ABSTRACTS

SYMPOSIUM ON EPIDERMOLYSIS BULLOSA: MOLECULAR GENETICS OF THE CUTANEOUS BASEMENT MEMBRANE ZONE

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7 Mosaicism in HERITABLE SKIN DISEASES. AS Palmer. Departments of Pediatrics and Dermatology, Northwestern University Medical School, Chicago, Ill. A mosaic individual is composed of more than one genetically different population of cells. Mosaicism originates from a genetically homogenous zygote. Mosaic skin conditions often manifest along lines of Blaschko, which are thought to represent the patterns of embryologic development. Functional mosaicism occurs in X-linked disorders because of X-inactivation. Mosaicism is less frequently seen in dominant disorders. Mosaic somatic mosaicism results in a mutation on an autosomal chromosome, with expression limited to cells that carry the mutant gene. If the genomic mosaicism involves germline cells, the mutation may be transmitted to all cells of the offspring. Theoretically, mutations that are lethal to the organism early in embryogenesis may be expressed in the mosaic state in a viable organism. Mosaicism can also be observed in cells selected by immortalization. The mechanism by which cells express mutated genes and replicate in the fetus by contiguous normal cells.

8 EB SIMPLEX AND THE GROWING FAMILY OF KERATIN DISEASES. W.M. Irwin-LeMone, Elizabeth L. Engar, Frances J.D. Smith, Susan M. Morley, Carrie C. Gliemann, Laura J. Gordon, Colin S. Morris, Irene M. Leggo, Robin A.J. Emery, and E. Burgess Smith. Departments of Dermatology, London, England, and Department, Southern General Hospital, Glasgow; Experimental Dermatology, Royal London Hospital, London, England, and Department of Medicine, University College Hospital, London, UK.

9 HOMOZYGOUS FRAMESHIFT MUTATIONS IN THE PLECTIN GENE CAUSE EPIDERMOLYSIS BULLA MUCHARA-DICKENSON. Theresa L. Smith, Lamia Pulkkinen, Elizabeth L. Rusty, Elizabeth Rusie, Robin A.J. Emery, Brenda L. Oates, Angela Memmel, and John A. McKeon. The Department of Dermatology, St. James's University Hospital, Leeds, UK; Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia, PA; University of Dander, Dundee, UK; Kelo University School of Medicine, Tokyo, Japan.

10 HOMOZYGOUS DELETION MUTATIONS IN THE PLECTIN GENE CAUSE EPIDERMOLYSIS BULLA MUCHARA-DICKENSON MUSCULAR DYSTROPHY. Lamia Pulkkinen, Frances J. Smith, W.M. Irwin-LeMone, Susan M. Morley, Carrie C. Gliemann, and Angela Memmel. The Department of Dermatology, St. James's University Hospital, Leeds, UK; and the Department of Dermatology, University of Pennsylvania, Philadelphia, PA.

11 JUNCTIONAL AND HEMIDESMOSONAL VARIANTS OF EB: MUTATIONS IN THE HEMIDESMOSE-ANCHORING FILAMENT COMPLEX. PHENIX Jost, B. McGrath, and D. Christiano. Departments of Dermatology and Cutaneous Biology, and Biochemistry and Molecular Biology, Jefferson Medical College, Philadelphia, PA.

12 LAD4, THE LINEAR IGA BULLOUS DERMATOSIS AUTOANTIGEN, IS ABSENT IN A SUBSET OF JUNCTIONAL EB PATIENTS. Patschke, M. Varga, P. Spiekerman, M. Murankovic, J. Offelt, B. Trax, S. Rau, G. Glading, S. Balder, M. Loppnow, H. H. de Boer, A. Tugum. Departments of Dermatology at Stanford University School of Medicine, Stanford, CA; Medical College of Wisconsin, Milwaukee, WI; University Hospital, Grazing, the Netherlands.

