Acne and Telomere Length: A New Spectrum between Senescence and Apoptosis Pathways


TO THE EDITOR

Acne is a multifactorial disease with many factors thought to play a role, including skin microflora and nutrition as well as hormonal influences and stress (Suh and Kwon, 2015). Acne patients have increased sebum secretion, and both acne and activity of the sebaceous glands are under significant genetic control (Bataille et al., 2002; Mourelatos et al., 2007). Recent genome-wide association studies have identified several variants linked to acne susceptibility (He et al., 2014; Navarini et al., 2014; Wang et al., 2015; Zhang et al., 2014).

It has long been noticed by dermatologists that acne patients have reduced skin aging, often observed many years after the acne has recovered. Signs of aging, such as wrinkling and skin thinning, appear later in acne patients compared with nonaffected individuals. This was speculated to be due to increased sebum secretion during the lifetime, but other factors are likely involved (Downing et al., 1986).

In this study, we investigated leukocyte telomere length (LTL) in subjects with acne compared with control subjects using data from the TwinsUK registry (http://www.twinsuk.ac.uk/).

Telomeres are repeat TTAGGG sequences at the end of linear chromosomes guarding against loss of genetic material during cellular replication. Repeated cell cycles eventually lead to a critically shortened LTL, signaling cellular senescence and triggering apoptosis. Hence, LTL has been shown to be predictive of biological aging (Hewitt et al., 2012).

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Volunteers in the TwinsUK cohort were not recruited on the basis of any specific trait or disease and have been shown to have diseases and lifestyle characteristics similar to those of the general population (Andrew et al., 2001). Guy’s and St. Thomas’ Hospital NHS Trust Research Ethics Committee approved the study, and all twins provided informed written consent. For historical reasons the TwinsUK registry involves mainly women, and men were therefore excluded from this study. The history of acne was self-reported during a nurse-administered questionnaire, and the female twins were asked if they had ever suffered from acne and whether their acne was self-treated, treated by a general physician or treated by a dermatologist (Bataille et al., 2002). A total of 293 out of 1,205 twin volunteers (24.3%) had experienced acne in their lifetimes.

LTL was measured using Southern blot analysis and was available for all subjects included in this study (Valdes et al., 2007) (see Supplementary Materials online for details). Mean LTL in the 1,205 subjects was 7.08 kilobase pairs (kb) (median = 7.06 kb, range = 5.70–8.67 kb). Mean weight was 67 kg (median = 65 kg, range = 40–115 kg), and mean height was 162 cm (median = 162 cm, range = 144–182 cm). The mean age of the twins at the time of DNA extraction was 48 ± 12 years.

Linear regression (see Supplementary Materials for details) showed that samples from acne patients had longer LTL (mean = 7.17 ± 0.64 kb) compared with those from control subjects (mean = 6.92 ± 0.02 kb) after adjustment for age, twin relatedness, weight, and height (β = 0.11; standard error = 0.05; P = 0.01). Using score tests under a logistic regression model, we further investigated the association between acne and a set of single-nucleotide polymorphisms (SNPs) previously reported to be associated with LTL in a sample of 1,893 patients with severe acne and 5,132 population controls from the UK Acne Genetic study (Codd et al., 2013; Mangino et al., 2015; Navarini et al., 2014). No LTL SNPs were significantly associated with acne after correction for multiple testing. However, rs3027234 in the CTC1 gene was nominally significant (see Supplementary Table S1 online). Finally, we performed a mixed-effect logistic regression analysis in whole-genome data from healthy skin samples comparing acne patients and control subjects. The expression data was measured in 705 women from the TwinsUK registry (http://www.muther.ac.uk/), of whom 346 had data on acne history. We selected 195 control twins who were perfectly age-matched to 39 twins with acne and gene expression data (see Supplementary Materials for details). Only the ZNF420 gene (probe ILMN_1720431) was significantly associated with acne history at a false discovery rate of 5%, showing a higher expression in control subjects (P = 7.73 × 10−7) (Table 1 and Figure 1). ZNF420 is one of the 30% most expressed genes in skin.

