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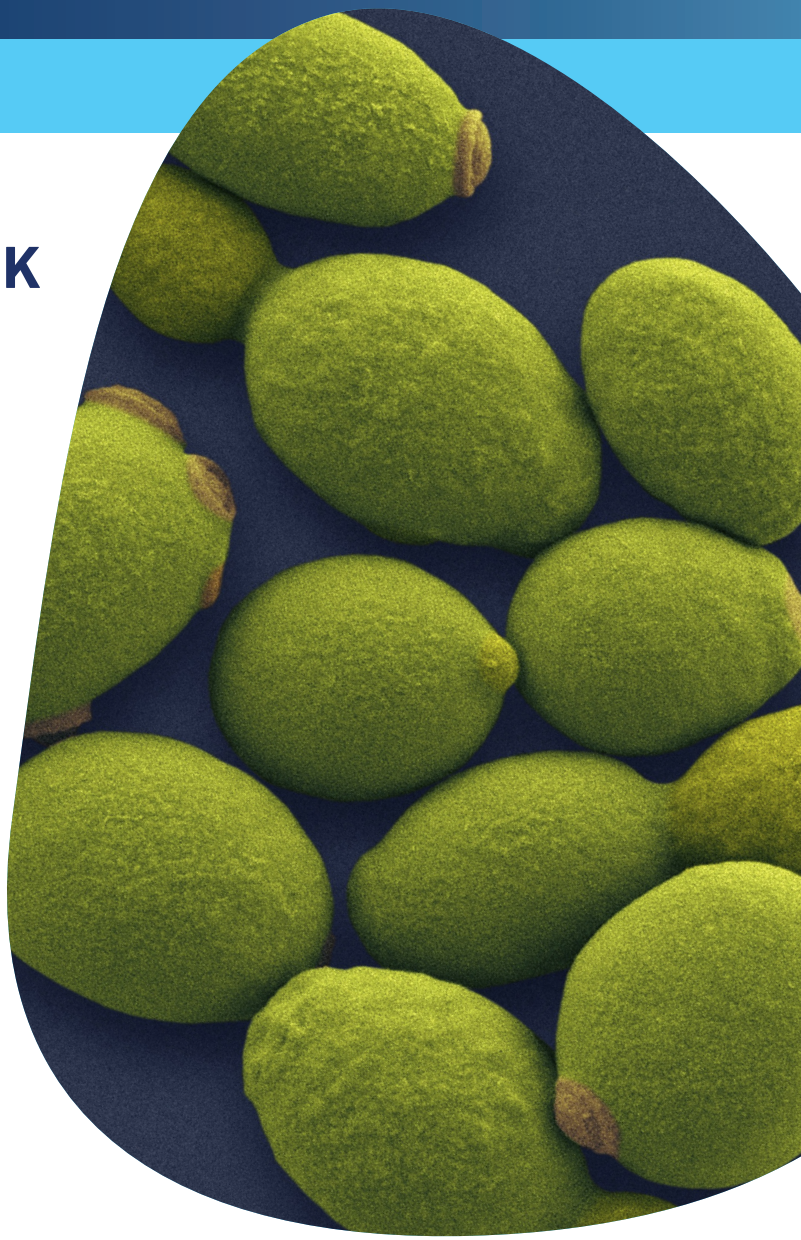
27–29 June 2018



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Poster Book Content

Poster Number: 01

Improvement of the cellobiose fermentation capability of engineered *Saccharomyces cerevisiae* through genome-wide perturbation library

Abstract

Saccharomyces cerevisiae is an industrially characterized microbe for ethanol production. However, wild type *S. cerevisiae* cannot ferment cellobiose, one of the most abundant components in plant biomass. In a previous study, we introduced a heterologous cellobiose assimilation pathway into *S. cerevisiae* to enable cellobiose fermentation. Because one molecule of cellobiose is cleaved into two molecules of glucose, we assumed that the ability of the engineered yeast to foment cellobiose was similar to that of the yeast to ferment glucose. However, the cellobiose fermentation efficiency of the engineered yeast was significantly lower than that of the glucose. Thus, we implemented a genome-wide perturbation library to discover gene targets to enhance the cellobiose fermentation ability of the engineered yeast. We found that the addition of β-glucosidase (*gh1-1*) gene led to the fastest cellobiose-fermenting transformant among those evaluated. We estimated that this occurred due to homologous recombination between the plasmids. Enzyme activity assay showed a significant increase of β-glucosidase activity in strains containing additional *gh1-1*, especially during early exponential phase, as compared to the β-glucosidase activity of the control strains. This result suggests that high expression levels of the *gh1-1* gene during early exponential phase are crucial for an efficient cellobiose fermentation.

