TRANSCRIPTOMICS

Common disease pathogenesis pathways

Several observations indicate that various human diseases might be biologically connected. In particular, some data suggest that metabolic, inflammatory and autoimmune diseases increase the risk of developing cancer, so Kevin Struhl and colleagues investigated whether their underlying biology overlaps.

Hirsch and colleagues generated expression profiles of cell transformation using two isogenic cell models — MCF10A cells expressing tamoxifen-inducible SRC (MCF10A–ER–SRC cells) and three isogenic fibroblast cell lines representing different stages of HRAS-G12V transformation. They combined the SRC and HRAS transformation profiles to produce the 'cancer gene signature' (CGS), comprising 343 differentially expressed genes, which was validated by literature mining and comparison to published expression profiles associated with cancer. They found that the genes in the CGS that associated with the widest range of cancer types were predominantly those involved in inflammation. Next, using ingenuity pathway analysis, they identified three groups of biofunctions and diseases that correlated with the CGS: cancer-related, inflammation and immunity, and, unexpectedly, lipid metabolism. They also found that the CGS overlapped with published expression profiles from individuals with obesity, atherosclerosis and metabolic syndrome.

They then organized the two transformation expression profiles into a network, which they compared with expression profiles from individuals with metabolic syndrome to identify 24 common nodes, including insulin, low density lipoprotein (LDL) and proteins involved in inflammation such as interferon-γ (IFNγ), interleukin-6 (IL-6) and nuclear factor-κB (NF-κB). Suppressing the activity of each of the 24 common nodes in the transformed MCF10A–ER–SRC cells reduced transformation, as determined by morphology or focus formation in soft agar. These data suggest that these groups of diseases exhibit overlapping alterations in certain pathways, which are defined by the nodes in the transformation-associated network.

This suggests that drugs used to treat one disease could be used to treat cancer (or other diseases). Therefore, the authors tested the ability of 13 drugs, including metformin, which are used to treat patients with metabolic syndrome (among others), to inhibit the transformation of MCF10A–ER–SRC cells treated with tamoxifen. They found that most drugs prevented colony formation in soft agar, and intraperitoneal injection of nude mice bearing MCF10A–ER–SRC xenografts with each of the four drugs that had the biggest effects *in vitro* either suppressed (metformin and sulindac) or delayed (cerulenin and simvastatin) tumour growth.

The CGS includes several genes not previously associated with cancer. When expression of these genes was knocked down by small interfering RNA in either model, four of the nine genes shown to be important for transformation were involved in lipid metabolism (associated with the LDL node): oxidized low density lipoprotein receptor 1 (*OLR1*), synaptosomal-associated protein, 23 kDa (*SNAP23*), vesicle-associated membrane protein 4 (*VAMP4*) and stearoyl-CoA desaturase (*SCD*). Of these, knock down of OLR1, which is overexpressed in patients with atherosclerosis, had the strongest effect on transformation, and genes involved in inflammation and the response to hypoxia were down-regulated when OLR1 expression was knocked down. In addition, the growth of transformed MCF10A-ER-SRC xenograft tumours was inhibited by treatment of mice with *Olr1* small interfering RNA. Finally, the authors report that *OLR1* and to a lesser extent the other lipid metabolism genes are overexpressed in some patients with mammary adenocarcinoma or prostate adenoma and that the expression levels increased with tumour grade.

Therefore, the authors suggest that the lipid metabolism pathways might be coordinately deregulated in cancer and other inflammatory and metabolic diseases, the pathogenesis of which may indeed overlap.

Gemma K. Alderton

> "lipid metabolism pathways might be coordinately deregulated in cancer and other inflammatory and metabolic diseases"

ORIGINAL RESEARCH PAPER Hirsch, H. A. *et al.* A transcriptional signature and common gene networks link cancer with lipid metabolism and diverse human diseases. *Cancer Cell* **17**, 348–361 (2010)