

# Annual Scientific Meeting 2001

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## Recent Advance in Melanogenesis

Speaker: Prof. M. Ichihashi

Solar radiation induces both acute and chronic responses in the skin. Sun burn, sun tan, generation of reactive oxygen species and immunosuppression are acute responses. Wrinkles, lentigines, post-inflammatory pigmentation are chronic damages. According to one study done in Japan, it was found out that the annual ultraviolet dose received by people living in Kagoshima was 1.6 times higher than those living in Akita, noting that their latitudes were 32 degree North and 40 degree North respectively. The amount of freckles in the face of a 40-year-old lady living in Kagoshima is the same as a 60-year-old lady in Akita. It is obvious that UV light plays an important role in melanogenesis. DNA fragments produced after UV exposure also stimulate melanogenesis. It is estimated that one hour of sun exposure at noon in a locality like Hong Kong may result in as much as 1,000,000 DNA damages. Cytokines, alpha-melanocyte stimulating hormone (alpha-MSH) and Vitamin D are reported to be factors important in UV-melanogenesis.

Some genes are responsible for melanogenesis. Some of them work at the subcellular level and control tyrosinase, tyrosinase related protein-1, tyrosinase related protein-2. Some genes work at the cellular level, for example, the agouti(a) gene exerts an inhibitory effect on alpha-MSH; C-kit genes and steel(SI) genes influence melanocyte proliferation. Furthermore, superoxide anion has also been shown to play a role in the activation of tyrosinase.

Recently, it was discovered that adult T-cell leukaemia derived factor (ADF) may play a role in UV-melanogenesis via a paracrine manner. ADF is a human homolog of thioredoxin and has a molecular weight of 13KD. UVB radiation stimulates keratinocytes to

produce ADF, which in turn stimulates melanocytes for melanogenesis. ADF also upregulates alpha-MSH-induced DNA synthesis. Moreover, after UVB exposure, keratinocytes produce more MSH and ACTH, which in turn stimulate the expression of MSH receptors on melanocytes cell surface.

Understanding the mechanism of melanogenesis enables us to design the potential approach to skin whitening. Melasma, senile and solar lentigo, post-inflammatory hyperpigmentation, naevus spilus and cafe au lait spots are examples of pigmented skin diseases that need whitening treatment. Protecting the skin from solar radiation is obviously important. Whitening of pigmented skin could successfully be accomplished by reducing or inhibiting melanin synthesis, accelerating destruction of melanin-forming enzymes and inhibiting melanosomes transfer from melanocyte to keratinocytes. Enhancing turnover of epidermis which efficiently discards melanin in epidermal keratinocytes is also effective. Chemical peeling and exfoliation of skin cells using, for example, alpha-hydroxy acids (AHAs) may be employed. Inhibition of melanogenesis can be achieved by agents like hydroquinone, ascorbic derivatives, arbutin, kojic acid and AHAs. The expression of alpha-MSH receptors on melanocytes surface can be decreased by down regulation of cytokines like ACTH and MSH elaborated by keratinocytes.

Diacylglycerol (DAG) and one synthetic DAG (1-oleoyl-2-acetyl-sn-glycerol:OAG) have been demonstrated to cause increase in melanin content of cultured human melanocytes without the need of UV light exposure. Topical DAG induces a long-lasting increase in epidermal pigmentation, presumably through protein kinase C activation. DAG may thus play a role in skin tanning in the future, as exposure to harmful UV light is not necessary.

### **Learning points:**

*Adult T-cell leukaemia derived factor is recently found to play a role in UV-melanogenesis. DAG may play a role in tanning of the skin in the future.*

## **Dermatomycoses of the Feet – More than Meets the Eye at First Sight?**

Speaker: Dr. B. Sigurgeirsson

### **Introduction**

Dermatomycoses of the feet were common skin disease. Recent studies had shown a prevalence of two to 10% for onychomycosis and 10-20% for tinea pedis. Its prevalence in Iceland was about 8.6%. Both conditions were sometimes considered trivial but they could have severe impact on quality of life.

### **Classification**

The disease was classified according to the clinical features: dermatophytosis simplex, (or complex when concurrent bacterial infection was present), moccasin type, vesicular type and onychomycosis.

### **Risk factors and clinical presentations of dermatophytosis of the feet**

The risk factors of dermatophytosis of the feet included age, family history, warm/humid climate, occlusive footwear, close contact with infected people, diabetes mellitus and immunocompromised state.