We have recently described LAD-1, a novel 120 kD anchoring filament protein which is the target of autoantibodies in the acquired blistering disorder linear IgA bullous dermatosis. Anti-LAD-1 mab 123 induces dermal-epidermal separation of human skin in vivo. LAD-5, 248 integrin and BPIV-3 mab's have been demonstrated to be present in some patients with junctional epidermolysis bulla (JEB) but the expression of LAD-4 in JEB patients was unknown. The purpose of this study was to identify and characterize expression of LAD4 in JEB patients. Of the JEB patients tested, only those with generalized atrophic benign IgA (GABE) showed LAD4 autoantibodies. Skin biopsies and primary keratinocytes from 6 GABE patients showed the following results: a) 2 patients' biopsies and keratinocytes showed normal BP180 and LAD-4 expression but decreased expression of laminin-5. b) Biopsies from 2 patients showed normal laminin-5 expression but decreased expression of both LAD-1 and BP180. Keratinocytes cultures from each of these 2 patients showed normal laminin-5 but undetectable LAD-1 and BP180 expression by IF microscopy and immunoblot analysis. Radioimmunoassay showed substantially decreased binding of GABE antibodies to laminin-5 and laminin-10. The expression of LAD4 was not associated with autoantibodies to other epidermal components in the 1 of the 2 patient keratinocyte cultures. Skin biopsy from 1 patient showed normal expression of laminin-5 and LAD-4 but absent expression of BP180. The density of LAD4 expression by IF microscopy was reduced in the autoantibody positive and immunoprecipitation analysis of patient cells. The other patient's skin biopsy showed normal staining for laminin-5, LAD-4 and laminin-10. This is the first report of an absent or reduced expression of LAD4 and BP180 exist in the skin of these patients. These features were similarly noted in immunoblots, IF, and immunoprecipitation analysis of patient cells. These results indicate that the GABE/EB phenotype is associated with multiple defects in the anchoring filament cytoskeleton. The pathogenesis and clinical correlation of these defects remain to be determined.
DYSFIBRIN EBN AND MUTATIONS IN TYPE VII COLLAGEN. Angela M. Christiansen and Joseph D. Venge. University of California and Cardiology and Cardiovascular Research Institute, University of Pennsylvania, Philadelphia, PA.

A wealth of information on specific mutations in the type VII collagen gene in different forms of DEB has allowed us to begin to establish genotype-phenotype relationships. Following the synthesis of type VII collagen, the procollagen is transported to the cell membrane where it is subsequently, consequently, mutated. Following the synthesis of type VII collagen or its interaction with collagen fibers, it is expected that the mutant collagen will result in a DEB phenotype. In HS-DEB, the persistent mutation contains a premature termination codon in both alleles of the affected individual. The PTC results in the failure of all type VII collagen mRNA which are therefore unable to function properly for assembly into anchoring fibrils. This observation is consistent with the ultrastructural demonstration of complete absence of the anchoring fibrils in HS-DEB, and explains the extreme fragility of the skin characteristic of the phenotype. In the milder forms of DEB, at least one of the alleles encodes for a full length type VII collagen polypeptide. However, this allele usually contains a missense mutation which can change the conformation of the protein. As a result of these two mutations, type VII collagen molecules may be able to assemble into anchoring fibrils, which are, however, unlikely to be stabilized by disulfide bonding. Thus, these attachment structures, although present, are weakened, resulting in the moderate severity of the skin observed in the milder forms of DEB. Within the dominantly inherited form, the recurrent mutation detected thus far is the substitution of a glycine residue which occurs within the collagenous domains of the molecular characteristic of the repeating Gly-X-Y amino acid sequence. These amino acid substitutions destabilize the collagen triple-helix and render the molecules susceptible to intrinsic degradation. However, some of these non-functional molecules are able to associate with type VII collagen synthesized from the normal allele, through a mechanism known as dominant negative interference. A strain responsible for negative interference in the collagen fibrils can form, consistent with ultrastructural demonstration of relatively thin anchoring fibrils in DEDEB, and the relatively mild clinical phenotype. Collectively, the type and combination of mutations are able to predict, in general, the mildness of the clinical phenotype observed in the disease. The new nature of the genetic lesion, their positions along the type VII collagen gene, and the dynamic interplay of the two mutant alleles on the individual's genetic background will determine the precise phenotype of the patient.

