What are 'model organisms'?

28/8/02 By Richard Twyman

A model organism is a species that has been widely studied, usually because it is easy to maintain and breed in a laboratory setting and has particular experimental advantages.

Over the years, a great deal of data has accumulated about such organisms and this in itself makes them more attractive to study. Model organisms are used to obtain information about other species – including humans – that are more difficult to study directly.

We can distinguish three major types of model organism:

Genetic model organisms

These are species that are amenable to genetic analysis, i.e. they breed in large numbers and have a short generation time so large-scale crosses can be set up and followed over several generations. Many different mutants are generally available and highly detailed genetic maps can be created. Examples include baker's yeast (Saccharomyces cerevisiae), the fruit fly (Drosophila melanogaster) and the nematode worm (Caenorhabditis elegans).

Experimental model organisms

These species may not necessarily be genetically amenable (i.e. they may have long generation intervals and poor genetic maps) but they have other experimental advantages. For example, the chicken and the African clawed frog Xenopus laevis have many disadvantages in terms of genetics but they produce robust embryos that can be studied and manipulated with ease. These species are widely used model organisms in developmental biology.

Genomic model organisms

Regardless of their genetic or experimental advantages and disadvantages, certain species are chosen as model organisms because they occupy a pivotal position in the evolutionary tree or because some quality of their genome makes them ideal to study.

An example is the puffer fish (Fugu rubripes) which has a similar gene repertoire to humans but a much smaller genome (400 million base pairs instead of 3000 million). The difference in size is mainly due to the presence of more repetitive DNA, larger segments of DNA between genes and larger introns in the human genome.

Another consideration that must be addressed is the relevance of model organisms to humans. Surprisingly, over 60 per cent of the human disease genes that have been identified thus far have counterparts in the fly and worm, revealing a core of about 1500 gene families that is conserved in all animals.

Genes affecting more evolutionarily advanced features, such as our immune system, are less likely to have direct counterparts in simple animals. For these systems, we require closer models such as the mouse . A great deal has been learned about humans by mapping and isolating mouse genes and using these as a

short cut to find corresponding human genes. The mouse genome is similarly organised to the human genome and large blocks of genes are even arranged in the same order (see Comparative genomics). Mice have been extensively used to establish disease models by mimicking the gene defects seen in humans, and these models can be used to test the efficacy of new drugs.

Model organisms: The mouse

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The mouse is closely related to humans so most human genes have functional mouse counterparts and the genome is organised in a very similar manner.

The mouse is the model organism most closely related to humans. The mouse and human genomes are approximately the same size, contain the same number of genes and show extensive synteny (conserved gene order). Most human genes have mouse counterparts and the functions of these genes are closely related. Mutations that cause diseases in humans often cause similar diseases in mice. Importantly, mice have genes that are not represented in other animal models (the fruit fly and nematode worm), including the genes of the immune system.

The similarities discussed above probably apply to most mammals, but the mouse has further properties that make it an ideal model organism. Mice are small, easy to maintain in the laboratory and (compared to most mammals) have a short breeding cycle (about 2 months). They can produce 10-15 offspring per litter and approximately one litter every month. This makes them suitable for genetic analysis. Many mutants are available and new mutations can be introduced easily by irradiation, feeding with chemical mutagens or inserting DNA fragments into the genome to interrupt genes.

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The suitability of mice for genetic analysis is enhanced by the availability of different species, such as Mus musculis and Mus spretus, which can be used for interspecific crosses. The advantage of this approach is that the different species are likely to have different DNA sequences at most polymorphic sites in the genome. Therefore, the interspecific hybrids produced from such crosses are extensively heterozygous and can be used to make finely detailed genetic maps (see Linkage analysis). Large-scale crosses can therefore be carried out to accurately map disease genes. It is often quicker to map a mouse disease gene and use its location to find the position of the equivalent human gene than it is to map the human gene directly. Advanced breeding strategies can be used to make specialised strains such as congenics, which are genetically identical with the exception of polymorphism for one specific gene.

As if the above were not enough, the mouse also has a string of unique technological advantages. Gene transfer technology is highly advanced, so transgenic mice can be created carrying any foreign gene of interest. Also, the mouse is the only vertebrate species in which pre-selected genes can be deliberately mutated in a precise manner (see Knockout mice). This means it is possible to create exact replicas of the

genetic defects that cause diseases in humans. For some reason, certain complex diseases are difficult to replicate in the mouse and in such cases the rat is often a suitable alternative.

Model organisms: Yeast

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Baker's yeast is one of the simplest eukaryotic organisms but many essential cellular processes are conserved between yeast and humans.

Baker's yeast (Saccharomyces cerevisie) is a single celled organism used in the bread-making industry. It would appear initially to have little in common with human beings. However, an important feature of yeast cells is that they are eukaryotic - they have a nucleus containing chromosomes just like our cells. Furthermore, S. cerevisiae cells divide in a similar manner to our own cells, and there are many other basic biological properties that are shared.

