there is only one copy of each of the α_1 (I), α_2 (I) and α_1 (I)-like genes per haploid genome in humans. The genes coding for the two chains of human type I collagen are located on different human chromosomes[12,13]: α_2 (I) on chromosome 7 and α_1 (I) on chromosome 17 (E. Solomon, ICRF, London; F. Ramirez). The presence of the genes for the different chains of heteropolymer on different chromosomes has many well known precedents, and does not allow prediction of whether other related genes will be clustered near either gene.

One of the most studied systems of collagen gene regulation has been the Rous sarcoma virus (RSV)-transformed chick embryo fibroblast (CEF) where the production of type I collagen is dramatically decreased on transformation, probably by regulation at the transcriptional level[14,15]. The availability of temperature-sensitive strains of the virus has allowed analysis of both the induction and reversal of the transformed state (M. Sobel, NIDR, Bethesda) and has prompted studies of the transcriptional regulatory signals of the chick α_2 (I) collagen gene. The promoter of this gene has been inserted into a hybrid SV40/pBR322 shuttle vector (B. de Crombrugghe, NCI, Bethesda) which makes possible detection of promoter activity by measurement of the activity of the product of the *Escherichia coli* chloramphenicol acetyl transferase gene. Analysis of deletion mutants in the α_2 (I) collagen promoter region of this vector has provided some evidence for regulatory sequences, particularly those potentially capable of forming hairpin structures[16]. Neither this approach, nor attempts to correlate methylation of the α_2 collagen gene with its activity[17] (C. McKeon, NCI, Bethesda), have been successful in yielding clues to the precise nature of transcriptional regulatory mechanisms. However, a role for methylation in the reduction of activity of type I procollagen gene expression on transformation of human lung fibroblasts with SV40 has recently been reported[18].

Chick embryo chondroblasts, which normally produce type II collagen, when transformed with RSV strain show decreased synthesis of type II collagen and decreased levels of type II collagen mRNA (ref. 19 and S. Adams, University of Philadelphia). Surprisingly, type I collagen mRNA begins to accumulate, but is not used by the cells to make type I collagen. This is clearly a regulation at the level of translation. Other examples of translational regulation are seen in the effects of the N-terminal propeptides on collagen synthesis in normal and dermatosporatic sheep fibroblasts (P. Müller, Max Plank Institut, Munich) and in the regulation of collagen gene expression in fetal sheep skin development[20] and human lung fibroblasts[21]. Clearly, continued analysis of these and other systems using cloned probes will reveal the exact details of the variety of mechanisms cells use to modulate their collagen production.

A variety of human genetic disorders may be due to a structural defect of collagen. These include Ostrogenesis imperfecta, several of the Ehlers-Danlos syndromes and the Marfans syndrome. These disorders, while normally inherited in simple mendelian fashion, vary greatly in the severity of their clinical symptons. Biosynthetic studies of collagen production in cultured fibroblasts from affected individuals show abnormal secretion of collagen in all the three types of disease (P. Byers, University of Washington). The abnormality may be due to underproduction or lack of one constituent α chain, an abnormally long or short chain causing incorrect assembly of the precursor, or inefficient cleavage of the terminal peptides. The wide variability of symptoms has long caused difficulties of classifications of heritable disorders of connective tissue and of meaningful genetic counselling. Classification using biochemical methods is being attempted (D. Rowe, University of Connecticut), but DNA analysis is obviously of prime importance in the understanding of these disorders. Such analyses for two individual cases were reported. A fibroblast culture from an affected individual with the severe perinatal lethal form of OI type II demonstrated both shorter mRNA molecules for α_1 (I) chains and a deletion in the α_1 (I) chain gene in the DNA (M.L. Chu, Rutgers University). The second case is another, less severe form of Ostrogenesis imperfecta, where, remarkably, no α_2 (I) collagen chains are found at all in the skin[22]. While this case is obviously also a prime suspect for a deletion, in fact both pro-α_1 (I) and pro-α_2 (I) mRNAs are present in normal amounts in fibroblasts (D. Prockop, Rutgers University). An intriguing study was mentioned (P. Byers; J. Phillips, John Hopkins University) of a large Osteogenesis imperfecta family in which the disease segregates completely with a restriction site polymorphism near a growth hormone gene on chromosome 17. The suggestion is one of linkage of the disease gene (possibly the α_1 (I) chain gene) with the polymorphism, and is the first instance of this kind of analysis for a connective tissue disease. The analysis of more cases of the genetic connective tissue disorders is underway with the probes that are available, and the results will be of great basic as well as clinical interest. □

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Onco Gen

from Peter Newmark

A paper on page 607 of this issue implicates the cellular gene known as c-*mos* in malignancies of antibody-producing cells or their precursors and illustrates a novel way of activation of an oncogene.

The c-*mos* gene is so called because it is the cellular homologue (and presumably the precursor) of the oncogene carried by the Moloney murine sarcoma virus. Whereas the viral gene is oncogenic, c-*mos* is not unless activated. In 1980 Blair *et al.* (*Science* **212**, 941) demonstrated activation of c-*mos* by the attachment to it of the long terminal repeat sequences of the Moloney murine sarcoma virus, probably on account of increased expression of c-*mos* under the influence of the long terminal repeats.

Rechavi *et al.* now demonstrate a completely different mechanism of activation of c-*mos* by — strange though it may seem — the replacement of a sizeable chunk of the gene by extraneous DNA. The mechanism is all the more important because it is not the result of an artificial construct but has been discovered in a chemically induced mouse myeloma.

The evidence comes from a comparison of the sequences of the normal c-*mos* gene and an abnormal version in the myeloma. The abnormal version, which was able to transform NIH 3T3 fibroblasts — the standard assay for an oncogene — had lost over 500 nucleotides from one end, including the information for the first 88 amino acids of the c-*mos* protein.

Intriguingly, a 159-nucleotide block of DNA immediately adjacent to what is left of c-*mos* has the hallmarks of a transposable genetic element, suggesting that a transposition has displaced some c-*mos* nucleotides and activated what is left.

The mechanism of the presumed activation is as much, if not more, of a mystery than in the case of the point mutation that seems to have produced the human bladder carcinoma oncogene (*Nature* **300**, 143 & 149).

In a note added in proof, Rechavi *et al.* claim that they have also detected a rearranged c-*mos* gene in a Burkitt's lymphoma. It is not yet known if the rearrangement involves a transposition but it does seem to be the consequence of a translocation from chromosome 8 to 14, bringing the c-*mos* gene into the proximity of the variable-region heavy-chain immunoglobulin gene in a fashion similar to that already reported for the c-*myc* gene (see *Nature* **300**, 403).

Peter Newmark is deputy editor of Nature.

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