Skin Immune Cells Modulate Bone Health

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INTRODUCTION: Inflammatory diseases can be associated with poor bone health and osteoporosis, but the mechanism underlying this relationship is poorly understood. Patients with the autoimmune disease systemic lupus erythematosus (SLE) are photosensitive, developing inflammatory skin lesions from even ambient sun exposure[2], and they also have a 2.53-fold increased occurrence of osteoporosis and fractures compared to healthy controls[4,5]. Photosensitive skin is associated with increased ultraviolet radiation-induced keratinocyte death, suggesting a compromise in epidermal generation of vitamin D or other bone-trophic factors. We have shown that Langerhans cells, an antigen-presenting cell that resides in the epidermis, normally promotes keratinocyte health by expressing ADAM17, a metalloproteinase that activates epidermal growth factor to promote keratinocyte survival, but are dysfunctional in SLE[3]. These findings suggest the hypothesis that dysfunctional Langerhans cells in SLE, by causing poor epidermal health, may contribute to osteoporosis associated with SLE. Here, we examine mouse models in which Langerhans cells are either deleted or are lacking ADAM17 and assess for bone microarchitecture changes consistent with an osteoporosis phenotype.

METHODS: LC-DTA and LCAd17 models were used. LC-DTA mice constitutively express attenuated diphtheria toxin in epidermal Langerhans cells and are thus depleted of Langerhans cells, while LCAd17 mice have Adam17 deleted in epidermal Langerhans cells[3]. Male and female LC-DTA mice and corresponding controls were exposed to ultraviolet radiation (1000J/m2 UVB) weekly x 6 weeks starting from 8 weeks onward prior to examination. Male and female LCAd17 mice were examined at 13-16 weeks of age at steady state. We evaluated the cortical and trabecular bone microarchitecture by MicroCT. Femurs from LC-DTA (n=4), corresponding wildtype (n=3), and LCAd17 (n=7) and corresponding wildtype littermates (n=4) were scanned at 6 µm resolution using a SCANCO vivaCT-45 system (SCANCO Medical AG, Fabrikweg, Switzerland), 70 peak kilovoltage and 145-µA X-ray source. 3D reconstruction and analysis of the µCT images were performed with the SCANCO Evaluation and Illustration software. Trabecular bone measurements were taken 0.33 mm proximally from the distal epiphyseal growth plate, with 1.2 mm in height, and cortical bone parameters were measured at mid-diaphysis (which was located by taking the midpoint between the greater trochanter and intercondylar notch), extending to a length of 1.2 mm.

RESULTS: In the LC-DTA mice, there was a significant reduction in both cortical bone area (Ct.BA, p=0.029), total area (Ct.TA, p=0.049) and trabecular thickness (Tb.Th, p=0.034). In LCAd17 mice, there was a decreasing trend found in trabecular thickness (Tb.Th, p=0.054), number (p=0.064) and bone volume fraction (BV/TV, p=0.070), without changes in cortical bone parameters. These results are consistent with a phenotype suggestive of early osteoporosis in mice lacking Langerhans cell ADAM17 at steady state and osteoporosis in mice lacking Langerhans cells that received ultraviolet radiation, suggesting that immune cells in the skin can modulate bone health.

DISCUSSION: Leveraging models with Langerhans cell dysfunction and compromised Langerhans-cell mediated skin protection, we investigated the role of epidermal Langerhans cells on bone health. Our results suggest that compromise of Langerhans cells in skin at steady state can lead to bone changes consistent with early osteoporosis and that lack of Langerhans cells with ultraviolet radiation can lead to changes consistent with osteoporosis. Together, these results suggest a model whereby Langerhans cell dysfunction, by causing poor skin health, can lead to osteoporosis. As this initial investigation looked at mouse models with constitutive Langerhans cell dysfunction, a limitation is the potential for developmental defects that led to the observed phenotypes. We plan to address this limitation by also studying inducible models. Further studies will also be needed to understand the extent to which our murine model observations are relevant to human conditions where Langerhans cells are compromised, such as in lupus or with sunburn or skin excoriation.

SIGNIFICANCE/CLINICAL RELEVANCE: Our results suggest that dysfunction of epidermal Langerhans cells leads to osteoporosis. These results suggest that immune cells in skin can have far reaching effects including regulation of bone health, by their actions on skin and suggest that examination of Langerhans cell function in patients with lupus and other skin diseases may be useful in predicting risk for osteoporosis, leading to early preventative measures to protect bone. These results also suggest that outcomes of bone fracture and surgery healing may be influenced by the health of the skin, raising the possibility that skin and skin immune cell health may need to be considered in assessing patient risks and stratification.

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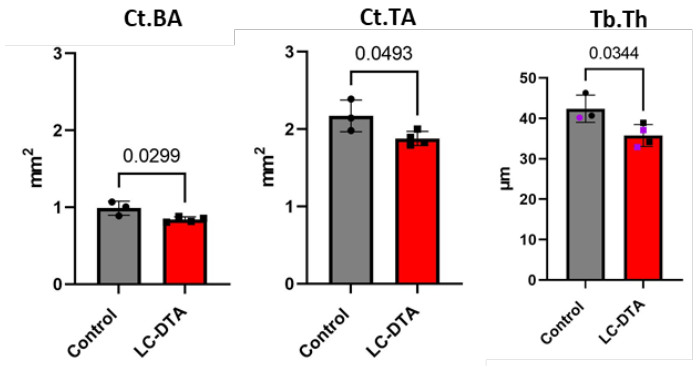

Figure 1. Control vs LC-DTA mice cortical bone area (Ct.BA), total area (Ct.TA) and trabecular thickness (Tb.Th).