Medical genetics: advances in brief

Frataxin gene of Friedreich's ataxia is targeted to mitochondria

Priller J, Scherzer CR, Faber PW, *et al.* *Ann Neurol* 1997;42:265-9.

Those of us with a suspicious nature might well have selected a nuclear encoded mitochondrial protein as a prime suspect for frataxin. Friedreich's ataxia predominantly involves the central nervous system and heart, the only two organs which rely on mitochondrial oxidative phosphorylation. The clinical picture of the disease, with optic atrophy, deafness, and diabetes being common, is very reminiscent of some of the known mitochondrial diseases. Biochemical studies have found raised levels of blood lactate in the condition, and a phenocopy of the disease is produced by deficiency of vitamin E, which is abundant in mitochondrial membranes and prevents mitochondrial peroxidation reactions. The data presented in this paper explore these suspicions. Chimeric genes composed of frataxin and the reporter gene, green fluorescent protein (GFP), were created within a cytomegalovirus expression vector, which was then transfected into COS cells. Similar constructs containing fusion genes of GFP and an N-terminal segment of the Huntington's disease gene containing a 23 residue length polyglutamate tract, and of GFP with human succinate dehydrogenase flavoprotein (SDH), were used as controls. Huntingtin is known to have a cytoplasmic localisation, whereas SDH is mitochondrial. The experimental system allows expression of the chimeric genes within the COS cells, giving rise to fusion proteins comprising full length frataxin bound to GFP, SDH bound to GFP, or an N-terminal huntingtin fragment bound to GFP. The fluorescent properties of GFP can then be used to localise the fusion product within the COS cells. The frataxin-GFP fusion product signal was spherical, in a typical pattern for mitochondria. This organellar location was confirmed by co-staining with CMXRos, a mitochondrial fluorescent dye, whose fluorescent emission can easily be resolved from that of GFP. The fluorescent pattern of the SDH-GFP fusion protein strongly resembled that of frataxin, whereas the pattern obtained with the huntingtin-GFP protein was diffusely spread throughout the cytoplasm. Thus, these data strongly suggest that frataxin is a nuclear encoded protein which is located in mitochondria.

EVAN REID

Relationship between lifetime ovulatory cycles and over-expression of mutant P53 in epithelial ovarian cancer

Schildkraut JM, Bastos E, Berchuk A. *J Natl Cancer Inst* 1997;89:932-8.

The authors hypothesise that a greater number of ovulatory cycles increases the risk of ovarian cancer by inducing proliferation associated DNA damage. A total of 197 patients with invasive ovarian epithelial cancer and 3363 control participants, between the ages of 20 and 54 years of age, were studied. Proliferation associated DNA damage was assessed indirectly by observation of P53 mutation status in the tumour samples. The authors found an association between lifetime ovulatory cycles and over-expression of the mutated P53 tumour suppressor gene in ovarian cancer. Results show that women whose tumours over-express P53 had the greatest mean number of lifetime ovulatory cycles (388), than women who had P53 negative tumours (342 cycles). Case control analyses were consistent with these findings. The findings are supportive of the hypothesis that mutations in P53 tumour suppressor gene in ovarian cancer may arise as a result of spontaneous errors in DNA synthesis that occur during ovulation induced epithelial proliferation. The findings are also consistent with the known heterogeneity of ovarian cancer, in terms of described molecular alterations, histopathology, growth rate, metastatic potential, chemosensitivity, and prognosis. This study suggests the possibility of several alternate molecular pathways, one of which being the result of spontaneous errors in DNA replication and consequent on ovulation related ovarian epithelial proliferation.

An editorial by Whittemore and McGuire in the same issue of the Journal (p 906) welcomes the results as direct support for the Fathalla-Pike hypothesis. Fathalla originally hypothesised that cancers arise as a concomitant of ovulation, such as increased cellular proliferation. Pike quantified this hypothesis in terms of ovarian cancer incidence rates and ovarian tissue age measured in units of mitoses. The Fathalla-Pike hypothesis predicts each year of ovulation increases the ovarian cancer incidence rate by a fixed (absolute) amount. Whittemore and McGuire also raised the important questions of the aetiology of P53 negative tumours and the role of ovulation in borderline epithelial cancers, usually P53 negative, but surprisingly with similar risk pro-

files to invasive cancer (and one would have thought similar relationships to ovulation).

JONATHON GRAY

Trinucleotide repeat expansion at the myotonic dystrophy locus reduces expression of DMAHP

Klesert T, Otten A, Bird T, Tapscott S. *Nat Genet* 1997;16.4:402-6.

Expansion of the myotonic dystrophy CTG repeat reduces expression of the flanking DMAHP gene

Thornton C, Wymer J, Simmons Z, *et al.* *Nat Genet* 1997;16.4:407-9.

Myotonic dystrophy (DM) is an autosomal dominant multisystem disorder with variable expression showing anticipation. The causative mutation was identified about five years ago as a triplet repeat expansion in the 3' untranslated region of a gene subsequently named the myotonin protein kinase gene (DMPK). However, the pathophysiology of the multisystem degeneration in this disease is still not understood and it has been suggested that DMPK alone cannot account for this. The findings that both mice deficient for the DMPK gene and over-expressing mice exhibit only minor abnormalities and that the repeat expansion in humans disrupts a DNase hypersensitivity site immediately upstream of the homeobox gene DMAHP, adjacent to DMPK, prompted Klesert *et al* and Thornton *et al* to analyse expression of DMAHP in DM patients. The former describe in fibroblasts and skeletal muscle cells a decrease in DMAHP transcript levels from the chromosome with the expansion compared to the wild type homologue. The latter similarly show that DMAHP expression in muscle, myoblasts, and myocardium is reduced by the repeat expansion in cis, the reduction increasing concomitantly with the size of the expansion. Both groups note that DMAHP is similar to a murine transcription factor regulating expression of the Na⁺ K⁺-ATPase alpha 1 subunit in developing muscle. These observations support the hypothesis that DMAHP is implicated in the disease phenotype. It will be of interest to see whether mice deficient for DMAHP more closely resemble the human disease than those deficient for DMPK, or perhaps both of these genes and possibly more are implicated.

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