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Poster Number: 02

Factors required for peroxisome biogenesis and inheritance converge at the peroxisomal membrane protein Pex3p

Abstract

Efficient compartmentalisation of a eukaryotic cell requires temporal and spatial control. Peroxisomes are single membrane bound organelles required for many biochemical reactions. In the budding yeast *S. cerevisiae*, peroxisomal inheritance depends on a balance between two opposing processes, transport and retention. Peroxisomes are transported to the daughter cell along actin cables via the myosin motor Myo2p or retained in the mother via Inp1p, a peripheral peroxisomal membrane protein. Inp1p interacts directly with the integral peroxisomal membrane protein Pex3p and tethers peroxisomes to the periphery of the cell. Pex3p is also known to bind to Pex19p, an interaction essential for peroxisome biogenesis, absence of Pex3p or Pex19p in humans results in a lethal Zellweger spectrum disorder.

In vivo and *in vitro* techniques uncovered a highly conserved region within Inp1p required for Pex3p binding. Bioinformatic analysis showed high similarity between this Inp1p motif and the known Pex3p binding motif of Pex19p. Overexpression of Inp1p results in an absence of peroxisomes and a range of *in vivo* techniques were used to accumulate data which suggests Inp1p and Pex19p directly compete for the same binding site on Pex3p.

Pex3p could be described as a hub, it binds a number of proteins required for processes which encompass the lifespan of a peroxisome, from biogenesis to inheritance and degradation. The underlying mechanisms of these processes remain unknown. This work shows that peroxisome biogenesis and inheritance appear to be coordinated by Inp1p and Pex19p binding to the same site on Pex3p via a similar protein motif.

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Poster Number: 03

Phenotypic profilling of double non-coding RNA deletion yeast mutants

Abstract

Background: Previously, we have performed a large scale phenotypic screening of the haploid non-coding RNA (ncRNA) deletion collection in a single condition (YPD, 30°) and observed significant variations in fitness. Here we present a large scale phenotypic analysis of double ncRNA mutants generated using Synthetic Genetic Array (SGA).

Aims: Screening of the double knock-out (KO) haploid library in various stress conditions to learn about the functions of ncRNAs.

Methods: Double KO mutants were generated using SGA by crossing a query strain (carrying single gene deletion) with the ncRNA KO collection. Generated double KO mutants have been screened in various conditions, including for example oxidative, temperature and respiratory stresses, and compared to the standard condition (YPD, 30°), and to the WT.

Results: In total, 27 query strains have been crossed with the library of ~450 single ncRNA mutants. Several gene interactions have been discovered in the standard condition showing either loss or gain in fitness, such as for example ΔSUT193-ΔSUT055 or ΔSNR13-ΔSUT347. Phenotypic analysis of double KOs in stress conditions revealed significant variations in fitness, such as for example ΔtI(AAU)P2-ΔSUT211 being lethal in oxidative stress but not in other tested conditions.

Conclusions: The SGA analysis on a small number of query strains showed a number of positive and negative genetic interactions, with a few being lethal. Phenotypic analysis of double mutants will help us determine the function of ncRNAs.

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Poster Number: 04

Distinct biological functions of fission yeast CSL transcription factors mediated by different DNA binding modes

Abstract

Cbf11 and Cbf12 proteins, members of the CSL transcription factor family, are involved in a wide range of cellular processes in the fission yeast *Schizosaccharomyces pombe* – e.g. they regulate cell adhesion and they have also been implicated in maintenance of genome integrity. Many of the target sites bound by CSL proteins *in vivo* do not contain any consensus CSL-binding element. CSL proteins may bind to their target loci in different ways, directly and also indirectly.

We aim to characterize the DNA binding modes of each CSL protein and link them with specific biological functions. To this end, we employed a point mutation in the CSL DNA binding domain (DBM = DNA binding mutation) which prevents canonical direct DNA binding. We introduced DBM directly into the *cbf12* chromosomal locus, and construction of a scar-less DBM mutation in the *cbf11* endogenous locus using the CRISPR/Cas9 system is in progress.

