The Editor's Choice

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Evaluating differential expression of fibrosis-related genes and their correlation with blood vessel density in chronic cutaneous graft-versus-host disease

Sclerodermoid graft-versus-host disease (GVHD) is the most severe form of chronic GVHD (cGVHD) and represents a considerable therapeutic challenge. Due to the scarcity of human studies on sclerodermoid cGVHD, the pathogenesis of this entity is not fully understood. Greenberger S et al identified the differential expression of fibrosis-related genes in skin lesions of human lichenoid and sclerodermoid cGVHD and to assess the expression of their corresponding proteins. The authors identified 44 upregulated and 14 downregulated genes in the skin samples of sclerodermoid cGVHD compared to the control group. TIMP3 was positive in 13/21 biopsies of cGVHD and in one biopsy of the control group. The average staining intensity was significantly higher in the cGVHD group compared to the control group. TIMP3 was expressed mainly in dermal blood vessels. cGVHD specimens with positive TIMP3 staining had a statistically significantly higher total microvascular area than the negative specimens. TIMP3 levels are increased in both subtypes of cGVHD and are associated with increased dermal vascularity.

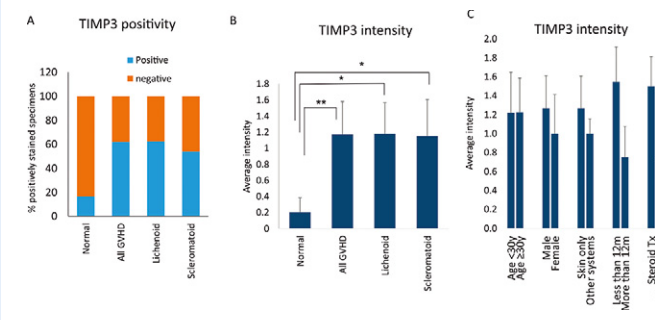

Fig. 2. TIMP3 expression in cGVHD skin tissue A. Percent of specimens positively stained for TIMP3 in cGVHD (n = 21), lichenoid cGVHD (n = 8), sclerodermatoid cGVHD (n = 13) and control (normal skin, n = 6), B. Staining intensity in cGVHD (n = 21), lichenoid cGVHD (n = 8), sclerodermoid cGVHD (n = 13) and control, (normal skin, n = 6). Results are expressed as means; error bars represent ± s.e.m. * indicates $p < 0.05$; * * indicates $p < 0.01$, C. Effect of age, gender, non-cutaneous GVHD and steroid treatment on TIMP3 staining intensity. Results are expressed as means; error bars represent ± s.e.m. * indicates $p < 0.05$.

Anti-inflammatory effects of differential molecular weight hyaluronic acids on UVB-induced calprotectinmediated keratinocyte inflammation

The biological functions of hyaluronic acid are related to its molecular weight and binding to its receptor, TLR4 or CD44. Recent studies have shown that low-molecular-weight Hyaluronic acid (LMW-HA) exhibits proinflammatory effects, while high-molecular-weight Hyaluronic acid (HMW-HA) functions as an anti-inflammatory factor. UVB-induced epidermal inflammation is mainly mediated by endogenous molecules, such as DAMPs, that cause severe skin damage by activating TLR signaling pathways. Since both LMW- and HMW-HA have inhibitory functions on TLR-mediated macrophage inflammation, HA is assumed to suppress UVB-induced DAMP-mediated inflammation in the skin. By competitively binding to TLR4, uLMW-HA downregulated Calprotectin-induced TRAF6 expression, which might be the direct process by which uLMW-HA decreased UVB-induced IL-6 secretion. Reduced CD44 variant (CD44v) expression in keratinocytes attenuated the inhibitory effect of both uLMW-HA and HMW-HA on UVB-induced inflammation, which indicated the involvement of CD44v in HA-regulated anti-inflammatory activity. Hyaluronic acid is a biologically effective material that can prevent the excessive skin inflammation caused in daily life, especially in the late stages after sunburn.

