Support for the Role of Collagen in Bone Growth

Type 1 collagen has been extensively studied for many decades. Consequently, its ability to perform as a site for cell attachment, migration, proliferation, and differentiation is well documented. The extracellular matrix (ECM) within all tissues and organs provides a physical scaffolding for cellular constituents as well as initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation, and homeostasis. Collagen is the most abundant fibrous protein within the interstitial ECM and constitutes up to 30% of the total protein mass of a multicellular animal.[1] This document provides a sampling of research articles providing evidence for the role of collagen in bone growth.

[1] Frantz et al., 2010 The extracellular matrix at a glance. Journal of Cell Science 123, 4195-4200)

Somaiah, et al., 2015, Collagen Promotes Higher Adhesion, Survival and Proliferation of Mesenchymal Stem Cells, PLoS ONE 10(12): e0145068. doi:10.1371/journal.pone.0145068.

"We found that collagen promoted cell proliferation, cell survival under stress and promoted high cell adhesion to the cell culture surface. Increased osteogenic differentiation accompanied by high active RHOA (Ras homology gene family member A) levels was exhibited by MSC cultured on collagen. […] [O]ur study shows that collagen will be a suitable matrix for large scale production of MSC with high survival rate and to obtain high osteogenic differentiation for therapy. […] Coating the cell culture surface with collagen alone or in combination with other scaffold material induced osteogenic differentiation of MSC in some cases, in the absence of osteo-inductive factors. […] High cell proliferation and decreased doubling time was seen in MSC cultured on [collagen]. […] Increased proliferation on [collagen] was further evidenced by high percentage of [collagen] cultured MSC in S phase compared to other matrices. To check the surface which promotes faster and higher cell adhesion, cell attachment on different matrices was determined after 2hr and 12hr of cell seeding. We found a significantly higher cell adhesion on [collagen] matrix. […] While cell proliferation was negligible during serum starvation, cell death was significantly lower in cells grown on [collagen]. […] Active migration of cells in the scaffold is required for functional remodeling. For this, the migration rate of MSC on different matrices was assessed by wound healing migration assay. […] Maximum migration speed was observed on [collagen]. […] [O]steogenic differentiation […] was significantly high on [collagen] surface. […] [I]n the presence of differentiation factors, [collagen] surface has a synergistic effect in promoting high osteogenic differentiation. […] [W]e studied different cell matrices that could protect MSC from oxidative/nutrient stress and promote cell growth and migration in in vitro and in vivo conditions. […] We found that [collagen] fibers significantly promoted cell proliferation resulting in short doubling time. […] Additionally, [collagen] matrix was efficient in protecting MSC from oxidative and nutrient stress induced cell death that might occur in vivo during ischemia. The cell adhesion on [collagen] was also high and it occurred within a short period of cell seeding. […] These results suggest that culturing MSC on [collagen] will help us to achieve high cell proliferation and survival and [collagen] can be used as a coating on scaffold for in vivo administration of MSC to protect them from stress induced cell death. Moreover, high osteogenic differentiation was observed when MSC were differentiated on [collagen]. […] [Collagen] promoted higher cell migration and cell attachment with more cell to cell surface contact points. […] In conclusion, our study demonstrates that extracellular matrices induce differential cell behavior of MSC by altering their cell proliferation, migration and differentiation. […] [W]hen used in tissue engineering [collagen] coated scaffolds will also promote high cell migration, proliferation, survival and osteogenic differentiation."

Aruta, et al., 2009, Biocompatibility of Collagen Membranes Assessed by Culturing Human J111 Macrophage Cells, Materials, 2009, 2, 945-957; doi:10.3390/ma2030945.

"Type I collagen has been well characterized and is ubiquitous across the animal kingdom. Its excellent biocompatibility and safety, due to biological characteristics, such as biodegradability and weak antigenicity, made this matrix constituent a primary resource in biomedical applications. […] Scaffolds of type I collagen are excellent matrix substrates providing adhesive properties for cells proliferation, migration and differentiation. […] Collagen substrates, in fact, have been shown to influence proliferation, migration and differentiation of a number of different cells in vitro."

