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Editors

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Introduction

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TE has been defined as “the application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes that restore, maintain, or improve tissue function”. There are serious prognoses that the economical volume of TE soon will exceed that of gene therapy, and that it may be one of the developments in biotechnology with the most impact. Notably tissue engineering may offer more functional solutions in chronic diseases and degenerative ailments compared to conventional treatments. These chronic deficiencies constitute an increasing social and economic burden, especially in western societies with aging populations.

Two relatively simple tissue types—epidermis and cartilage—have already been introduced into clinical practice. They share the peculiarity that they do not need an intrinsic vascular system for parenchymal cell survival and function. Other clinically relevant tissue defects currently under investigation for this kind of substitutive treatment include nervous tissue, cornea, liver, endocrine pancreas, kidney tubules, urothelium and bladder, cardiovascular and musculoskeletal tissues (bone, cartilage, muscle).

For practical application, tissue engineering approaches can be categorized into more *substitutive* approaches, where the aim is the *ex vivo* construction of a living tissue or organ similar to a transplant, versus *histeoconductive* or *histeoinductive* concepts. The latter rather attempt to optimize the structure and composition of biogenic or (semi)synthetic matrix materials, boost or select living cells for optimal proliferation *in vivo*, and to use highly specific growth factors or gene therapy transfecting for such cytokines.

To succeed in developing products applicable in TE a close cooperation between material sciences, biology (cell biology, molecular biology, genetics), medicine (clinical sciences, embryology, anatomy, physiology) and industry is a prerequisite. Only a comprehensive understanding of the

involved components (biomaterials, cells, cytokines, genes) can lead to a successful manipulation of reparative processes.

Biomaterials

Materials used for TE applications must be biocompatible, non-toxic (including their breakdown products), non-carcinogenic, sterilizable and surgically handable. They should have an intrinsic mechanical stability as requested for the tissue type to be substituted for. In most cases they should be restorable in an order as they are replaced *in vivo* by the newly produced matrix. They also should be tissue conductive (guide migrating and proliferating cells) and possibly tissue inductive (induce specifically the proliferation of cells). To permit the survival of living cells they must be permeable for nutrients, cytokines and waste products. Preferably they can contain binding sites for cells (e.g. fibronectins).

Currently used materials meeting some of these criteria are open pore polymers and ceramics with pore sizes in the range of 100–500 μm , woven fibre fleeces and gels (fibrin, alginates). Biomaterials can be categorized into biogenic (from animals or human sources), semisynthetic or synthetic. Biogenic materials (e.g. acellular matrices, collagens, glycosaminoglycans, fibrin) have the advantage that they naturally meet many of the requested criteria. Disadvantages include the possibility of disease transmission and limited availability. Synthetic polymers currently under investigation include PLA, PGA and their copolymers, PEG, polyphosphazenes, polyanhides and various hydrogels.

Cells

The progress of cell biology has made it possible to culture virtually all mammalian cells under specific culture conditions. Most tissues are constituted of a variety of different cell types (parenchymatous and interstitial) in a specific topological and functional relationship. So far it is not possible to coculture these interdependent cells in an analogous way *in vitro*. When differentiated cells are cultured in flasks they tend to dedifferentiate. Using adequate matrix materials this dedifferentiation can be reversed. Recently it has been found that there are a number of pluripotent stem cell types for various parenchymatous cells. These cells have a high potential for proliferation (e.g. keratinocyte stem cells) and some of them may differentiate into different cell types depending on culture conditions and their matrix. By selecting such specific stem cells and the corresponding optimal matrix material and by boosting these cells (e.g. by growth factors) it may be

possible to use precursors rather than inactive differentiated cells for implantation. Future progress in cell biology may permit to use even more pluripotent embryonic stem cells of allogenic origin for transplantation.

Cytokines

Cytokines are mostly polypeptides that act as local hormones by selectively regulating the proliferation, differentiation migration, and function of specific target cells. They play an important role in homeostasis and adaptation to changing requirements. Cytokines may perform by an autocrine (targeting the same cell type) or paracrine (targeting other cells) mechanism. Growth factors are cytokines that are of special importance in TE, as they can stimulate the proliferation of cells included in a TE construct or in the host (e.g. the ingrowth of blood vessels—angiogenesis). All cell culture techniques rely on the *in vitro* use of growth factors in the culture medium. Growth factors may also be added to the matrix material, either as a simple additive or bound to the polymers for a more controlled drug release.

Genetic Engineering

Under the bottom line all tissue proliferation and differentiation is programmed by the genetic code. By gene therapy specific genes coding for a desired protein are introduced into cells. Genetic vectors (plasmids) attractive for the use in tissue engineering are the ones which code for growth factors. In this way a controlled and continuous release of such cytokines by the implanted cells can be achieved. This may circumvent the problem of the short *in vivo* stability of added recombinant growth factors. The plasmids may either be introduced by *ex vivo* transfection of the cultured cells or by binding the plasmid on the matrix material.

Conclusion

The complex mammalian organism has to be considered as the gold standard and a model for perfect tissue engineering conditions. The challenge of the ordered integration of a complex arteriovenous and capillary vascular tree into large living tissue engineered organs *ex vivo* still has to be solved. The functional three-dimensional and dynamic stratification between different cell types and matrix components in most organs is part of our exceedingly genetic code as well as determined by ontogenetic ordered processes that often involve many interrelated systems. Surgery, on the other hand has relied empirically since centuries, on the *in vivo* “bioreactor” capacity of the human body. In postnatal mammals this reparation commonly is deficient. Taking biological processes and materials as a model, it may be more practical to specifically substitute for deficient components (cells, matrix, materials, cytokines, gene expressions) *in vivo*, while relying onto the modulating and regulating control within the recipient organism, than to construct a complete complex organ *ex vivo*.

This approach has been rather successful for the treatment of skin wounds and in cartilage repair. In this concept the tissue engineer (as any good surgeon) rather acts as a gardener than a carpenter.

TE is a fascinating challenge for applied research to improve the health care by totally new therapeutic options. This requires the close cooperation and new platforms of communication between basic and clinical scientists, chemical engineering, industry and public funding.

The 2nd BioValley Tissue Engineering Meeting which is sponsored by the Tissue Engineering Society (TES) has the goal to be a forum for the exchange of concepts and results for this purpose.