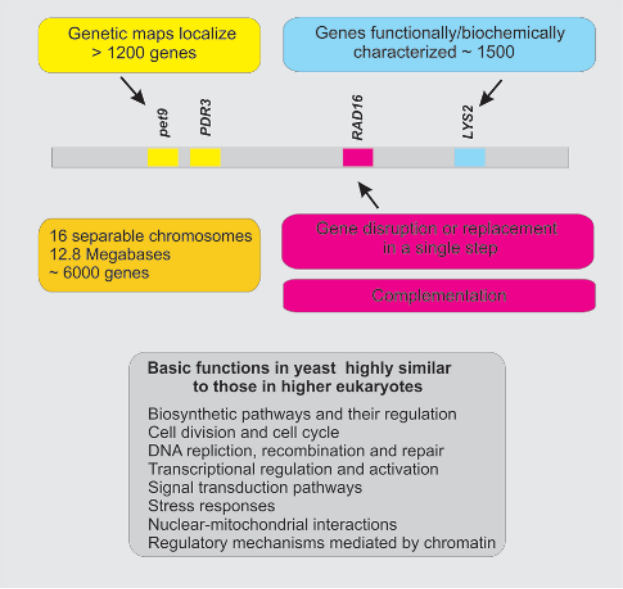

Fig. 1.2 Yeast around the start of the Yeast Genome Sequencing Project.

Summary

- There is no doubt that yeast, *S. cerevisiae*, is one of the oldest domesticated organisms. It has served mankind for thousands of years for baking bread, and making beer and wine. We owe a first glimpse of its nature to van Leeuwenhoek's microscopic description at the end of the seventeenth century. Still, the capability of yeast of fermenting sugar remained a mystery until the middle of the nineteenth century when fermentation could be correlated with yeast metabolism. Indeed, the expression "enzymes" describing the cellular compounds involved in this process is derived from this organism (*en zymi* = in yeast).

- Around 1930, it was recognized that yeast represents an ideal system to investigate cell architecture and fundamental cellular mechanisms, successfully competing with other model organisms such as *Drosophila* or *Neurospora*. Yeast combines several advantages: it has a propagation time comparable to bacterial cells and can be used for mass production of material, it is a unicellular eukaryote that can be grown on defined media, and it is easily tractable to classical genetic analysis including mutational analysis, thus allowing genetic mapping. No wonder then that yeast qualified as a model organism to study metabolic pathways by biochemical and genetic approaches at the same time. Another benefit offered by the yeast system was the possibility to isolate its subcellular components in sufficient quantity and to dissect their functional significance.

- As soon as molecular approaches became available in the mid-1950s, they were successfully applied to yeast. Finally, with the deciphering of its complete genome sequence in 1996, yeast became the first eukaryotic organism that could serve as a model for systematic functional analysis, and as a suitable reference for human, animal, or plant genes and those of a multitude of unicellular organisms. In fact, these comparisons provided evidence that substantial cellular functions are highly conserved from yeast to mammals.

Further Reading

Goffeau, A., Barrell, B.G., Bussey, H. *et al.* (1996) Life with 6000 genes. *Science*, **274**, 546, 563–567 (review).

Hartwell, L.H. (2002) Yeast and cancer. *Nobel Lecture Bioscience Reports*, **22**, 373–394. http://nobelprize.org/nobel_prizes/medicine/laureates/2001/hartwell-lecture.html.