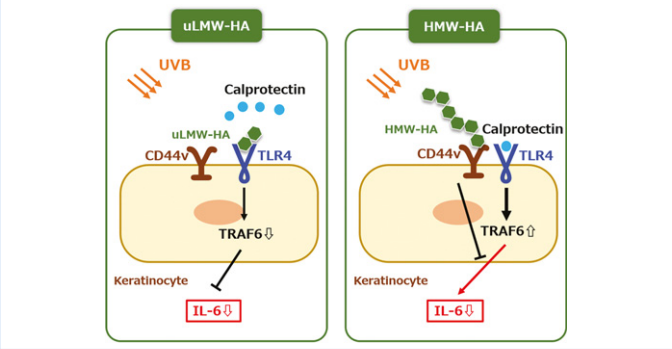

Fig. 6. Schematic of HAs functions on UVB-induced inflammation. uLMW-HA attenuates the TLR4 signaling via TRAF6 by blocking the stimulation of TLR4 agonists such as calprotectin, which can be produced by UV radiation. HMW-HA suppresses inflammatory responses by inflammatory ligands such as calprotectin through binding to CD44v, although HMW-HA upregulates TRAF6 expression.

Actinic lentigines from Japanese and European volunteers share similar impaired biological functions

Hyperpigmented spots develop earlier and with a higher incidence in Asian individuals compared with Europeans. Although actinic lentigines (AL) are very common, the biological events underlying their formation remain ill-defined. Warrick E at al showed AL from Japanese individuals revealed deep epidermal invaginations with melanin accumulation in the depth of epidermal rete ridges. Transcriptomic data identified 245 genes differentially expressed in AL versus NL skin samples, associated with the different skin compartments and multiple functional families and biological processes, such as epidermal homeostasis, extracellular matrix organization and ion binding/transmembrane transport. Strikingly, melanogenesis-related genes were not significantly modulated in AL compared with NL skin. Comparison of the molecular profiles of Japanese and European AL showed that a huge majority of genes were modulated in the same way, recapitulating the overall biological alterations. AL from Japanese volunteers exhibited morphological and molecular alterations of the whole skin structure with impairment of multiple biological functions similar to that found in European women. These findings will contribute to the development of efficient treatments of AL lesions

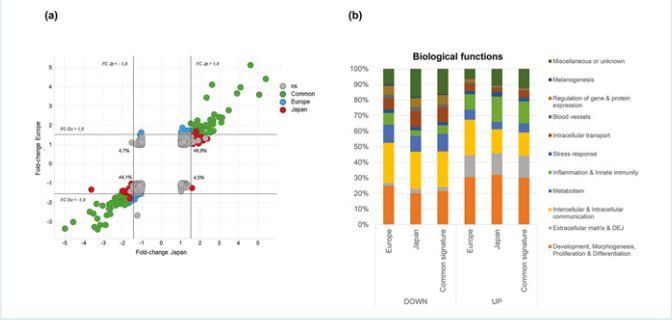

Fig. 3. Comparison of gene expression profiles and functional families in AL versus NL skin in Japanese and European studies. (a) Comparison of lists of probesets with a Pvalue < 0.05 in at least 1 study using TIBCO Spotfire (TIBCO Software, Palo Alto, USA). Fold-change values in the European study and in the Japanese study are represented on the vertical and horizontal axes, respectively. This global comparison shows that more than 90% of all probesets were modulated in the same way in European and Japanese AL. FC Eu: Fold-change European study; FC Jp: Fold-change Japanese study. Green: common probesets significantly modulated in both studies with mean FC value ≥ 1,5 (for up-regulated genes) or ≤ −1,5 (for down regulated genes) and an adjusted P-value < 0.05; Blue: probesets significantly modulated in the European study only; Red: probesets significantly modulated in the Japanese study only. ns: not significantly modulated. (b) Comparison of biological functions associated with genes differentiating AL from NL skin in European (n = 196) and Japanese (n = 245) volunteers with the biological functions associated with common genes, modulated in both studies (n = 245). Note that the same functional families are similarly represented in European and Japanese AL, and that the common signature recapitulates this biological profile.