Using washing assays we have found out that the functional DNA binding domain of Cbf12 is necessary for the regulation of cell adhesion as Cbf12DBM cells lose the ability to adhere to agar. These results correlate with a pilot ChIP-qPCR study where we observed reduced Cbf12DBM ability to bind promoters of adhesion-related genes (*cbf12*, *gsf2* and *pfl7*). Our results further show that the ability of canonical direct DNA binding is not required for the role of Cbf12 in maintenance of genome integrity. Thus, DBM is a separation-of-function mutation and a useful tool to dissect the complex CSL roles in *S. pombe*.

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Poster Number: 05

Encoding yeast genomic diversity using variation graphs

Abstract

Linear reference genomes have been used traditionally to guide the assembly of sequence reads, in particular prior to variant calling. However, they are a poor representation against which to study an entire species and inadequate for organisms such as yeast which display a high level of sequence diversity. Variation graphs provide a more flexible reference structure in which the genomes of many individuals within a species population can be incorporated as variants within a bi-directed sequence graph. The use of variation graphs has been shown to mitigate reference allele bias and improve read mapping, thereby increasing the accuracy of variant calling.

The National Collection of Yeast Cultures (NCYC; http://www.ncyc.co.uk) contains approximately 4,000 diverse strains from over 530 species. A recent project has led to the whole genome sequencing of ~1,000 NCYC strains, with the large species group belonging to *Saccharomyces cerevisiae*. Here, we describe an evaluation of variation graphs as yeast reference structures. In particular, we use Illumina sequence read sets for both NCYC and third-party *S. cerevisiae* strains to quantify read mapping and variant calling, comparing the use of linear genomes, single-strain variation graphs and multi-strain variation graphs (i.e. pan genomes) as reference structures. In all experiments conducted, we show that multi-strain variation graphs improve both the quantity of sequence reads mapping to the reference structure and the quality of the mapping itself. These findings support the future use of variation graphs as reference structures for yeast genomes.

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Poster Number: 06

Investigating the role of yeasts as potential probiotics to control enteropathogenic bacteria in the chicken gut

Abstract

Background: *Saccharomyces cerevisiae* var. *boulardii* is a well-known yeast probiotic that has been effectively used in treating gastroenteritis. The main aim of this research is to isolate yeast like organisms from chickens to screen for novel strains with potential probiotic properties to be used in poultry feed for controlling enteropathogens in chicken gut.

Methods: general microbiological methods were used to isolate yeasts from chicken gut and environment. The isolated strains were biochemically identified by using API 20C AUX strips and investigated for their potential 'probiotic activity' against a common poultry pathogen known as Avian Pathogenic *E. coli* (APEC). The antibacterial activity of the yeast isolates was tested using agglutination and inhibition assays.

Results: 6 yeast strains were isolated from litter and small intestine of 48 broilers. The yeast isolates were identified by API 20C AUX biochemical testing as different species of *Candida* (*C. famata, C. rugose, C. boidinii, C. zeylanoides, C. dubliniensis and C. thermophile*). Most isolates showed positive agglutination whereas only one strain of *Candida famata* designated as E11 significantly ($P<0.05$) decreased the growth of the challenged bacterial strains when statistically analysed using Two Sample T-test assuming equal variances.

Conclusion: Suppression of APEC strains by E11 suggests that there is some form of chemical activity such as acid or toxic enzyme produced by this yeast as an antibacterial mechanism of action. This means that *C. famata* has an antagonistic activity against *E. coli* and might work as a potential probiotic.

Maha Aldeieg, Martin Woodward

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Poster Number: 07

Probing the Mitotic Exit Network with Synthetic Physical Interactions

Abstract

The Spindle Pole Body (SPB) is the microtubule organizing centre of budding yeast and acts as a signalling hub, controlling the timing and fidelity of cell division. The dynamics of protein regulation by the SPB are not fully understood; particularly in terms of which proteins are recruited there, when and why. One way to study these protein associations is to use Synthetic Physical Interaction screens, which make use of a strong interaction between GFP and GBP (GFP Binding Protein) to force tagged proteins to physically interact. Using a library of GFP strains, these screens may be performed in a high-throughput manner, allowing over 4,000 forced interactions to be tested. Proteome-wide screens with structural SPB proteins found that forcing Mitotic Exit Network (MEN) proteins to interact with the SPB protein Nud1 caused a slow growth phenotype. The screens also identified the mitotic phosphatases PP1 and PP2A as causing a growth defect when targeted to Nud1, potentially indicating a role at the SPB for these complexes. Further screens were conducted with the SPB component Spc72 and the temperature sensitive allele nud1-2. Comparison of these screens suggest the regulation of the MEN protein Tem1 at the SPB depends specifically on interaction with Nud1. These findings offer an insight into the role of the SPB as a signaling scaffold in the MEN and indicate an active role for SPB proteins in the regulation of the MEN.

