Further support for the idea that an immune response originally directed against BSA may cross-react with an islet antigen comes from the finding, by the same group[2], that anti-BSA antibodies found in patients also bind to p69.

Karjalainen and colleagues offer a hypothesis which is elegant and simple. The ABBOS peptide is immunogenic in hosts with a diabetogenic haplotype, and is absorbed from the immature gut. The resulting ABBOS-specific immune response could mediate destruction of β-cells through the "shared epitope", p69. Unrelated infectious events that generate the release of γ-interferon would induce expression of p69, transiently exposing β-cells to immune-mediated destruction (see figure). The long preclinical course preceding the onset of diabetes could be explained by the temporary nature of such episodes of p69 expression on β-cells.

There are, however, some problems inherent in this study as it stands. The authors boldly state that ABBOS and p69 share an antigenic epitope based on cross-reactive antibody binding. As destruction of β-cells is believed to be primarily T-cell mediated, T-cell reactivity is of greater significance than antibody specificity and, in any case, would be necessary for a secondary anti-p69 antibody response. Therefore Karjalainen *et al.* must imply that p69 and BSA contain a homologous linear peptide sequence in order to trigger the T-cell response. A further difficulty is that binding of antibody to a molecule does not necessarily indicate biological relevance, as it says nothing of binding affinity or ability to mediate effector functions[3]. These points are not just academic. Diabetic patients have long been known to have a variety of autoantibodies, including those against insulin[4] and a 64K islet-cell protein[5], and although they are of predictive value they have failed to tell us much about the pathogenesis of β-cell destruction.

So, intriguing though it is, the hypothesis requires further testing. It remains to be seen whether ABBOS and p69 do have a similar amino-acid sequence, whether the T cells of diabetics are responsive to p69, and whether reactivity to p69 is pathogenic, or results from spreading of autoimmunity to secondary antigens following tissue destruction. □

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CYSTIC FIBROSIS

More from the modellers

James M. Wilson and Francis S. Collins

THE mouse model for cystic fibrosis published last month[1,2] (and discussed by us in News and Views[3]) was a remarkable scientific achievement and has had an immediate influence on investigations of this deadly disease. That model was developed by a group at the University of North Carolina (UNC) using homologous recombination in embryonic stem cells. On page 211 of this issue[4], David Porteous from Edinburgh and his collaborators (Dorin *et al.*) now announce the generation of another murine model of cystic fibrosis with embryonic stem cell technology. This new model expresses a surprisingly different phenotype to that found in the UNC animals.

A litter of mice resulting from the mating of two CF insertional mutant heterozygotes; the litter consists of five wild type (+/+), three heterozygotes (*cf*/+) and one CF insertional mutant homozygote (*cf*/*cf*). The *cf*/*cf* mutant is the black mouse. Coat colour variation is independent of the CF gene, but the animal's genotype was identifiable by electrophysiology and histological abnormalities. (Picture courtesy of J. R. Dorin *et al.*)

In our previous News and Views article we described the salient features of the cystic fibrosis (CF) model from the UNC group. Animals homozygous for the disrupted CF gene, subsequently referred to as *cf*/*cf*, develop an extremely reproducible phenotype characterized by death within 30 days of birth due to bowel obstruction, a condition that closely resembles the syndrome of meconium ileus in humans. Pathology of the bowel, nasal mucosa and submaxillary glands was characteristic of the disease, but there was a notable absence of symptoms in the lungs, pancreas, hepatobiliary system and reproductive tract.

The *cf*/*cf* mouse described in this issue differs in several ways. Evaluation of the new model was restricted to eight *cf*/*cf* mice for a period up to 30 days postpartum. Electrophysiological abnormalities were identified in epithelia of each animal consistent with defective transport of chloride ions. Unlike the UNC animal model, however, these *cf*/*cf* mice developed a variable spectrum of pathological features and remained free of overt clinical disease. Most animals had characteristic pathology in gut mucosa, but two of the eight *cf*/*cf* animals were indistinguishable from non-CF animals in terms of gross and histological pathology. In addition, the authors describe focal pathology in lung, vas deferens and salivary glands of single animals; the relevance of these isolated observations to the expression of CF in this model will require longitudinal blinded studies with larger numbers of animals.

Several mechanisms could explain the variation in phenotype observed between the two models. Both of them were developed from a line of embryonic stem cells in which the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) had been disrupted at exon 10 by homologous recombination. The UNC group used a replacement vector to introduce an in-frame stop codon in the coding sequence of exon 10, whereas the Edinburgh group used an insertional vector to introduce a duplication of genomic sequences spanning intron 9 and exon 10. An advantage of the insertional strategy is that it can be used in subsequent steps to introduce specific mutations into the CF gene such as the common ΔF508 mutation (in fact Dorin *et al.* state that such a cell line has been generated). The disadvantage is that the transcript derived from this kind of gene disruption may splice out the duplication at a low level thereby reconstituting small amounts of normal CF gene function. The milder phenotype of the *cf*/*cf* animal described by Dorin *et al.*, therefore, may be explained by low levels of residual CFTR function. Other causes of phenotypic heterogeneity between and within *cf* genotypes include environmental influences and the genetic background into which the *cf* mutation has been bred (into three different inbred strains in the study by Snouwaert *et al.*[1]

or into an outbred strain in the study by Dorin *et al.*[4]).

