Stem cells and cancer: Evi-1 in hematopoiesis and cancer

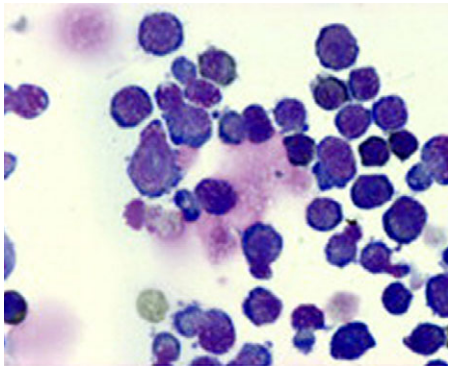

Image reproduced from Angelin-Duclos et al. (2005). *Development* **132**, 925-934.

Elevated expression of Evi-1 is associated with acute myeloid leukemia (AML), where it confers resistance to current cancer treatments. Altered expression of Evi-1 has also been found in a variety of solid tumors. Deletion of Evi-1 in embryonic mice is lethal but its role in embryogenesis and development is not currently understood.

Researchers at the University of Tokyo recently created an inducible knockout of Evi-1 in mice and showed that it is essential for proliferation and maintenance of hematopoietic stem cells. They found that Evi-1 was necessary for normal production of hematopoietic cells both during development and in adult animals in a dose-dependent manner. Deletion of Evi-1 also inhibited transformation of myeloid cells. They suggest that the ability of Evi-1 to enhance proliferation and survival of stem cells may similarly contribute to the self-renewal capacity of cancer stem cells, and therefore offer a potential target for future therapy.

Goyama, S., Yamamoto, G., Shimabe, M., Sato, T., Ichikawa, M., Ogawa, S., Chiba, S. and Kurokawa, M. (2008). Evi-1 is a critical regulator for hematopoietic stem cells and transformed leukemic cells. *Cell Stem Cell* **3**, 207-220.

Cancer: targeting Myc for cancer therapy

The transcription factor Myc regulates the expression of genes that promote cell proliferation and growth. Mutations in, and overexpression of, Myc are closely associated with many types of cancer, making it a seemingly attractive target for therapeutic inhibition. However, there are concerns that anti-Myc therapy would result in a multitude of undesirable side effects since normal cells rely on Myc-regulated pathways for proliferation during tissue turnover and regeneration. Technical issues in the selective inhibition of Myc have also impeded progress in this area.

Researchers at the University of California, San Francisco (UCSF) have tested the effects of a systemic, dominant-interfering mutant of Myc on normal versus cancer cells in a mouse model of *Kras*-induced lung adenocarcinoma. Using a switchable expression system they show that even established lung tumors regress in the presence of the dominant-interfering Myc mutant. Myc inhibition also affected normal, continuously proliferating tissues, causing thinning of the epidermis, inhibition of hair growth, testicular atrophy and erosion of intestinal villi. However, animals tolerated these side effects well and quickly recovered following reversal of mutant expression. Thus, this work suggests renewed potential for anti-Myc therapy for cancer despite anticipated side effects.

Soucek, L., Whitfield, J., Martins, C. P., Finch, A. J., Murphy, D. J., Sodir, N. M., Karnezis, A. N., Swigart, L. B., Nasi, S. and Evan, G. I. (2008). Modelling Myc inhibition as a cancer therapy. *Nature* Aug 17 [Epub ahead of print] [doi:10.1038/nature07260].

Infectious disease: PON protection against *Pseudomonas aeruginosa*

Host susceptibility to bacterial infection is influenced by a complex interaction of pathogen- and host-derived molecules. *Pseudomonas aeruginosa* is an opportunistic bacterial pathogen that causes a substantial number of clinically relevant, hospital-acquired infections. Many bacterial genes thought to contribute to its pathogenesis are regulated by the bacterial protein N-3-oxododecanoyl homoserine lactone (3OC12-HSL), which is degraded by a conserved family of host enzymes known as paraoxonases (PONs). The ability of PONs to degrade 3OC12-HSL suggests that PONs may offer protection against bacterial-induced pathology; however, this hypothesis has not been tested due to the complexity of generating a knockout model lacking all PON family members.

