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BEST ORAL PRESENTATION AWARD (Euro 500.)

FC-9 **12R-LIPOXYGENASE DEFICIENCY LEADS TO A LOSS OF SKIN BARRIER FUNCTION IN MICE ACCOMPANIED BY ULTRASTRUCTURAL CHANGES IN THE UPPER GRANULAR LAYER**
Nikolas Epp[1], Ingrid Hausser[2], Gerhard Fürstenberger[1] and Peter Krieg[1]
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BEST POSTER PRESENTATION AWARD (Euro 500.)

P-6 **EPIDERMAL MORPHOLOGICAL FEATURES IN ORGANOTYPIC CULTURES OF NORMAL HUMAN BREAST SKIN: A LIGHT AND ELECTRON MICROSCOPY STUDY**
M. Bedoni, C. Sforza and E. Donetti
Department of Human Morphology, University of Milan, Italy

The whole Final Programme can be found at: http://orgs.dermis.net/content/e04scur/e03meetings/e775/e896/index_ger.htmlor http://www.scur.org and click ''Meetings'' and the sublink: 'Previous Meetings'

ABSTRACTS

INVITED LECTURES

IL-1

A possible role of epidermodysplasia verruciformis-associated human papillomaviruses in the pathogenesis of psoriasis

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In our previous studies we found a high prevalence of epidermodysplasia verruciformis-associated human papillomaviruses (EV HPV) DNA in the skin of patients with psoriasis. Moreover specific antibodies to EV HPV5L1 capsid protein were detected in a proportion of psoriatic patients but not in the controls, except for patients with extensive burns in whom the antibodies were only transiently detected. Recently we searched for antibodies to EV HPV5 E6 and E7 oncoproteins and examined cell-mediated immune (CMI) responses to EV HPV5 proteins in patients with psoriasis. Using a radio-immunoprecipitation assay with *in vitro* translated HPV5 E6/E7 proteins, specific antibodies were found in 15/29 patients with psoriasis, 5/9 with EV but only in 1/32 with atopic dermatitis and 1/42 healthy individuals. EV HPV5 VLPs (virus like particles) stimulated proliferation of T cells from patients with psoriasis but not with EV and healthy persons. This was associated with a significant ($P<0.05$) increase in production of interferon gamma (IFNg) by psoriatic PBMC in spite of normal levels of IL-18 and IL-10. In contrast in supernatants of cultured PBMC from EV patients an increased levels of IL-10, normal levels of IL-18 and decreased levels of IFNg were detected. In addition, immunohistochemical studies showed the expression of HPV5 L1 protein in the upper parts of psoriatic epidermis, i.e. in the area of Munro abscess formation. The results indicate that EV HPVs may be involved in the pathogenesis of psoriasis by direct stimulation of keratinocyte proliferation (E6.E7 oncoproteins) and by induction of both humoral and cell mediated immune responses to EV HPV proteins. Recently introduced immunosuppressive therapies for psoriasis, by inhibiting immune responses against EV HPV antigens, could result in a decreased EV HPV expression and in consequence in a decrease of keratinocyte proliferation. Our hypothesis on a possible role of EV-HPVs in pathogenesis of psoriasis is also strengthened by the studies showing an association between presence of HPV5 DNA and severity of the disease (Prigano *et al.*, 2005) as well as by the detection of HPV5 mRNA in cultured primary keratinocytes from psoriatic skin (Simeone *et al.*, 2005).

IL-2

Blistering mechanisms of pemphigus vulgaris: Biochemical and ultrastructural studies

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Since both monoclonal anti-desmoglein 3 (Dsg3) antibodies and a complete loss of Dsg3 function, as in Dsg3-knockout mice, can cause a blistering disease with clinical and histological characteristics very similar to pemphigus vulgaris (PV), the disruption of the adhesive function of Dsg3 by autoantibodies against Dsg3 is thought to be a fundamental cause. The blistering mechanisms after autoantibodies bind to Dsg3, however, is not yet clear. Two principal hypotheses emerge as pathomechanisms underlying generation of PV blisters. The first proposes that anti-Dsg3 antibody-dependent steric hindrance interferes with intercellular adhesive function(s) of Dsg3, leading directly to dissociation of desmosomes (DSs). Alternatively, myriad PV-IgG-induced intracellular signaling events could lead to DS dissociation. These signaling-related events include not only phosphorylation of Dsg3, which has been linked to its depletion from DS, but also urokinase-type plasminogen-activator (uPA) secretion, apoptosis signaling, as well as modulations of plakoglobin, p38MAPK, heat shock protein 27 and c-Mic functions. By immuno-electron microscopy (IEM), we have shown that PV-IgG binding to Dsg3 on the keratinocyte surface does not inhibit calcium-induced DS formation, suggesting that the steric hindrance of Dsg3 adhesion alone does not appear sufficient to inhibit DS formation and to cause DS detachment. We have shown also that PV-IgG and pathogenic anti-Dsg3 monoclonal antibodies (mAb) treatments cause endocytosis of Dsg3 and deplete the membrane fraction of Dsg3 within 20 min and DS of Dsg3 within 48 hr in culture, as revealed by IEM, fluorescence microscopy and immuno-blotting. We showed also Dsg3-depleting activities were proportional to their pathogenicities. The combination of 4 different Dsg3-mAbs augmented the activities more than any two-Dsg3 mAb combination or any single Dsg3 mAb stimulation. In addition, Dsg3 depletion from DS was associated with the decreased in their mechanical adhesive function as examined in culture. Taken together these results, the association of Dsg3-depletion with Dsg3-phosphorylation may suggest that PV-IgG binding to Dsg3 on the cell surface activates a variety of intracellular signaling pathways, some of which are possibly linked to Dsg3-depletion from DS, and that the Dsg3-depletion from DS is a principal outcome directly explain the decrease in mechanical strength of DS leading to cell-cell detachment.

