Chapter 1

The excitement of developmental biology

Developmental biology is the science of how biological form changes in time. Development occurs most obviously in the embryo, where the fertilized egg develops into a complex animal containing many cell types, tissues, and body parts. But development also occurs in other contexts, for example during regeneration of missing body parts, during metamorphosis of larval animals to the adult form, and even within our own bodies as the continuous differentiation of new cells.

Developmental biology occupies a unique central position in modern biology. This is because it unites the disciplines of molecular/cellular biology, genetics and morphology. Molecular and cell biology tell us about how individual genes and cells work. In development this means the operation of intercellular signaling factors, their receptors, intracellular signal transduction pathways, and the transcription factors that regulate gene expression. Genetics tells us directly about the function of an individual gene and how it relates to the activities of other genes. Morphology, or anatomical structure, is both a consequence and a cause of the molecular events. This is because the first processes of development create a simple subdivision of parts in the embryo which then serves as the basis on which further rounds of signaling and responses can occur, creating a progressively more complex morphology.

So developmental biology is a discipline involving contributions from these three areas of science. When thinking about developmental problems it is necessary to be able to use concepts from the three areas simultaneously because they are all required to achieve a complete picture.

Where the subject came from

One of the most amazing conclusions of modern research is that the mechanisms of development are very similar for all animals, including humans. This fact has only been known since it has become possible to examine the molecular basis of developmental processes. Before 1980, we knew virtually nothing of these mechanisms but 40 years later we know a lot and there are several undergraduate textbooks on the subject. Over this period, developmental biology has been one of the most exciting areas of biological research. Each of the components of the modern

discipline has its own historic tradition: experimental embryology, developmental genetics, and molecular biology, that eventually became fused together into the present single world view.

Experimental embryology had been going since the late nineteenth century. In its early decades it consisted mainly of microsurgical experiments on embryos of frogs and sea urchins. These demonstrated the existence of **embryonic induction**: chemical signals that controlled the pathways of development of cells within the embryo. The experiments showed where and when these signals operated, but they could not identify the signals nor the molecular nature of the responses to them.

Developmental genetics has existed since the early twentieth century, but it really flowered in the late 1970s when mass genetic screens were carried out on the fruit fly *Drosophila melanogaster,* in which thousands of mutations affecting development were examined. These **mutagenesis screens** resulted in the identification of a high proportion of the genes that control development, not just in *Drosophila*, but in all animals. The curious names that developmental genes often have, even in humans, reflect their original names on the basis of their effects in *Drosophila*.

Molecular biology effectively started with the discovery of the three dimensional structure of DNA in 1953, and became a practical science of gene manipulation in the 1970s. The key technical innovations were methods for **molecular cloning** to enable single genes to be amplified to a chemically useful quantity, methods for **nucleic acid hybridization** to enable the identification of DNA or RNA samples, and methods for **DNA sequencing** to determine the primary structures of genes and their protein products. Once this toolkit had been assembled it could be applied to a whole range of biological problems, including those of development. It was used initially to clone the developmental genes of *Drosophila*. This turned out to be of enormous importance because most of the key *Drosophila* genes were found to exist also in other animals, and frequently to be controlling similar developmental processes. Molecular biological methods were also applied directly to vertebrate embryos and used to identify the previously mysterious inducing factors and the genes regulated by them.

The application of molecular biology techniques meant that the mechanisms of development could, for the first time, be understood in molecular detail. It also meant that the path of development could be experimentally altered by the introduction of new genes, or the

selective removal of genes, or by an alteration of the regulatory relationships between genes. It also showed that all animals use very similar mechanisms to control their development. This is particularly exciting because it means that we really can learn about human development by understanding how it happens in the fruit fly, zebrafish, frog, or mouse.

Impact of developmental biology

Apart from its intellectual excitement, some areas of developmental biology have had a significant practical impact on society. ***In vitro* fertilization (IVF)** is now a routine procedure and has enabled millions of previously infertile couples to have a baby. It is estimated that about 2–3% of births in developed countries now arise from IVF. Its variants include artificial insemination by donor (AID), egg donation, and storage of fertilized eggs by freezing. In 2011, Robert Edwards (1925-2013) received the Nobel Prize in Physiology/ Medicine for introducing this technique. It is less widely appreciated that AID, IVF, embryo freezing, and embryo transfer between mothers are also very important for farm animals. These techniques have been used for many years in cattle to increase the reproductive potential of the best animals.

Developmental biology also led to the understanding that human embryos are particularly sensitive to damage during the period of **organogenesis** (i.e. after the general body plan is formed, and while individual organs are being laid down). The science of **teratology** studies the effects of environmental agents such as chemicals, viral infection, or radiation on embryos. This has led to an awareness of the need to protect pregnant women from the effects of these agents. For example the statin drugs, used to lower cholesterol levels, can compromise the cholesterol modification of the signaling molecule Sonic hedgehog. This can lead to a variety of defects in systems dependent on hedgehog signaling during development: the central nervous system (CNS), limbs, and vertebrae. Although normal doses of statins are unlikely to be teratogenic in humans, this provides a good reason to avoid them during early pregnancy.

Developmental biology is responsible for an understanding of the genetic or chromosomal basis of many human **birth defects**. For example, Down syndrome is due to the presence of an extra chromosome 21, and there exist a number of relatively common abnormalities of the sex chromosomes. These can be detected in cells or DNA taken from the amniotic fluid and form the basis of the **amniocentesis** tests taken by millions of expectant mothers every year. They can also

be detected in **chorionic villi**, a part of the placenta derived from the conceptus, which may be sampled in the early stages of pregnancy. It is also now possible to screen for defects in single cells removed from the early conceptus following IVF (**preimplantation diagnosis**). Many other birth defects are due to mutations in specific genes that control development. These may be screened for in the DNA of the parents, or that of the preimplantation conceptus, or that of the chorionic villi, using molecular biology techniques.