Frantz et al., 2010, The Extracellular Matrix at a Glance, Journal of Cell Science 123, 4195-4200.
"The extracellular matrix (ECM) is the noncellular component present within all tissues and organs, and provides not only essential physical scaffolding for the cellular constituents but also initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation and homeostasis. [...] Cell adhesion to the ECM is mediated by ECM receptors, such as integrins, discoidin domain receptors and syndecans. Adhesion mediates cytoskeletal coupling to the ECM and is involved in cell migration through the ECM. [...] In addition, the ECM directs essential morphological organization and physiological function by binding growth factors (GFs) and interacting with cell-surface receptors to elicit signal transduction and regulate gene transcription. [...] The ECM is composed of two main classes of macromolecules: proteoglycans (PGs) and fibrous proteins. The main fibrous ECM proteins are collagens, elastins, fibronectins and laminins. [...] Collagen is the most abundant fibrous protein within the interstitial ECM and constitutes up to 30% of the total protein mass of a multicellular animal. Collagens, which constitute the main structural element of the ECM, provide tensile strength, regulate cell adhesion, support chemotaxis and migration, and direct tissue development."

Parenteau-Bareil, et al., 2010, Collagen-Based Biomaterials for Tissue Engineering Applications, Materials, 2009, 2, 945-957; doi:10.3390/ma2030945.
"The use of biological material for medical applications requires making a distinction between immunogenicity and antigenicity. Immunogenicity is about triggering an immune response while antigenicity refers to the interaction between the antibodies and the antigenic determinants or epitopes. An immune response against collagen mainly targets epitopes in the telopeptide region at each end of the tropocollagen molecule. [...] Type I collagen is a suitable material for implantation since only a small amount of people possess humoral immunity against it. [...] Modern extraction methods are based on three basic principles of solubilisation: in acid solutions, in neutral salt solutions and in proteolytic solutions. [...] Even if some sterilization of collagen-based biomaterials is done by low dose gamma irradiation (γ-ray), this method alters molecular structure and decreases mechanical and enzymatic resistance of the collagen scaffold. [...] Research groups use collagen scaffolds to study cell behavior such as migration and proliferation, as well as differentiation."

Takata et al., 2001, Migration of Osteoblastic Cells on Various Guided Bone Regeneration Membranes, Clin. Oral Impl. Res. 12, 2001; 332-338.
"On the collagenous membranes, [...] cells seemed to migrate mainly along with fibrous structures of the membranes. [...] For a barrier membrane to be successful, cell migration, attachment and proliferation to the materials is essential and for this to take place the material must have no deleterious effects on osteoblasts. [...] Furthermore, it should also encourage cell spreading to a degree which promotes cell proliferation and migration. [Collagenous membranes] showed migration rates equal to or higher than the culture dish, on which cells generally grow favorably. [...] In addition, for [some collagenous membranes] it was noted that cells proliferated with time, however with [others] the cells remained at the same level after initial attachment. [...] Based on these preliminary in vitro results, it appears that [some collagenous membranes] promote osteoblastic cell migration better than other tested barriers."

Kleinman, et al., 1981, Role of Collagenous Matrices in the Adhesion and Growth of Cells, Journal of Cell Biology, 88(3):473.
"Collagen substrates enhance the growth, as well as the differentiation, of many cells in culture above that observed with other substrates such as plastic and glass. [...] [C]ollagen substrates alter the morphology, migration, and adhesion of cells and, in some cases, differentiation. [...] Thus, collagen and degradation products of collagen may be attractants for fibroblasts in vivo during wound repair, fracture healing, and embryogenesis. [...] Purified collagen substrates and collagenous matrices have been shown to maintain differentiated functions as well as to induce differentiation in cultured cells. [...] Because collagens can interact with various attachment proteins and proteoglycans, it is likely that unique and complex matrices are formed that maintain the cells within the tissue and direct their differentiation growth and differentiation."

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