IL-3

New insight into the pathomechanism of bullous pemphigoid: Update from Sapporo

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Bullous pemphigoid is the most common autoimmune blistering skin disease in which patients have autoanbibodies to BPAG1 and BPAG2 at the epidermal basement membrane. Autoantiboides against BPAG2, known to be type XVII collagen (COL17), is thought to be pathogenic for skin lesion. The lack of expression of COL17 molecule due to mutations in the gene COL17A1 leads to human inherited blistering disease, called non-Herlitz junctional epidermolysis bullosa (EB). A number of murine models that mimic the features of EB have been developed by targeted ablation of the candidate genes, including type VII collagen (COL7A1), or subunit polypeptides of laminin 5 (LAMA3, LAMB3, and LAMC2). However, most of them are lethal or die soon after birth. In order to further clarify the function of COL17 as well as its role in the pathomechanism for bullous pemphigoid, we have generated the COL17 knockout mice. In this lecture, I will introduce some update data from my department in Sapporo.

IL-4

X-linked dominant ichthyosis: Chondrodysplasia punctata, the Conradi-Hünermann-Happle syndrome

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Inborn defects of cholesterol biosynthesis are a group of metabolic disorders often presenting with ichthyosiform skin symptoms. Conradi-Hünermann-Happle syndrome, also known as X-linked dominant chondrodysplasia punctata (CDPX2-MIM302960), a rare form of ichthyosis primarily affecting females. CDPX2 is presumed lethal in males, although a few affected males have been reported. The disease is characterized by a changing skin phenotype, mild or more severe skeletal abnormalities like punctate calcification in infancy, limb length discrepancies, growth retardation as well as by hair anomalies and cataracts. CDPX2 is caused by mutations within emopamil-binding protein (EBP) resulting in deficient function of the 3-beta-hydroxysteroid- delta(8), delta(7) isomerase in the cholesterol biosynthesis pathway. The disease is an interesting example of X-linked dominant diseases rendering data on close correlation of lipid metabolism and cornification. Characteristic features of mild or changing skin phenotype as well as skin ultrastructure can be summarized.

IL-5

Ultrastructure of unusual epidermolysis bullosa phenotypes

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The exact blister level in the basement membrane determines the classification of the major forms of epidermolysis bullosa (EB). Although molecular biology has advanced our understanding of the genetic causes of EB, electron microscopy is still the golden standard for diagnosis. However, the ultrastructure may be misleading as to pointing to the candidate gene. For instance, an intracellular blister level is possible in aberrant ''junctional'' adhesion molecules, such as integrin beta4 and type XVII collagen, confusingly leading to the diagnosis EB simplex. Moreover, electron microscopy cannot differentiate between high and low splits in the lamina lucida. IF antigen mapping using monoclonal antibodies does allow differentiation between lamina lucida splits with laminin 5 in the floor (high LL) and those with laminin 5 in the roof and in the floor of the blister (low LL). Moreover, conspicuous tonofilament clumping may be absent in EB simplex Dowling-Meara and in mild bullous congenital ichthyosiform erythroderma, thus possibly leading to a missed diagnosis. New are desmosomal skin fragility diseases, such as lethal acantholytic EB, and skin fragility - ectodermal dysplasia syndrome due to mutations in desmoplakin and plakophilin 1 genes respectively. Breakage occurs between the tonofilaments and the inner dense plaque of desmosomes. The challenge for the electron microscopist is to find a clue for diagnosis in these diseases, since IF antigen mapping is found of little help. In this presentation unusual phenotypes will be presented that challenge the current classification based on electron microscopy.

IL-6

Inherited disorders of desmosomes

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Desmosomes are highly organised intercellular junctions that provide mechanical integrity to tissues by anchoring intermediate filaments to sites of strong adhesion. These cell-cell adhesion junctions are found in skin, heart, lymph nodes and meninges. Over the last nine years, several naturally occurring human gene mutations in structural components of desmosomes have been reported. These comprise autosomal dominant or recessive mutations in plakophilin 1, plakophilin 2, desmoplakin, plakoglobin, desmoglein 1, desmoglein 4 and corneodesmosin. Clinically, these discoveries have often highlighted novel or unusual phenotypes, including abnormal skin fragility and differentiation, and developmental anomalies of various ectodermal appendages, especially hair, as well as cardiac disease resulting from some mutations. Ultrastructurally, desmosomes in these disorders show variable abnormalities. Some mutations, for example in plakophilin 1, lead to smaller, fewer desmosomes with increased keratinocyte cell migration and reduced calcium stability of desmosomes. In such cases, the plane of cell fragility is just within the cell such that the desmosomes have a pinched off appearance with no signs of extracellular cleavage. Other mutations, for example in desmoglein 1, may alter the ultrastructural appearances of the mid-line extracellular plaque. Collectively, inherited disorders of desmosomes give rise to a spectrum of clinicopathological features and highlight the key functions of several of the desmosomal proteins in tissue adhesion and cell biology.