The extracellular matrix of the dermis is degraded through the activation of angiogenesis due to paracrine signaling from keratinocytes

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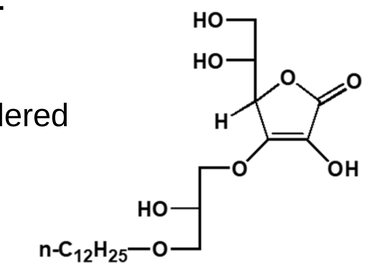
Introduction:

The ultraviolet (UV) ray in sunlight accelerates the progression of skin aging characterized by sagging and deep wrinkles. One of the main causes of skin wrinkles originates from the degradation and/or denaturation of the extracellular matrix (ECM) not only as a result of autocrine signaling in fibroblasts, but also of paracrine signaling from neighboring cells such as keratinocytes. Recently, it was suggested that angiogenesis of capillary vessels in the papillary dermis is also involved in the formation of wrinkles, because the ECM is degraded by neutrophil elastase secreted from newly synthesized capillary blood vessels [1]. Angiogenesis is caused by the migration of vascular endothelial cells in response to vascular endothelial growth factor (VEGF) secreted by epidermal keratinocytes [2]. Since the secretion of VEGF from keratinocytes is enhanced by reactive oxygen species (ROS) and inflammatory cytokines [3], we hypothesized that interactions between keratinocytes and vascular endothelial cells are involved in the formation of wrinkles.

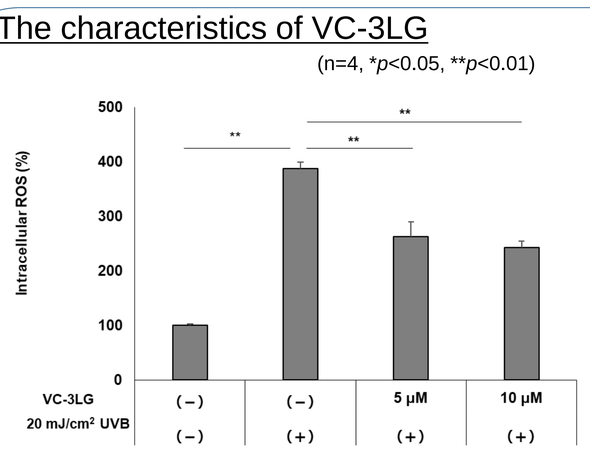
In this study, we first clarified interactions between keratinocytes and vascular endothelial cells that result in the formation of wrinkles. In addition, since it was considered that suppression of ROS production was useful for suppression of VEGF production in keratinocytes, we evaluated the effects of 3-*O*-laurylglyceryl ascorbate (VC-3LG), which is an ascorbic acid derivative and exhibits a high antioxidant effect, on interfering with those interactions.

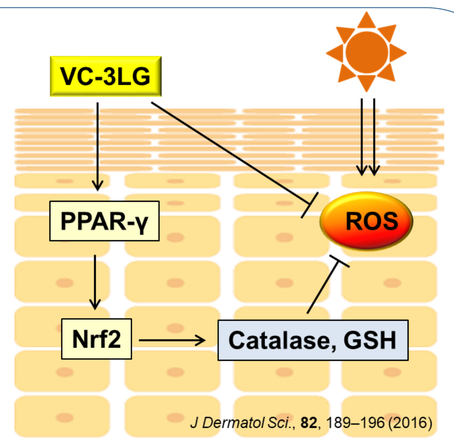


3-*O*-laurylglyceryl ascorbate (VC-3LG)

The characteristics of VC-3LG

(n=4, **p*<0.05, ***p*<0.01)





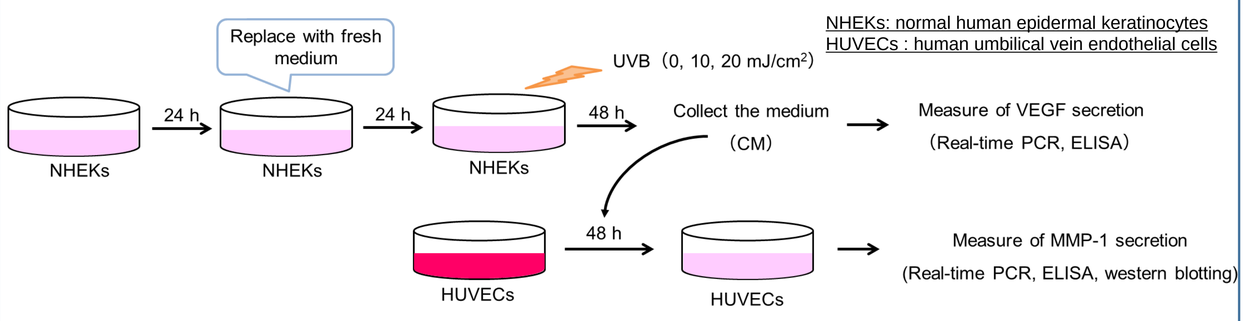
VC-3LG enhances intracellular antioxidation defense through activation of the PPAR-γ-Nrf2.

