

## New from NPG

**Suppression of the antiviral response by an influenza histone mimic**

Marazzi, I. *et al. Nature* doi:10.1038/nature10892 (14 March).

The authors describe a new mechanism by which a virus can hijack the host cell. They show that the influenza A H3N2 subtype nonstructural protein 1 has a histone-mimicking sequence that allows the virus to target and suppress a transcription elongation complex important in the human antiviral response.

**Signaling-mediated bacterial persister formation**

Vega, N.M. *et al. Nat. Chem. Biol.* doi:10.1038/nchembio.915 (18 March).

The authors show that the bacterial signaling molecule indole is important for allowing *Escherichia coli* cells to enter a protected 'persister' state, where the cells cannot be eradicated by antibiotic treatment. Indole activates oxidative stress and phage-shock responses that are involved in persister formation in *E. coli*.

**Mutations in SWI/SNF chromatin remodeling complex gene *ARID1B* cause Coffin-Siris syndrome**

Santen, G.W.E. *et al. Nat. Genet.* doi:10.1038/ng.2217 (18 March).

**Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome**

Tsurusaki, Y. *et al. Nat. Genet.* doi:10.1028/ng.2219 (18 March).

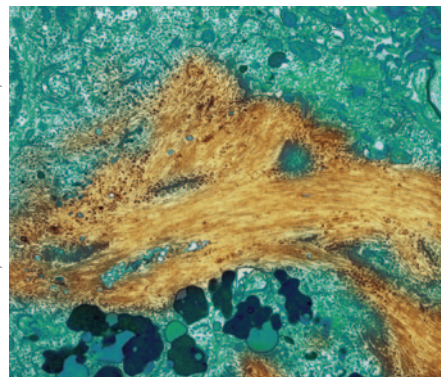
Two papers highlight mutations in the SWI/SNF chromatin remodeling complex as a cause of the developmental syndrome Coffin-Siris syndrome (CSS). In the first study, the authors identify truncating mutations in the SWI/SNF complex gene *ARID1B* in three individuals with CSS. In a second study, the authors find mutations in six SWI/SNF subunit genes in individuals with CSS.

**N-terminally cleaved Bcl-x<sub>L</sub> mediates ischemia-induced neuronal death**

Ofengeim, D. *et al. Nat. Neurosci.* doi:10.1038/nn.3054 (26 February).

The authors show that an apoptosis-inducing drug used for cancer chemotherapy, ABT-737, can protect against neuronal death in a rat model of ischemia. The authors find that ABT-737 prevents the generation of a prodeath cleavage fragment of Bcl-x<sub>L</sub>, suggesting that this fragment could be a potential therapeutic target against ischemic neuronal death.

mice show that this spread of tangles occurs across synapses and along neuronal circuits (*Neuron* **73**, 685–697; *PLoS ONE* **7**, e31302).



Thomas Deerinck, NCMIR / Photo Researchers, Inc.

Alex de Calignon *et al.* and Li Liu *et al.* created transgenic mice that expressed human tau only within neurons in their entorhinal cortex, the part of the brain where tangles are initially found in humans in the early stages of Alzheimer's disease. The researchers found that the human tau was able to cross the synapse into brain regions to which the entorhinal cortex projects, such as the hippocampus, an area of the brain involved in learning and memory. They could also detect human tau in areas of the brain that in turn received projections from the hippocampus, which indicates that tau was able to spread through the brain following existing neuronal circuits.

Although the mechanism by which tau propagation across synapses remains to be elucidated, the findings suggest that blockade of neuron-to-neuron spread of tau could be a promising approach to block disease progression in Alzheimer's disease. —EC

**■ CANCER****Complex cancer roles for telomerase**

Erosion of telomeres—for example, through loss of telomerase activity—activates p53, leading to cell cycle arrest, apoptosis and/or senescence, which together restrain tumorigenesis. Ron DePinho and his colleagues previously reported that in transformed mouse cells deficient in the RNA template subunit of telomerase (mTerc), alternative lengthening of telomeres (ALT) by homologous recombination could maintain telomere length and enable continued subcutaneous but not metastatic tumor cell growth, which required reexpression of mTerc (Chang *et al. Genes Dev.* **17**, 88–100, 2003). These and other findings are consistent with a role

for telomere dysfunction in contributing to chromosomal abnormalities during tumor initiation and, conversely, with the need for telomere length maintenance during tumor progression.

DePinho's team now extends these results in two new papers (Hu *et al. Cell* **148**, 651–663; Ding *et al. Cell* **148**, 896–907). Using a mouse model of spontaneous T cell lymphoma or a prostate tumor model, the authors showed that in the absence of telomerase the time to tumor emergence is increased, whereas reactivating telomerase in previously telomerase-deficient cells shortens the tumor latency and results in more aggressive malignancy. Hu *et al.* found that turning off telomerase in lymphoma cells causes compensatory activation of ALT, extending telomere length. In lymphoma cells, ALT activation was associated with increased expression and copy number gain of the transcriptional coactivator PGC-1 $\beta$ , which regulates mitochondrial function. Moreover, silencing PGC-1 $\beta$  reduced the survival of tumor cells dependent on ALT.

These results are consistent with this group's previous findings that telomere dysfunction, by activating p53, represses PGC-1 $\alpha$  and PGC-1 $\beta$ , thereby impairing mitochondrial function and that reexpression of PGC-1 $\alpha$  in telomerase-deficient cells restores mitochondrial respiration (Sahin *et al. Nature* **470**, 359–365, 2011).

In addition, Ding *et al.* found that telomerase restoration in prostate tumor cells that had previously experienced telomere deficiency induced a new metastatic phenotype, namely lumbar spine metastases. These metastases were associated with *Smad4* deletion in some tumors, and *Smad4* knockout in the prostate tumor model similarly induced bone metastasis in some mice. These results complement this group's earlier work showing that *Smad4* deletion is required for the metastatic outgrowth of *Pten*-null prostate tumors in mice (Ding *et al. Nature* **470**, 269–273, 2011).

Altogether, these results indicate that telomere dysfunction can activate DNA-damage-sensing checkpoints that then shut down cellular metabolism. Abrogating the checkpoint and/or restoring mitochondrial function in tumor cells can enable their continued survival, and the accumulated genomic alterations caused by telomere dysfunction contributes to their genetic instability, increased malignancy and altered metastatic phenotype. —AF

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