The Editor's Choice

Y. Tokura

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Prognostic factors in 105 Japanese cases of mycosis fungoides and Sézary syndrome: Clusterin expression as a novel prognostic factor

Clusterin is a ubiquitous 80 kDa heterodimeric glycoprotein expressed on tumor cells of systemic and primary cutaneous anaplastic large cell lymphoma. The expression of clusterin in mycosis fungoides (MF) and Sézary syndrome (SS) has only been sporadically reported in a small number of cases. Tobisawa S et al conducted a study to determine the long-term prognosis of Japanese patients with MF and SS, to identify clinical and pathological factors predictive of survival, and to evaluate the prognostic significance of the International Society for Cutaneous Lymphomas (ISCL) revised staging system (2007). They performed a retrospective cohort study of 105 Japanese patients with MF and SS. Biopsied specimens of MF and SS were immunostained for clusterin, CD30, and Ki-67. In the multivariate analysis, T classification, extracutaneous disease, increased serum LDH level, clusterin expression, and performance status were the significant independent prognostic factors. Japanese stage IIIA MF/SS patients contain a subpopulation with a favorable prognosis. The most significant prognostic factor for survival of MF and SS was the presence of extracutaneous disease. Clusterin expression was shown to be a novel unfavorable prognostic factor.

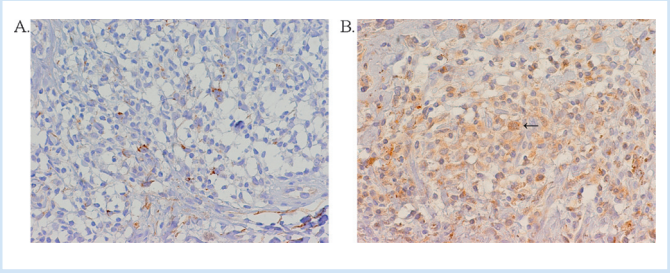

Fig. 2. Clusterin immunostaining. (A) Clusterin immunostaining: focal (reactive cells fewer than 25%) 400×, (B) clusterin immunostaining: most of the lymphoid cells are positive for clusterin. The percentage of positive cells was less than 75% in this case. Note characteristic dot-like Golgi staining pattern (arrow) 400×.

Ultraviolet B enhances DNA hypomethylation of CD4+ T cells in systemic lupus erythematosus via inhibiting DNMT1 catalytic activity

$CD4^+$ T cells DNA hypomethylation is involved in the pathogenesis of systemic lupus erythematosus (SLE). Ultraviolet B (UVB) might induce the exacerbation of SLE by decreasing the DNA methylation level. However, the role of DNA methyltransferase 1 (DNMT1) remains unclear in the UVB-induced $CD4^+$ T cell DNA hypomethylation. Wu Z et al elucidated the role of DNMT1 in lupus CD4+ T cells global DNA hypomethylation enhanced by UVB. They analyzed $CD4^+$ T cells from SLE patients and healthy controls exposed to different dosages of UVB. The level of global DNA methylation and DNMT1 mRNA expression in $CD4^+$ T cells from SLE patients were significantly lower than those from the control group. DNA methylation was decreased after UVB exposure in a dosage-dependent manner in SLE patients, but not in the control group. DNMT1 mRNA and protein expression level were not affected by UVB exposure in both SLE patients and healthy controls. DNMT1 catalytic activity was significantly decreased in $CD4^+$ T cells from SLE patients after UVB exposure in a dosage-dependent manner. DNMT1 catalytic activity was lower and more sensitive to UVB exposure in $CD4^+$ T cells from active SLE patients that from stable ones. Thus, UVB enhanced DNA hypomethylation of CD4+ T cells in SLE via inhibiting DNMT1 catalytic activity in a dosage-dependent manner.

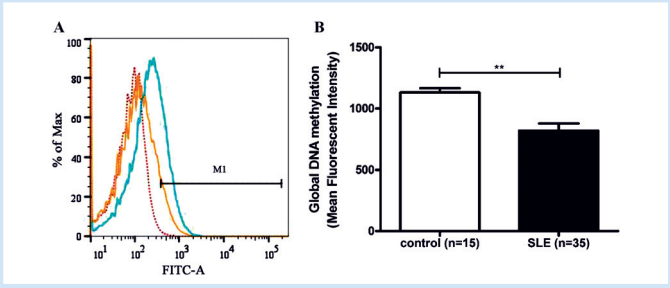

Fig. 1. The level of CD4+ T cells global DNA methylation in SLE patients and control group. Representative FACS histogram overlays (red dotted line: isotype control; blue line: healthy controls; yellow line: SLE patients). (A) And quantitative analysis (B). CD4+ T cells global DNA methylation in SLE patients (n = 35) significantly decreased when compared with healthy controls (n = 15). $^{**}P < 0.01$.