A recent report from Stoltz et al. exploits the fact that Drosophila lack all PON proteins to test the protective potential of PONs in this model organism. They found that expression of an activated form of PON1 protected flies against the toxicity of *P. aeruginosa* infection and promoted host survival. The protective effect of PON1 was dependent on its ability to inactivate 3OC12-HSL. This work provides insight into pathogen-host interactions and suggests that therapeutic induction of PON activity could have beneficial effects for infected patients.

Stoltz, D. A., Ozer, E. A., Taft, P. J., Barry, M., Liu, L., Kiss, P. J., Moninger, T. O., Parsek, M. R. and Zabner, J. (2008). Drosophila are protected from Pseudomonas aeruginosa lethality by transgenic expression of paraoxonase-1. *J. Clin. Invest.* Aug 14 [Epub ahead of print] [doi:10.1172/JCI35147].

Stress response and aging: zebrafish screens identify genes involved in aging

Image reproduced from *Development* (2003) **130**, (15).

Neurodegeneration and neuromuscular disease both seem to be correlates of aging. These pathological processes are thought to result, at least in part, from the chronic accumulation of reactive oxygen species (ROS) generated through normal cellular metabolism.

A recent report from Kishi et al. demonstrates the utility of zebrafish in the identification of genes that regulate oxidative stress and aging in vertebrates. Using both *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis and retroviral insertion methods to induce genetic mutations in zebrafish embryos, they identified genes that alter the expression of a senescence-associated β-galac-

tosidase under conditions of oxidative stress. Their study shows that biomarkers of stress response in embryos are consistent with degeneration and advanced aging phenotypes in adults since many of the genes identified in the screen also induce aging-related phenotypes in adult zebrafish. Two genes identified in this screen included homologs for Drosophila *spinster*, which regulates neurodegeneration and lifespan in flies, and human *TERF2*, which produces a telomere-nucleoprotein complex protein that is important in telomere regulation. This work demonstrates the potential for zebrafish as a tractable vertebrate model for identification of aging-related genes.

Kishi, S., Bayliss, P. E., Uchiyama, J., Koshimizu, E., Qi, J., Nanjappa, P., Imamura, S., Islam, A., Neuberg, D., Amsterdam, A. et al. (2008). The identification of zebrafish mutants showing alterations in senescence-associated biomarkers. *PLoS Genet.* Aug 15 [Epub ahead of print] [doi:10.1371/journal.pgen.1000152].

Neuronal injury and repair: for glial scar protein, timing is everything

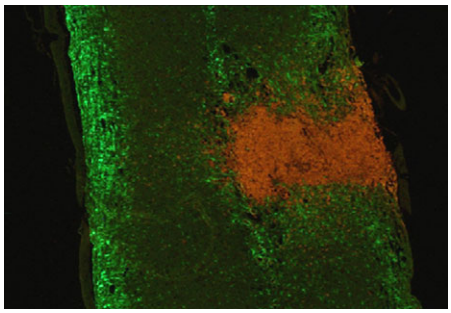

Image reproduced from *PloS Med.* (Rolls et al., 2008).

Spinal cord injuries can cause paralysis, loss of sensation and loss of muscle control. The inflammatory response triggered by injury results in abundant production of chondroitin sulfate proteoglycan (CSPG), an extracellular matrix protein that makes up most of the resulting glial scar tissue. Since CSPG has been shown to inhibit axonal growth, regenerative therapy has focused on degradation of CSPG.

