Symposium on epidermolysis bullosa

A symposium on epidermolysis bullosa (EB) was held on 4 and 5 October 1991, at Jefferson College of Medicine, Thomas Jefferson University, Philadelphia, on the occasion of celebrating the new Blumele Life Science Building housing research areas for dermatology, biochemistry, molecular biology, and other disciplines.

At no previous meetings devoted to these mostly inherited blistering diseases has so dramatic a breakthrough in our understanding of basic molecular mechanisms been presented. The keynote lecture was by Elaine Fuchs on 'Mice and men: genetics of epidermolysis bullosa simplex'. At the the Howard Hughes Medical Institute, University of Chicago, Fuch's group has studied the effect of mutations in keratin genes both by fibril reassembly analysis and by introducing site-directed mutated keratin genes into transgenic mice. On electron microscopy the resulting blistering forepads showed similarities with the findings in basal keratinocytes in EB simplex in man.

Concurrently, Ervin Epstein's group at the University of California, San Francisco, had picked the keratins as candidate genes for EB simplex and initially showed genetic linkage of EBS kindreds to the RFLPs flanking the keratin gene clusters on chromosomes 12 and 17. Since K5 (58 kD) on chromosome 12 and K14 (50 kD) on chromosome 17 make the keratin pair expressed in the basal cells and constitute the proteins of the cytoskeletal tonofibrils, restriction cutting of their corresponding genes allowed Epstein to spot one specific mutation in K5 in local EBS Weber-Cockayne and one small deletion in K14 in generalised EBS Köbner.

Contrary to these EBS forms which on electron microscopy show cytolytic changes, the group of dominant herpetiform EB(S) Dowling-Meara patients have from studies in the late 70's been clear candidates for keratin mutations, since tonofibrillar clumping is a hallmark of the basal cell abnormality. Consequently, Fuch's group concentrated on such patients and was able to show a specific C-T (arg-lys) mutation in K14 exon 125 in one patient and an arg-his K14 exon 125 mutation in another. This indicates a critical role for this exon in the NH2 terminal end of the gene. Site directed mutations in this end of K14 before fibril reassembly and transgenic mice experiments had a more severe effect and created tonofibrillar clumping in the blistering mice, whereas COOH-terminal mutations showed milder effects and did not give tonofibrillar clumping. Hence, the striking clinical difference between classical EBS and the herpetiform EBH-DM can be explained by different mutations in the same gene(s).

Other types of EBS also need to be explored, but no keratin-like sequence has been found on 8q24 where EBS1 is mapped. Three further EBS families were reported to map on chromosome 12 (M Rynänen (Finland, Philadelphia), P Humphries (Ireland), B Höyheim (Norway)). Locus EBS2 is now used for chromosome 12 and EBS3 for chromosome 17 until keratin specific mutations are proven. EBS4 (HGM11) is free for any other locus as the family provisionally assigned to chromosome 1 was found to have a higher lod score for a chromosome 12 marker (P Humphries).

The host institution, led by Jouni Uitto, has excelled in characterising, cloning, and mapping genes expressed in the basal membrane zone (BMZ). An excellent review was given by Uitto, including their own cloning and mapping of bullous pemphigoid antigen 1 (BPA1) on chromosome 6p and mapping (cloned by others) of antigen 2 (BPA2 on 10q). Important groups of blistering diseases are created by autoantibodies to these antigens. Since electronmicroscopic studies by German and Japanese workers in the 1970's showed reduction and abnormalities in anchoring fibrils (AF) in dominant dystrophic EB, and Bourgeson and others in the early 1980's showed type VII collagen to be the structural protein of AF, COL7A1 has been a candidate gene for these diseases (the same applies to the recessive severe dystrophic EB that Briggaman found devoid of AF). However, scant amount of protein has delayed proper aa sequencing. Uitto's group (A Christiano and others) in Philadelphia reported on the cloning of COL7A1 by using antibody screening of a keratinocyte cDNA expression library and of an RFLP. R Knowlton, from the same group, reported on the linkage (without recombination) of this and flanking RFLPs on chromosome 3p21 to dominant dystrophic EB in three different families. The search is now directed towards proving the EBD1 mutations are in COL7A1 itself. For recessive dystrophic EB (EBR1) studies with COL7A1 have not yet been reported. A Hovnanian (France) has shown PCR primer polyorphism within the collagenase gene and studied eight recessive EBD families. In one of them he was able to exclude collagenase (CLG on 11q) as the candidate gene. Hence, the meeting did not report decisive progress in recessive dystrophic EB, although it promises well for the future. L Briggaman (Zürich) reported on the animal model, sheep lacking AF, and expression of COL7A1.

M-L Chu (Philadelphia) presented the unexpected discovery of a new collagen by applying molecular techniques and the attempts to show its function. Proteins unique to the hemidesmosomes (HD), several of which are considered candidate genes for recessive junctional EB, were discussed by G Giudice (Milwaukee). J-D Fine of the University of North Carolina gave an interesting overview of the immunofluorescence (IF) testing of epitopes of the human skin and their use in diagnosis.
and research in EB. This practical side was enhanced by R Eady's report on the London experience in prenatal diagnosis of various severe types of EB, reasonably safe diagnosis now being possible by using either EM or IF (so far both) on skin biopsies taken in the 15th week instead of the 20th week as before. The clinical phenotypes of the numerous EB types and variants (some say 23) were reviewed by T Gedde-Dahl Jr (University of Tromsø).

In the final panel discussion of research needs in EB, two points are worth mentioning. R Briggaman (University of North Carolina) addressed the issue of raising false hopes of a cure when new discoveries of the Fuchs/Epstein (see above) type were spread to the press. D Prockop (Philadelphia) counteracted this by mentioning the fantastic developments in collagen gene engineering. Gedde-Dahl stressed that despite EBS being the result of keratin mutations, the natural course of Dowling-Meara signified a considerable contribution of environment to the severity of the disease, and therefore hope for better treatment. The second and clear ethical issue was addressed in the concluding remarks of I Hashimoto (Hirosaki) quoting the reaction of a counselled Japanese mother who had lost a child with junctional Herlitz type EB. After having understood the high risk of a future child, and that this child in all probability would also die, she said: "Then there is no problem. I will have another child." Hashimoto concluded: The research challenge is above all severe dystrophic epidermolysis bullosa.

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