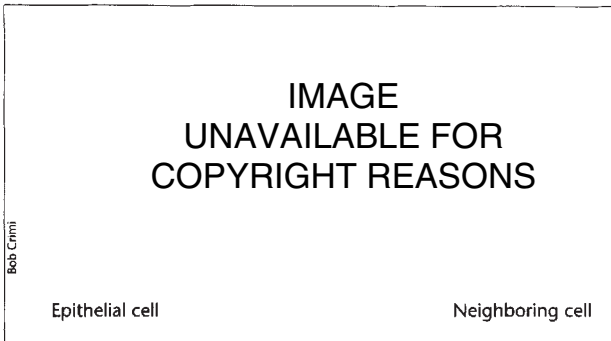

Fig. 2 Through their effects on prostaglandin synthesis, COX-1 and COX-2 mediate many cellular processes including apoptosis, cell migration and angiogenesis. Recent findings indicate that COX-2 induces colon cancer cells to release prostaglandins that then stimulate endothelial cells to form new blood vessels.

els of COX-2. Offspring of a genetic cross between $Apc^{\Delta 716}$ mice and COX-2 homozygous null animals have fewer polyps than offspring of the $Apc^{\Delta 716}$/COX-2 wildtype cross[5]. Recently, chemoprevention by selective COX-2 inhibitors has been demonstrated in cell culture[6], in the azoxymethane-treated rat model of colon cancer[7] and in $Apc^{\Delta 716}$ mice[5].

Despite the many studies that correlate increased expression of COX-2 with colon cancer development, the molecular mechanisms underlying COX-2's contribution to carcinogenesis are still not clear. Overexpression of COX-2 in intestinal epithelial cell lines results in resistance to sodium butyrate-induced apoptosis, possibly mediated by Bcl-2, and downregulation of E-cadherin (a cell adhesion protein)[8,9]. Given the high frequency of *APC* gene mutations and COX-2 overexpression in colonic polyps, it is tempting to speculate (although by no means substantiated) that dissociation of APC–β-catenin proteins results in β-catenin-mediated activation of COX-2, and modulation of E-cadherin activity.

In a recent *Cell* paper, Tsujii *et al.*[10] advance the notion of a novel paracrine mechanism by which COX-2 might promote tumor development. Using a coculture of endothelial cells and colon cancer cells, they demonstrated that COX-2 stimulates colon cancer cells to release proangiogenic prostaglandins that stimulate endothelial cell migration and tube formation—the initial steps in the formation of new blood vessels (angiogenesis). This was prevented by aspirin, NS-398 (a selective COX-2 inhibitor) and by a cocktail of antibodies against angiogenic factors. They then showed that COX-1 expression in endothelial cells directed these cells to form new blood vessels, a process that could be inhibited by aspirin and a COX-1 antisense oligonucleotide. Selectively blocking COX-1 activity may be a valuable chemotherapeutic strategy for combatting the small number of colon cancers that do not express COX-2.

1. Giardiello, F.M. *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N. Engl. J. Med.* **328**, 1313–1316 (1993).
2. Shiff, S.J. & Rigas, B. Nonsteroidal anti-inflammatory drugs and colorectal cancer: evolving concepts of their chemopreventive actions. *Gastroenterology* **113**, 1992–1998 (1998).
3. Piazza, G.A. *et al.* Sulindac sulfone inhibits azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. *Cancer Res.***57**, 2909-2915 (1997).
4. Kalgutkar, A.S. *et al.* Aspirin-like molecules that covalently inactivate cyclooxygenase-2. *Science* **280**, 1268–1270 (1998).
5. Oshima, M. *et al.* Suppression of intestinal polyposis in APC delta 716 knockout mice by inhibition of prostaglandin endoperoxidase-2 (COX-2). *Cell* **87**, 803–809 (1996).
6. Sheng, H. *et al.* Inhibition of human colon cancer cell growth by selective inhibition of cyclooxygenase-2. *J. Clin. Invest.* **99**, 2254-2259 (1997).
7. Reddy B.S., Rao, C.V. & Seibert, K. Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. *Cancer Res* **56**, 4566–4569 (1996).
8. Tsujii, M. & DuBois, R.N. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase-2. *Cell* **83**, 493–501 (1995).
9. Tsujii, M., Kuwano, S. & DuBois, R.N. Cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential. *Proc. Natl. Acad. Sci. USA* **94**, 3336–3340 (1997).
10. Tsujii, M. *et al.* Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell* **93**, 705–716 (1998).

Gastrointestinal Unit
Massachusetts General Hospital
Boston, Massachusetts 02114, USA
email: rustgi@helix.mgh.harvard.edu

The Tao of tau

After years of fruitless searching for mutations in *TAU*, a prime candidate gene for Alzheimer's Disease (AD), a trio of research teams has now discovered missense *TAU* mutations in individuals with a type of frontotemporal dementia, FTDP-17. The disorder is heterogeneous with respect to age of onset, typically involving an unlikely alteration in personality, such as compulsive obsession, and is physically characterized (upon autopsy) by neurofibrillary tangles of tau protein and atrophy of the frontotemporal lobes. Tau tangles are also observed in AD patients, in the form of paired helical filaments, although in AD these tangles are always preceded by amyloid deposition.

Initial investigations of *TAU* sequence integrity of affected members of FTDP-17 kindreds also yielded nothing but, on closer inspection, one of nine candidate polymorphisms was discovered by Parvoneh Poorkaj *et al.* (*Annals Neurosci.* **43**, 815–825, 1998) to be a mutation—and a mutation that lies in a conserved region encoding a microtubule-binding motif (MBM). In contrast, the mutation described by Maria Spillantini and colleagues (*PNAS* **95**, 7737–7741, 1998) lies directly 3′ of the alternatively-spliced exon 10. They also detected a distortion in the composition of alternatively-spliced *TAU* isoforms in affected individuals (a preponderance of isoforms containing four MBMs over the three-MBM variety), which suggests that the mutation interferes with the excision of exon 10. Uniting these two types of mutations, is a study presented by Michael Hutton and co-workers (*Nature* **393**, 702–705, 1998) in which they describe six mutations: three splice-site mutations (although these are situated just 5′ of exon 10) and three missense mutations, two of which occur in microtubule-binding domains. The authors went on to show that the splice-site mutations do, in fact, interfere with exon-10 excision.

Isoforms that include exon 10 and therefore sport four MBMs appear to be more soluble than the three-MBM variant; a distortion in isoform ratio may affect the binding of tau to (and consequently the structural integrity of) microtubules. Given the lack of obvious adverse effects in the *tau*-null mouse, however, it seems more likely that the aggregation of unbound tau is critical to neuronal atrophy. The fact that tau dysfunction is now demonstrated to lead to neurodegeneration will be gratifying to AD researchers. As Rudy Tanzi (Massachusetts General Hospital) points out, however, the formation of amyloid plaques before the appearance of paired helical filaments in AD suggests a fundamentally different genetic etiology, although some reassessment of the AD risk of *TAU* polymorphisms is warranted. Those in the politically scarred field of AD research might do well to take a leaf from the book of Lao Tsu, who advocated empathy, humility and aspiration to communal harmony.

Bette Phimister, Nature Genetics