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THE DEVELOPMENT, STRUCTURE AND REPAIR OF ARTICULAR CARTILAGE

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de Vrije Universiteit Amsterdam,
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THE DEVELOPMENT, STRUCTURE AND REPAIR OF ARTICULAR CARTILAGE

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Hunziker EB, Spector M, Libera J, Gertzman A, Woo S L-Y, Ratcliffe A, Lysaght M, Coury A, Kaplan DL, Vunjak-Novakovic G. Tissue Engineering: Translation from research to applications. Tissue Eng, 2006, 12(12): 3341-3364.

Quinn TM, **Hunziker EB**, Häuselmann HJ. Variation of cell and matrix morphologies in articiular cartilage among locations in the adult human knee. Osteoarthritis Cartilage, 2005, 13(8): 672-678.

Hunziker EB, Driesang IMK. Functional barrier principle for growth-factor-based articular cartilage repair. Osteoarthritis Cartilage, 2003, 11(5): 320-327.

Hunziker EB, Quinn TM. Surgical removal of articular cartilage leads to loss of chondrocytes from cartilage bordering the wound edge. J Bone Joint Surg (Am), 2003, 85A: 85-92.

Hunziker EB. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. Osteoarthritis Cartilage, 2002, 10(6):432-463.

Hunziker EB, Quinn TM, Häuselmann HJ. Quantitative structural organization of normal adult human articular cartilage. Osteoarthritis Cartilage, 2002, 10(7): 564-572.

Hunziker EB. Growth-factor-induced healing of partial-thickness defects in adult articular cartilage. Osteoarthritis Cartilage, 2001, 9(1): 22-32.

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Chapter 1

General Introduction and Aims

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A layer of articular cartilage lines each of the synovial joints. This tissue transmits loads and forces between the skeletal elements, absorbs peak stress events, and assures frictionless joint movement. The key to these mechanical functions lies in the structure and composition of articular cartilage. In mature organisms, this tissue consists predominantly of intercellular material. The extracellular matrix, which constitutes 98 per cent of the tissue mass, is maintained and remodelled by an exceedingly small population of chondrocytes (representing 2 per cent of the tissue mass), which are organized in a highly characteristic anisotropic manner. Articular cartilage is aneural, avascular and alymphatic. Having only a limited access to the immune system via the synovial fluid, it is immunologically privileged.

The articular cartilage layer is highly susceptible to structural lesioning, which can be occasioned either traumatically, or pathologically during the course of osteoarthritis (a prevalent disease affecting aging Western populations). If these lesions are confined to the articular cartilage layer, they do not heal spontaneously. Indeed, the lesioning process is exacerbated with time, leading to extensive destruction of the surrounding tissue. If the lesion penetrates the sanginous bony compartment, then a spontaneous repair response is mounted. However, the tissue formed is structurally and functionally inferior to native cartilage: it is unstable and degenerates after a short time.

In the field of tissue engineering, many research groups are engaged in attempts to improve the quality and functionality of the repair tissue laid down within articular cartilage defects. Most approaches involve the implantation of a matrix bearing growth factors and/or a homogenous population of potentially chondrogenic cells. The unifying principle behind the different strategies is the desire to restore the native, highly anisotropic structure of adult articular cartilage, which is crucial for its functional competence.

It is the aim of this thesis to address various issues relating to the repair of articular cartilage tissue.

In Chapter 1, the postnatal development of the adult structural architecture of mammalian articular cartilage is analyzed from a mechanistic point of view. The mechanism is based on a continuous process of tissue neoformation, stemming from the very surface of the articular cartilage layer. This process is coordinated with a likewise continuous process of cartilage resorption, which is mediated by the degradative activity of cathepsin-K-producing osteoclasts (mineralized tissue) and monocytes/macrophages (unmineralized tissue).

In Chapter 2, the potential and limitations of available articular cartilage treatment strategies are scrutinized. This review article brings to light the generally poor clinical outcomes of current surgical approaches, thereby underlining the need for considerable improvements in cartilage repair techniques.

