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Characterization and tissue incorporation of cross-linked human acellular dermal matrix

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ABSTRACT

Here, we describe a novel human acellular dermal matrix (ADM) cross-linked using electron beam irradiation. Structural and biomechanical characteristics of the human ADM were assessed by infrared spectrometry and uni-axial tensile testing. Electron beam irradiation affects collagen secondary structure, which can be detected in the amide I spectral region (1660 cm^{-1} and 1690 cm^{-1}). At doses exceeding 25 kGy, cross-linking of the collagen matrix results in a denser, more stratified appearance and parallel arrangement, with significantly increased tensile strength and elastic modulus. In a micropig model, the implanted ADM elicits rapid host cell infiltration and extracellular matrix deposition; however, the delayed remodeling resulted in long-term structural integrity. Furthermore, mean densities of collagen and elastin, expression of extracellular matrix proteins, and microvessel formation within the implanted ADM increased significantly, whereas the thickness of the implanted ADM did not decrease during the course of the study. Compared with normal adjacent tissue, type I collagen mRNA levels in the ADM increased 12-fold at 3 months after implantation, and transforming growth factor-β mRNA levels increased 3.3-fold at 2 months. Matrix metalloproteinase (MMP)-1 and MMP-9 mRNA levels were also elevated. Collectively, these results demonstrate that the structural and biomechanical properties of this novel cross-linked human ADM are adequate for use as a biologic tissue substitute.

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1. Introduction

Acellular dermal matrix (ADM) is created from cadaveric skin using proprietary processing techniques that are reported to preserve the biochemical and structural components of the extracellular matrix (ECM), thereby promoting tissue regeneration. Human ADM is extremely useful in burn care and reconstructive surgery, such as breast reconstruction, abdominal hernia repair, and cleft palate repair [1–10]. In addition, ADM graft can be combined with autologous thin split-thickness skin graft for safe and effective reconstructive procedures [11–14].

Acellular dermal matrix contains collagen and elastin, which contribute tensile strength and elasticity; proteoglycans, which induce angiogenesis; laminin, which maintains binding with connective tissues; and basement membrane, which consists of collagen type IV. This material acts as a biologic scaffold for re-epithelialization, neovascularization, and fibroblast infiltration [15–17], but does not induce an immune response. Critical requirements for materials used in surgical implantation procedures include biocompatibility, potential for tissue integration and remodeling, strength, and durability. Cross-linking of human ADM can increase its resistance to degradation by collagenases, but may affect angiogenesis, tissue formation, and the inflammatory response, potentially altering the strength, durability, and incorporation of the implant [16,18,19].

The two approaches to cross-linking of collagen materials are chemical and physical methods. For example, Permacol™ is a porcine dermal matrix chemically cross-linked using hexamethylene diisocyanate [20,21] that has been well characterized and

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is used in reconstructive surgery. Physical cross-linking of ADM using ultraviolet irradiation and microwaves produces materials that differ with respect to microvascular architecture, degree of density, and dermal epidermal integration. Here we describe a novel, cross-linked human ADM (MegaDerm™) that is minimally processed to remove epidermal and dermal cells using patented techniques that do not damage essential biochemical and structural components (e.g., collagen, elastin, proteoglycans) or dermal structure. Preparation of this material uses electron beam (e-beam) irradiation, which is used for sterilization and collagen cross-linking. Moderate cross-linking treatment can improve durability and strength, and result in controlled tissue integration and remodeling [19,22]. Although MegaDerm™ has been used as a dermal implant and filler in various reconstructive procedures (e.g., facial augmentation, breast reconstruction) and after thyroidectomy and parotidectomy in Korea, its histologic appearance and biomechanical properties have not been reported. In addition, the expression of proteins involved in wound healing and remodeling, such as collagen type 1 and transforming growth factor-β (TGF-β), is poorly understood.

In the present study, we evaluated the structural and biomechanical properties of this novel cross-linked human ADM. Using a micropig model, we evaluated neovascularization, soft tissue ingrowth, and integration into the host tissue to determine the usefulness of this material as a biological scaffold. In addition, the effect of this cross-linked human ADM on the expression of proteins involved in ECM remodeling was assessed by immunohistochemistry and quantitative polymerase chain reaction (qRT-PCR).

2. Material and methods

2.1. Preparation of the cross-linked human ADM

Cross-linked human ADM (MegaDerm™; L&C BIO, Seongnam-Si, Gyeonggi-Do, Korea) is derived from donated human skin supplied by U.S. tissue banks under the guidelines of the American Association of Tissue Banks (AATB) and the U.S. Food and Drug Administration. Donor medical history and results of serological testing were reviewed by the medical director, and fresh human cadaver skin was procured by tissue banks in accordance with these guidelines. Epidermal and dermal cells were removed without damage to essential biochemical and structural components including collagen, elastin, and proteoglycans. The remaining acellular, dermal layer was preserved by using a proprietary freeze-drying method, which retains the native extracellular architecture and vascular channels. MegaDerm™ is packaged in this freeze-dried form and can be stored up to 5 years. E-beam irradiation was used to cross-link collagen and eliminate viruses, bacteria, and spores to achieve a sterility assurance level of 10^{-6}.

