EBV Ig-like domains

SIR—Two proteins encoded in the genome of Epstein–Barr virus (EBV) possess regions with sequence similarity to the immunoglobulin domain of the immunoglobulin superfamily[1]. We now report a third domain in p140, an EBV envelope protein.

A neural-network computer search program trained to recognize immunoglobulin domains[2] was used to scan amino-acid sequences stored in the National Biomedical Research Foundation (NBRF) protein database (release number 19). As well as detecting virtually all known members of the immunoglobulin superfamily, the program identified viral proteins with previously unrecognized superfamily similarity including the p140 envelope protein of EBV (NBRF filename QQBE1).

The immunoglobulin-like domain of p140 comprises 106 amino acids between the cysteines at positions 888 and 994, and is thus similar in length to some T-cell receptor variable (V) immunoglobulin domains[3]. Chou–Fasman and Garnier-Osguthorpe–Robson algorithms predict 5 β strands of 5–12 amino acids between the cysteines and 2 flanking β-strands, consistent with the secondary structure of an immunoglobulin fold[3]. Alignments between members of the immunoglobulin superfamily and the immunoglobulin-like domain of p140 using the ALIGN program (Protein Identification Resource, NBRF) indicate that the highest similarity scores (standard deviation > 3) are usually obtained with human or mouse T-cell receptor γ chains. The alignment of the immunoglobulin-like domain of p140 with the V region of human T-cell receptor γ-chain K20 (filename A24574) scored highest (s.d. = 5.41), with 25 per cent sequence identity and 10 per cent conservative substitutions. Similarity with s.d. > 4 is also observed with other superfamily members (such as human IgG γ 1 constant region GHHU and rat Ig κ chain V region B23986). The carboxyl-terminal region of the immunoglobulin-like domain of p140 displayed the most marked sequence similarity with known immunoglobulin domains, including those in T-cell receptor α, β and γ V-chains (see figure).

The occurrence of several immunoglobulin-like domains in EBV-encoded proteins indicates a novel mechanism by which molecular mimicry might participate in multiple sclerosis (MS), which is serologically and epidemiologically associated with exposure to several viruses, EBV[4] included. One of us has previously proposed that non-specific 'mitogenic' activation of central nervous system T cells could result in bystander demyelination, and has demonstrated that activating anti-T-cell receptor antibodies are efficiently presented by glial cells *in vitro*[5,6].

It is possible that activating anti-T-cell receptor antibodies would arise in certain predisposed individuals as a consequence of epitopes shared with viral proteins bearing immunoglobulin-like domains, such as EBV. Anti-T-cell receptor antibodies may be more effectively mitogenic in the central nervous system than in the periphery because of its low constitutive activity of complement and the lack of effective reticuloendothelial sequestration.

It is noteworthy that the murine homologue of a human T-cell receptor V β-gene linked with MS[7] has significantly similarity (s.d. > 3) with the carboxyl-terminal region of the EBV p140 immunoglobulin-like domain. It will be interesting to compare T-cell receptor amino-acid sequences of T-cell clones over-represented in the central nervous system or T-cell receptor susceptibility genes in MS, with protein sequences of other viruses associated with MS.

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QQBE1   EV L Q T L R S MNM Y PAVLG R VG E Q G - P DQM FEV QHG PET VLRQA L RLLLGTWSSF A SEQ Y E C
A24574  EV I Q F L V S IS- Y DGTV- R K- E S G I P SGK FEV DRI PET STS-T L TIHNVEKQDI A T-- Y Y C
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Local alignment of the carboxyl-terminal region of the immunoglobulin-like domain of Epstein-Barr virus envelope protein p140 (QQBE1) with a human T-cell receptor γ chain (A24574) (s.d. = 5.35 by ALIGN program, bias =6, gap penalty = 6). Identical residues (34 per cent) are boxed; conservative substitutions according to Dayhoff Matrix (19 per cent) are denoted by bars.

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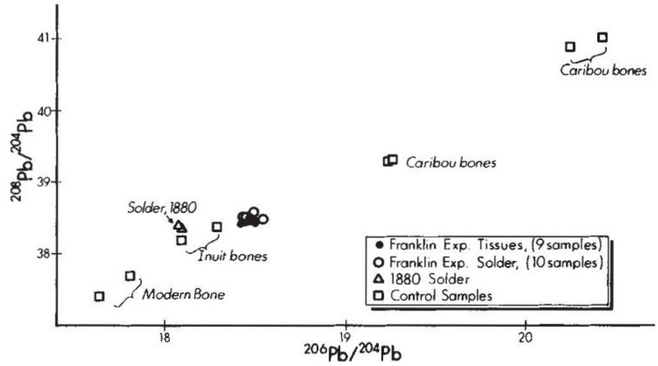
Did solder kill Franklins men?

SIR—One of the greatest mysteries of Arctic exploration is the loss of the 129 crewmen and officers of the Sir John Franklin expedition (1845–48) in search of a North-West Passage[1]. As part of a forensic investigation of recently discovered human remains from the expedition, atomic absorption analysis yielded levels of lead in tissues consistent with acute lead intoxication[2]. These findings indicate that it was exposure to toxic levels of lead that adversely affected the health, judgement and ultimate survival of the expedition members. It has been hypothesized[2,3] that food preserved in soldered tins was the source of the high lead levels. Because lead isotopes do not fractionate in biological systems, their ratios within human tissues are a reflection of the ratios from the contaminating source[4]. Matching lead isotope ratios would indicate that the lead in the human remains came from the soldered tins. We have carried out isotope studies of lead from the human remains and tins to test the hypothesis.

The materials used in the analyses were collected from Beechey and King William Islands, Northwest Territories, Canada. Bone samples from Inuit and caribou from the same time period and geographical



Lead isotope analyses, carried out by thermal ionization mass measurement using a VG-Micromass-30 mass spectrometer. The measured lead isotope ratios were corrected for mass fractionation, as determined by repeat analyses of US. National Bureau of Standards NBS SRM 981 standard lead. The precision of the lead isotope ratios was established by replicate analyses and indicated a variation of one part per thousand at the 95% confidence level. Error limits are indicated (approximately) by the size of the circular symbols.