Research Briefings

Jamie Davies
The building and rebuilding of mammalian organs

ONE OF THE OUTSTANDING PROBLEMS IN 21ST CENTURY SCIENCE IS HOW CELLS IN AN EMBRYO MANAGE TO ORGANIZE THEMSELVES INTO THE PRECISE AND COMPLEX TISSUES AND ORGANS OF THE ADULT BODY. WE USE ORGAN CULTURE, MOLECULAR BIOLOGY, BIOINFORMATICS, SYNTHETIC BIOLOGY AND STEM CELL TECHNIQUES TO INVESTIGATE MECHANISMS OF TISSUE SELF-ORGANIZATION, FOR BASIC SCIENCE AND FOR REGENERATIVE MEDICINE.

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The big questions

How do relatively unorganized populations of cells in an early embryo organize themselves to produce the complex, highly-ordered architecture typical of adult tissues and organs? How can we use an understanding of these mechanisms to build or rebuild organs and tissues for medical purposes? These questions are the focus of the research in the Davies laboratory, and we and our collaborators tackle them in a variety of ways including organ culture, molecular biology, bioinformatics, synthetic biology and stem cell techniques.

The kidney as a model for organ development

In seeking to understand general principles of tissue and organ development, we have decided to concentrate mainly on the mammalian kidney. This is partly because there is an urgent and growing need to find ways to repair damaged kidneys or to make new ones, the number of human organs available and suitable for transplant never being enough. It is also because the kidney is particularly suited for research; it develops autonomously so it can be separated from the rest of the embryo and can be grown in organ culture (Fig1), where it can be easily observed and subjected to various experimental treatments; it begins as a relatively simple mixture of just two cell types but produces, of the course of a week or so, a spectacularly ordered arrangement of many different cell types, each specialized to perform a particular task in the adult organ; most of the events that take place in kidney development are also central events in the development of other organs such as lung, pancreas, mammary gland etc, so that what we learn easily in kidney can be applied to other organs.

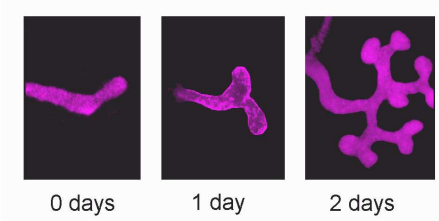

Fig 1: A kidney rudiment developing in culture (the immunostain shows just one tissue in the kidney, the developing collecting duct)

Our major interest is in understanding how groups of cells act together to create biological organization and anatomical shape. For this reason, much of the work in the lab is concerned with identifying how and when cells communicate with one another, how this communication can be used to drive cells to make appropriate decisions, and how cell communication can lead to anatomical change. Having identified individual signalling events, we take systems approaches to studying how their integration drives self-organization

of tissues.

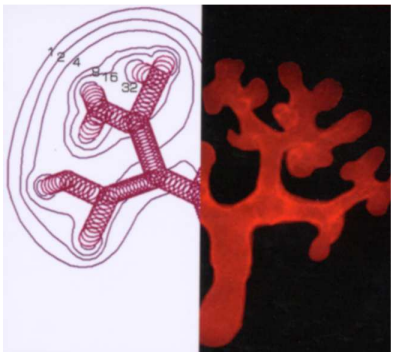

Fig 2: A side-by-side comparison of real morphogenesis of the renal collecting duct (fluorescent half-picture right) and predicted 'morphogenesis' in a computer model that incorporates of some of of the signals we have identified (left half-picture). This figure appears on the cover of Davies (2005) Mechanisms of morphogenesis.

Building kidneys from cell suspensions

Using what is already known about kidney development, we are currently developing culture systems in which simple suspensions of cells are brought together so that they organize themselves spontaneously into tissues characteristic of embryonic kidney. We are using this system to make immortalized lines capable of making kidney tissue, so that we can reduce animal use in our research, and also to program human stem cells to make renal tissue (Fig3): this work is being done with the eventual hope of translation to clinical use.

Bioinformatics

To make the vast volumes of gene expression data in developing kidneys easier to use, this lab created a web-based database of kidney gene expression back in 1994 (when it was the first ever such database). The project has grown, and we now host the editorial office of the international GUDMAP altas of urogenital gene expression (www.gudmap.org).

Synthetic Morphology

For both basic science and clinical translation, we are pioneering the application of the techniques of synthetic biology to the artificial control of cell shapes, cell associations and ultimately the formation of artificial tissues. This field is 'synthetic morphology'. At present, we are at the first stage of this work – producing a library of effector modules that can be controlled by existing synthetic genetic circuits and will result in cells undergoing a specific one of the ten basic events (eg adhesion, migration) by which most biological shape is formed).

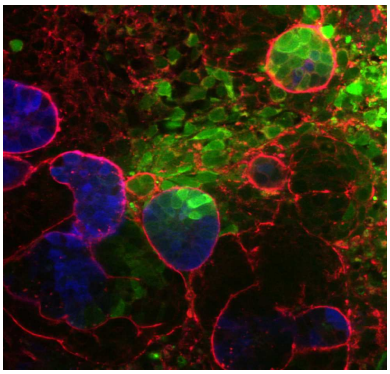

Fig 3: Renal tubules formed from mixed cell suspensions: the green cells, some of which have integrated into the tubules, derive from human amniotic stem cells. Photo: Mathieu Unbekandt

Selected references

Davies JA (2005) *Mechanisms of Morphogenesis* (book: Elsevier). http://www.amazon.co.uk/Mechanisms-Morphogenesis-Jamie-Davies/dp/012204651X/ref=sr_1_1?ie=UTF8&s=books&qid=1251721748&sr=1-1

Sweeney D, Lindström N, Davies JA (2008) Developmental plasticity and regenerative capacity in the renal ureteric bud/collecting duct system. *Development* 135:2505-2510.

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