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Poster Number: 08

Tracking of metabotype heterogeneity of *Saccharomyces cerevisiae* at a single cell level via microfluidics

Abstract

In previous work it has been shown that metabolic exchange in *Saccharomyces cerevisiae* can be generated in auxotrophic strains by progressive loss of plasmids carrying the complementing metabolic markers (Self-establishing metabolic cooperating communities, SeMeCos). These SeMeCo demonstrated growth efficiency and biomass formation as well as extracellular metabolite concentrations akin to the wild type under nutrient limited conditions. This indicates that similar cooperation also occurs naturally. However, upon co-culturing two, in theory complementing, auxotrophic strains they are unable to compensate for each others metabolic deficiencies. We investigate how metabolic heterogeneity, and the associated cooperation, can evolve in genetical homologous *S. cerevisiae* communities

We adapted a microfluidic device intended for the visualization of cell monolayers, which enables us to track the budding time on a single cell level under different nutrient availabilities. This allows us to study metabolic heterogeneity and the effects of cooperation in a highly controlled environment. Adjustment of the flow rate of the chamber can simulate sharing and non-sharing conditions. Alongside auxotrophic and prototrophic strains, combining the SeMeCo model with fluorescent labelling will allow us to track cells of known metabotypes in this system.

The study of metabotype heterogeneity in single-cellular eukaryotes like *S. cerevisiae* can help advance the understanding of the high variability of cellular metabolism, with possible implications for the evolutionary development of multicellular eukaryotes.

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Poster Number: 09

Uncovering novel genetic mechanisms of the DNA damage response using a yeast QTL analysis approach

Abstract

Genotoxic stress (DNA damage) is paradoxically both a hallmark of cancer and target in genotoxic therapies. DNA damage response differs from cell to cell and person to person. Further insights into the mechanisms of genotoxic response are challenging to obtain through animal studies. DNA damage response renders a quantitative (complex) trait, as many other traits in physiology and disease, which depend on multiple loci and on genetic and environmental interactions.

We sought to develop and employ QTL-mapping approaches in yeast to uncover novel genes and pathways influencing DNA-damage responses. Our QTL-mapping provides advancements by using: the unique population derived from 4 wild isolate strains founders (Cubillos et al, 2009), densely mapping unites of 16K SNPs, our adapted R/QTL script: Shmootl and a sensitive and our high-throughput phenotyping platform: PHENOS (Barton, et al, 2018). Our analyses included X-Ray irradiation, phleomycin, hydroxyurea and methyl methanesulfonate treatments. There was minimal overlap in the genetic architecture among genotoxic agent responses mirrored by the low correlation value and limited overlap across agents' QTL.

Through our poster we would highlight findings of our validation experimental phase. *LIF1, SOK2, DUF1* are genes that appeared as single-gene-QTL and validated across a number of treatments. We identified examples of background-specific and treatment-specific liabilities to the same genetic. Moreover, we unravelled a potential novel role of protein mannosylation in genotoxic-stress response.

Our study underscores the complexity in understanding the inter-individual variation in cancer predisposition and genotoxic therapy response. Genetics insights are provided to pursue gene-focused assays in human-cell studies.

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Poster Number: 10

Yeast Quantitative Genetics to study Human Drug Response

Abstract

Understanding the genetic basis of variability in drug responses is a step towards personalised treatments. This study explores the genetic variation in responses to chemotherapeutic and cancer chemopreventive agents by Quantitative Trait Locus (QTL) mapping in *Saccharomyces cerevisiae* yeast and extrapolates findings to humans. This was possible due to the conservation of genes between these two organisms. It is also enhanced by the whole genome sequencing of the naturally variable wildtype yeast isolates in 2009.

Here, we aim to test whether we can use the yeast QTL system to identify genetic variants influencing the differences in drug responses to agents implicated to benefit cancer patients. This sophisticated system has yielded interesting findings and shed light into different pathways by which the agents can exhibit their anti-cancer properties.

We followed a multi-parent QTL mapping approach. Yeast segregants from the SGRP-4 project were used and phenotyped by PHENOS which quantified yeast growth in different drug treatments. These phenotype values were then analysed along with their genotype data by linkage-based gene mapping using the R-QTL software package. Various database tools were then used to identify and annotate genes controlling the phenotype of interest.

