TRANSCRIPTOMICS

Common disease pathogenesis pathways

Several observations indicate that various human diseases could be biologically connected. In particular, some data suggest that metabolic, inflammatory and autoimmune diseases increase the risk of developing cancer, so a new study has investigated whether there is overlap in the underlying biology of these diseases.

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 gene expression profiles to produce a 'cancer gene signature' (CGS) that comprised 343 differentially expressed genes; the CGS was then validated by literature mining and comparison to published expression profiles associated with cancer. The genes in the CGS that associated with the widest range of cancer types were predominantly those involved in inflammation. Furthermore, the CGS correlated with three groups of biofunctions and diseases: cancer-related, inflammation and immunity and, unexpectedly, lipid metabolism. The CGS also overlapped with published expression profiles from individuals with atherosclerosis, metabolic syndrome and obesity.

The authors then organized the two sets of transformation-associated differentially expressed genes 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. 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 that are known to work on one disease can also be used to treat cancer or other diseases. The authors selected 13 drugs that are used to treat metabolic syndrome (among other diseases), then tested the ability of these drugs to inhibit transformation of MCF10A–ER–SRC cells treated with tamoxifen. Most drugs prevented colony formation in soft agar and the four drugs that had the biggest effects *in vitro* either suppressed or delayed tumour growth in nude mice.

The CGS includes several genes that have not previously been associated with cancer. When expression of these genes was knocked down by small interfering RNAs (siRNAs) in either model, it was found that out of the nine genes that are important for transformation, four are involved in lipid metabolism (that is, they are associated with the LDL node). Of these four genes, knockdown of oxidized low density lipoprotein receptor 1 (*OLR1*) — which is overexpressed in atherosclerosis patients — had the strongest effect on transformation and led to the downregulation of genes involved in inflammation and the response to hypoxia. In addition, treatment of mice with *Olr1* siRNAs inhibited the growth of transformed MCF10A–ER–SRC xenograft tumours. Finally, *OLR1* is overexpressed in some patients with mammary adenocarcinoma or prostate adenoma, and expression levels increase 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 pathogeneses of which may indeed overlap.

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