Suppressive effects of antimycotics on thymic stromal lymphopoietin production in human keratinocytes

Thymic stromal lymphopoietin (TSLP), produced by epidermal keratinocytes, induces Th2-mediated inflammation. TSLP expression is enhanced in lesions with atopic dermatitis and is a therapeutic target. It is known that antimycotic agents may improve the symptoms of atopic dermatitis. Hau CS et al examined whether antimycotics suppress TSLP expression in human keratinocytes. Normal human keratinocytes were incubated with poly I:C plus IL-4 in the presence of antimycotics. Poly I:C plus IL-4 increased the secretion and mRNA levels of TSLP, which was suppressed by an NF-kB inhibitor, and also enhanced NF-kB transcriptional activities and induced the degradation of IkBa in keratinocytes. The antimycotics itraconazole, ketoconazole, luliconazole, terbinafine, butenafine, and amorolfine suppressed the secretion and mRNA expression of TSLP, NF-kB activity, and IkBa degradation induced by poly I:C plus IL-4. These suppressive effects were similarly manifested by 15- deoxy-D-12,14-PGJ2 (15d-PGJ2), a prostaglandin D2 metabolite. Antimycotics increased the release of 15d-PGJ2 from keratinocytes and decreased the release of thromboxane B2, a thromboxane A2 metabolite. Antimycotic-induced suppression of TSLP production and NF-kB activity was counteracted by an inhibitor of lipocalin type-prostaglandin D synthase. These antimycotics may block the overexpression of TSLP in lesions with atopic dermatitis.

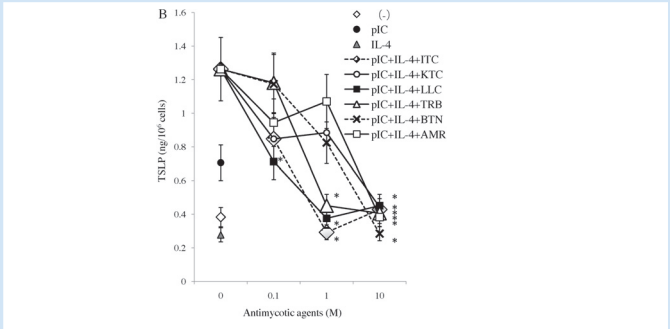

Fig. 1. Antimycotics suppress poly I:C plus IL-4-induced TSLP secretion and mRNA expression. (A and C) Keratinocytes were preincubated with the vehicle (DMSO) or 1 μM helenalin for 30 min, and incubated with 10 μg/ml poly I:C and/or 10 ng/ml IL-4. TSLP secretion or mRNA levels were measured at 48 h or at 24 h, respectively. $^*P < 0.05$, by one-way ANOVA with Scheffe's test. Means ± SD (n = 4) are shown. (B and D) Keratinocytes were preincubated with the vehicle (DMSO) or the indicated concentrations of antimycotics for 30 min, and incubated with poly I:C and/or IL-4. TSLP secretion or mRNA levels were measured at 48 h or at 24 h, respectively. $^*P < 0.05$ vs. poly I:C plus IL-4, by oneway ANOVA with Dunnett's test. Means ± SD (n = 4) are shown. pIC, poly I:C; ITC, itraconazole; KTC, ketoconazole; LLC, luliconazole; TRB, terbinafine; BTN, butenafine; AMR, amorolfine.

Activation of the epidermal growth factor receptor promotes lymphangiogenesis in the skin

The molecular mechanisms involved in the regulation of lymphangiogenesis remain incompletely characterized. Marino D et al aimed to identify new pathways involved in the promotion of skin lymphangiogenesis. They used a mouse embryonic stem cell-derived embryoid body vascular differentiation assay. A subcutaneous Matrigel assay was also used to study candidate lymphangiogenesis factors as well as skin-specific transgenic mice. Compounds inhibiting the epidermal growth factor (EGF) receptor (EGFR) led to an impaired formation of lymphatic vessel-like structures. In vitro studies with human dermal lymphatic endothelial cells, that were found to express EGFR, revealed that EGF promotes lymphatic vessel formation. Incorporation of EGF into a mouse matrigel plug assay showed that EGF promotes enlargement of lymphatic vessels in the skin in vivo. Transgenic mice with skin-specific overexpression of amphiregulin, another agonistic ligand of the EGFR, displayed an enhanced size and density of lymphatic vessels in the skin. The authors' findings reveal that EGFR activation is involved in lymphatic remodeling. Specific EGFR antagonists might be used to inhibit pathological lymphangiogenesis.

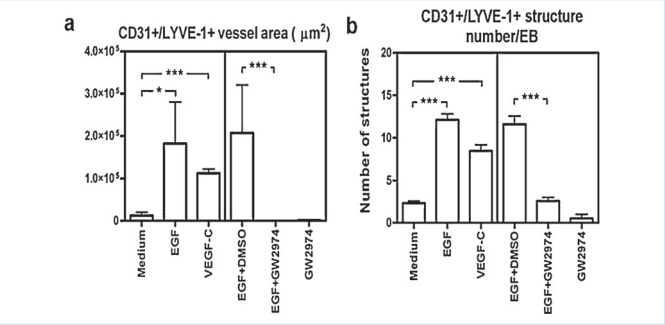

Fig. 2. EGF promotes the formation of CD31+/LYVE-1+ lymphatic vessel-like structures in mouse embryoid bodies. EGF (100 ng/ml) and GW2974 (10 µM) were added to embryoid bodies either alone or together. VEGF-C and medium alone served as positive and negative controls, respectively. After 4 days, the EBs were stained for CD31 (red; c, d, e and f) and LYVE-1 (green; c', d', e' and f'). The overlays of the resulting images are shown in c", d", e" and f". The area covered by CD31+/LYVE-1+ vessels (a) and the number of vessel-like structures per embryoid body (b) were assessed. Data are expressed as mean values ($n = 9$) + SEM; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Scale bars: 50 µm.