In Chapters 3-5, the structure of normal mammalian articular cartilage is analyzed. In Chapter 3, the structural organization of knee-joint cartilage in adult humans is evaluated quantitatively. The baseline data presented in this study represents the ideal towards which any tissue-engineering approach is aimed. In Chapter 4, the mechanism underlying the postnatal evolution of an immature, isotropic articular cartilage structure into a mature, highly anisotropic one is evaluated. A knowledge and understanding of this physiological mechanism is important in guiding cartilage-engineering approaches in a fruitful direction. In Chapter 5, the heterogeneity of articular cartilage structure within different regions of the adult human knee joint is revealed. Of all human joints, the knee is the most susceptible to traumatic or pathological lesioning. The analysis undertaken in this study serves as an important basis for a topographically-orientated approach to tissue engineering, which is required to yield optimal repair results.

In Chapters 6-8, the use of growth factors in articular cartilage repair is dealt with. In Chapter 6, the local biological conditions that must be satisfied for an optimal growth-factor-induced repair response are elucidated. Growth factors are highly versatile signalling molecules, which can have opposing effects above and below a critical threshold concentration. This threshold level will be influenced not only by the total dose administered, but also by the rate of drug delivery (temporal release profile) and by the local environment within which the agent is acting. One adverse effect to be avoided within a cartilaginous environment is an induction of bone formation. Chapters 7 and 8 deal with alternative measures that can be adopted to physically (Chapter 7) or functionally (Chapter 8) impede the upgrowth of osseous tissue from the bony into the cartilaginous compartment of full-thickness defects.

Chapters 9 and 10 deal with surgical steps that can be injurious to articular cartilage repair. Before a construct is implanted within an articular cartilage defect, it is customary to smooth and level the fibrillated, irregular surfaces of the lesion floor and walls. This procedure involves the surgical removal of articular cartilage tissue. In Chapter 9, the surgical removal of articular cartilage tissue is shown to be associated with the loss of healthy chondrocytes from the wound edges. And in Chapter 10, even simple surgical suturing is shown to be associated with the loss of viable chondrocytes from the walls of the channels thereby created. Furthermore, these channels widen and elongate with time. This finding indicates that the surgical suturing of, for example, a tissue flap to articular cartilage (to secure an implanted construct) should be avoided if possible. Alternative modes of tissue securance should be sought.

The concluding Chapter 11 deals with the planning and execution of tissue-engineering approaches, and with the choice of appropriate parameters to gauge the quality and quantity of the repair tissue formed. Many investigations are marred by a faulty experimental design, which renders the biological meaningfulness and the validity of the data questionable. This article points out the common pitfalls and their remedies.

The following specific questions were addressed in this thesis:

1. *What is the current status of articular cartilage repair in experimental laboratories and clinical practice?*
2. *On a quantitative and topographic basis, how is the articular cartilage layer of the human knee joint structured?*
3. *By what physiological mechanism does the immature, isotropic structure of mammalian articular cartilage evolve into the mature, highly anisotropic architecture during postnatal development?*

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

Articular Cartilage Repair: Basic Science and Clinical Progress. A Review of the Current Status and Prospects

Chapter 2

Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects
[Hunziker EB. Osteoarthritis Cartilage, 2001, 10(6): 432-463]

Chapters 3-5

The Structural Organization of Articular Cartilage Tissue as a Fundament for Repair

Chapter 3

Quantitative structural organization of normal adult human articular cartilage [Hunziker EB, Quinn TM, Häuselmann HJ. Osteoarthritis Cartilage, 2002, 10(7): 564-572]

Chapter 4

The structural architecture of adult mammalian articular cartilage evolves by a synchronized process of tissue resorption and neoformation during postnatal development
[Hunziker EB, Kapfinger E, Geiss J. Osteoarthritis and Cartilage, 2007, 15(4): 403-413]

