CHARACTERIZATION OF SKIN ABNORMALITIES ASSOCIATED WITH OSTEOGENESIS IMPERFECTA VIA HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING

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Introduction

OI is a rare heritable bone disease characterized by a mutation in the type I collagen-producing genes COL1A1 and COL1A2. Resulting structural changes in the type I collagen heterotrimer are thought to disrupt formation of the triplex helix structure by the decreased abundance of the hydrophobic collagen α2 chain.[1] Patients with this disorder exhibit a number of clinical manifestations, the most prominent of which are frequent bone fractures. Diagnosis in patients with moderate disease requires lengthy fibroblast culture studies. The *oim/oim* mouse has been used as model for the human disease of OI for evaluation of both bone pathology and therapeutic interventions. While bone abnormalities in OI are of dominant importance, we hypothesized that alterations in collagen I would also be manifest in the skin, particularly with respect to hydration and collagen packing in the dermal layer. Such changes are accessible to a number of MR measurement techniques. If it is confirmed that non-invasive MR evaluation of skin is useful in diagnosis and characterization of OI, this could lead to improved diagnostic capabilities in clinical settings in which rapid diagnosis is of value.

Given the demonstrated ability of T_2 and density-weighted proton MRI to characterize hydration and water mobility in the layers of skin in both normal and pathological skin samples[2] and the well-established sensitivity of magnetization transfer (MT) MRI to collagen concentration in cartilage,[3] we utilized these contrast mechanisms to non-invasively characterize dermal abnormalities in OI.

Methods

Images, ca. 15 mm x 10 mm, were obtained from samples harvested from the backs of *oim/oim* and wild type mice. Samples were stretched onto non-magnetic planar sample holders and immersed in protease inhibitor solution within a standard 15 mm NMR tube. Images were acquired at 9.4 T using a Bruker DMX 400 NMR spectrometer equipped with a 15 mm birdcage resonator and 1000 mT/m three-axis microimaging gradients. Cold air generated using an Exair vortex tube was used to cool samples to 4ºC. All samples were imaged in 12 equally spaced axial planes. Geometric parameters included a field of view of 0.75 x 1.5 cm, slice thickness = 1mm, and a matrix size of 512 x 256, resulting in a resolution of 15 x 60 µ with the read direction perpendicular to the Bo magnetic field. Total scan times for T_2 weighted images were approximately 2 hours, and 8 hours for MT images. Transverse MRI slices were compared to geometrically equivalent histological sections stained with Masson Trichrome to delineate collagen.

Results

In addition to notable visual differences in the T_2-weighted contrast seen in OI (n=6) and wild type (n=6) skin samples, the dermal skin layer in OI skin samples was also considerably thinner compared to the WT skin samples. Further, in the dermis,T_2 values were greater in OI skin, consistent with greater water mobility. This may be due to the absence of the hydrophobic α2 collagen chain. MRI also documented the formation of a characteristic skin layer in the *oim/oim* samples; the presence of this layer was confirmed by histology. Overall, this additional skin layer was similar to the WT hypodermis in terms of MR parameters.

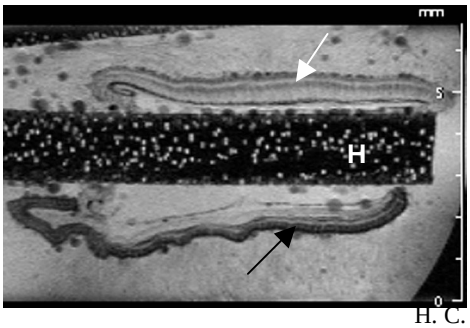

Fig. 1 T_2-weighted image showing OI skin sample (white arrow) and WT skin (black arrow) separated by a planar sample holder (H).

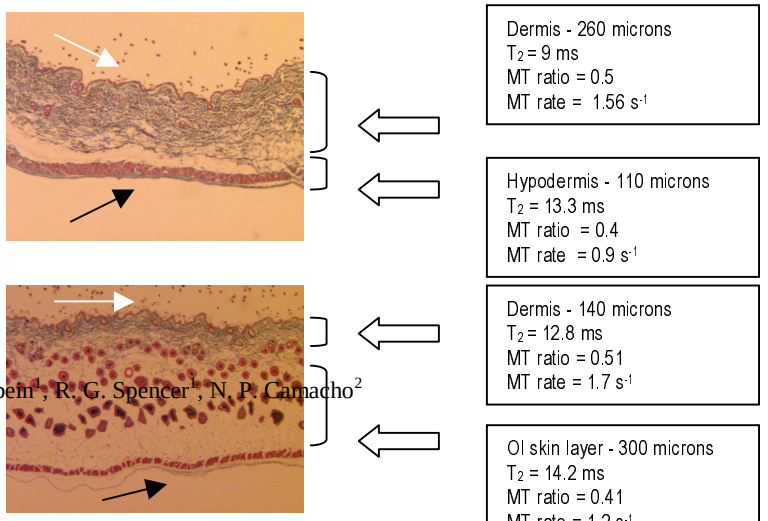

Fig. 2 WT (top) and OI (bottom) skin samples with Masson Trichrome staining for collagen. White arrow indicates fur; black arrow indicates muscle.

Conclusion

We found significant and highly reproducible differences in thickness, layer distribution, relaxation times, and magnetization transfer parameters between skin samples from wild-type and oim/oim mice. These results can be interpreted in terms of the known molecular basis for OI, including differences in type I collagen fibril packing. Current efforts are directed towards determining whether such results will also be found in human OI patients. If so, MRI may represent an important modality in the rapid detection of OI as well as in the study of OI-associated abnormalities in connective tissue.

References

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