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Growth and development: eukaryotes

Judith Berman

Judith Berman received her Ph.D. at the Weizman Institute of Science, Israel. Her early independent work concerned *S. cerevisiae* telomeres and chromatin. Her studies of *Candida albicans* began with a focus morphogenesis and cell-cycle progression. She now researches centromere dynamics and genome instability and their responses to antifungal drug stress. She is currently Distinguished McKnight University Professor in the Department of Genetics, Cell Biology and Development at the University of Minnesota.

Eukaryotes generate diverse responses to their environment using both genetic and epigenetic mechanisms. Our focus on eukaryotes in this issue of *Current Opinion in Microbiology* centers on these mechanisms, primarily as they are executed by fungi, a diverse group of organisms with a high degree of genotypic and phenotypic plasticity. Here we gathered ten experts to focus on mechanisms for generating new phenotypes, many of them heritable. The topics are diverse and range from mechanisms of sexual, parasexual and asexual cellular interactions to their use of non-Mendelian mechanisms to generate diversity in the proteome, transcriptome or genome, and to their use of transcriptional and post-transcriptional circuits to regulate cell identity, cell morphology and the relationship between the two.

We start with a focus on cell-cell interactions with two chapters on different aspects of sex in fungi and one on asexual cell fusions. **Clifford Zeyl** provides an evolutionary perspective on the role of sex in pathogenic fungi, highlighting some of the new discoveries of sexual cycles in organisms that were previously thought to be asexual. In light of the prevalence of homothallic mating, he suggests that despite the absence of an increase in allelic diversity, the benefit of homothallic sex may arise through recombination events that result in the homozygosis of adaptive mutations. **Racquel Sherwood** and **Richard Bennett** review meiosis and parasexual processes in *S. cerevisiae*, *Schizosaccharomyces pombe*, *Candida albicans* and *Candida lusitanae*, highlighting the similarities and striking differences between them.

In the third chapter, **Nick Read** together with **Alexander Lichius**, **Jun-ya Shoji** and **Andrew Groyachev** then highlights the process of self-self hyphal fusion occurring between genetically identical individuals. They discuss exciting new results in which conidial anastomosis tube formation involves a 'ping-pong' oscillation mechanism that mediates the communication between two hyphal tips germinating from conidia. The process ensues over a short time frame that most likely does not involve regulation at the transcriptional level.

We then move to four chapters that delve into a range of different epigenetic mechanisms from centromere specification to prion dynamics. First, **Kojiro Ishii** reviews new work on how centromere position is determined epigenetically. While *S. cerevisiae* has point centromeres, which require a specific DNA binding site, most other organisms have regional centromeres in which centromere establishment and maintainance is epigenetically determined. New work

on neocentromere formation at ectopic loci reveals that *S. pombe* centromeres must form at telomeres, which can assemble heterochromatin, while *C. albicans* centromeres do not require heterochromatin but do form within large intergenic regions that have moderately repetitive DNA sequences in close proximity. In addition, while DNA sequence divergence is higher at centromeres than at other loci, the mechanism for generating it remains a mystery.

Next, **Suzanne Sindi** and **Tricia Serio** discuss mechanisms of prion dynamics, in which the conformation of a protein with the ability to form prions becomes a self-replicating entity, with potentially profound effects on phenotypic outcomes. They use mathematical modeling to illustrate how the size of protein aggregates in the prion state affects the ability to efficiently transmit the prion-associated phenotype to progeny cells. They demonstrate that smaller sized aggregates are more effectively propagated, such that they are maintained during many cell divisions.

Manuel Santos, together with **Gabriela Moura** and **Laura Carreto**, review codon ambiguity as a completely different set of mechanisms for generating diversity at the protein level. They discuss t-RNA mischarging as a way to reassign UGA and UAG stop codons to selenocysteine and pyrrolysine and also outline tRNA-dependent asparagine, glutamine, and cysteine biosynthesis in organisms without tRNA synthetases for these three amino acids. They outline their elegant work with *Candida albicans* and related members of the clade that uses CUG codons to specify serine instead of leucine. Interestingly, these organisms tolerate occasional misincorporation of leucine at CUG codons and, under stress conditions, misincorporation levels are higher and lead to phenotypic effects such as increased filamentous growth. Intriguingly, the phenotypic defects exposed by CUG misincorporation resemble defects seen with the [PSI⁺] prion in *S. cerevisiae*, which causes defects in translation termination, the production of aberrantly long proteins. Finally, they discuss ‘translational stress mutagenesis’ as an indirect mechanism in which defects in translation result in elevated mutation rates that generate advantageous phenotypes.