THE NATIONAL EPIDEMIOLOGY BULGOSA REGISTRY: A LONGITUDINAL EPIDEMIOLOGIC PROJECT WHICH CAN FACILITATE THE PERFORMANCE OF BASIC SKIN RESEARCH. E. D. Fine and a M.A. R. Ruggles. Department of Dermatology and Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Approximately 1500 patients with X-linked dominant and skin-related conditions (including X-linked recessive disorders, skin cancer, multiple epidermolysis bullosa) have been enrolled in the federally funded, multicenter National EB Registry (NEBR) since its inception in 1986. Exhaustive data have been collected on each subject, including details of medical, family, and social histories, as well as details on their specialized diagnostic studies, to include transmission electron microscopy and EB-specific monoclonal antibody immunohistochemistry, which have been performed to precisely classify each patient as to EB type. Cell and DNA banking has become an increasingly important activity in the NEBR, both within the core laboratories of its Data Coordinating Center in Chapel Hill and at several of its regionally situated Clinical Centers. Over many years the NEBR has served as an important resource to the general scientific community, both in the width of its collected data and in the availability of its investigators, especially when attempting to study specific phenotypes, such as the clinical characteristics of a characterized patient population. Indeed, the existence of the NEBR has already facilitated the performance of several large-scale research studies, each of which has provided important contributions to the understanding of the number of EB cases in the general population and at the availability of detailed data on the clinical phenotypic features and associated laboratory findings present in these patients. The data and the findings generated through the NEBR will be used for educational purposes, and then applied prospectively for purposes of counseling and prognosis. Investigators interested in accessing selected NEBR data and/or in planning formal research proposals for consideration by the project's national Steering Committee, can obtain IRB approval has been obtained at their local institutions.

GENE THERAPY STRATEGIES USING EPIDERMAL KERATOCYTES. Elizabeth S. Fenyes, Department of Oral Biology and Pathology, SUNY at Stony Brook University, Stony Brook, NY.

Gene therapy offers a potential approach for the treatment of inherited disorders through the introduction and expression of new genetic information. Among the many cell types that can be considered as targets for introducing genes, epithelial keratocytes have emerged as a tissue with great potential. The choice of keratinocytes as recipient cells for genetic therapy both in vivo and ex vivo will be discussed. Their application in treating inherited dermatologic disorders will also be reviewed. A dermatologic disorder in which the mutated gene has been identified and the normal allele is cloned is a candidate to be treated with keratinocyte-based gene therapy. The differences between dominant and recessive disorders in terms of their suitability for gene therapy will be evaluated. In the treatment of an autosomal dominant disorder such as EB, the expression of a normal allele will not ameliorate the disorder. It would therefore be necessary to biologically affect epithelial cells directly to suppress the mutant gene product in vivo and expand the corrected keratocytes to produce epithelium suitable for grafting. Selective inactivation can be achieved using either homologous recombination, antisense or inactivating drugs in adult tissues. Selective inactivation of Keratinocytes in a single copy of the mutant allele and are phenotypically normal, inserting a normal allele into an affected individual is likely to recreate a normal phenotype. Insertion of the normal allele can occur in an ex vivo strategy such as the gene gun or by inserting the normal allele into cultured patient keratocytes which can then be used to replace affected as an autograft. In any type of disease, if the current gene therapy has had a selective advantage over photodynamic skin it could repopulate the affected parts of the patient's body.

DIAGNOSIS OF EARLY EPIDERMOLYSIS BULGOSA USING ELIMINATED TERTIARY COMBINATION CONFIRMATORY GENIC MUTATION. Angela M. Christiansen and Joseph D. Venge. Department of Dermatology and Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

