The molecular nature of the cystic fibrosis antigen

SIR—Cystic fibrosis is the most common autosomal recessive genetic disease among Caucasians. About 1 in 20 people, though healthy, is a carrier, and 1 in 2,000 newborns is affected by the disease. No reliable biochemical marker is available for the defective gene which has been localized on chromosome 7 (ref. 1). However, using isoelectric focusing, a serum factor (*p*I 8.4 and 8.5) has been identified[2] which is present at elevated levels in patients and obligate heterozygotes (parents). The gene for this factor, called the cystic fibrosis (CF) antigen, was assigned to chromosome 1 (ref. 3). Dorin *et al.*[4] described the molecular cloning of a myeloid leukaemia protein which could be isolated with a monoclonal antibody for the CF-antigen. Recently we described the isolation and molecular cloning of a pair of proteins, MRP-8 and MRP-14, from peripheral blood leukocyte cultures[5], which both map to chromosome 1 (K.H. Grzeschik, personal communication). The sequence of MRP-8 is identical to the sequence of Dorin *et al.*[4] with the exception of one additional nucleotide, which alters the predicted last 15 amino acids, due to a shift in the reading frame.

With monospecific antisera against the recombinant proteins we are able to titrate MRP-8 and MRP-14 at levels of less than 1 ng ml^{-1}. Unexpectedly, on screening many sera and plasmas of carriers and non-carriers, we detected MRP-8 in only three cases (2–5 ng ml^{-1}), whereas we always found MRP-14. For cystic fibrosis patients, the plasma levels of MRP-14 were in the range 250–5,500 ng ml^{-1} (n = 16), and for obligate heterozygotes in the range 120–380 ng ml^{-1} (n = 23) with one sample at 75 ng ml^{-1}. For control individuals, values of 2–50 ng ml^{-1} were found in 32 cases, and values of 55–135 ng ml^{-1} in seven cases. These data suggest that MRP-14 is the CF-antigen. Because we isolated MRP-8 and MRP-14 as a complex[5], Dorin *et al.* probably isolated the CF-antigen as a complex of MRP-8 and MRP-14 as well. If so, they obtained only MRF-8 sequence because, as shown by our own data, MRP-14 is N-terminally blocked. Another possibility, though remote, would be that a protein with the 15 C-terminal amino acids as reported[4] represents a different allele of MRP-8 not recognized by our antiserum. In that case more than one CF-antigen would exist.

The increased level of CF-antigen(s) might not be unique to cystic fibrosis; in plasma of patients suffering from other diseases (for example polyarthritis) we also find levels well above the normal average. It will be intriguing to discover the common denominator.

In our preliminary study there is a minor overlap between the MRP-14 plasma levels of obligate heterozygotes for the CF gene and other healthy volunteers. This overlap is probably caused by samples from unidentified carriers (1 in 20) and unrecognized disease cases. Nevertheless, it so far seems possible to distinguish most non-carriers from carriers of the CF gene, by a simple enzyme-linked immunosorbent assay (ELISA) test using our monospecific anti-MRP-14 serum. This will be important for relatives of CF patients.

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Eustatic sea-level change

SIR—Gaffin[1] has demonstrated a negative correlation, with a phase difference of 10 Myr, between geomagnetic reversal rate and recent data on long-term eustatic sea-level change[2]. He continues, "it is reasonable to demand that the dominant mechanism controlling eustasy be plausibly linked to reversals too" and assumes that oceanic ridge volume is the controlling factor. His calculation of ocean basin volume takes other variables (such as continental hypsometry and water volume) to be fixed. With these constraints he calculates the seafloor creation rate required to cause the long-term eustatic sea-level change, and finds a positive correlation, again with a 10-Myr phase difference. Such a result is of great theoretical interest.

There are, however, other possible controls on sea level that need to be considered. For example: (1) change in the age distribution of oceanic crust has been shown to have an effect on ocean-basin volume[3,4]. The development of 'Atlantic' type oceans (with no marginal subduction) at the expense of 'Pacific' type oceans (where the age of oceanic crust being subducted is essentially random) is not the same as a simple change in spreading rate (as suggested by Gaffin[5]), as the age distribution of non-subducted crust will change. The development of the Atlantic and Indian oceans over the past 150 Myr, the timespan considered by Gaffin[1], would give rise to a rise and subsequent fall in sea level of the order of tens of metres. A fall of roughly 100 m since the mid-Cretaceous has been suggested[4].

(2) The similarity of modern normalized hypsometric curves[6] and the apparent relationship between modern continental area and elevation[7,8] suggests that former continental masses should have conformed to the same patterns. Using modern data on continental hypsometries[9] it is possible to calculate the effect on global sea level of the split up of Pangaea[8]. This gives a predicted rise in sea level of some 130 m between about 140 and 50 Myr before present, and a small drop (of the order of 10 m) since then.

(3) Massive mid-plate volcanism from about 110 to 70 Myr before present in the Western Pacific has been used to suggest a sea-level rise at that time of a minimum of 40 m and probably nearer 100 m (ref. 10).

All these changes need to be removed from whatever eustatic sea-level curve is used before ascribing the remaining variation to change in ridge volume. The large differences in absolute values of sea-level change between some recently published curves[2,11], and the view that in any case we are unable to isolate eustatic changes from other sea-level change[12] suggest caution in applying Gaffin's correlations.

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Any old iron?

SIR—Martin and Fitzwater (*Nature* **331**, 341–343; 1987) suggest that the growth of phytoplankton in ocean waters at high latitudes is restricted today by the limited amount of iron available, and that during recent ice ages the carbon dioxide content of the atmosphere was reduced because there was then more dust in the air. This suggests a possible way to alleviate the anthropogenic greenhouse effect, which is at present a cause for concern. By adding iron compounds to the oceans, a 'technological fix' to remove carbon dioxide from the air might be practicable.

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