This new animal model of CF has several features that will greatly enhance its usefulness. The apparent absence of lethal bowel obstruction may allow survival until pathology in other organ systems such as lung, pancreas or liver can be further elicited. In addition, the marked variation of phenotype in animals with the same *cf* genotype provides an excellent opportunity to identify environmental and additional genetic factors that contribute to expression of disease. This heterogeneity in phenotypic expression, however, will need to be taken into account in studies of potential therapies that use clinical or pathological endpoints.

The apparent differences in the first two mouse models of CF underscore the complexities of modelling human diseases in animals. They are a timely reminder of the value of having important problems tackled by more than one research group, even if the differences in strategy seem minor. The challenge remains to use the full power of mouse genetics to understand the basis of the differences between these models in the context of the pathophysiology of CF in humans. □

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PALAEOCLIMATOLOGY

Avoiding a permanent ice age

William R. Kuhn

ALTHOUGH the Earth's climate is clement, on our neighbouring planets things are different. The greenhouse effect has run away on Venus, giving the planet a scorching atmosphere. And Mars is a frozen world. How lucky are we? Calculations by Caldeira and Kasting on page 226 of this issue[1] suggest that climate cooling when the Earth was young would have triggered the growth of carbon dioxide ice clouds high in the atmosphere, locking the Earth into a permanent ice age. The present warmth of our climate might be taken to indicate that previous notions of an early ice age are wrong.

One of the vexing problems of palaeoclimate is known as the faint young Sun paradox[2]. Models of solar evolution and observations of stars like our Sun in various stages of evolution indicate that solar luminosity was significantly less — by 25–30 per cent — than it is today — so much so that the Earth would have been a frozen world if all else remained the same. Yet there is geological evidence that there was liquid water on the planet up to 3.8 billion years ago[3]. Speculation has centred on increased concentrations of certain gases in the atmosphere that create a greenhouse effect, most notably carbon dioxide, and arguments have been put forth that the resulting warming could counteract the faint young Sun and save the planet from total glaciation.

Although the earlier studies of palaeoclimate recognized that carbon dioxide, in large enough amounts, could have counteracted the lower solar luminosity, they did not include the possibility that carbon dioxide ice crystals could have formed. Caldeira and Kasting speculate that air temperatures could have fallen enough for carbon dioxide ice clouds to have appeared in the young atmosphere. These clouds might have looked much as cirrus water ice clouds do today, which frequently appear as white, wispy or filamentary clouds above about 6 km. But there is a substantial difference: water ice clouds generally heat the Earth because of their substantial greenhouse effect[4], whereas carbon dioxide ice clouds would have more of a tendency to cool the surface because they are good scatterers of radiation, including solar radiation.

The possible existence of carbon dioxide clouds in the early atmosphere has implications for what are known as runaway effects. Could some transient change in the Earth or its atmosphere have made the early climate unstable, causing polar ice sheets to grow and cover the Earth? If so, then obviously the process was reversible.

Simple models have been developed that indicate the number and stability of climate states for different solar luminosities, and limit the ranges of those parameters that affect climate. For example, studies have shown that decreases of solar luminosity of perhaps only a few per cent could cause polar ice to spread over the whole planet[5,6]. In the light of Caldeira and Kasting's work, it seems unlikely that this happened even with a 25–30 per cent difference in solar luminosity. Carbon dioxide clouds may have formed that would have prevented the Earth from ever returning from its frozen state. (Even the build-up of gaseous carbon dioxide — cut off by ice from the Earth's rocky surface, a carbon dioxide sink — would not have negated this.) If Caldeira and Kasting are correct, then the Earth may have been warm from its birth and remained warm with an abundance of greenhouse gases such as carbon dioxide and water vapour.

Our recent awareness that we have the potential to alter global climate has accelerated the interest in and importance of climate modelling. Much of what we learn from those studies is applicable to our efforts to understand what Earth was like billions of years ago. However, we are finding that the Earth system is vastly complex, and it is not obvious whether the relative importance of a process in the geological past was the same as it is today.

For example, the biosphere plays a strong role in regulating climate today, but could hardly have done so a few billions of years ago. And what fraction of the Earth was covered by land? Rapid continental growth occurred 2.7–3 billion years ago[7], so that before then, there was probably little exposed land. How would this have affected the change in atmospheric carbon dioxide through rock weathering?

Solar radiation is clearly the most important determinant of the Earth's temperature. Last year, Graedel *et al.* called into question the magnitude of the solar flux early in Earth's history[8]. It is possible that the young Sun was not as faint as we thought. New solar models, albeit speculative, include an early solar mass loss that leads to luminosities larger than the 75–80 per cent generally assumed.

Another important uncertainty in modelling both palaeoclimate and present climate is the treatment of clouds. If it weren't for clouds in the present atmosphere, the temperature would be some 20 °C higher. Most clouds in our present-day atmosphere are more effective at reflecting solar radiation away from the surface than they are at trapping heat by the greenhouse effect. Cirrus clouds are the exception. It is not only cloud amount, thickness and droplet size that are important, but also

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