Recent work by Rolls et al. suggests that upregulation of CSPG after injury is part of a beneficial healing response. Using mouse models of spinal cord injury, they demonstrated that CSPG inhibition in the immediate post-injury acute phase decreased recovery of movement, but CSPG inhibition during the later subacute phase improved recovery. CSPG acts, in part, via the CD44 receptor to activate microglia/macrophages, and to spatially organize these cells at the lesion site. Furthermore, CSPG and CSPG degradation products stimulate release of insulin-like growth factor 1 (IGF-1), and attenuate the effects of TNF-α. In light of the dual activity of CSPG, therapies targeting this protein must take the temporal context of spinal cord injury into consideration.

Rolls, A., Shechter, R., London, A., Segev, Y., Jacob-Hirsch, J., Amariglio, N., Rechavi, G. and Schwartz, M. (2008). Two faces of chondroitin sulfate proteoglycan in spinal cord repair: a role in microglia/macrophage activation. *PLoS Med.* Aug 19 [Epub ahead of print] [doi:10.1371/journal.pmed.0050171].

Cardiovascular disease: RNAi therapy hits the mark for lowering cholesterol

Image reproduced from Ferreira-Cornwell et al. (2002). *J. Cell Sci.* **115**, 1623-1634.

High blood cholesterol, or hypercholesterolemia, is a major risk factor for atherosclerosis and heart disease. Some patients using current cholesterol-lowering therapies are still unable to reach target LDL level recommendations, demonstrating the need for additional therapeutic targets to further reduce hypercholesterolemia. Proprotein convertase subtilisin-like kexin type 9 (PCSK9), a protease that decreases LDL receptor levels in the liver, is an interesting potential target since PCSK9 gain-of-function mutations increase plasma cholesterol levels, and PCSK9 loss-of-function mutations decrease cholesterol levels.

Frank-Kamenetsky et al. demonstrate the therapeutic potential of RNAi to target PCSK9 in rat and mouse models, including transgenics expressing the human *PCSK9* gene. The siRNA treatment effectively lowered LDL via specific silencing of PCSK9. RNAi silencing of PCSK9 also effectively lowered LDL in cynomolgus monkeys, without affecting HDL or triglyceride levels. These results indicate potential for RNAi therapies and the targeting of PCSK9 as a way to treat high cholesterol.

Frank-Kamenetsky, M., Grefhorst, A., Anderson, N. N., Racie, T. S., Bramlage, B., Akinc, A., Butler, D., Charisse, K., Dorkin, R., Fan, Y. et al. (2008). Therapeutic RNAi targeting PCSK9 acutely lowers plasma cholesterol in rodents and LDL cholesterol in nonhuman primates. *Proc. Natl. Acad. Sci. USA* **105**, 11915-11920.

Autoimmune disease: pre-eclampsia IgG produces a murine model of maternal morbidity

Pre-eclampsia is a disease affecting up to 5% of pregnant women – its key symptoms include high-blood pressure and compromised renal function. In advanced stages, pre-eclampsia can cause placental damage, liver and kidney dysfunction, and cerebral hemorrhaging, which is sometimes fatal for the mother, baby, or both. Previous work demonstrates that autoantibodies from women with pre-eclampsia stimulate AT_1 angiotensin receptors, highlighting a possible mechanism for this disease.

To further test this model, Zhou et al. treated mice with IgG from pregnant women with pre-eclampsia and found significant increases in blood pressure and urine protein levels. This effect was prevented by peptide block, or by using antagonists, of the target angiotensin receptor. IgG or affinity-purified AT_1 autoantibodies also caused tissue damage in the kidneys and placenta, and smaller fetus sizes. Non-pregnant mice did not show the same physiological responses or kidney damage from IgG treatment, demonstrating that the symptoms were specific to pregnancy. This study establishes a new mouse model for pre-eclampsia and supports screening for angiotensin autoantibodies as an early test for this disease.

Zhou, C. C., Zhang, Y., Irani, R. A., Zhang, H., Mi, T., Popek, E. J., Hicks, M. J., Ramin, S. M., Kellems, R. E. and Xia, Y. (2008). Angiotensin receptor agonistic autoantibodies induce pre-eclampsia in pregnant mice. *Nat. Med.* **14**, 855-862.