Developmental biology research has also led to the identification of several new growth regulatory substances, some of which have entered clinical practice. For example the hematopoietic growth factors erythropoietin and granulocyte–macrophage colony-stimulating factor (GM-CSF) have both been used for some years to treat patients whose blood cells are depleted by cancer chemotherapy, or for other reasons. Some others, such as the platelet derived growth factor (PDGF) have been used to assist the healing of wounds.

Developmental biology has also impacted in a major way on other areas of science. This is especially true of the methods for making genetically modified mice, which are now commonly used as **animal models** of human diseases, enabling more detailed study of pathological mechanisms and the testing of new experimental therapies. These are by no means limited to models for genetic disease as often a targeted mutation in the mouse can mimic a human disease that arises from non-mutational causes.

Last but not least, developmental biology has been the "midwife" of stem cell biology. **Embryonic stem cells** were discovered by developmental biologists and human embryonic stem cells were first isolated in 1998. These are **pluripotent** cells, which means that any cell type in the body can be obtained from them using methods for **directed differentiation** *in vitro*. These methods depend very largely on the understanding of the normal sequence of signals and responses in the embryo, which has been built up by developmental biologists. It is now also possible to make **induced pluripotent stem cells (iPS cells)** from any individual by overexpressing certain genes in normal cells from the skin or blood. Functional cell types obtained from human pluripotent stem cells, particularly heart muscle and liver, are now used for safety screening of new drugs. Several clinical trials are investigating the use of cell transplants derived from pluripotent stem cells for the treatment of various diseases, for example retinal

pigment epithelium for treatment of macular degeneration, and dopaminergic neurons for the treatment of Parkinson's disease.

Future impact

Although the past impact of developmental biology is considerable, the future impact will certainly be much greater. Some of the applications, particularly those involving human genetic manipulation, may cause some serious ethical and legal problems. These problems will have to be resolved by society as a whole and not just the scientists who are the current practitioners of the subject. For this reason it is important that an understanding of developmental biology becomes as widespread as possible, because only with an appreciation of the science will people be able to make informed choices.

The scope for assisted reproduction will increase as methods are perfected to create gametes from pluripotent stem cells. This will enable completely infertile people to have children derived from their own iPS cells, although for the foreseeable future the resulting conceptuses will still need to be implanted in the womb of either the biological mother or a surrogate mother to enable development to term.

We can expect to see an extension of **prenatal screening** to encompass the whole variety of single-gene disorders. Although this is welcome as a further step in the elimination of human congenital defects, it also presents a problem. The more tests that are performed on an individual’s genetic makeup, the more likely they are to be denied insurance or particular career opportunities because they are found to have a susceptibility to some disease or other.

The application of developmental biology to the production of human cells, tissues, or organs for **transplantation** will certainly expand. There is now the possibility of making grafts from patient-specific iPS cells, which will be a perfect immunological match for the patient him- or herself. Stem cell technology is becoming fused with the methods for **tissue engineering**, which can potentially generate more complex tissues and organs starting with the constituent cell types. This involves the production of novel types of three-dimensional extracellular matrix, or **scaffold**, on which the cells grow and with which they interact. Tissue engineering will need more input from developmental biology in order to be able to create tissues containing several interacting cell types, or tissues with appropriate vascular and nerve supplies. Stem cell

technology will also embrace **gene therapy**, which relates to the introduction or modification of specific genes for therapeutic purposes. So transplants derived from stem cells may also carry specific genetic modifications to rectify problems suffered by the patient.

Finally, we should not overlook the likely applications of developmental biology to agriculture. With farm animals the possibilities are likely to be limited by a public wish to retain a "traditional" appearance for their cows, pigs, sheep, and poultry, but already technologies have been developed to produce rapidly growing fish, pharmaceuticals in the milk of sheep, vaccines in eggs, and other opportunities will doubtless present themselves in the future.

Further reading

Useful web sites

Society for Developmental Biology: Education section
http://www.sdbonline.org/education
British Society for Developmental Biology: Advocacy
http://bsdb.org/advocacy/

Textbooks, mainly descriptive

Gilbert, S.F. & Raunio, A.M., eds. (1997) *Embryology: Constructing the Organism*. Sunderland, MA: Sinauer Associates.

Hildebrand, M. & Goslow, G.E. (2001) *Analysis of Vertebrate Structure*, 5th edn. New York: John Wiley & Sons.

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Textbooks, mainly analytical

Wolpert, L. & Tickle, C.A. (2015) *Principles of Development*, 5th edn. Oxford: Oxford University Press.

Gilbert, S.F. and Barresi, M.J.F (2016) *Developmental Biology*, 11th edn. Sunderland, MA: Sinauer Associates.

Reproductive technology and teratology

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Stem cells and regenerative medicine

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Trounson, A., DeWitt, N.D., (2016). Pluripotent stem cells progressing to the clinic. *Nat Rev Mol Cell Biol* 17, 194-200.

Shafiee, A., Atala, A., (2017). Tissue engineering: toward a new era of medicine, in: Caskey, C.T. (Ed.), *Annual Review of Medicine*, 68. Annual Reviews, Palo Alto, pp. 29-40.

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Dunbar, C.E., High, K.A., Joung, J.K., Kohn, D.B., Ozawa, K., Sadelain, M., (2018). Gene therapy comes of age. *Science* 359.