cortex (Fig. 1). Finally, it will be important to integrate current knowledge about the intracellular and genomic targets of addictive drugs—such as protein kinases, calcium signals, transcription factors and growth factors affecting membrane remodeling—with the notion that messages from nAChRs may also converge on these cascades. Intriguing data indeed suggest that nAChRs regulate phosphorylation of CREB, a transcription factor known to mediate the neuronal response to dopamine and other neurotransmitters[16]. But, it seems, activation of CREB by nAChRs occurs under conditions very different from that invoked by other receptors. We are only just beginning to tease out the complex neuronal and molecular interactions that underlie the brain's response to drugs—and that's just the first step to an antidote for the hardship of addiction.

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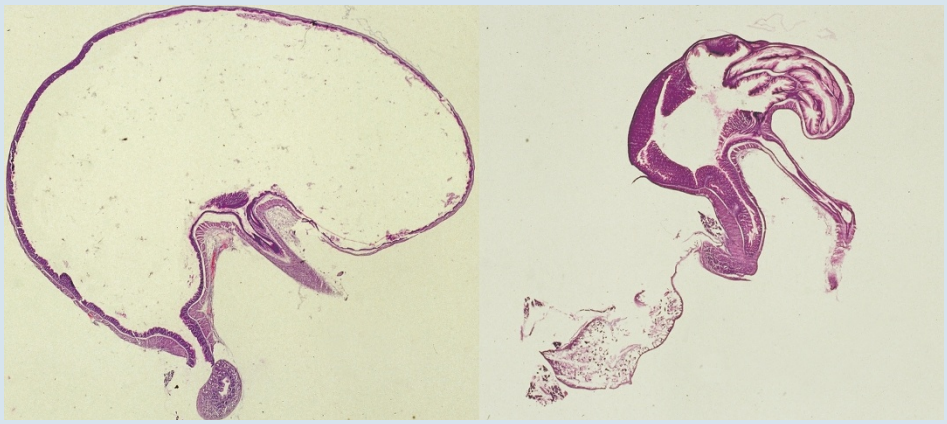
Gastric cancer gets the run-around



Gastric cancer is a major cause of death worldwide, and is particularly common in certain Asian populations. Now, with the goal of understanding the molecular events causing the disease, Suk-Chul Bae, Yoshiaki Ito and colleagues describe in the 5 April issue of *Cell* a link between the development of gastric cancer and reduced expression of *RUNX3*, a gene encoding a transcription factor influenced by the transforming growth factor-β (TGF-β) signaling system.

Beginning their studies in laboratory mice, Bae, Ito and colleagues found that the absence of *Runx3* leads to increased cell growth in the stomach mucosa (on right) compared with wild-type tissue (left). Wild-type stomachs were slightly larger and their walls thinner. The authors go on to show that *Runx3* is required for the growth suppressive actions of TGF-β in this tissue. They conclude that *Runx3* probably functions under normal conditions to rein in the growth of gastric epithelial cells. In humans, expression of the corresponding *RUNX3* gene was also significantly reduced, when examined in clinical specimens from gastric tumors. The *RUNX3* gene itself was found to be deleted in some gastric cancer specimens, most frequently in advanced tumors.

One hallmark of cancer cells is that genes encoding proteins that put a brake on cell growth—commonly known as tumor suppressor genes—are turned off by DNA methylation. The authors duly describe that DNA sequences regulating expression of the *RUNX3* gene are methylated in tumor specimens but not in normal gastric epithelia. A search for DNA sequence mutations in *RUNX3* which might affect the encoded protein's function, and thereby predispose individuals to develop gastric cancer, yielded only one abnormality in more than 100 tumor samples. Paradoxically, the apparent rareness of *RUNX3* mutations provides a possible therapeutic route for future testing—*RUNX3* genes silenced by DNA methylation could potentially be reactivated by the use of chemical agents such as histone deacetylase inhibitors, which can unmask genes that have been turned off by DNA methylation.

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