Chapter 5

Variation of cell and matrix morphologies in articular cartilage among locations in the adult human knee
[Quinn TM, Hunziker EB, Häuselmann HJ. Osteoarthritis Cartilage, 2005, 13(8): 672-678]

Chapters 6-8

Growth Factors in Articular Cartilage Repair

Chapter 6

Growth-factor-induced healing of partial-thickness defects in adult articular cartilage
[Hunziker EB. Osteoarthritis Cartilage, 2001, 9(1): 22-32]

Chapter 7

Structural barrier principle for growth factor-based articular cartilage repair
[Hunziker EB, Driesang IMK, Saager C. Clin Orthop Rel Res, 2001, 391S: 182-189]

Chapter 8

Functional barrier principle for growth-factor-based articular cartilage repair
[Hunziker EB, Driesang IMK. Osteoarthritis Cartilage, 2003, 11(5): 320-327]

Chapters 9-10

The Need for Improving Surgical Techniques in Articular Cartilage Repair

Chapter 9

Surgical removal of articular cartilage leads to loss of chondrocytes from cartilage bordering the wound edge
[Hunziker EB, Quinn TM. J Bone Joint Surg (Am), 2003, 85A: 85-92]

Chapter 10

Surgical suturing of articular cartilage induces osteoarthritis-like changes
[Hunziker EB, Staehli A, Kapfinger E. Ostearthritis Cartilage, 2008: in press]

Tissue Engineering: Translation from Research to Applications

Chapter 11

Tissue Engineering: Translation from research to applications
[Hunziker EB, Spector M, Libera J, Gertzman A, Woo S L-Y, Ratcliffe A, Lysaght M, Coury A, Kaplan DL, Vunjak-Novakovic G. Tissue Engineering: Translation from research to applications, 2006, 12(12): 3341-3364].

Summary and Conclusions

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.

Samenvatting

Samenvatting

Samenvatting en conclusies

Een kritische analyse van de beschikbare literatuur gecombineerd met onze onderzoeksresultaten toont de noodzaak aan om op het gebied van herstel van het articulair kraakbeen tot aanzienlijke verbeteringen te komen. De hyalien-achtige eigenschappen van het reparatie kraakbeen dienen verbeterd te worden om functie en levensduur te waarborgen. Recentelijk heeft een aantal onderzoeken op het gebied van *tissue engineering* veelbelovende resultaten laten zien die verbeteringen voorspellen bij toekomstig klinisch handelen.

De specifieke onderzoekvragen die gesteld zijn in de inleiding van dit proefschrift kunnen als volgt worden beantwoord:

1) *Wat is de huidige status van articulair kraakbeen genezing in experimentele laboratorium opstellingen en in klinisch gebruik?*

   Geen van de in de huidige klinische praktijk geïmplementeerde genezing-inducerende behandelstrategieën laat resultaten zien die superieur zijn aan de resultaten van behandelingen gericht op spontane (wondgeïnduceerde) stimulatie van het beenmerg. Verschillende veelbelovende behandelstrategieën zijn nog steeds in een experimenteel stadium en de verwachting is dat we nog ver weg zijn van de klinische toepassing ervan.

2) *Hoe is in kwantitatieve en topografische zin het articulair kraakbeen van de humane knie gestructureerd?*

   De structurele organisatie van het kraakbeen in de humane knie is heel specifiek voor dit type kraakbeen. De celdichtheid is extreem laag, veel lager dan in elk ander zoogdier dat ooit hierop is onderzocht, en de macromoleculaire organisatie van de extracellulaire matrix is uitermate complex. Verder zien we dat de architectuur van de verschillende lagen van het articulair kraakbeen verschilt afhankelijk van de locatie binnen het kniegewricht. Om therapeutisch succesvol te kunnen zijn moet een behandelstrategie rekening houden met deze specifieke gelaagde opbouw van het kraakbeen.

