

Cartilage Development in an MRI-Compatible Hollow-Fiber Bioreactor

Richard G. Spencer

National Institute on Aging, NIH, Baltimore MD

Osteoarthritis is the leading cause of joint pathology in the older population. Given the limited intrinsic self-repair capacity of cartilage, a great deal of activity is ongoing to establish conditions under which cartilage regeneration might be achieved. In addition, the potential for use of engineered cartilage as a therapeutic implant is also under active investigation. Finally, the ability to assess cartilage status noninvasively through MRI analysis may play an important role in the development of therapeutics.

Motivated by these considerations, we have explored cartilage growth and development in an MRI-compatible hollow fiber bioreactor (HFBR) system (Fig. 1).



Figure 1. A: Hollow fiber bioreactor. The version shown has 6 longitudinal fibers. B: Development of cartilage from bovine chondrocytes after 4 weeks of growth.

In this system, a high-purity glass tube is fitted with one or more longitudinal porous hollow fibers made of polypropylene or polyvinylidene fluoride. The fibers are potted at the ends of the HFBR with silicone rubber. Chondrocytes ($\sim 10^7$) obtained from embryonic chick sterna or from bovine articular cartilage via collagenase digestion are inoculated into the HFBR through the side port, and the system is then perfused with media using a pin-compression flow pump.

Studies of the three-dimensional matrix elaborated by chondrocytes can be studied longitudinally for several weeks using this approach. Pathomimetic interventions for cartilage degradation through use of IL-1, retinoic acid, chondroitinase, trypsin, and collagenase have all been evaluated using this system. MRI outcome measures have been correlated with the biochemical sequelae of these agents, establishing a further basis for eventual non-invasive analysis of cartilage degradation in situ. Similarly, the effect of anabolic interventions, such as high-dose ascorbate and mechanical stress, on matrix development from chondrocytes has been evaluated.

The macroscopic amounts of neocartilage produced in the HFBR and the nondestructive nature of the MRI analysis permit a number of complementary studies to be performed on the tissue. These include histology and biochemical matrix analysis, optical spectroscopy, gene expression studies, and mechanical testing.

Our results support the hypothesis that tissue development in the HFBR follows a favorable trajectory of increasing matrix volume and proteoglycan and collagen content over development times of several weeks. Both the dynamic and equilibrium tissue moduli increase over time as well. Systematic variations in cartilage properties along the length and along the diameter of the HFBR have been demonstrated by both MRI and optical spectroscopic imaging. Gene expression studies establish the maintenance of the hyaline cartilage phenotype. MRI-derived parameters, including T_1 , T_2 , magnetization transfer, apparent diffusion coefficient, and fixed charge density correlate well with biochemical and biomechanical properties of the engineered cartilage. These relations have been demonstrated under a number of degradative and regenerative paradigms. Finally, the response of the developing tissue to such interventions supports the utility of this approach to characterize cartilage under a number of conditions.