

## Immunity and infection: a smart way to fight infection

Innate immunity is the front-line defense for combat of invading microorganisms. Several recent studies point to the nervous system as the key regulator of the innate immune response, promoting its speed and accuracy, but it is not yet understood how this process occurs. Recent work from Styer et al. deciphers part of the communication pathway that relays messages between neurons and the immune system. In a genetic screen using the model organism *C. elegans*, they identified G-protein-coupled receptor (GPCR) mutations that impact worm survival following bacterial infection. A loss-of-function mutation in the gene *npr-1* was found to decrease the worm innate immune system response after infection. NPR-1 is expressed in neurons that function as part of a neural circuit responsible for coordinating the worm's behavioral response to the environment. Since *npr-1* encodes a GPCR related to the mammalian neuropeptide Y receptor, it is likely that this type of neural-immune system communication will be conserved in other organisms as well.

Styer, K. L., Singh, V., Macosko, E., Steele, S. E., Bargmann, C. I. and Aballay, A. (2008). Innate immunity in *Caenorhabditis elegans* is regulated by neurons expressing NPR-1/GPCR. *Science* **322**, 460-464.

## HIV: protein binding elicits antibody response



Image reproduced from *PLoS Pathog.* (Forsell et al., 2008).

Development of HIV-1 vaccines has been hampered by the virus's ability to rapidly

evolve through structural changes to its envelope glycoprotein (Env) that allow it to evade host antibody responses during persistent infections. A particularly interesting candidate for vaccine development is the viral glycoprotein gp120, which binds to CD4 on host cells to create a second co-receptor site needed for entry into the cell. Although HIV-infected individuals make many neutralizing antibodies to this co-receptor site, these antibodies are largely ineffective. Now, Forsell et al. show that in both primates and rabbits, antibodies are only induced in the presence of primate CD4 binding to gp120. They suggest that naive B cells require gp120 to bind to primate CD4 in order to recognize the co-receptor site, and that the conformation of this interaction is an important determinant of HIV-1 immunogenicity.

Forsell, M. N., Dey, B., Mörner, A., Svehla, K., O'dell, S., Högerkorp, C. M., Voss, G., Thorstensson, R., Shaw, G. M., Mascola, J. R. et al. (2008). B cell recognition of the conserved HIV-1 co-receptor binding site is altered by endogenous primate CD4. *PLoS Pathog.* **4**, e1000171.

## Stem cells: a niche in the sea



Image reproduced from Voskoboynik et al. (2004). *J. Exp. Biol.* **207**, 2409-2416.

The microenvironment surrounding stem cells, their niche, is thought to provide the conditions necessary for maintaining the ability of stem cells to self-renew and differentiate into a variety of mature cell types. The characteristics of these niches provide valuable information regarding the factors that contribute to the characteristic traits of stem cell populations. Voskoboynik et al. have now extended the list of organisms with defined adult stem cell niches to include the golden star tunicate *Botryllus schlosseri*. They report that cells in the anterior ventral region within *Botryllus*'

pharynx can proliferate and migrate to developing areas, unlike other cells in the organism. This suggests that stem cell niches are highly conserved among species and illustrates the potential for this urochordate as a tractable model organism for defining the shared characteristics of adult stem cell niches.

Voskoboynik, A., Soen, Y., Rinkevich, Y., Rosner, A., Ueno, H., Reshef, R., Ishizuka, K. J., Palmeri, K. J., Moiseeva, E., Rinkevich, B. et al. (2008). Identification of the endostyle as a stem cell niche in a colonial chordate. *Cell Stem Cell* **3**, 456-464.

## Development: kinase crucial for cardiac development

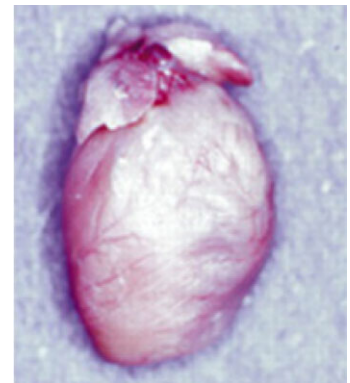


Image reproduced from Sibilias et al. (2003). *Development* **130**, 4515-4525.