The disease affected both sexes with male more common, and increased with age. However, there was increasing incidence of dermatophytosis noted in the west. It might be related to the increasing number of elder people, use of public facilities and occlusive footwear coming into fashion.

Fissuring, inflammation, itching and pain were common presenting features. Dermatophytosis affected the quality of life by causing embarrassment, difficulty in nail trimming or discomfort in wearing shoes, etc. Pain and id reaction were frequently overlooked in patients suffering from dermatophytosis of feet. Pain could be due to paronychia, onychogryphosis, fissure from dry skin and bullae.

Dermatophytosis, frequently presenting as intertrigo, was an important risk factor for bacterial infection such as erysipelas and cellulitis of the legs. Overlook of it could be fatal.

### **Other presentations and associations**

Dermatophytosis could occasionally cause otitis externa and autoinoculation.

There were reports of dermatophytosis leading to flares of atopic eczema, to trigger asthma and perennial rhinitis. Erythema nodosum, erythema multiforme and other reactive dermatoses have also been found to be associated with dermatophytosis.

### **Treatment aspects**

The speaker highlighted the importance of treating any concurrent bacterial infection in associated with dermatophytosis. Patients with onychomycosis should be followed up long enough after treatment to ensure complete cure of the disease, as relapse was common.

#### ***Learning points:***

*Dermatomycoses of the feet are common, which may be associated with severe symptoms and complication and have significant adverse impact on quality of life.*

## **New Entities of Bullous Disease**

Speaker: Prof. X. J. Zhu

Bullous disease is a special entity of skin dermatoses that characterized by vesicle, blister or simply erosion. These can be further classified as congenital and acquired blistering dermatoses. With the great achievements made in the last 20 years on molecular biology, electron microscopy and genetic analysis, new entities of immuno-bullous disease such as paraneoplastic pemphigus (PNP) and IgA pemphigus were defined. The gene mutations of rare congenital epidermolysis bullosa (EB) such as dominant dystrophic epidermolysis bullosa pruriginosa (DDEB-P) and generalized atrophic benign epidermolysis bullosa (GABEB) were also identified.

In the past two years, a total of four cases of PNP were diagnosed in Peking University First Hospital in

Beijing. Three male and one female patients, aging from 17 to 44, presented with severe oral and conjunctival mucosal involvement that was not responded to high dose systemic therapy. The clinical features of PNP resemble pemphigus vulgaris, pemphigus foliaceus, erythema multiforme and lichen planus. All histological specimens of four cases showed lymphocytic infiltration at dermoepidermal junction, suprabasal cleft, sparse necrotic keratinocyte and basal cell liquefaction. IgG and C3 were positive at intercellular and dermoepidermal junction by direct immunofluorescence method. The autoantigens were identified as 190 kd and 210 kd by immunoblotting method that is corresponding to desmoplakin located in cytoplasmic plaques of desmosome. Extensive investigations of the underlying neoplasm showed all of them had Castleman disease, a benign lymphocytic neoplasm. And all patients improved gradually after surgical excision of the Castleman disease.

Dominant dystrophic epidermolysis bullosa pruriginosa (DDEB-P) is a new variant of dystrophic epidermolysis bullosa characterized by prurigo-nodularis-like features over limbs and dystrophic nail. Dr. Yu-Yun Lee and Dr. Uitto demonstrated a G-to-A transition at nucleotide 6724 with exon 85, which converted a glycine to an arginine within the triple-helical domain of the type VII collagen, COL7A1 gene. A big Chinese family with DDEB-P were extensively studied by PCR-based molecular technologies. It revealed a G-to-A transition at nucleotide 6110 with exon 73 of COL7A1 that converted a glycine substitution mutation within the triple-helical domain of the type VII collagen. The affected family individuals bear the mutation and such mutation was not found in unaffected family member, healthy individuals and unrelated DEB patients.

