TUMOUR SUPPRESSORS

Conflict resolution

The activity of the peroxisome-proliferator-activated receptor (PPAR) family members has been implicated in various tumour types, although the evidence for one of these proteins — PPARβ/δ — has been contradictory. Raymond DuBois and colleagues have therefore used a mouse model of colorectal cancer, along with a Pparβ/δ selective agonist, to more clearly demonstrate the role of Pparβ/δ in tumour growth.

PPARs are a family of nuclear hormone receptors that function as ligand-activated transcription factors. PPARβ/δ is involved in development, wound healing, fatty-acid metabolism and repression of the inflammatory response. More importantly, the expression and activity of PPARβ/δ are increased after loss of the adenomatous polyposis coli (APC) tumour suppressor, which implicates it in the pathogenesis of colorectal cancer. To support this, a study showed that loss of both *PPARβ/δ* alleles from a colorectal cancer cell line slowed tumour growth. A separate study, however, reported that disruption of *Pparβ/δ* did not affect polyp formation in Apc^{min} mice — a model of intestinal polyposis that progresses to colorectal cancer, in which *Apc* is mutated. DuBois and colleagues therefore tested another approach to this problem — they treated Apc^{min} mice with the selective Pparβ/δ agonist GW501516.

Pparβ/δ is expressed primarily in the intestinal epithelial cells of both the normal intestinal epithelia and adenomas of Apc^{min} mice. Treating these mice with GW501516 led to a twofold increase in polyp number in the small intestine, but no change in the number of colon polyps. The mice that were treated with the Pparβ/δ agonist also showed a five-fold increase in polyps larger than 2 mm, so Pparβ/δ activation seems to affect the rate of polyp growth more than polyp formation. The polyps in these mice also had a slightly higher degree of dysplasia, indicating a more advanced stage of progression.

How does Pparβ/δ activation promote tumour growth? Although GW501516 had no effect on proliferation of colorectal cancer cells *in vitro*, it suppressed apoptosis in a dose-dependent manner. DuBois concluded that Pparβ/δ stimulates the growth and development of intestinal adenomas by activating anti-apoptotic pathways in intestinal epithelial cells.

This finding has important implications for the clinic, as activating ligands of PPARβ/δ (including GW501516) are in the later stages of development as drugs to treat dyslipidaemia syndromes, obesity and atherosclerosis. PPARβ/δ agonists should be administered with caution, as they might increase the risk of cancer in individuals with familial adenomatous polyposis — a disease in which *APC* mutations lead to a high incidence of colorectal cancer.

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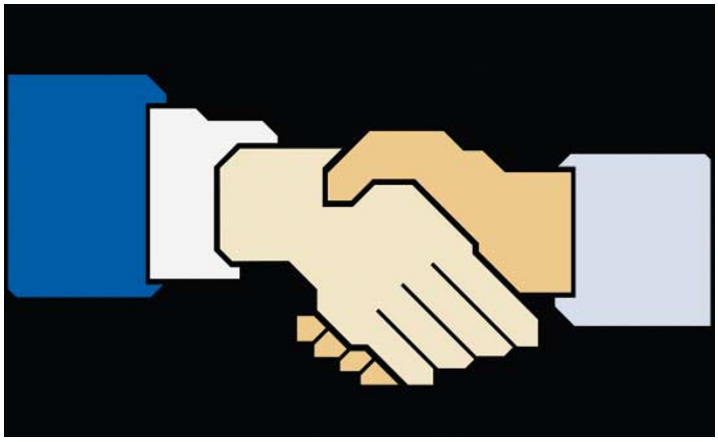

References and links

ORIGINAL RESEARCH PAPER Gupta, R. A. *et al*. Activation of nuclear hormone receptor peroxisome proliferator-activated receptor-δ accelerates intestinal adenoma growth. *Nature Med*. 1 Feb 2004 (doi:10.1038/nm993)

FURTHER READING Michalik, L., Desvergne, B. & Wahli, W. Peroxisome-proliferator-activated receptors and cancers: complex stories. *Nature Rev. Cancer* **4**, 61–70 (2004)

WEB SITE
Raymond DuBois' lab:
https://medschool.mc.vanderbilt.edu/facultydata/php_files/show_faculty.php?id3=760