Materials & Methods:

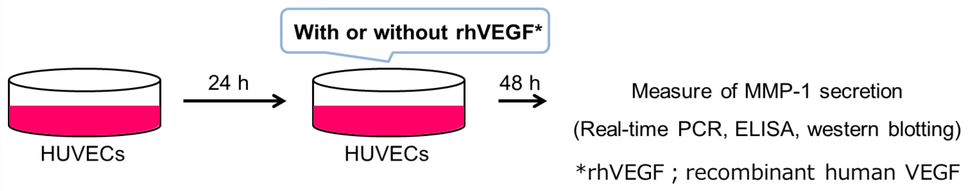
1. A role of VEGF from UVB-irradiated keratinocytes on the secretion of matrix metalloproteinase-1 (MMP-1) from endothelial cells

1-1. The VEGF secretion and the influence of the CM on HUVECs

NHEKs: normal human epidermal keratinocytes
HUVECs : human umbilical vein endothelial cells



1-2. The influence of VEGF on HUVECs on the secretion of MMP-1



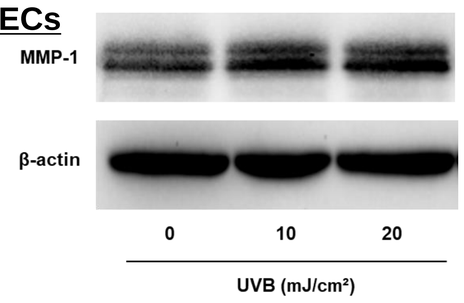
2. The effect of VC-3LG on interactions between NHEKs and HUVECs

- NHEK pretreated with VC-3LG for 24h was irradiated with UVB.

  ⇒ The effects of VC-3LG was evaluated following the method 1-1.

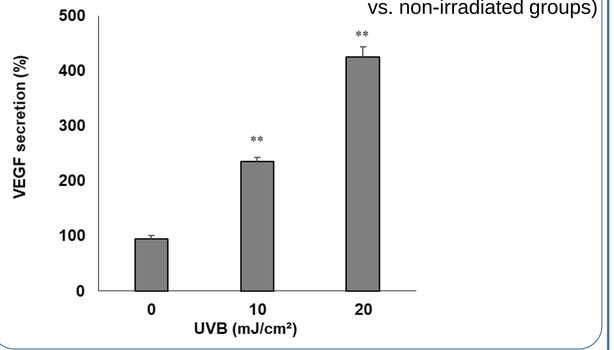
Results & Discussion:

1. CM of UVB-irradiated NHEKs enhanced MMP-1 production in HUVECs

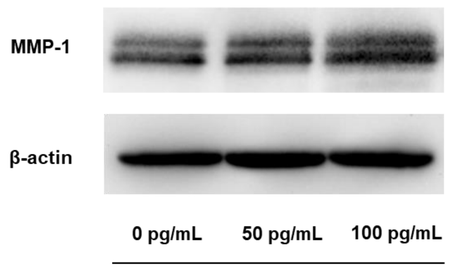


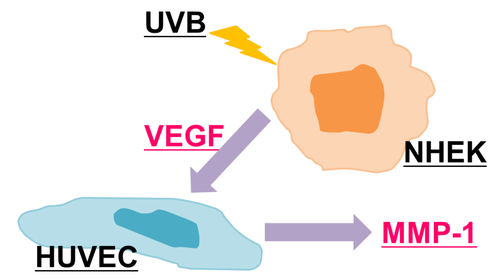
2. UVB-irradiated NHEKs increased the secretion of VEGF

(n=3, **p*<0.05, ***p*<0.01 vs. non-irradiated groups)



