Gene expression in children with Fabry disease

This study examined the effect of enzyme replacement therapy on differential gene expression in peripheral blood mononuclear cells of children with Fabry disease who had not previously been exposed to enzyme replacement therapy.

Thirteen children with Fabry disease were enrolled in this study. Paired blood samples were taken at the start of the study and after 6 months of enzyme replacement therapy. Further blood samples were also taken from 16 age-matched control subjects. Peripheral blood mononuclear cells were isolated and, following RNA extraction, differential gene expression analysis was performed using the Human Genome U133 Plus 2.0 microarray.

Twenty-one genes were determined to be differentially expressed in peripheral blood mononuclear cells of enzyme replacement therapy-naïve children with Fabry disease compared with healthy controls; neuronal apoptosis inhibitory protein ranked as the most significantly differentially expressed gene. Comparison of gene expression in children with Fabry disease before and after enzyme replacement therapy showed that two genes were significantly expressed following treatment. The expressed sequence tag was downregulated, while expression of apoptosis-inducing factor was increased, possibly as an antioxidant counter-regulatory response.

The study concluded that the two differentially-expressed genes may relate to the underlying biologically abnormalities in Fabry disease.

Moore D, Goldin E, Gelderman M et al (2008) Apoptotic abnormalities in differential gene expression in peripheral blood mononuclear cells from children with Fabry disease. *Acta Paediatr* **97**: 48–52

Disuse atrophy of diaphragm fibres in mechanical ventilation

The combination of complete diaphragm inactivity and mechanical ventilation elicits disuse atrophy of myofibres in animals. The authors of this study hypothesized that the same would also occur in the human diaphragm.

Biopsy specimens were obtained from the costal diaphragms of 14 brain-dead organ donors before organ harvest and compared with intraoperative biopsy specimens from the diaphragms of eight patients who were undergoing surgery for either benign lesions or localized lung cancer. Case subjects had diaphragmatic inactivity and underwent mechanical ventilation for 18–69 hours; among control subjects diaphragmatic inactivity and mechanical intervention were limited to 2–3 hours. Histological, biochemical and gene-expression studies were performed on these specimens.

As compared with diaphragm-biopsy specimens from controls, specimens from case subjects showed decreased cross-sectional areas of slow-twitch and fast-twitch fibres respectively, decreased glutathione concentration, increased active caspase-3 expression, a 200% higher ratio of atrogin-1 messenger RNA (mRNA) transcripts to MBD4 (a housekeeping gene), and a 590% higher ratio of MuRF-1 mRNA transcripts to MBD4.

The study concluded that a combination of 18–69 hours of complete diaphragmatic inactivity and mechanical ventilation results in marked atrophy of human diaphragm myofibres. These findings are consistent with increased diaphragmatic proteolysis during inactivity.

Levine S, Nguyen T, Taylor N et al (2008) Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* **358**: 1327–35

Statins and cancer risk

Despite numerous randomized clinical trials and observational epidemiological studies, evidence of the potential effectiveness of statins for prevention of cancer remains controversial. The aim of this study was to investigate the relation between lipophilic statin use and cancer occurrence.

A retrospective observational study was carried out, based on a medical administrative database in Quebec, Canada. Patients aged 45 years or above and discharged from the hospital alive after admission for acute myocardial infarction were included. High- and low-dose statin use were defined as a filled prescription, within 3 days after index discharge, at or above the statin-specific target dose for any of the four lipophilic statin medications: atorvastatin, simvastatin, lovastatin or fluvastatin. A total of 30 076 patients were followed for up to 7 years.

The crude incidence rates of hospital admission with the diagnosis of any type of cancer were 13.9, 17.2 and 26.0 per 1000 person-years in statin high-dose users, low-dose users and non-users respectively.

It was concluded that the use of lipophilic statins at sufficiently high doses might be associated with a clinically important reduction in the incidence of cancer.

Karp I, Behlouli H, LeLorier J, Pilote L (2008) Statins and cancer risk. *Am J Med* **121**: 302–9

Germline genomic homozygosity association with cancer cases

While studying loss of homozygosity in cancer tissues, a low frequency of homozygosity has been observed in cancer patients compared with controls, raising the question whether homozygosity could play a role in cancer predisposition.

The objective of this study was to determine the frequency of germline homozygosity in a large series of patients with three different types of solid tumours compared with population-based controls.

Germline and corresponding tumour DNA isolated from 385 patients with carcinomas (147 breast, 116 prostate and 122 head and neck carcinomas) were subjected to the whole genome (345-microsatellite marker) loss of heterozygosity analysis. The main outcome measures of the analysis were the frequency of homozygosity at microsatellite cancer cases *vs* controls and frequency of somatic loss of heterozygosity in cancers at loci with the highest homozygosity.

It was found that in the solid tumour types studied, increased germline homozygosity occurred at specific loci. When the germline was heterozygous at these loci, high frequencies of loss of heterozygosity/allelic imbalance occurred at these loci in the corresponding carcinomas.

Assié G, LaFramboise T, Platzer P, Eng C (2008) Frequency of germline genomic homozygosity associated with cancer cases. *JAMA* **299**: 1437–45