Correlation of increased MYG1 expression and its promoter polymorphism with disease progression and higher susceptibility in vitiligo patients

MYG1 (Melanocyte proliferating gene 1 or C12orf10) -119C/G promoter and Arg4Gln structural polymorphisms have a functional impact on its regulation. The promoter polymorphism was shown to be associated with vitiligo in Caucasian population. Dwivedi M et al investigated MYG1 polymorphisms and correlated them with MYG1 mRNA expression and clinical courses. They genotyped MYG1 -119C/G promoter (rs1465073) and 11-12AA/GC structural polymorphisms in 846 vitiligo patients and 726 age-matched unaffected controls. MYG1 mRNA levels were assessed in whole blood of 166 patients and 175 controls. The authors found that the MYG1 -119C/G promoter polymorphism was in significant association with vitiligo being 'G' allele prevalent in patients. However, 11-12AA/GC structural polymorphism was prevalently monogenic in patients and controls with only MYG1 GC (4Arg) allele being present. Significant increase in MYG1 mRNA expression was observed in vitiligo patients compared to controls, especially in patients with active and generalized vitiligo. MYG1 mRNA expression was increased in patients with susceptible -119 GG genotype. Patients with age groups 1–20 years and 21–40 years showed increased expression of MYG1 mRNA. Female patients showed significant increase in MYG1 mRNA and early age of onset of vitiligo. Thus, MYG1 -119C/G promoter polymorphism may be a genetic risk factor for susceptibility and progression of vitiligo, suggesting the crucial role of MYG1 in autoimmune pathogenesis of vitiligo.

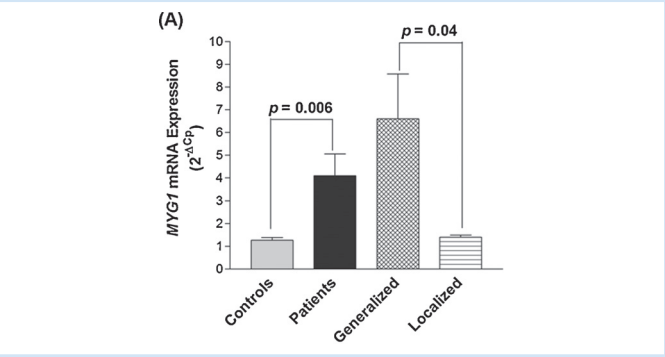

Fig. 2. Relative gene expression of *MYG1* in controls and vitiligo patients: (A) Expression of *MYG1* mRNA in 175 controls, 166 vitiligo patients, 122 generalized vitiligo patients and 44 localized vitiligo patients, as suggested by Mean $2^{-\Delta Cp} \pm$ SEM [Controls vs. Patients: 1.27 ± 0.12 vs. 4.09 ± 0.97 ($p = 0.006$); generalized vs. localized: 6.61 ± 1.97 vs. 1.41 ± 0.087 ($p = 0.04$)].

A failure in endothelin-1 production from vitiligo keratinocytes in response to ultraviolet B irradiation

Elevated circulating soluble interleukin-2 receptor in patients with non-segmental vitiligo in North American

In addition to the above paper, there are two other papers regarding vitiligo in this issue. Although the dysfunction of melanocytes occurs in vitiligo, its pathogenesis still remains unknown. Autoimmunity to melanocytes or their specific organelles has been proposed to be involved in the pathogenesis of vitiligo. Alternatively, impairment in the melanogenic cytokine network between melanocytes and epidermal keratinocytes has also been regarded as a possible cause of vitiligo. It has recently been reported the number and functional defects in peripheral blood invariant natural killer T (iNKT) cells, or regulatory T lymphocytes.

Takata T et al showed that narrowband-UVB-induced endothelin-1 expression by keratinocytes derived from vitiligo lesions is significantly attenuated, while non-lesional keratinocytes showed normal response to UVB. Therefore, tanning-effect by UVB is impaired in vitiligo lesion, at least in part, through the failure of keratinocytes in up-regulation of endothelin-1. The abnormality in lesional keratinocytes might confer the intractability of this disease, but probably represents a collateral damage of consequence of the depigmentating process.

Shi Y-L showed that elevated serum sIL-2R levels and positive correlation with disease severity in active non-segmental vitiligo patients in a North American patient population. This suggests that serum sIL-2R may be a potential immunological marker for vitiligo prognosis, as well as for response to therapy. sIL-2R levels could serve as biomarkers for response to immunotherapy or phototherapy in vitiligo.