Screening results have shown interesting novel outcomes and some hits that have been previously supported by the literature providing validation of this screening approach. Conserved genes identified will be studied in human cell culture to understand the biological and potential clinical relevance. This study can identify unexplored therapeutic opportunities for biomarker development of drug response and applications in pharmacogenomics.

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Poster Number: 11

Ras signalling regulates nutrient acquisition and senescence in*S. cerevisiae*

Abstract

Ras proteins are small GTPases that function as regulatory switches linking external environmental stimuli with intracellular effectors to control cell growth and proliferation. Mutations that lead to the constitutive activation of Ras proteins are associated with the development of several human cancers. The localisation of Ras is crucial for its function and this is controlled by post-translational modifications. We have identified that the phosphorylation of Serine^{225} plays an important role in the localisation and function of Ras2p in *S. cerevisiae.* Modification of this residue leads to changes in Ras localisation that drives cells towards a senescence phenotype via a previously unidentified cAMP/PKA signalling pathway. We propose that the control of Ras signalling regulates the ability of cells to acquire nutrition from growth media, which in turn has a significant influence upon the viable cell fraction within a population.

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Poster Number: 12

Genome-wide profiling of histone modifications in *Candida albicans* using ChIP-Seq.

Abstract

Candida albicans is a highly successful human pathogen, due in great part to its genomic plasticity and instability. Clinical isolates are often characterised by gross chromosomal rearrangements and aneuploidy, which can confer anti-fungal drug resistance due to altered copies of specific genes. Mechanisms underlying *C. albicans* genome plasticity are still largely not well understood. However, it is clear that DNA repeats play an essential role in this process. In many organisms, repetitive DNA regions, such as those found at telomeres, centromeres and the rDNA locus, are assembled into transcriptionally repressed chromatin, known as heterochromatin. The presence of heterochromatin at these regions suppresses recombination and promotes stability of the genome.

We have shown previously that, contrary to other model systems, *C. albicans* DNA repeats are assembled into distinct chromatin states differentially regulating transcription and recombination. To gain a deeper understanding of the role of histone modifications as epigenetic regulators of genomic stability in this organism, we have performed for the first time genome-wide profiling of histone modifications H2AS129p, H3K4me3, H3K9ac and H4K16ac in a BWP17 (wt) strain. We have also performed ChIP-Seq analyses of H3K4me3, H3K9ac and H4K16ac in histone modifying enzyme deficient mutant strains. Our analyses reveal that chromatin-mediated epigenetic mechanisms strongly influence transcriptional regulation and genomic stability in *C. albicans*.

Jordan Price, Alessia Buscaino

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Poster Number: 13

Investigating interactions between *Candida albicans* and *Pseudomonas aeruginosa* in a clinically relevant mixed biofilm model

Abstract

Many bacterial and fungal organisms, including opportunistic pathogens, grow as sessile, surface-associated communities known as biofilms. Biofilms confer many advantages to the organisms within them, including increased resistances to sheer forces, host immune responses and antibiotics. Biofilms that grow on medical devices such as tracheostomy tubing, can act as a source of future infection and as a threat to patient health. Many investigations have been carried out into the formation of biofilms, but fewer into the interactions between species in mixed biofilms – which appears to be the more clinically relevant scenario.

Candida albicans is a potentially pathogenic yeast that can be found within mixed biofilms and is known to interact with the gram negative bacterial pathogen *Pseudomonas aeruginosa*. Interactions between the two species are documented and both organisms, and their interactions, have clinical relevance. Here we investigate the interaction with respect to the colonisation of plastics commonly used in medical devices.

The initial stage of biofilm formation is that of attachment, when planktonic cells bind irreversibly to a surface (such as the PVC wall of a tracheostomy tube). Our initial investigations strongly suggest that the presence of *P. aeruginosa* promotes the attachment of *C. albicans,* in both ambient air and air containing a high percentage (~5%) of CO_2 (similar to exhaled air). Elucidation of the mechanisms and factors of this interaction may point to improved methods of prevention or control of biofilm growth on prostheses such as tracheostomy tubing.