Generalized atrophic benign epidermolysis bullosa (GABEB), characterized by generalized blisters, skin atrophy, alopecia, scarceness of eyelashes, eyebrows and suprapubic hair, nail dystrophy and dental anomalies, was first described by Hashimoto in 1976. The ultrastructural examination of a Chinese family with GABEB revealed fissures in lamina lucida of basement membrane zone (BMZ). Immunofluorescence assay using a monoclonal antibody recognizing the extracellular domain of the 180 kDa bullous pemphigoid antigen (BPAg2) showed a loss of fluorescent signal in BMZ of the skin. DNA sequencing reveals a homozygous mutation of C899G in exon 11 of

COL17A1 gene. It results in a substitution of S265C, which located in a highly conserved region of the intracellular domain of BPAg2. A novel polymorphic substitution of C798G in exon 10 of COL17A1 gene, which results in a 1233M change in BPAg2, is a common polymorphic allele in a limited Chinese population.

#### **Learning points:**

*Paraneoplastic pemphigus is characterized by severe mucosal involvement with typical direct immunofluorescence and autoantigens that is not responded to systemic steroid. The principle management is to identify and remove the underlying neoplasm.*

## **The Implications of Acute HIV Infection**

Speaker: Dr. S.S. Lee

In the past, Human Immunodeficiency Virus (HIV) infection has long been viewed as a chronic infection and its management is not different from cancers. However, the discovery of different phases of HIV infection which include uninfected, primary and chronic phase, has changed this concept and hence its clinical and public health implications.

### **Different phases of HIV infection**

HIV infection can be viewed as three different phases, an uninfected phase, primary phase and chronic phase. Uninfected phase simply means before the exposure of HIV. The primary phase can be divided into an acute phase and an early phase. The acute phase, occurring in the first three months after contracting HIV, is characterized by the presence of HIV antigen without HIV antibody. The early phase occurs around three to five months after contracting HIV and is characterized by the presence of both HIV antigen and antibody. After the primary phase, viral dynamics reach a steady state or a viral set point in which there is a balance between viral replication and destruction, marking the onset of chronic phase.

In fact, the term acute HIV infection is interchangeable with primary HIV infection that states the early phase of disease progress shortly after HIV inoculation. In clinical practice, non-specific sign and

symptom of fever, malaise, lymphadenopathy and pharyngitis occur at one to three weeks after exposure in 50-90% of patients with serological evidence of seroconversion.

### **Diagnosis of acute HIV infection**

In clinical setting, the symptomatology of acute HIV infection is not different from other viral infections like Epstein Barr Virus, hence making definitive clinical diagnosis not possible. At some stage, objective measurements of p24 antigen and HIV RNA by laboratory method are advocated in differentiating the primary infection. However, the high specificity but low sensitivity of p24 antigen test and high sensitivity but low specificity of HIV RNA test make them unreliable laboratory methods for determining recent HIV infection objectively when used separately. The yield would be greatly improved if both of them are used at the same time, but the high cost limits their use in research laboratory.

### **The implications of acute HIV infection**

The accurate diagnosis of acute HIV infection in the population may facilitate an early treatment and the development of an effective control programme. In the era of Highly Active Anti-Retroviral Therapy (HAART), HIV infection or AIDS can be viewed as a chronic suppressible infection. The concept of early treatment strategy is based on the fact that early treatment may suppress viral burst, decrease the dissemination of HIV inside the body, decrease the symptomatology of acute disease, lowering the viral set point, and hence may preserve the host's immunity. However, there is no consensus on the treatment strategy for acute HIV infection and the idea of structured treatment interruption may enlighten us a new direction in the future treatment strategy.

#### ***Learning points:***

***Even in the era of Highly Active Anti-Retroviral Therapy (HAART), HIV infection or AIDS can only be viewed as a chronic suppressible infection. Viral containment either by acute HIV treatment or structured treatment interruption may give us a hope for better disease control in the future.***

### **Corrigendum**

The publisher wishes to draw attention to the following errors in the Hong Kong Dermatology & Venereology Bulletin, Vol.9 No.3, September 2001:

- 1) On the back page of the table of contents, the name of Dr TANG Yuk-ming, the immediate past chairman of the Hong Kong Dermatology & Venereology Bulletin, should be included in the list of Council Members.
- 2) On page 125, the legends of the figure 1 and 2 of the article "Pretibial Epidermolysis Bullosa" by Dr CK Ho were labelled wrongly and should be switched.
- 3) On page 138, the learning points of the scientific meeting "Update on the Treatment of Onychomycosis" reported by Dr YLS Ngai should be "Subtypes of onychomycosis may require different or combination of topical, oral and chemical-surgical treatment".

The publisher apologises for these errors and any inconvenience that may have caused.