Flexible throughout life by varying numbers of chromosome copies

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The yeast Saccharomyces cerevisiae, which normally occurs as a single cell, has the ability to form colonies as it is able to duplicate single chromosomes.

Baker's yeast is a popular test organism in biology. Yeasts are able to duplicate single chromosomes reversibly and thereby adapt flexibly to environmental conditions. Scientists from the Luxembourg Centre for Systems Biomedicine (LCSB) of the University of Luxembourg, in collaboration with colleagues from the US Institute for Systems Biology (ISB) in Seattle, have now systematically studied the genetics of this process, which biologists refer to as aneuploidy. The team's new insights will allow a new medical evaluation of aneuploidy, which is associated with certain diseases when it occurs in multicellular organisms. Their results appear in the scientific journal *PNAS*.

Chromosomes are molecular complexes built out of the genetic material DNA and proteins. They are duplicated before a cell divides and then shared between the daughter cells. In yeast cells, the cell division cycle takes only 1.5 hours – meaning yeast have a very rapid succession of generations. That makes them capable of adapting very quickly to changing environmental conditions. The yeast Saccharomyces cerevisiae, which normally occurs as a single cell, has the ability to form colonies featuring multicellular structures with divided responsibilities, meaning the cells differentiate to perform different tasks. "The genetic basis for this change in the yeast's external appearance has remained unknown until now," says Dr. Alexander Skupin, a major contributor to the cooperative project.

Detailed genetic analyses have now shown that the yeast cells individually multiply as many as six of their 16 total chromosomes during cell division, and can reverse this multiplication again. "The organization of cell colonies and phenotypic switching between different types of colonies becomes a lot more flexible and rapid with reversible aneuploidy than if it depended on random mutations in the genes," Skupin says. "The duplication of a single chromosome is enough to

change the yeast from a relatively smooth colony to one with what we describe as a 'fluffy' morphology."

If the cells reduce the copy number of this specific chromosome again – say upon another change in environmental conditions – then they turn back into a smooth colony. "So, the flexibility of yeast cells does not arise from the activity or inactivity of a single gene," project head at ISB, Dr. Aimée Dudley, explains. Rather gene dosage, which depends on the number of chromosome copies, is responsible for this: "If the chromosome is multiplied, then more copies of the same gene will be transcribed. That means it has a stronger effect than if it is active only once on one chromosome in the cell," Dudley concludes. These cells can change very rapidly.

The researchers now intend to find out what molecular mechanisms result from the activity of a gene transcribed from multiplied chromosomes. "Only then can we understand in detail how the different cell colonies arise," Skupin asserts.

Prof. Dr. Rudi Balling, director of LCSB, explains the medical implications of the new insights: "We have long known of aneuploidy in multicellular organisms. One well-known example is Down's syndrome, in which the 21st chromosome, or part thereof, exists in triplicate. Recently, however, the phenomenon has also been observed in cancer cells and has even been connected with brain development. Given the rapid succession of generations in yeast, we can use it as a model organism – and study the mechanisms of aneuploidy in much greater detail to find out whether we can derive from it new approaches for diagnosing and treating human diseases."

More information: Tana, Z. et al. Aneuploidy underlies a multicellular phenotypic switch, *PNAS* 2013. www.pnas.org/cgi/doi/10.1073/pnas.1301047110