Research News

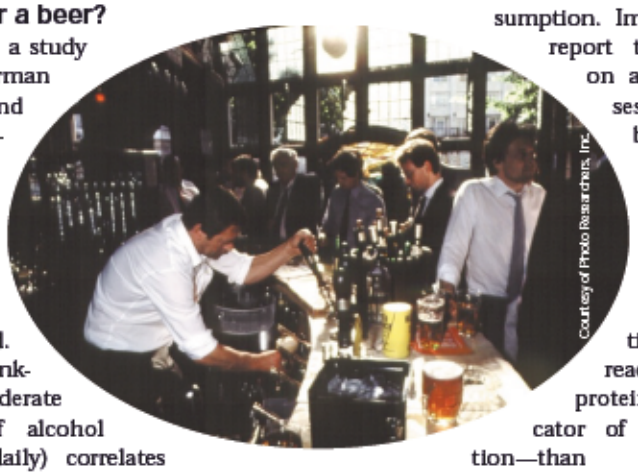
A is for anti-angiogenic

Cyclosporin A (CsA) may someday be used to treat rheumatoid arthritis, but not because of its immunosuppressive ability. In the 5 March issue of the *Journal of Experimental Medicine*, Hernandez *et al.* report that CsA inhibits VEGF-mediated angiogenesis. The authors made this discovery in a roundabout manner, coming across COX-2 in a search for novel VEGF-regulated genes. Analysis of the *COX-2* gene promoter revealed a binding site for the transcription factor NFAT, which was able to bind the COX-2 promoter and induce its expression in response to VEGF stimulation. The drug CsA is known to inhibit NFAT, so Hernandez *et al.* investigated whether this drug could block COX-2 expression and VEGF-induced angiogenesis. Indeed, CsA did inhibited endothelial cell migration and angiogenesis in a corneal neovascularization assay. Hernandez *et al.* suggest that the CsA should be considered for treating diseases associated with VEGF-induced neovascularization, such as rheumatoid arthritis, psoriasis and diabetic retinopathy.

Hunger strike

Muscarinic acheylcholine receptors are involved in controlling smooth muscle contraction, but a recent study suggests they also regulate food intake. There are five members of this receptor family, and one of these, M3, is expressed in the central nervous system, although its function is unknown. Yamada *et al.* created M3 knockout mice, and in the 8 March issue of *Nature*, report that they weigh about 20% less than their wildtype littermates, have 50% less fat, and eat 30% less food. Yamada *et al.* attribute this weight loss to appetite reduction, as M3 deletion did not affect salivation, gastrointestinal motility, or metabolic rate, and the mice performed normally in behavioral tests. The mice did, however, have significantly reduced levels of serum leptin and insulin. The hormones are continuously monitored by hypothalamic neurons, which respond by stimulating or suppressing food intake. M3 is expressed in the hypothalamus, so the authors investigated whether its absence interferes with the leptin/insulin appetite-regulating signaling pathways. They report that the M3-null mice have altered expression levels of several hypothalamic neuropeptides that act downstream of the leptin system. This suggests a new role for cholinergic receptors in the appetite signaling pathway, as well as new therapeutic targets for obesity.

Aspirin, or a beer?



Based on a study of 2006 German men and women, scientists have concluded that a little tipple does a heart good. In fact, drinking a moderate amount of alcohol (20-60 g daily) correlates with a lower risk of coronary heart disease than abstention or heavy consumption (>60g). The reason, according to a paper in the 10 March issue of *The Lancet*, appears to be anti-inflammatory properties associated with alcohol consumption. Imhof *et al.*, report that based on a 7-day assessment, both teetotallers and heavy drinkers had higher concentrations of C-reactive protein—an indicator of inflammation—than moderate drinkers. Inflammation has been linked to atherosclerosis and other diseases. Interestingly, C-reactive protein values were lowest at a slightly higher alcohol intake for women than men, 40-60g and 20-40g respectively.

De-cloaking cancer

Heparin, an anticoagulant, may be revived as an anticancer agent after spending 30 years on the back burner. Animal studies performed in the '60s and '70s showed that heparin had anti-metastatic effects, which researchers believed depended on its ability to prevent blood clotting. However, follow-up studies involving orally-administered anticoagulants, which are easier to manage than heparin, failed to show clinical benefit. Heparin has since been found to have other biological functions, such as the ability to bind cell adhesion molecules known as selectins. These cell adhesion proteins are expressed on the surfaces of platelets and other blood cells. Selectins bind mucin-type glycoproteins, which are present on the surface of tumor cells and associated with a metastatic phenotype. This selectin/mucin interaction allows platelets to bind tumor cells and form a 'cloak' around foci, protecting tumors from immune detection. In the 13 March issue of *PNAS*, Borsig *et al.* report that heparin disrupts mucin/selectin binding, interfering with platelet/tumor interactions *in vitro* and *in vivo*. Heparin-treated mice developed fewer metastatic foci than normal mice after intravenous injection of tumor cells, and the 'de-cloaked' tumor cells were susceptible to attack by cytotoxic immune effectors. The authors suggest that heparin might be given to patients as soon as a primary tumor is identified, to prevent circulating tumor cells from becoming established metastatic deposits.

An antibiotic switch

The identification of a switch that allows bacteria to turn on antibiotic resistance genes may arm researchers in the fight against drug-resistant strains. β–lactam antibiotics such as penicillin are the most effective treatments for staphylococcal infections, yet physicians constantly battle bacteria that develop resistance. Many of the enzymes that are involved in resistance have been identified, but the detailed sequence of events in this pathway has not been determined. One of these enzymes, β-lactamase, is known to inactivate penicillin by hydrolysis. In the 9 March issue of *Science*, Zhang *et al.* investigated the mechanism by which the transmembrane protein, BlaR1, can detect the presence of antibiotics and turn on expression of β-lactamase. They found that BlaR1 is an antibiotic sensor that binds penicillin, and then cleaves itself to release an active metalloprotease fragment. This protease in turn cleaves the DNA-binding protein, BlaI, that usually represses transcription of the β-lactamase gene. BlaI cleavage causes it to be released from its intergenic operator sites, allowing transcription of the gene encoding β-lactamase to proceed, along with antibiotic resistance. The authors suggest that although other chromosomal elements may be involved in resistance, compounds that disrupt this regulatory pathway could restore activity of antibiotics against drug-resistant bacterial strains.

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