2.2. Characterization of ADM morphology by scanning electron microscopy

A scanning electron microscope (Hitachi S-800, Japan) was used to characterize the morphology of the cross-linked human ADM before and after e-beam irradiation. After ADM specimens were irradiated (25, 30, 50, or 70 kGy), the specimens were sputter-coated with platinum, and cross-sectional images were obtained at an accelerating voltage of 20 kV.

2.3. Infrared spectrophotometry

Fourier transform infrared (FT-IR) spectra for e-beam–irradiated ADM (0, 10, 15, 25, and 35 kGy) and unirradiated ADM (controls) were determined by using a Spectrum GX spectrometer (Perkin–Elmer, UK) in attenuated total reflection mode using a single diamond crystal window. Diffuse reflectance was measured using powdered samples mixed with spectroscopic grade KBr (1:10); background noise was corrected with spectra of pure KBr powder. Spectra were obtained from six scans per sample at a resolution of 1 cm^{-1} (4000–400 cm^{-1}). The background spectrum of the crystal (without sample) was collected and subtracted from scans of

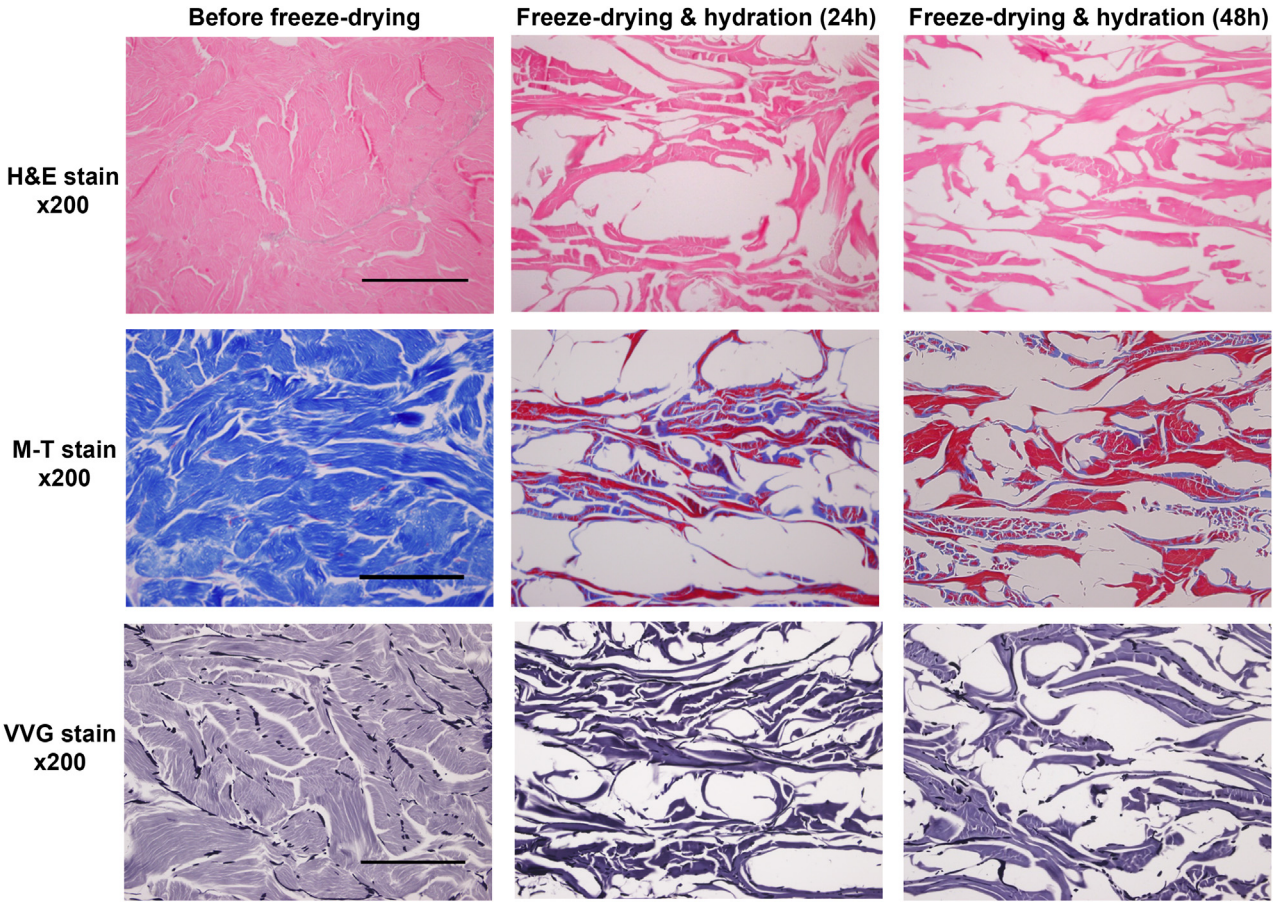

Fig. 1. Histologic appearance of MegaDerm™ before and after freeze-drying and rehydration. The essential biochemical and structural components (e.g., collagen and elastin) and three-dimensional natural dermal structures were preserved. The extracellular matrix was preserved after rehydration, and the ultrastructure was more porous, as assessed by hematoxylin and eosin (H&E), Masson's trichrome stain, and Verhoeff–Van Gieson stain (× 200, scale bar = 200 μm).

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