The diagnosis of HS-DEB in a patient with severe, mutilating, scarring, with clinically unrestrained is usually made by clinical examination and histology. In the nonfamilial, relatively mild scarring phenotype in a vertical pattern, with multiple affected family members in hemizygous situations, it may be difficult to distinguish between a dominant trait and a recessive trait. The use of COL7A1 mutations has shown that the dominant and recessive form of DEB can be differentiated by using COL7A1 mutations thus far, has revealed only one case derived from a de novo dominant mutation. Based on these considerations, for genetic counseling purposes, it appears appropriate to consider each "new" case of a recessively inherited form of DEB to be treated as a genetic mutation. The re-classification of DEB on the basis of the underlying mutation clearly impacts on the potential likelihood of the affected individual of having an affected offspring. The precise understanding of the underlying mutations in different forms of DEB could reveal the development of DNA-based prenatal diagnosis which can be performed as early as the 10th week of gestation through chorionic villus sampling or 12-15 week of gestation through amniocentesis. These approaches have already been applied to DNA-based prenatal diagnosis in 20 families at risk for recurrence of the severe, mutilating form of DEB. The genetic information also provides the basis for development of preimplantation diagnosis through blastomere analysis in the future, an advance which would obviate the necessity of termination of the pregnancy.

NOVEL ALTERNATIVE GENIC THERAPIES: POSSIBLE LINKS TO EB. F. H. F. and H. J. M. van der Heide, Department of Cell Biology and Dermatology, Baylor College of Medicine, Houston, TX.

The structural integrity of epithelial cells is maintained by a filamentous network made up of keratin filaments. The basic structure of keratin filaments is a lateral network of keratin filaments which is cross-linked by disulfide bonds, resulting in a rod domain of keratin as a core in common intrinsic skin diseases, including epidermolysis bullosa simplex (EBS), epidermolysis bullosa dystrophica (EBD), and recessive dystrophic epidermolysis bullosa (RDEB). These domains are generally inherited in an autosomal dominant, recessive, or X-linked recessive pattern. Disorders resulting from mutations, leading to abnormal keratine with mutations in one of three genes: K5, K14, and KDS. In RDEB, KDS has been identified as the cause of a keratinocyte that is defective in keratinization. The presence of keratinocytes that do not properly keratinize, but maintain normal function, may have a pathologic effect on the skin. Therefore, for a gene therapy approach to be efficacious for a long period of time it must control the expression of the gene in the skin. This approach would be to inhibit expression of the mutant allele. This may be achieved using antisense RNA or ribozymes expressed from viral-based vectors. However, to date, therapeutically acceptable methods to modulate expression of viral-based vectors have not been achieved in keratinocytes in vivo. An alternative approach would be to target keratin-specific promoters to achieve expression of keratin-specific vectors in keratinocytes of the skin. The goal of this strategy is to deliver keratin-specific promoters to keratinocytes in vivo. This approach could be achieved by using viral-based vectors. However, to date, therapeutically acceptable methods to modulate expression of viral-based vectors have not been achieved in keratinocytes in vivo. An alternative approach would be to target keratin-specific promoters to achieve expression of keratin-specific vectors in keratinocytes of the skin.
GENE THERAPY FOR JUNCTIONAL EB: REVERSION OF PHENOTYPE, FUNCTIONAL ASSAYS, AND FUTURE GRANTED SCIENTIFIC ABSTRACTS.

21 CHARACTERIZATION OF GENERALIZED ATROPHIC BENIGN JUNCTIONAL EPIDERMOLYSIS BULLOSA (GABEB) KERATOCYTE CELL LINES WITH HETEROGENEOUS MOLECULAR DEFECTS. M. Jonoff, H. Tan, G. Galvin, S. Building. Mayo Clinic, Rochester, MN; L. Wilson, J. L. H. Blumen, P. Reep, M. J. Nathan, Stanford, CA; Medical College of Wisconsin, Milwaukee, WI; University Hospital, Groningen, The Netherlands; and University of Colorado, Denver, CO.

GABEB is an inherited blistering disorder characterized by subepidermal blistering of the skin and mucous membranes. Affected individuals have recurrent and extensive dermal and epidermal blistering that can lead to scarring. This study aimed to characterize five GABEB keratinocyte cell lines with diverse genetic backgrounds to better understand the pathophysiology of GABEB. We investigated five primary cultures of GABEB patient keratinocytes with HPV E6 and E7 genes. Immunohistochemical and IF microscopy analysis of these cell lines showed several distinct patterns of aberrant protein expression. 2 GB cell lines showed absent expression of one or both and 1 normal and normal E5 expression. 1 GB cell line showed absent expression of the BP180 ectodomain with normal expression of the BP180 endodomain and normal expression of the BP230 in normal GB and GB74 in the GB cells. Expression of BP230 was also normal. IF microscopy showed that the type I collagen expression was reduced in all cell lines. The results show that the clinical phenotype is not always associated with the specific genetic defect. Further studies are needed to determine the functional implications of these findings.

