The development, structure and repair of articular cartilage

Hunziker, E.B.

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Summary and Conclusions

A critical analysis of the current literature and of our own experimental findings reveals the need for considerable improvements in the field of articular cartilage repair. The hyaline-like qualities of the repair cartilage must be bettered to enhance its durability and its functional competence. However, several tissue-engineering approaches being currently developed have yielded promising results, which bode well for their future utility in clinical practice.

The specific questions posed in the General Introduction to this thesis can be answered as follows:

1. *What is the current status of articular cartilage repair in experimental laboratories and clinical practice?*

   None of the biologically-based repair-induction strategies currently implemented in surgical practice yield a result that is superior to that elicited by a spontaneous (injury-induced) stimulation of the bone marrow. Several promising strategies are still at an experimental stage of development; but as yet, the ideals towards which they aim are a long way from realization in a clinical setting.

2. *On a quantitative and topographic basis, how is the articular cartilage layer of the human knee joint structured?*

   The structural organization of human knee-joint cartilage is highly specific. The numerical cell density is extremely low – much lower than in any other mammal that has been investigated – and the macromolecular organization of the extracellular matrix is extraordinarily complex. Furthermore, the architecture of the articular cartilage layer differs according to its topographic location within the knee joint. To be therapeutically successful in the long-run, a repair strategy must take into account this latter circumstance.

3. *By what physiological mechanism does the immature, isotropic structure of mammalian articular cartilage evolve into the mature, highly anisotropic architecture during postnatal development?*

   The structure of mature mammalian articular cartilage is achieved by a process of tissue resorption and replacement, not by one of internal remodelling and reorganization. Hence, engineered constructs with a chaotic (unphysiological) organization are unlikely to remodel into the mature anisotropic structure after implantation within an articular cartilage defect. Tissue-engineering approaches must therefore aim to re-establish the mature native organization from the onset, or within a very short time of implantation. Once the construct is *in situ*, the postnatal growth process will not be recapitulated. In the light of our finding, investigators must now reconceive their notions of an optimal tissue-engineering approach for articular cartilage repair.

4. *Is it possible to induce the repair of articular cartilage without surgically transplanting cells or tissue, viz., can local populations of stem cells be recruited to repair a defect merely by applying an appropriate growth factor?*
   Partial-thickness defects in small mammalian species can be successfully repaired using such a growth-factor-based strategy. However, the agent cannot

be directly injected into the joint. The growth factor must be introduced into the defect via a space-defining matrix within which it is entrapped both in a free form, for immediate release, and in a liposome-encapsulated one, for slow delivery. Such a system generates the critical local concentrations at timely junctures to induce, sequentially, the recruitment and proliferation of synovial mesenchymal stem cells and their subsequent differentiation into chondrocytes, which then remodel the matrix into a cartilage-specific one. This system must now be optimized to elicit the repair of more voluminous defects in large mammalian species.

5. *Can current open or arthroscopic surgical techniques be applied without endangering healthy articular cartilage, and thus without exacerbating the existing condition?*

   Surgery is always associated with iatrogenically-induced trauma. But our investigations have revealed that even simple trimming procedures and suturing could have a deleterious effect on healthy chondrocytes at the edges of an articular cartilage defect. To minimize this damage, care must be exercised in the choice of surgical instruments, and alternative modes of tissue securance should be sought.