3) *Volgens welk fysiologisch mechanisme ontwikkelt de premature isotrope structuur van het humane articulair kraakbeen zich gedurende de postnatale ontwikkeling in de anisotrope architectuur die daaruit ontstaat?*

   De structuur van volgroeid humaan articulair kraakbeen ontstaat door een proces van weefselresorptie en -vervanging. Het is de verwachting dat door *tissue engineering* gevormde constructies met een niet-fysiologische (chaotische) organisatie, na implantatie in een kraakbeen defect, niet zullen remodelleren in de anisotrope structuur die we zien bij volgroeid gezond kraakbeen. De fysiologische mechanismen hiervoor ontbreken. De benadering vanuit *tissue engineering* moet gericht zijn op het direct of snel na het aanbrengen van het construct laten ontstaan van een anisotrope structuur zoals we die kennen bij gezond en volgroeid kraakbeen. Als het transplantaat is aangebracht zal het postnatale groeiproces niet meer plaatsvinden. In het licht van de resultaten van ons onderzoek behoeft het onderzoek op het gebied van de behandeling van articulair kraakbeen van de knie mogelijk een andere benadering.

4) *Is het mogelijk om de reparatie van articulair kraakbeen te induceren zonder cellen of weefsels te transplanteren? Anders gesteld kunnen specifieke stamcellen worden gestimuleerd door een passende groeifactor te appliceren?*

   Partial thickness defecten in kleine zogdieren kunnen op een succesvolle wijze genezen door een op groeifactoren gebaseerde behandel strategie te volgen. De factoren kunnen echter niet direct in het gewricht worden gespoten, maar dienen ingebracht te worden middels een *space defining matrix* waarbinnen ze opgesloten zitten in een vrije vorm voor onmiddellijke afgifte of opgesloten in liposomen voor een vertraagde afgifte. Een dergelijk systeem genereert kritische locale concentraties op verschillende tijdsintervallen om zo over een langere periode de proliferatie van synoviale mesenchymale stamcellen te stimuleren. Deze cellen kunnen differentiëren tot chondrocyten die vervolgens de matrix remodelleren tot een specifieke kraakbeen matrix. Dit systeem moet verder geoptimaliseerd worden om toegepast te kunnen worden in defecten van een fors volume in grotere zoogdieren.

5) *Kunnen de huidige open of gesloten arthroscopische chirurgische technieken worden toegepast zonder het gezonde articulair kraakbeen in gevaar te brengen, ergo zonder de bestaande situatie te verergeren?*

   Chirurgie wordt vaak geassocieerd met een iatrogeen geïnduceerd trauma. Ons onderzoek heeft uitgewezen dat zelfs een eenvoudige *shave* en hechtprocedure een negatief effect kan hebben op gezonde chondrocyten aan de randen van een kraakbeendefect. Om dit effect zo klein mogelijk te houden moet naar een minimaal invasief instrumentarium gezocht worden alsook naar alternatieven voor de huidige hechttechnieken.

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Acknowledgements

An acknowledgement should be composed in the manner of a good oral presentation, abiding by the principles of “*docere, delectare, movere*” (teach, entertain and emotionally move), as the Romans were wont to say. A PhD title defines a person as being knowledgeable, viz., “*doctus*” (taught) in his or her chosen field. Most persons are awarded this degree at the onset of their professional careers. However, in geardagum, the title was conferred upon Dutch academics, usually professors, towards the end of their life’s work, which makes perfect sense, since it takes a lifetime of experience to become thoroughly knowledgeable in one’s chosen discipline. Moreover, the term “*doctus*” does not appertain to erudition in exclusively one field, but to a broad knowledge of the life-sciences, the arts, languages, philosophy and different cultures. Such a multifaceted consciousness is incompatible with youth. Indeed, advancement in a professional career is often made at the expense of this broader schooling – most regrettably.

