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Letter to Editor Open Access

CCN3 and CCN5, New Factors Associated with Skin Pigmentation

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The CCN family of matricellular protein is composed of 6 members which are differentially expressed in the skin. CCN3 mRNA has been shown to be mostly expressed in the epidermis whereas mRNA of CCN2 and CCN5 were mostly expressed in the dermis [1]. However according to Rittie et al., CCN2 seemed expressed in melanocytes [1]. We have shown that melanocytes express CCN3 [2]. In melanocyte, CCN3 is implicated in melanocyte homeostasis by regulating the collagen-receptor DDR1 [3]. CCN proteins are regulated by various factors implicated in melanogenesis such as FGF2, endothelin [1], estrogens and progesterone and the receptors for estrogens and progesterone are increased in melasma, a common acquired hyperpigmentary disorder [4]. In non-segmental vitiligo, an hypopigmentary disorder with loss of melanocytes, we have shown that the expression of CCN3 was increased in keratinocytes of lesional skin and that the expression in melanocytes was variable in perilesional skin [2]. In systemic scleroderma, a fibrotic disease due to excessive secretion of collagen by activated fibroblasts and associated in around 40 % of cases with hypo or hyperpigmentary troubles [5] CCN3 was found increased in lesional fibroblasts [6] whereas CCN2 was increased in lesional epidermis [6,7]. CCN1 was found greatly increased in dermal fibroblasts from elderly individuals as compared to young ones [8] and its expression was suppressed by retinoic acid [9] which is commonly used for treatment of melasma [10]. Under UV irradiation, a well know activator of melanogenesis, CCN mRNA were diversely modulated in full thickness skin, CCN1 and CCN2 were significantly upregulated whereas CCN3-6 were significantly downregulated [11]. We have recently demonstrated that incubation of pigmented reconstructed epidermis supplemented with medium conditioned by irradiated fibroblasts originating from old patients modeled senile lentigo, a hyperpigmentary disorder [12]. All these results let us suspect a link between level of CCN and regulation of pigmentation. To look further at variations of CCN proteins expression in normal pigmentation, we investigated CCN1,2,3 and 5 in 30 skin samples (foreskin or mammary skin) with a wide range of ages (9 months to 75 years) and phototypes (I to VI). We performed immunohistochemistry and measured fluorescence of CCN in epidermis and dermis using NIS Element Br (Nikon) software. Comparing our data with those of Rittie et al. [1], we confirmed that CCN1 and CCN2 were mostly expressed in the dermis but we could not confirm a greater expression of CCN5 in the dermis. We observed that the level of fluorescence was not modified by age at variance with Quan et al. [8] for CCN1, 2 and 3 but we did not test samples from patients over 80 years. CCN5 presented a peak of expression in the 10-30 years old age group. We found no difference of expression of CCN 1 and 2 according to phototype (Supplemental Figures 1 and 2).

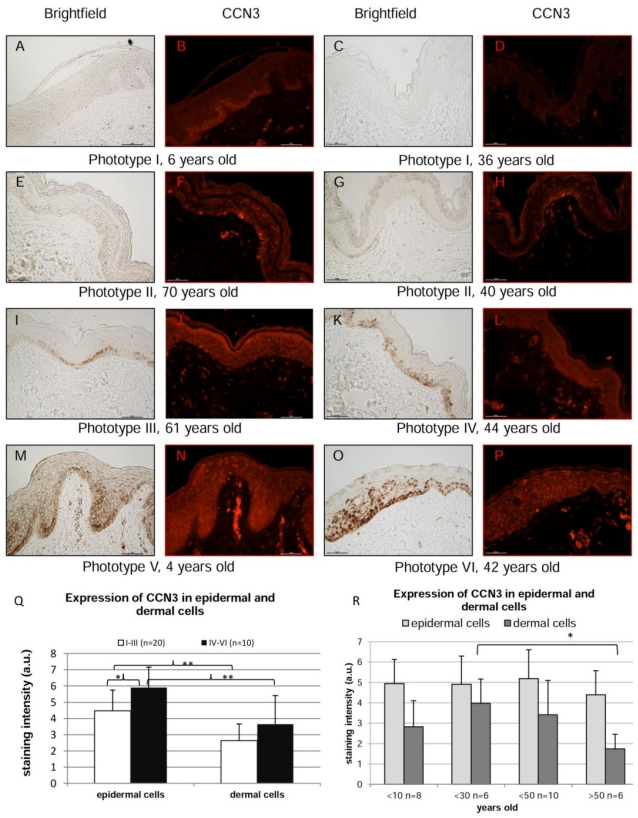

Figure 1: Expression of CCN3 in human skin according to phototype. Bright field pictures of human skin were taken to asses level of melanin (A, C, E, G, I, K, N, P) prior to observe CCN3 expression detected using ab 137677 followed by anti-rabbit alexa 555 (B, D, F, H, J, L, N, P). Scale bar : 50 µm. Q Histogram of CCN3 expression in epidermis and dermis according to phototype I-III and IV-VI R, histogram of CCN3 expression in epidermis and dermis according to age . Student t-test $^{*}p<0.05$; $^{**}p<0.01$.

We confirmed the results of Rittie et al. [1] of a higher expression of CCN3 in epidermis than in dermis (Figure 1). Surprisingly CCN3 expression increased significantly when comparing low *vs* high phototypes in both epidermal and dermal compartments (Figure 1). On the contrary, CCN5 decreased significantly with phototype in the epidermal compartment (Supplemental Figure 3).

We confirmed the expression of CCN3 in melanocytes but did not detect CCN2 in melanocytes as indicated by Rittie et al. [1]. However Rittie et al., have not done a double staining melanocyte /CCN2, thus basal cells overexpressing CCN2 in their case may be Merkel cells. Moreover, occasionally CCN5 was expressed in melanocytes at the difference of CCN1 which was always detected in melanocytes (Supplemental Figure 4).

In conclusion, CCN 1 and 2 were not altered by age until 75 years old and were not modified according to phototype. CCN3 expression was also not influenced by age but was increased according to phototype. As for CCN5, it was the only CCN tested which was influenced by age with a peak around 20. CCN5 expression decreased with phototype. Moreover, independently of phototype, CCN 1,3,5 but not CCN2 were expressed in melanocytes. Due to the differential expression of CCN3 and CCN5 according to phototype, an investigation of their expression in pigmentary disorders which have a differential prevalence in Caucasian, Asian and African skin types such as melasma or solar lentigines might be relevant.

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