GLYCOGEN SUBSTITUTION TREATMENTS IN THE GENE (COL7A1) FOR TYPE VII COLLAGEN IN DYSTROPHIC EPIDERMOLYSIS BULLOSA: IMPLICATIONS FOR GENETIC COUNSELING. Atsushi Kon, John A. McGrath, Kojiro Nagai, Naoko Saito, Yoko Nakamura, Yoshiko Nakazawa, Masakatsu, Masakazu M. I. Yamamoto, Jinji Uehata, Takanori, Angel M. Christiansen, Issach Hashimoto, and Joanni Uehata. Department of Dermatology and Cutaneous Biology, Jefferson Medical College, Philadelphia, PA; Department of Dermatology, Hiroaki University School of Medicine, Hiroaki, Japan; and Division of Dermatology, Kumamoto National Hospital, Kumamoto, Japan.

Dystrophic epidermolysis bullosa (DEB) is an inherited multigenic disorder characterized by fragility of the skin and mucous membranes. The anchoring fibril protein, type VII collagen is encoded by COL7A1 which harbors mutations in this group of diseases. In this study, we report novel glycine substitution mutations in COL7A1 in two Japanese families with DEB. The mutation detection strategy consisted of PCR amplification of genomic DNA, followed by heteroduplex analysis and nucleotide sequencing of the PCR products demonstrating the mutation.

Recent progress in molecular-based analysis of genetic abnormalities in the patients with dystrophic epidermolysis bullosa has led to the general understanding of correlations between disease mutations in type VII collagen (COL7A1) and their clinical phenotype. In this study, we identified two novel splice site mutations in COL7A1 in two Japanese families. These cases were clinically severe blistering type but mild syndactyly. Substitution of glycine to cysteine at donor splice site of exon 81 (6575+1 G to C) and 1 base pair deletion of thymine at acceptor splice site of exon 108 (9798+1 T) were identified in allele 1 and 2, respectively. In RT-PCR study, size of the type VII collagen mRNA from the patient's keratinocytes was heterogeneous, with splicing by length and splicing by size. In the transcripts of allele 1 and 2, the predicted size of the final transcript is 108 and ~50 bp shorter one in the region of exon 81, suggesting exon 108 skipping and alternative splicing in the intron following exon 81. These novel splice site mutations may explain the unique clinical phenotype of severe blistering with mild syndactyly in this patient with RDEB.
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Dystrophic Epidermolysis Bullosa with prurigo-like lesions: an ultrastructural study and a pathogenetic hypothesis. G. Tagliarini, A. Brusasco, S. Cangini, E. Cavalli and R. Rappaport. Center for Inherited Cutaneous Diseases, Institute of Dermatology, University of Milano. University of Trieste. Italy

Recently, a new variant of EBBD with a peculiar "prurigo-like" lesions has been proposed. In this patient, two sporadic cases and three patients of the same family suffering from a dystrophic EB, immunohistochemically and ultrastructurally diagnosed, with a similar phenotype. These patients presented in childhood a classic bullous lesions distribution and developed progressively during the adolescence a pattern of grouped papulos-nodular lesions, particularly in the external surfaces. These lesions are very numerous and intermingled with hemidermis cysts. Albumpoid lesions were also visible on the trunk. These lesions are always accompanied with an incoercible pruritus that obtains very scarce relief using any local or systemic therapy. We performed a biopsy of one of the lesions in these one patient. The histological examination showed orthokeratotic hyperkeratosis, a flattened dermal-epidermal junction and thickened sub-papillary collagen with enlarged vessels; some small infundibular cysts were also present. At the ultramolecular level we observed in a reduced number of hypertrophic anchoring fibrils without dermal-epidermal separation. The striking ultrastructural abnormality was observed in the presence of the presence of collagen fibrils that sometimes hides the lamina densa itself. A similar aspect of the dermo-epidermal junction has been never reported in any bullous disorder. The immunofluorescence studies could show the reduced presence of collagen VII by the reactivity of both LH-72 and KP-1. On the basis of these findings we propose that the prueral-nodules in these patients represent an abnormal dermal defensive response to the mechanical injuries such as occurs in keloids and hypertrophic scars.