The persons who have contributed most to my scientific development are Robert Schenk and Luis Manuel Cruz Orive. They ignited my latent enthusiasm for research and at the same time taught me the importance of strict and thorough analytical thinking. Larry Rosenberg, Klaus Küttner, Joe Buckwalter and Alain Grodzinsky have likewise figured prominently in my scientific development, and I was most fortunate to make their acquaintance at a very early stage in my professional career. All of these persons have remained my close friends.

The idea of submitting a doctorate thesis to the VU University Amsterdam was actually prompted by my friend John Jansen during one of his visits to Bern, and I am grateful to him for this suggestion and for inciting me to pursue it. Klaas de Groot also encouraged me greatly in this endeavour. And apropos of my Dutch colleagues, I call to mind Clemens van Blitterswijk, with whom I have enjoyed many stimulating, albeit often heated, discussions without loss of friendship. Indeed, the capacity to deal with conflicting opinions without sacrificing friendship is essentially necessary for a healthy scientific atmosphere.

In realizing this doctorate thesis, the support of Vincent Everts and Daniel Wismeijer is warmly acknowledged. And last but not least amongst my Dutch associates, I would like to thank Yuelian Liu for her continuous encouragement, support and optimism. Other persons, too numerous to mention, are also silently acknowledged. But by name, I would particularly like to recognize the exceptional technical expertise of Eva Kapfinger and Wolfgang Herrmann. Finally, I cannot close without expressing my indebtedness to my former wife Ruth and to our four children, Raphael, Manuel, Samuel and Stephanie, who have greatly enriched my life and have furnished a basis of joy and happiness which has been reflected also in my professional career. To be a scientist and to be scientifically active is not just a profession, it is much more; it is a vocation and an integral part of one’s being. This spark of fascination for science was lighted in me thirty years ago and is still burning.

Curriculum Vitae

Curriculum Vitae

I, Ernst Bruno Hunziker, grew up in Schönenwerdt, Switzerland, where my basic education was undertaken. After completing this at the age of twenty years, I was unsure whether to pursue a course of higher education in Roman history and Latin, in the natural sciences, or in medicine / dentistry. I opted for the former, but then, after a year of study at Zurich University, switched to medicine and dentistry at the University of Bern, where a new curriculum and a novel teaching approach had been recently introduced. I soon realized that dentistry was too narrow a field for my interests and therefore followed exclusively the medical course, which I successfully completed in 1976. Immediately thereafter, I took a course in tropical medicine, and gained practical experience in Bolivia (South America) and Gabon (Central Africa). After returning to Switzerland, I worked awhile in general surgery at the cantonal hospital in Olten, and gained further practical experience in this discipline and in clinical paediatrics at the University of California in San Francisco. After further travelling experiences on the American continent and in Africa and Asia, I worked for six months in clinical pathology before embarking on a scientific and academic career at the Institute of Anatomy in Bern, initially undertaking a one-year postgraduate course in experimental medicine and biology at the University of Zurich to gain more insight into and to broaden my knowledge of scientific methodologies. I was engaged at the Institute of Anatomy for the next twelve years, where I delivered lectures to the first- and second-year medical students and conducted research in the field of the musculoskeletal system, with special emphasis on cartilage tissue. In 1989, I became a full professor of the University of Bern and was appointed director of the MEM-Institute for Biomechanics. My research activities were then extended to include the micro-biomechanics and repair of cartilage tissue. In 2002, I became director of the ITI Research Institute for Dental and Skeletal Biology of the University of Bern. My research interests were further broadened to embrace dental implantology and tissue engineering. Currently, I am director of the Dental and Skeletal Tissue Research Centre within the Department of Clinical Research at the University of Bern, and continue to pursue all of my research interests. Several of my more recent publications form the basis of this doctorate thesis, which has been submitted to the VU University Amsterdam – the professional seat of my two promoters, Vincent Everts and Daniel Wismeijer.

So, I am on the verge of attaining after thirty years what the youth of today achieves in three or four. After all, "*Life can only be understood backwards: but it must be lived forwards.*" (Søren Kierkegaard)