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Thematic Minireview Series: Complexities of Cellular Signaling Revealed by Simple Model Organisms*

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All cells discriminate environmental signals and generate appropriate intracellular responses. Our understanding of these signal transduction mechanisms has benefitted from studies across the kingdoms of life, from fungi and fish to mice and men. This thematic minireview series examines lessons learned from three of the simplest (and best understood) eukaryotic model organisms. The first article focuses on the mating pheromone pathway in budding yeast *Saccharomyces cerevisiae*. The second describes stress-mediated signaling in the roundworm *Caenorhabditis elegans*. The third outlines some of the signaling pathways that dictate growth and development in the fruit fly *Drosophila melanogaster*. Each system has provided unique insights into hormone and neurotransmitter signaling mechanisms, in particular those mediated by the MAPKs. The advances described in these articles will continue to improve our understanding of human physiology and pharmacology.

There is a long tradition of cellular and molecular biology research in simple eukaryotes including yeast, worms, and flies. Each organism has distinct advantages for conducting and interpreting genetic experiments. All have much to offer the broader signaling community.

Yeast has been popularized in large part because it has the ability to grow stably as a haploid, which is especially useful for the identification of recessive gene mutations. Homologous recombination is unusually efficient, which has allowed the systematic disruption of most non-essential genes and regulated expression of most essential genes. Nearly all of the genes have been fused to the green fluorescent protein, for the purpose of visualization in live cells, and have been affinity-tagged, for the purpose of rapid and large-scale protein purification.

Studies in yeast have led to some important advances in signaling, particularly in the area of signal amplification, cross-talk, and desensitization. Much of the work has focused on a signaling pathway required for mating of the two haploid cell types, known as **a** and α. The mating pathway is composed of a G protein-coupled receptor and ERK family MAPK similar to those found in humans. This pathway is the topic of the first minireview, authored by Christopher G. Alvaro and Jeremy Thorner (1) at the University of California, Berkeley.

Another versatile model is the nematode *Caenorhabditis elegans*, which has gained much traction for the study of neural development. It is one of the simplest organisms with a nervous system and it exhibits characteristic neurological behaviors including mechanosensation, memory, and even sleep. Given that the organism is transparent, it is possible to visualize all cells (including all 302 neurons) during development. This feature led to the startling realization that many cells are culled through apoptosis during normal growth and development.

Signaling in *C. elegans* is the topic of the second minireview, authored by Matthew G. Andrusiak and Yishi Jin at the University of California, San Diego, and Howard Hughes Medical Institute (2). Their study focuses on two stress-activated MAPKs, JNK and p38. Although ERK is usually activated by hormones, JNK and p38 are activated by adverse stimuli such as osmotic stress, heat shock, cellular damage, and infection. The signaling role for p38 was first revealed through genetic screens for mutants defective in nervous system development, but later studies revealed a requirement for p38 after infection by the opportunistic pathogen *Pseudomonas aeruginosa*. Other screens revealed a role for stress-activated MAPKs in olfactory memory, where the organism learns to associate chemical cues with positive or negative experiences. The JNK pathway is needed to detect nutrient stress; it has long been known that dietary restriction increases the lifespan of the organism.

Signal transduction in *Drosophila* is the subject of the third minireview, authored by Ben-Zion Shilo (3) of the Weizmann Institute of Science. *Drosophila* was one of the first model organisms to gain widespread popularity, and it is the source of much of what we know today about the genetic basis of heredity and development. This particular review considers multiple aspects of cell signaling, ranging from molecular details of ligand-receptor (*e.g.* Wnt-Frizzled) interaction to the signaling function of cellular structures such as cytonemes and nanotubes. Collectively, these features provide the spatial and temporal cues necessary for proper development.

All three organisms have a rich history of innovation and discovery. All have had a similar trajectory, with studies becoming progressively more mechanistic over time. Early genetic studies were often done one gene at a time, typically with some qualitative phenotype as the readout. Later genome sequencing efforts led to more systematic screens and more quantitative measures of function. When just a small percentage of the yeast genome is required for proper MAPK function, and the importance of each gene can

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be ranked in some quantitative way, it is far easier to determine which proteins merit further investigation.

Gene silencing and editing technologies are now used routinely in animal cells. Nevertheless, there will always be a role for simpler alternatives. Current research is benefitting from advances in single cell analysis including single cell sequencing, reporters of activity, and metabolomics. Such technologies are usually "beta-tested" in simple organisms before they are implemented in animals. Those who keep abreast of these advances will surely benefit from the knowledge and the tools they provide. It is our hope that this series will promote communication by scientists working on the disparate branches of the tree of life.

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