Bridging the gap

Tissue engineering: mathematical models are helping to take tissue engineering from concept to reality.

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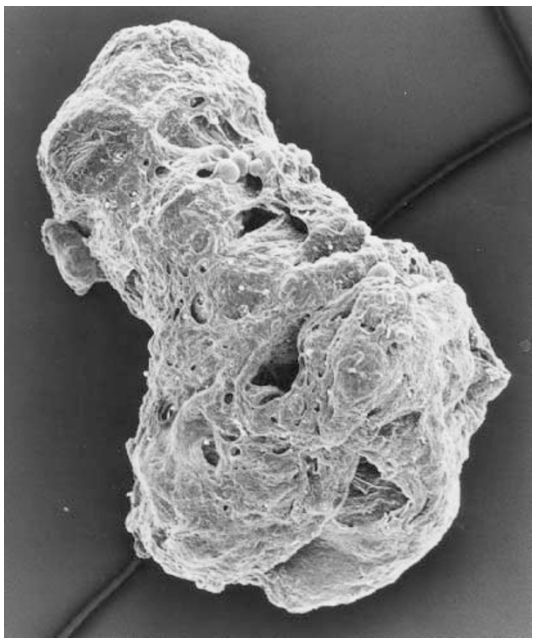
The emerging discipline of tissue engineering has the grand aim of understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use. There have been several remarkable successes. A recent example is the work of Patrick Warnke, Hendrick Terheyden and co-workers, in which a section of replacement jaw was generated inside a sculpted titanium mesh cage by coaxing appropriate stem cells (those elusive precursor cells that give rise to specialized body tissues) to form bone. But although successes such as this show that, in concept, tissue engineering is possible, routine implementation of such strategies remains some time off.

In fact, this is no big surprise, as such a broad implementation requires a much better understanding of the principles of tissue formation than we currently possess, from the fundamentals of stem-cell biology to the physics and biomechanics of pattern formation. To complicate (or perhaps, enrich) matters further, this mandate also calls on the specialist expertise of scientists from a wide variety of disciplines — such as cell and molecular biologists, clinicians and materials scientists — each of whom sees the various problems involved from the perspective of their own discipline. Practical integration of these seemingly disparate strands of understanding is proving to be a rich source of scientific challenge and opportunity. In particular, collaborations between biologists and mathematicians are now providing alternative and often innovative ways of thinking about tissue regeneration.

Reproducing functional tissue *ex vivo* requires an understanding not only of the behaviour of individual cells, but also of how global form and function arise from local cellular interactions. By looking at evolving tissue as a complex biological system, mathematical models can provide just such a holistic understanding. The use of agent-based models to interpret stem-cell systems is beginning to show promise in offering new ways of thinking about tissue evolution. In these models, cells are considered as distinct entities (or agents) positioned on an appropriate lattice, and simple cellular behaviours are prescribed, which, on their own or on the local scale, are insufficient to produce pattern. But on the global scale, structure is seen to emerge from long-range summation of these low-level behaviours. Such models are now being incorporated into practical work programmes to explore the behaviour of stem-cell systems and mechanisms of tissue regulation.



Growing bone (above) on a scaffold is still far from routine.

As a related example, our current work focuses on the behaviour of selected stem-cell populations *in situ*, as they progress through the osteogenic route to form bone. Behaviour here includes both the differentiation potential and the spatio-temporal patterns of adhesion, migration and proliferation of the cells. In particular, we are using mathematical models of cell-population behaviour in conjunction with experimentation to explore regulation of the osteoblast and bone-tissue phenotypes on various three-dimensional porous scaffolds. By combining expertise in biomimetic materials science and stem-cell biology with mathematical models, our aim is to select the tissue-engineering strategies that are most likely to be successful and offer creative ways of investigating tissue formation. This work is directing new experimental research that is helping to elucidate relationships between stem-cell activity, differentiation, nutrient delivery and evolving macroscopic tissue architecture.

A final and appealing new direction is the use of complex network theory to analyse the 'shape' of phenotypic regulatory mechanisms. In these models, topologically complex networks — consisting of all potential regulators of a cellular phenotype and their interactions — may be generated from the wealth of stoichiometric data that are becoming increasingly available. As there may be hundreds of factors implicated in a given phenotype, such networks may be bewilderingly entangled and appear intractable at first sight. But statistical comparison of such 'real-life' networks with properties of similar-sized random networks (those in which network topology is generated, in some prescribed sense, randomly) can begin to relate the shape of the real-life network to its function. For example, the features of the real-life network that occur significantly more often than in the random networks may be identified for further investigation, as may those vertices, edges or subnetworks whose presence or absence profoundly affect the global properties of the network. Such critical subnetworks may represent functionally significant control motifs, whereas the elements whose removal has little effect on global network properties may be considered to be more functionally peripheral. Thus, representing phenotypic regulatory mechanisms as complex networks may allow the fundamental functional units of morphogenesis to be redefined in terms of, for example, small networks of genes, transcription factors and proteins, rather than in terms of these elements in isolation.

These are bright times for tissue engineering. The integration of mathematical modelling with experimentation in an iterative framework — each informing and directing the other — is offering exciting challenges, as well as substantial scope to further our understanding of tissue regeneration. In the end, this may prove crucial in taking tissue engineering from concept to reality. ■

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FURTHER READING

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