The yeast genome is just over 12 million base pairs in length and contains about 6000 genes. Perhaps surprisingly, about 20 per cent of human disease genes have counterparts in yeast. This suggests that such diseases result from the disruption of very basic cellular processes, such as DNA repair, cell division or the control of gene expression .

It also means that yeast can be exploited to look at functional relationships involving these genes, and to test new drugs. A yeast mutant that has lost the functional equivalent of a human disease gene can be screened with thousands of potential drugs in order to identify compounds that restore normal function to the yeast cell. These compounds, or molecules like them, might also be useful in humans.

The yeast genome was completed in 1997 and other projects have been initiated to determine the functions of all 6000 genes. The Saccharomyces Genome Deletion Project, for example, aims to produce mutant strains of yeast in which each of the 6000 genes is mutated. Mutation is achieved using the same technique as that used to produce knockout mice , although the gene targeting process is much more efficient in yeast cells.

Another large project involves the yeast two-hybrid system and mass spectrometry to catalogue all the different protein interactions that occur in yeast cells. Interacting proteins often function in conserved complexes or pathways. A pathway found in yeast might therefore exist in humans, and characterising the interacting proteins in yeast might help to identify the corresponding proteins in humans. The identification of interacting proteins is useful because they may provide alternative drug targets. For example, the product of a human disease gene might be an unsuitable drug target, perhaps due to extensive polymorphism. However, interacting proteins in the same pathway might show less variability and would be better targets for drug development.

Model organisms: Frogs and chickens

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Frogs and chickens provide good experimental models of vertebrate development and have therefore been adopted as model organisms even though they are not suitable for genetic analysis.

The African clawed frog (Xenopus laevis) and the chicken (Gallus gallus) are important model organisms representing the amphibians and birds respectively. Both have similar genome sizes (about 1500 million base pairs). Unlike the other species described in this section, neither the frog nor the chicken is favoured for its genetic amenability. Xenopus produces large numbers of eggs but the breeding cycle is very long (it takes about four months to produce sexually mature adults). Chickens produce fewer eggs and the breeding cycle is even longer (over six months). Therefore, it is difficult and time-consuming to carry out large-scale crosses.

There are few well-characterised mutants for either species, but gene transfer is possible so transgenic frogs and transgenic chickens can be produced if necessary..

An additional disadvantage of Xenopus laevis for genetic analysis is that the species is tetraploid. This means there are four copies of each chromosome, rather than the two copies found in most vertebrates, including humans. The closely related species Xenopus tropicalis is therefore favoured where genetics is important since this frog is diploid and also has a shorter breeding cycle.

The African clawed frog (Xenopus laevis) is often used for studies of early development.

The predominant reason for the use of Xenopus and chickens as models is that they produce large, robust embryos whose development occurs outside the body of the mother. Since they are both vertebrates, their developmental processes have much in common with each other, and with humans. However, the embryos are much more accessible than those of mammals. Frog development occurs in water and can be observed at all stages. Chickens develop inside an opaque egg, but the shell can be cut open and covered with clear plastic or the embryos can be cultured outside the egg.

The accessibility of the embryos means they can be surgically manipulated or treated with proteins and chemicals that interfere with normal development. In many cases, the results from such experiments can be extrapolated to mammals.

Xenopus has been particularly useful for the analysis of events occurring very early in development, such as the formation of the neural plate, which gives rise to the entire nervous system.

Chickens have been invaluable for elucidating the molecular basis of limb development and cell migration in the nervous system. They have helped to uncover the molecular basis of many limb and neural defects in humans.

Model organisms: The nematode worm

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The nematode worm Caenorhabditis elegans is a very simple animal that can be handled like a microbe but it shares many genes and molecular pathways with humans.

Caenorhabditis elegans is a soil-dwelling nematode worm about 1 mm in length that feeds on bacteria. It is one of two major model organisms representing the invertebrates. The other is the fruit fly Drosophila melanogaster.

While the fruit fly has a long history as a model organism this is not the case for the nematode. C. elegans was chosen in 1963 specifically to provide a new model for scientists studying animal development. It was chosen because it is perhaps the simplest multicellular organism in existence, containing fewer than 1000 somatic cells. Despite this simplicity, C. elegans has a multitude of cell types and a fully functioning nervous system. It therefore shares enough characteristics with humans to be a useful model.

One of the most attractive features of C. elegans is that it can be handled like a microbe. Large numbers of worms can be maintained inexpensively on lawns of bacteria growing on standard agar plates, but viable cultures can be stored as frozen stocks and then revived when required. Unlike other animals, C. elegans does not have male and female sexes. Instead, there are males and hermaphrodites. A single hermaphrodite can self-fertilise and produce over 1000 eggs per day. If crosses need to be carried out, hermaphrodites can be mated with males. The life cycle of C. elegans is two weeks long, similar to that of the fruit fly, so it is very amenable to genetic analysis.

The rise of the nematode worm as a model organism began in 1963, when Sydney Brenner chose it for his studies of the role of genes in development and the nervous system.