In the last chapter on epigenetic mechanisms, **Mariusz Nowacki** and **Laura Landweber** discuss non-Mendelian inheritance in ciliates. They describe RNAi-like mechanisms as well as homology-dependent maternal effects that direct genome rearrangements, which occur in approximately one-third of the internal eliminated sequence (IES's) in *Paramecium*. These sequences are eliminated from the vegetative macronucleus, by a trans-nuclear genome sequence comparison that apparently protects homologous sequences from degradation. They also describe their exciting new work on RNA-mediated epigenetic reprogramming in *Oxytricha* where the transient RNA transcribed from the maternal somatic genome templates DNA rearrangements and ‘unscrambling’, which eliminates ~ 95% of the germline genome, retaining primarily the coding sequences. This provides a mechanism for the stable inheritance, from somatic genome to somatic genome, of spontaneous mutations that are perpetuated without requiring alteration of the germline genome.

In the last section we have three chapters that focus on mechanisms that regulate morphogenesis and development. In Chapter 8, **Yue Wang** reviews connections between cyclin dependent kinases, the Cdc42 GTPase module and the morphogenetic decision in both *S. cerevisiae* and *C. albicans*. He describes the role of cyclins in regulating polarized growth through phosphorylation of proteins that regulate Cdc42 activity, phosphorylation of septin ring components such as Cdc11p, and, in *C. albicans*, the action of the hyphal specific CDK^{Hgc1} in phosphorylating Egl1, a transcription factor that promotes filamentous growth, in part by repressing expression of genes that mediate cell separation. Finally, he highlights connections between cell cycle checkpoints and morphogenesis in both *S. cerevisiae* and *C. albicans*.

In Chapter 9, **Matthew Loese** and **Sandy Johnson** review the white-opaque transition, a unique developmental switch between two cell types found in *C. albicans* and very closely related species. These two cell types have distinctive features including different cellular and colonial morphologies, metabolic states, mating competence, interactions with the immune system and host niches in which they grow and/or form biofilms. The white and opaque state are heritable, yet a switch between cell types can be triggered by environmental conditions such as temperature, reagents that cause cell cycle delays or the availability of oxygen. The white-opaque switch is unique to *C. albicans*, yet is regulated primarily at the transcriptional level by a positive feed-back loop featuring the WOR-1 transcription factor, which is a member of a large family of fungal proteins, some of which also have critical regulatory roles.

Finally, Hugo Lavoie, Hervé Hogues and Malcolm Whiteway provide an overview of transcriptional circuitry that regulates metabolic pathways including fatty acid metabolism, phospholipid synthesis, carbohydrate metabolism, amino acid biosynthesis and ribosomal protein production and assembly. These pathways have become rewired over evolutionary time scales. Some networks, including those affecting the expression of the highly conserved ribosomal proteins, have undergone complete rewiring with replacement of many cis-regulatory components and trans-acting factors. In contrast, pathways in less obviously critical pathways are highly conserved or underwent only subtle changes, in which similar transcription factors are utilized, sometimes with some changes in their interactions or ultimate effects on gene expression. One intriguing observation is that some transcription factors in one organism have become regulators of chromosome components such as centromeres or telomeres. Nonetheless, a major unanswered mystery remains: How did large-scale rearrangements of cis-regulatory elements and trans-acting factors that regulate highly conserved, essential processes evolve in a manner that was heritable and adaptive.

In summary, the ten reviews presented here explore several mechanisms by which fungi and other eukaryotic microorganisms generate diversity at the DNA, RNA and protein level and how they establish and/or maintain that diversity. They use a broad range of mechanisms, many of which we are only beginning to be explored. It is our hope that these reviews remind us that the central dogma of molecular biology is only a starting point and that heritable phenotypes can be established and maintained through a diverse set of alternative mechanisms.