3. VEGF and also increased the secretion of MMP-1 from HUVECs





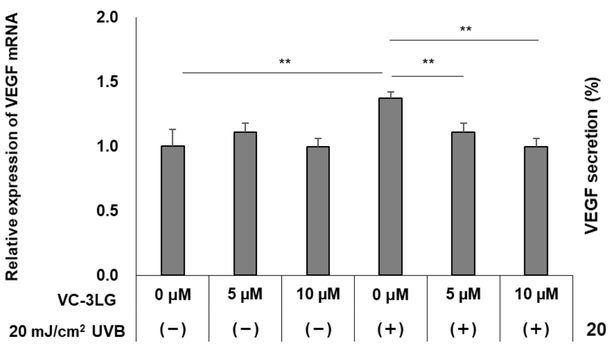
Interactions between NHEKs and HUVECs

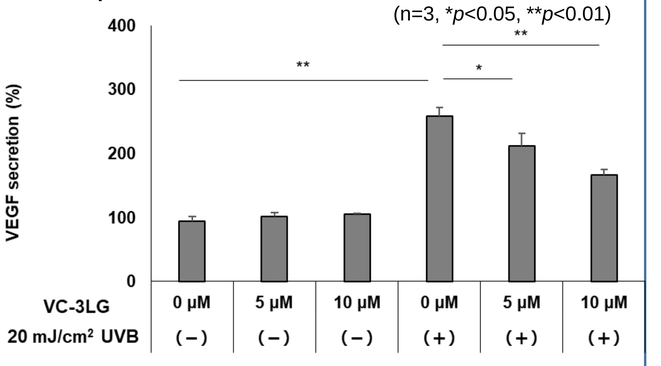
UVB causes collagen depletion through increasing MMP-1 of HUVECs by VEGF secreted from NHEKs

4. Interference of VC-3LG on interactions between NHEKs and HUVECs

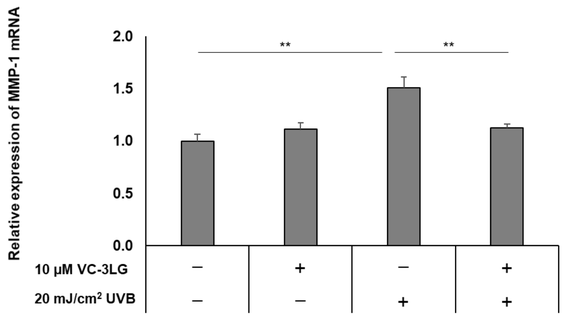
- The effect of VC-3LG on UVB-induced VEGF production from NHEKs

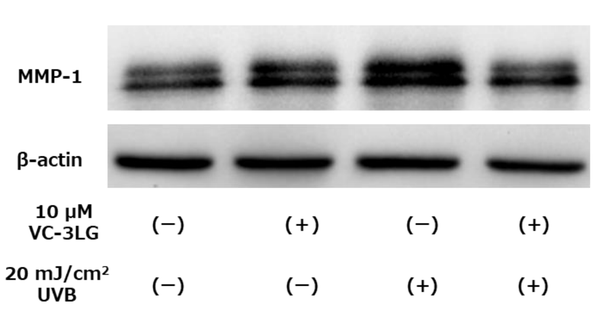
(n=3, **p*<0.05, ***p*<0.01)





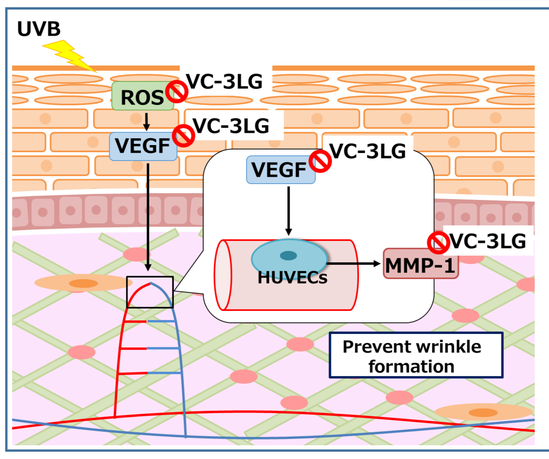
- The inhibitory effect of VC-3LG on MMP-1 production





VC-3LG reduces MMP-1 secretion from HUVECs through block the interaction between keratinocyte and vein endothelial cell

Conclusions:



・In the process of UVB-accelerated wrinkle formation, it was demonstrated a possibility of the presence of interaction between keratinocyte and vein endothelial cell.

・The study demonstrated that VC-3LG has the potential to be an effective anti-wrinkle agent by block UVB induced interaction between keratinocytes and vein endothelial cells.

References:

[1] Yano K, Kadoya K, Kajiya K, Hong Y-K, Detmar M (2005) Ultraviolet B irradiation of human skin induces an angiogenic switch that is mediated by upregulation of vascular endothelial growth factor and by downregulation of thrombospondin-1. *Br J Dermatol* 152:115-151.
[2] Ferrara N, Davis-Smyth T (1999) The biology of vascular endothelial growth factor. *Endocrine Rev* 18:4-25.
[3] Sen CK, Khanna S, Babior BM, Hunt TK, Ellison EC, Roy S (2002) Oxidant-induced vascular endothelial growth factor expresion in human keratinocytes and cutaneous wound healinig. *J Biol Chem* 277: 33284-33290.