Mitochondrial ribosomal RNA mutation associated with aminoglycoside-induced and non-syndromic deafness


Mutations of mitochondrial (mt) DNA have recently been identified in patients with sensorineural deafness and diabetes mellitus. Last year, this journal described a six-generation pedigree (including 55 affected subjects) with exclusively maternally transmitted deafness. Further work has strengthened the link between hearing loss and mt disease (J Med Genet 1992;29:86-90). The present paper describes the sequencing of the mtDNA in two subjects from this pedigree, together with the investigation of three Chinese families segregating for maternally inherited, aminoglycoside induced deafness. Many sequence alterations were identified in most of the mtDNA pairs which could explain the natural polymorphisms or previous sequencing errors. However, one point mutation was found in four families at 1555 A to G which codifies for the 12S RNA gene. Functional evidence strongly suggests that this mutation is causally related to the deafness. It lies in that part of the ribosome to which aminoglycosides bind and appears to alter translational fidelity in prokaryotes (mitochondria are thought to be evolutionary relics of symbiotic bacteria), and two point mutations of the adjacent factor which can only be observed in the small RNAs of aminoglycoside resistant yeast mt and Tetrahymena. This work, if replicated, will provide a whole new dimension to pharmacogenetics: if mt DNA mutates are found in sporadic aminoglycoside induced deafness, the service implications will be enormous.

ANDREW WILKIE

Functional interaction of the retinoblastoma protein with mammalian D-type cyclins


Physical interaction of the retinoblastoma protein with human D cyclins


The retinoblastoma tumour suppressor protein (pRb) is a negative regulator of cell proliferation. Its activity is modulated by phosphorylation. Hypophosphorylated pRb is found in resting cells and in early stages of cell cycle and inhibits cell cycle progression. Removal of pRb induced block and progression through cell cycle is associated with pRb hyperphosphorylation. It is suggested that pRb can regulate cell cycle by binding growth promoting proteins such as E2F transcription factors, which can only be associated with pRb in its hypophosphorylated form. Binding of E2F prevents it from acting as a positive transcription element for genes involved in cell cycle progression. These two papers report physical and functional interaction of the pRb with a subdomain of D-type cyclins. D-type cyclins form complexes with pRb by binding to the same sites as DNA tumor-suppressor proteins. Some cyclins (for example D2) appear to act by inducing hyperphosphorylation of pRb on binding, thus preventing its interaction with E2F. In contrast, other cyclins such as D1 are unable to phosphorylate pRb. Furthermore, the activity of D1 may be regulated through complex formation with E2F suggesting that D1 may have a similar role. These findings provide insight into the link between positive and negative regulators of cell cycle and fascination of this recent demonstration of cyclin D1 overexpression in a variety of epithelial and lymphoid tumours as a consequence of gene amplification and/or translocations occurring in these abnormalities. It is possible that overproduction of the D1 proteins outstrips the ability of pRb to bind them, thus allowing cells to overcome pRb regulation of cell cycle.

S N THAKKER

Charcot-Marie-Tooth disease type 1A: association with a spontaneous mutation in the PMP22 gene


Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy. CMT type 1A is associated with a 1.5 Mb DNA duplication at 17p11.2-12. Three patients. The PMP22 gene encodes a myelin protein and is mapped within the duplication. The myelin deficient trembler and trembler* mouse models of CMT type 1 contain point mutations in murine Pmp22. This paper describes 32 unrelated patients with CMT type 1 characterised by neuropathological features, including hypertrrophic neuropathy with ‘onion bulb’ formation and slowed motor nerve conduction, who did not have the 1.5 Mb tandem duplication at 17p11.2-12. This report describes the sequencing of the previous PMP22 mutations observed in patients. The sequencing of the present study is correlated with a point mutation in the PMP22 gene.

WILLIE REARDON

Mice with null mutation of the TGF-β gene have abnormal skin architecture, wavy hair and curly whiskers and often develop corneal inflammation


TGF deficiency results in hair follicle and eye abnormalities in targeted and Waved-1 mice


Transferring growth factor α (TGFα) is a member of the epidermal growth factor family and is expressed in a variety of normal tissues both in the adult and in the embryo. Functional roles for TGFα are implicated in wound healing, cell migration, angiogenesis, and cell differentiation. It is also expressed by neoplastic cells which also often coexpress EGF or the TGFα receptors suggesting the creation of autocrine loop which allows independent growth. These two papers report the changes in mice homozygous for null mutations of the TGFα gene. The mouse gene was disrupted by homozygous recombination in embryonic stem cells. The mice showed surprisingly few changes and were viable and fertile suggesting that recruitment of related molecules, that is, other members of the EGF family, may compensate for the lack of TGFα. The most pronounced and interesting changes were waviness of the coat and whiskers with derangement of the hair follicles. In addition, developmental abnormalities of the eye, open eyelids at birth, and corneal inflammation were observed in both the homozygous and, to a lesser extent, heterozygous mice. Waved-1 mice have been previously shown to have similar changes and both Northern analysis of TGFα expression in Wα-1 mice and Western blots of TGFα demonstrated the absence of Wα-1 and TGFα are allelic. These studies are interesting ontogenetically because they demonstrate the physiological role of TGFα but also because they suggest the disruption of genes of such growth factors may be important in human and mouse in which ectodermal dysgenesis is observed.

N S THAKKER