Immunity: Ars2 suppresses viral infection

Through innate immunity, organisms mount an immediate and nonspecific attack against infectious pathogens using mechanisms that are largely conserved from invertebrates to mammals. In healthy plants and animals, microRNAs (miRNA) influence gene expression by regulating the cleavage of mRNAs. Some innate immune systems also use RNA interference to suppress infection by targeting viral RNA for degradation. Sabin et al. have now identified Ars2 as a key regulator of the small interfering RNA (siRNA) pathway, where it is required for normal miRNA-mediated silencing and the innate immune response to RNA virus infection. Loss of Ars2 increases susceptibility to RNA viruses in cells and in flies. Ars2 interacts directly with key components of the inhibitory RNA processing machinery, Dicer and Drosha/Pasha, to enhance siRNA processing. Although Ars2 is conserved in mammals, it is not well characterized. This work in Drosophila suggests that the Ars2 homologue and RNA interference may also limit replication of RNA viruses in higher organisms.

Sabin, L. R., Zhou, R., Gruber, J. J., Lukinova, N., Bambina, S., Berman, A., Lau, C. K., Thompson, C. B. and Cherry, S. (2009). Ars2 regulates both miRNA- and siRNA-dependent silencing and suppresses RNA virus infection in Drosophila. *Cell* **138**, 340-351.

Cancer: yeast as a model for breast cancer

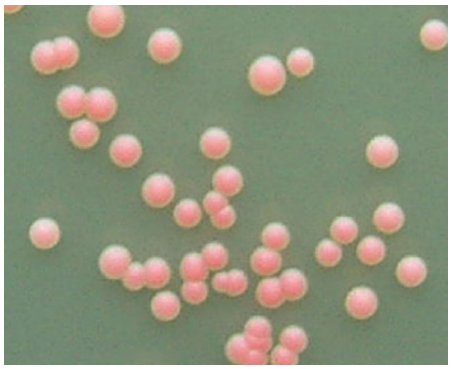

Image reproduced from *PloS Biol*. (Li et al., 2009).

One challenge to understanding cancer is identifying the meaningful genomic mutations that contribute to disease. Minichromosome maintenance (MCM) proteins are important regulators of the early steps in DNA replication. A mutation in the MCM4 protein, Chaos3, destabilizes the protein, inducing chromosome breaks and causing aggressive breast adenocarcinoma in female mice. A study by Li et al. shows that this mutation also causes genome instability and improved growth of the yeast, *Saccharomyces cerevisiae*. The yeast growth phenotype emerges simultaneously with aneuploidy, but aneuploidy does not contribute to the growth characteristics. Importantly, the growth phenotype induced by $MCM4^{Chaos3}$ in yeast cells involves mutations in only a few genetic loci, suggesting that it may be possible to define the growth-enhancing mutations that contribute to cancer in this simple model.

Li, X. C., Schimenti, J. C. and Tye, B. K. (2009). Aneuploidy and improved growth are coincident but not causal in a yeast cancer model. *PLoS Biol.* **7**, e1000161.

Stem cells: iPS mice

Image reproduced from Richmond and Su (2008). *Dis. Model. Mech.* **1**, 78-82.

Induced pluripotent stem (iPS) cells have successfully produced mice in experiments by two independent research groups, proving that, by expression of four key transcription factors, mature cells can be reprogrammed to have a similar pluripotency to embryonic stem (ES) cells. Two groups of researchers implanted iPS cells using tetraploid embryos to create a supporting placenta and now report healthy second and third generation offspring, albeit with low success rates and high embryonic and postnatal mortality. The plasticity and the complete pluripotency of iPS cells suggest a therapeutic potential for them in many human diseases. In addition, iPS cell-derived animals provide a new tool to understand cell programming in health and disease.

Zhao, X.-y., Li, W., Lv, Z., Liu, L., Tong, M., Hai, T., Hao, J., Guo, C.-l., Ma, Q.-w., Wang, L. et al. (2009). iPS cells produce viable mice through tetraploid complementation. *Nature* July 23 [Epub ahead of print] [doi: 10.1038/nature08267].

Neurodegenerative disease: preventing dyskinesia

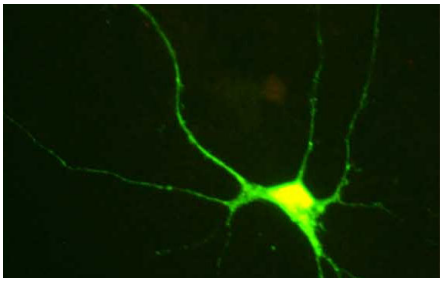

Image reproduced from Karumbayaram et al. (2009). *Dis. Model. Mech.* **2**, 189-195.

L-DOPA is an effective treatment for Parkinson's disease (PD), but long-term therapy is associated with a progressive loss of motor control. Using the well-established mouse model of PD, in which the nigrostriatal pathway is selectively damaged by the toxin 6-hydroxydopamine, Santini et al. show that dyskinesia may develop as repeated administration of L-DOPA promotes mammalian target of rapamycin (mTOR) signaling through dopamine D1 receptor-mediated activation of the mTOR complex 1 (mTORC1). Mice with induced PD activated mTORC1 and exhibited dyskinesia when treated with L-DOPA alone. Similar mice treated with L-DOPA and rapamycin, which inhibits mTOR, benefited from the therapeutic action of L-DOPA and remained free of motor side effects. This indicates that rapamycin and other drugs that target the mTORC1 signaling cascade may warrant further investigation for their potential as anti-PD therapies.

Santini, E., Heiman, M., Greengard, P., Valjent, E. and Fisone, G. (2009). Inhibition of mTOR signaling in Parkinson's disease prevents L-DOPA-induced dyskinesia. *Sci. Signal.* July 21 [Epub ahead of print] [doi: 10.1126/scisignal.2000308].