IN THE NEWS

To eat, or not to eat

The salmon-farming industry is in uproar over a comprehensive report in *Science* (9 January 2004) that shows that farm-raised salmon, particularly from Scotland and the Faroe Islands, contains more cancer-causing agents than wild salmon.

The study sampled 700 salmon that were bought in North America, South America and Europe and found that 13 organochlorine compounds were significantly higher in farmed Atlantic salmon than in wild Pacific salmon. "We think it is important for people who eat salmon to know that farmed salmon have higher levels of toxins than wild salmon from the open ocean" said the study leader Ronald Hites (*BBC News*, 8 January 2004).

Contamination with organochlorines — particularly polychlorinated biphenols (PCBs) and pesticides that contribute to the risk of liver and other cancers — could override the beneficial effects of eating this fish, which is a rich source of proteins, vitamin D and omega fatty acids, and can protect against heart disease and cancer. However, the chairman of the United Kingdom Food Standards Agency, Sir John Krebs, assures "This study shows that the levels of dioxins and PCBs in salmon are within internationally recognized safety limits. We advise that the known benefits of eating one portion of oily fish [per week] outweigh any possible risks." (*NewScientist.com*, 9 January 2004).

The study indicates that the contaminants come from the 'chow' that is fed to farmed salmon — a mixture of meal and oil made from other types of fish — thereby transferring toxins that have accumulated in the food chain. Steps are already being taken by the salmon-farming industry to find fish meal with low levels of contaminants.

Emma Croager

METASTASIS

CAV1 connection

During metastasis, changes in the tissue microenvironment allow cancer cells to escape the tumour and disseminate. Epidermal growth factor receptor (EGFR) overexpression

and downregulation of E-cadherin — a key component of intercellular junctions — are both known to disrupt cell-cell interactions and, according to a report by Tony Hunter and colleagues in *Cancer Cell*, these processes are connected by the caveolae-associated protein caveolin-1 (CAV1). Not only does EGFR overexpression initially cause cave-

olin-dependent internalization of E-cadherin, it also ultimately reduces CAV1 protein levels, which activates the β -catenin signalling pathway and downregulates E-cadherin expression.

In response to EGF, EGFR-overexpressing cancer cells undergo an epithelial-mesenchymal transition, which is caused by loss of cell-cell junctions and cell depolarization. In A431 human cancer cells, rapid internalization of E-cadherin was associated with the early stages of this process and, as EGF is known to trigger CAV1 redistribution, the authors investigated whether the internalization was mediated by caveolae. Chemical depletion of cholesterol, a key component of caveolae, prevented E-cadherin internalization, indicating that caveolae are needed to downregulate surface E-cadherin and cause rapid loss of intercellular contacts (see figure).

E-cadherin normally associates with β -catenin — a component of the WNT signalling pathway — at intercellular junctions, and immunofluorescence experiments showed β -catenin was reduced on the surface of the EGF-treated cells.

THERAPEUTICS

All exits blocked

One way that tumour cells inactivate tumour suppressors is through sub-cellular mislocalization. For example, in some cancer cells, the forkhead (FOXO) family of transcription factors, which normally inhibit cell proliferation, are functional, but are exported from the nucleus to the cytoplasm. Pam Silver's group has developed a screen for compounds that prevent FOXO transport out of the nucleus and lead to cell-cycle arrest.

FOXO localization is regulated by the PI3K–PTEN–AKT signalling pathway. *PTEN* is mutated in several tumours, leading to loss of its lipid phosphatase activity and constitutive activation of AKT

signalling. AKT phosphorylates FOXO transcription factors at several sites, which promotes nuclear export and thereby prevents their transcriptional activity. As studies showed that forcible localization of FOXO1A to the nucleus can reverse tumorigenicity of *PTEN*-null cells, Silver and colleagues developed a cell-based chemical screen for inhibitors of FOXO1A nuclear export. Using localization of FOXO1A as a visual assay, they screened over 18,000 compounds for their ability to relocate FOXO1A to the nucleus in *PTEN*-null cells. Eighty nine compounds were found to cause FOXO1A nuclear retention, 42 of which were selected for further characterization.

Of these 42 compounds, 19 were also able to block export of the human immunodeficiency virus rev protein — another nuclear factor — and were therefore considered to be 'general export inhibitors'. These compounds were found to function

by interfering with the activity of CRM1, an export receptor that shuttles proteins out of the nucleus. The other 23 compounds that were examined were only able to block nuclear export of FOXO1A, through several points along the AKT signalling pathway.

One of the compounds was identified as trifluoperazine, which acts as a calmodulin inhibitor, among other things. The authors therefore treated *PTEN*-null cells with other types of calmodulin inhibitor, and found that they all caused FOXO1A re-localization to the nucleus. This is the first report of a calmodulin-dependent regulatory mechanism of FOXO1A localization, and indicates that calmodulin could interact with the AKT signalling pathway.

So, the compounds that were identified in the screen cause FOXO1A to stay in the nucleus, but how do they affect tumour growth? Thirty of the nuclear-transport inhibitors that were discovered also