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Melanocyte-Epidermal twin nevus syndrome (Phacomatosis Pigmentokeratotica): a recently recognized ectodermal mosaicism. G. Tagliarini, R. Rappaport, R. Boccelli, C. Franceschini, C. Parisi, F. Serafini, N. Varesi, R. Collini, M. Bonadonna, I. Ragonese, G. Cianfarani. "Center for Inherited Cutaneous Diseases, Institute of Dermatological Sciences, IRCCS Policlinico-University of Milan, Italy; Dept of Dermatology, Philipps University, Marburg Germany

The genetic concept of twin spotting has been proposed to explain paired mosaic patches in plants and animals and, recently, also in humans. We have observed in two patients the co-occurrence of a verrucous epidermal nevus of a non-epidermotropic type and a speckled lentiginous nevus both arranged along the lines of Blaschko, associated with hyperhidrosis, painful parentheses and postural deviation. Meanwhile, a thorough review of the literature revealed the occurrence of different similar cases. We propose to delineate a further separate type of epidermal nevus syndrome and to explain it by the genetic concept of twin spotting. In an embryo heterozygous for two different recessive mutations, no localization of an epidermotropic naevus of an over or under expression could give rise to two homoygous daughter cells representing the stem cells of two different cutaneous abnormalities. We observed the existence of these two cutaneous abnormalities. In the nonepidermolytic, organoid type and a speckled lentiginous nevus may be explained by a similar mechanism. The somatic mutation give rise to the abnormalities of the peripheral nervous system. The reason of the identity of the nevus of an infrastructural level. Molecular studies are in progress in order to evaluate the presence of microdeletions or insertions using the cells obtained by the nevi and from the non affected counterparts.

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NORMALIZATION OF ULTRASTRUCTURE AND IMMUNOREACTIVITY OF DEFECTIVE HEMIDESMOSES BY ORAL DAPSONE IN PATIENTS WITH NOGUE/DEITHEL JUNCTURAL EB OF THE MITIS TYPE. L. Luengo-Palacios, I. Chosidow, C. Waksman, J. Tabar, J. Sainz-Buser, J. Java, J. A. Echevarria, F. G. Martinez, J. I. Sainz, L. L. Echevarria, Institute for Ultrastructure Research of the Skin, Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden; Department of Dermatology, Catholic University, Madrid; Department of Dermatology, University of La Laguna, Tenerife, Spain

Differences in the degree of hypoplasia and ultrastructural details of hemidesmosomes representing the basic defect in the pathogenesis of various subtypes of junctional EB (JEB) were found to be reliable and stable ultrastructural markers for their diagnostic distinction and to be a strong hint to considerable heterogeneity of candidate molecules and genes. The new molecular genetic data confirm the direct relationship of defective hemidesmosomes to the respective gene mutation in JEB.

As yet, no drug therapy is known that interferes directly with the pathogenetic pathway or may be able to compensate the effect of a gene mutation in any of the genodermatoses. We have controlled dapson treatment of JEB patients of various subtypes for clinical improvement of skin stability, immunological and ultrastructural response for more than 10 years. Here we report the complete ultrastructural normalization of previously hypoplastic hemidesmosomes and restoration of immunoreactivity for various junction related antigens in patients with the non-lethal, benign JEB mitis (or GABEB) type under dapson, in contrast to the lethal Herlitz type with only partial ultrastructural restoration but failure to normalize immunoreactivity for hemidesmosomes. It is for the first time that a gene-induced basic defect of a genodermatosis is completely normalized on the ultrastructural level by systemic dapson therapy. These unexpected findings are of special interest in view of recent progress in the identification of mutations in different candidate genes for various types of JEB, and might serve as a clue for better understanding molecular interactions and significance of intra- and extracellular protein complexes in the hemidesmosomes for junctional integrity and resistance to mechanical stress.
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