Glycogen synthase kinase-3 (GSK-3) is a proposed drug target for a wide variety of diseases, from stroke and diabetes to Alzheimer's disease and bipolar disorder. The element lithium is the only currently approved drug that inhibits GSK-3. However, since maternal lithium treatment has been implicated in congenital heart defects, this raises concern that new GSK-3-inhibitors might likewise cause similar abnormalities. In order to determine the role of GSK-3 in heart development, Kerkela et al. studied knockout mice lacking either GSK-3 $\alpha$  or GSK-3 $\beta$  isoforms. Whereas GSK-3 $\alpha$ -null mice had no heart defects, GSK-3 $\beta$ -null mice died before birth. Further analysis of GSK-3 $\beta$ -deficient embryos and embryonic stem cells demonstrated that hyperproliferation of cardiomyocytes during development caused congenital cardiomyopathy. This study shows that GSK-3 $\beta$  is a regulator of cardiac development,

and highlights potential problems in using GSK-3 antagonists in women of childbearing age.

**Kerkela, R., Kockeritz, L., Macaulay, K., Zhou, J., Doble, B. W., Beahm, C., Greytak, S., Woulfe, K., Trivedi, C. M., Woodgett, J. R. et al.** (2008). Deletion of GSK-3beta in mice leads to hypertrophic cardiomyopathy secondary to cardiomyoblast hyperproliferation. *J. Clin. Invest.* Oct 1 [Epub ahead of print] [doi:10.1172/JCI36245].

## Cancer: a new look at SIRT1 in tumor suppression and DNA repair

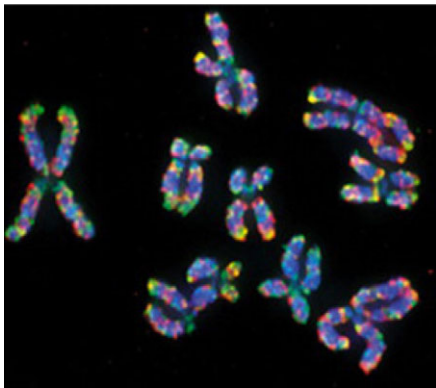


Image reproduced from Van Hooser et al. (2001). *J. Cell Sci.* **114**, 3529-3542.

SIRT1 is thought to underlie the link between caloric restriction and decreased cancer susceptibility. However, the role of mammalian SIRT1 in cancer is highly debated because of conflicting reports of its activity. Here, Wang et al. create a new mouse model in which the catalytic domain of SIRT1 is deleted, and no SIRT1 protein is expressed. They found that these mice have more severe phenotypes than other previously reported SIRT1 deletion models. SIRT1-null mice die before birth, and embryonic tissue analysis revealed that the SIRT1 deficiency leads to chromosome instability, impaired repair of DNA damage, and abnormal cell-cycle changes. Furthermore, *Sirt1* heterozygotes have a significant increase in spontaneous tumor formation. The authors analyzed tumor cells from human clinical samples and re-

ported that these cancer cells have decreased levels of SIRT1 expression. Taken as a whole, these studies of SIRT1 in mice and human tissue support the idea that SIRT1 acts as a positive regulator of tumor suppression.

**Wang, R. H., Sengupta, K., Li, C., Kim, H. S., Cao, L., Xiao, C., Kim, S., Xu, X., Zheng, Y., Chilton, B. et al.** (2008). Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. *Cancer Cell* **14**, 312-323.

## Cystic fibrosis: transgenic pigs mimic human symptoms

Although the specific gene responsible for cystic fibrosis (CF), *CFTR*, has been known for almost 20 years, the failure of *CFTR*<sup>-/-</sup> mice to develop human-like CF symptoms has limited the use of this animal model. In order to create an animal model that more closely represents human CF, researchers created transgenic *CFTR*<sup>-/-</sup> domestic pigs using tools and methods of mouse genetic manipulation. As with newborn humans, newborn pigs lacking *CFTR* initially showed no signs of disease. However, within a few days after birth they developed severe symptoms similar to the clinical manifestations of human CF. These symptoms included intestinal blockage (meconium ileus), exocrine pancreatic insufficiency and damage, and liver disease (focal biliary cirrhosis). Respiratory symptoms and lung disease are the primary causes of human CF mortality and morbidity, but symptom onset does not take place immediately; patients begin developing symptoms anywhere between 3 months to several years after birth. Similar to human neonates, the *CFTR*<sup>-/-</sup> piglets do not have obvious lung abnormalities at birth, but analyzing *CFTR*<sup>-/-</sup> pigs later in life might reveal progressive lung changes over time.

**Rogers, C. S., Stoltz, D. A., Meyerholz, D. K., Ostedgaard, L. S., Rokhlina, T., Taft, P. J., Rogan, M. P., Pezzulo, A. A., Karp, P. H., Itani, O. A. et al.** (2008). Disruption of the *CFTR* gene produces a model of cystic fibrosis in newborn pigs. *Science* **321**, 1837-1841.