This study investigated reduced skin aging observed in acne by assessing telomere length in circulating white blood cells and gene expression in the skin. Acne patients had longer telomeres after adjusting for age, height, and twin relatedness, suggesting that the delayed skin aging may be due to reduced senescence. Only one SNP predicting LTL was found to be associated with acne at nominal significance. This SNP is located within the CTC1 gene, which is a component of the CST complex and plays an important role in protecting telomeres against degradation (Sarek et al., 2015). The reduced expression of the gene ZNF420, which encodes the protein Apak, in the normal skin of acne patients suggests that p53 is up-regulated in acne patients, because the ZNF420 gene is a
negative regulator of p53-mediated apoptosis. Considering longer telomeres and the up-regulation of the p53 pathway in acne patients, it could be speculated that acne susceptibility may be linked to the biology of cancer. A recent study from the Nurses’ Health Study II, a large US cohort involving more than 99,000 female nurses (Zhang et al., 2015), found an increased risk of cancer in acne patients (Zhang et al., 2015). Additionally, recent genome-wide association studies have reported significant associations between acne and genes involved in cancer susceptibility, including the MYC gene and genes linked to the transforming growth factor-β cell signaling pathway (Navarini et al., 2014; Zhang et al., 2014). Further work is needed to investigate the associations between cell senescence, acne, and cancer susceptibility, but this work sheds light on this very common and often debilitating skin disease.

**CONFLICT OF INTEREST**
The authors state no conflict of interest.

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**SUPPLEMENTARY MATERIAL**
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.09.014.

**REFERENCES**

Bataille V, Snieder H, MacGregor AJ, Sasiemi P, Spector TD. The influence of genetics and environmental factors in the pathogenesis of
Allogeneic Hair Transplantation with Enhanced Survival by Anti-ICAM-1 Antibody with Short-Term Rapamycin Treatment in Nonhuman Primates


TO THE EDITOR

Autologous hair transplantation is an effective treatment option for permanent alopecia. However, patients with severe hair loss cannot benefit from autologous hair transplantation because of the shortage of donor hair follicles (HFs). In particular, childhood cancer survivors suffer from chemotherapy-induced permanent alopecia throughout life (Choi et al., 2014). In the clinical setting, parents may wish to donate some of their hair to their children; however, allogeneic hair transplantation cannot be successful without life-long immunosuppression. Although long-term immunosuppression may prevent allograft rejection, the side effects cannot be justified for non-life-threatening diseases.

Induction of T-cell tolerance to specific antigens has been attempted using dendritic cells as targets for tolerance induction (Steinman et al., 2003). Antigen presentation by semimature dendritic cells results in T-cell tolerance because of a failure to provide sufficient costimulatory signals (Shortman and Naik, 2007). Recently, the MD-3 antibody was developed as an anti-human intercellular adhesion molecule 1 (ICAM-1) antibody cross-functional in nonhuman primates (Jung et al., 2011). Antibody-mediated ligation of ICAM-1 in dendritic cells arrests dendritic cells in the semimature stage and induces antigen-specific T-cell tolerance against grafted antigens rather than generalized immunosuppression. MD-3 treatment has been shown to achieve long-term xenograft survival in nonhuman primates when combined with low-dose rapamycin and anti-CD154 blocking antibody.

Here, we evaluated the induction potential of T-cell tolerance by the MD-3 antibody in the skin immune system in a major histocompatibility complex-mismatched HF allograft model in nonhuman primates. Before transplantation, we prepared recipient sites on the upper back skin to prevent plucking of the transplanted HFs. Using a diode laser, the medullated hair was targeted, and we aimed to destroy the unmedullated hair simultaneously. After two sessions, monkey hairs were efficiently removed (Supplementary Figure S1 online). Sixteen cynomolgus monkeys were randomly coupled to eight donor-recipient pairs and participated as a recipient and donor after screening of donor-recipient pairs and as a recipient and donor after screening of donor-recipient pairs. Monkeys were divided into three groups (Figure 1a) and treated with the MD-3 antibody plus short-term low-dose rapamycin (n = 6, MD3+IS), short-term low-dose rapamycin only (n = 5, IS), or no treatment (n = 5, Con). MD-3 was injected twice (dosage 8 mg/kg) intravenously at 1 and 4 days before transplantation. Low-dose rapamycin (trough level 6–12 μg/ml) was administered for 3 weeks. Eyebrow HFs of the donor monkey were transplanted into the upper

Abbreviations: HF, hair follicle; ICAM-1, intercellular adhesion molecule 1; ORS, outer root sheath
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