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Poster Number: 14

Quantitative genetics and biotechnological uses of novel yeast hybrids

Abstract

Interspecies hybridization increases the genetic variations in natural yeast populations and it is also an important mechanism for the origin of novel lineages and adaptation to new environments. Hybrids among yeast species and strains are common and are key players in many industrial applications including various fermentations to produce alcoholic beverages. However, hybrids being sterile can't be used for strain improvement via breeding. In this study, we aim to overcome the hybrid sterility by generating allotetraploid (4n) strains, which can undergo meiosis and produce viable diploid (2n) hybrid spores. We created interspecific hybrids of *S. kudriavzevii* × *S. cerevisiae* and *S. jurei* × *S. cerevisiae* yeast strains possessing different mitochondria. We showed that upon meiosis the spore viability of the engineered *S. cerevisiae*×*S. jurei* tetraploids was 80-90% and of *S. cerevisiae*×*S. kudriavzevii* tetraploids was 80%. The fitness of the progeny with randomly assorted traits is tested in different environments and in the presence of different stressors to select the best performing hybrids. The genome of improved strains is sequenced and QTLs underpinning specific traits will be uncovered.

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Poster Number: 15

QTL analysis in yeast: identifying candidate therapeutic targets for Huntington's disease

Abstract

Huntington's disease (HD) is a hereditary neurodegenerative disease caused by the expansion of a CAG trinucleotide repeat in the huntingtin HTT gene. Though the number of repeats strongly correlates with severity of disease, there is still great variability in disease presentation among individuals with the same number of repeats. In order to find the genetic modifiers responsible for this variability, we plan to perform quantitative trait loci (QTL) analysis in yeast. Saccharomyces cerevisiae has been successfully used in the past to identify modifiers of mutant HTT toxicity, and thus will serve as a robust model for these analyses. To select our candidate strains we assessed the effect of mutant mHTT on 14 natural yeast isolates containing most of the genetic variation of the species (1 - 2 SNPs per 100 base pairs) and chose the ones with the most extreme phenotypes. We plan to intercross these strains to generate a large population of stains with a new combination of alleles that will be used for QTL analysis. The effect of mHTT toxicity on the growth of the descendants will be analysed by PHENOS, a high-throughput tool which facilitates QTL analysis with yeast, and strains will be genotyped using Next Generation Sequencing (NGS). SNP segregation frequencies of resistant and sensitive strains will be compared with the SNP frequencies of the whole population. Any difference found on the segregation of the SNP on resistant or sensitive strains will indicate the location of a possible modifier gene. These modifiers will be further validated in yeast via various approaches and ultimately tested in fruit fly models of HD.

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Poster Number: 16

Improving C5 Sugar utilisation in yeast for biotechnology

Abstract

Budding yeast is the microbe of choice for many biotechnological and industrial purposes. In second generation processes using lignocellulosic feedstocks, yeast fail to utilise almost half of the sugars available, C5 sugars such as xylose and arabinose. A screen of a wide variety of S. cerevisiae and its close relatives has identified some strains that can grow, albeit slowly, on xylose as a sole carbon source. We have developed genetic tools for increasing the rate of evolution in these isolates and crosses between them in order to increase the ability to metabolise five carbon sugars. Subtelomeres often harbour many genes and gene families involved in carbon source utilization and these are a target of increased evolution. We can enhance the rate of copy number variation changes at subtelomeres, recombination between subtelomeric homologous sequences and the mutation rate in terms of base substitutions. All of these are under control of a genetic switch allowing a return to the wild type rates of evolution once a desired state is attained.

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Poster Number: 17

Understanding the function of mitochondrial i-AAA protease Yme1

Abstract

Mitochondrial AAA (ATPases associated with diverse cellular activities) proteases are key components of the mitochondrial protein quality control systems. Mutations in these proteases cause mitochondrial dysfunction and diverse neurodegenerative disorders. There are two mitochondrial inner membrane anchored AAA proteases, i-AAA and m-AAA, which are highly conserved. i-AAA protease Yme1 is the only ATP-dependent protease with the functional domain located in the mitochondrial intermembrane space in yeast. Yme1 has dual functions: as a protease it degrades damaged and unwanted inner membrane and IMS proteins to prevent their potentially deleterious accumulation in mitochondria; as a chaperone it prevents aggregation of misfolded or unfolded proteins. We showed previously that unassembled Tim10 of the intermembrane space was effectively degraded by Yme1 in vivo but much less efficient for Tim10 homologue protein Tim9 (spiller et al. Biosci Rep. 2015). To further our understanding of the function and molecular mechanism of Yme1, in this study, we investigated how YME1 deletion affects yeast chronological life span and mitochondrial function. Our results show that Yme1 plays an important role in maintaining the chronological life span of yeast and mitochondrial respiration, as well as in preventing protein aggregation and oxidative stress.

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