C. elegans also has an impressive list of experimental advantages. The worm is transparent throughout its life. Therefore, the behaviour of individual cells can be followed through development and gene expression patterns can be monitored very easily. A unique feature of this animal is that development is stereotypical, i.e. cells divide and specialise in a totally characteristic way so that every normal worm has the same number and type of cells arranged in the same manner. This means that the lineage of every cell can be traced back to the egg. A complete wiring map of the 302 neurons that make up the nervous system is also available. C. elegans mutants can be produced very easily and gene function can also be studied using the relatively new technique of RNA interference.

The C. elegans genome is 97 million base pairs in length and contains about 20 000 genes. Many of these genes appear to have functional counterparts in humans, and whole pathways are often conserved. This makes C. elegans a useful model for human diseases. For example, the insulin signalling pathway is fully conserved between humans and nematodes so mutant worms impaired for insulin signalling are useful models of type II diabetes. Due to their microbe-like properties, these nematode mutants can be screened

with thousands of potential drugs to identify compounds that return the insulin-insensitive disease physiology to normal. C. elegans mutants provide models of many other diseases including neurological disorders, congenital heart disease and kidney disease. The molecular basis of cell death has been studied extensively in C. elegans and in the future this worm may even hold the key to counteracting the effects of ageing in humans.

Model organisms: The fruit fly

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The fruit fly Drosophila melanogaster has the longest history of any model organism and has been widely used to study genetics and developmental biology.

The fruit fly (Drosophila melanogaster) is a small insect that feeds and breeds on spoiled fruit. It has been used as a model organism for over 100 years and thousands of scientists around the world work on it. Part of the reason for this is historical. Scientists today choose to study the fruit fly because so many others have done so before them. There are established methods for handling flies in the laboratory and an immense volume of data has accumulated about fly biology. But why was the fruit fly chosen in the first place?

As with most of the long-established model organisms, the initial choice was for practical reasons. The fruit fly is small and has a simple diet. Therefore, large numbers of flies can be maintained inexpensively in the laboratory. The life cycle is also very short, taking about two weeks, so large-scale crosses can be set up and followed through several generations in a matter of months. Fruit flies also have large polytene chromosomes, whose barcode patterns of light and dark bands allow genes to be mapped accurately.

Due to these advantages, fruit flies were extensively used in the early 20th century to work out the principles of genetics. Indeed, they are still used in this capacity to teach genetics in schools. Mutants are available for a large number of genes and new mutations can be induced very easily by exposing flies to radiation or adding mutagenic chemicals to their food. This ability to recover mutants means that flies can be used to investigate the genetic basis of any conceivable biological process.

The fruit fly (Drosophila melanogaster) has been used as a model organism for nearly a century.

The relevance of the fruit fly to the human genome project reflects the remarkable conservation among genes in different animals. The fly genome, which was sequenced in the year 2001, is 165 million base pairs in length (spread over four chromosomes) and contains approximately 14 000 genes.

The human genome contains 3-4 times as many genes but most of these are thought to have arisen by two rounds of genome doubling during the evolution of vertebrates. Therefore, humans have more genes than flies but about the same number of gene families. Since it is easy to create mutants and carry out experiments on fruit flies, the functions of many fly genes have been established.

The relationship between fly and human genes is so close that the sequences of newly discovered human genes, including disease genes, can often be matched against their fly counterparts. This provides a lead towards the function of the human gene and could help in the development of effective drugs.

The analysis of fly embryonic development has made a particularly important contribution to the understanding of developmental processes in humans. The genetic basis of many human birth defects is now known thanks to experiments on developmental mutants in the fly.

In acknowledgement of this, Ed Lewis, Christiane Nusslein-Volhard and Eric Wieschaus, who led early work on Drosophila developmental genetics, were awarded the Nobel Prize in Physiology or Medicine in 1995.

Model organisms: Fish

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Two species of fish are widely used as model organisms: the zebrafish primarily because of its experimental and genetic amenability, and the pufferfish because of its extraordinarily compact genome.

Zebrafish (Danio reiro)

The zebrafish comes close to being the ideal model organism for vertebrate development because it appears to combine the best features of all the other models.

Like the frog , zebrafish embryos develop externally and can be viewed and manipulated at all stages. However, zebrafish development is more rapid than in the frog, the organisation of the embryo is simpler and (like worms and fruit flies) the embryo is transparent. Like the mouse , the zebrafish is amenable to genetic analysis and has a similar generation interval (2-3 months). However, zebrafish are smaller than mice and they produce more offspring in a shorter time. A female zebrafish can lay up to 200 eggs per week, while a mouse may produce a litter of up to 15 embryos in 21 days.

It is easy to induce new mutations in zebrafish and large-scale screens have been carried out to identify mutations causing defects in particular biological processes, such as the developing nervous system. The technology for gene transfer to zebrafish is highly advanced (alsoTransgenic mice).

These advantages have allowed the creation of dense genetic maps in the zebrafish, which have been useful for the comparative mapping of human genes (see Comparative genomics). There is extensive similarity between the zebrafish and human genomes so many human developmental and disease genes have counterparts in the zebrafish. The zebrafish genome is 1700 million base pairs in length, about half the size of the human genome.

A number of zebrafish mutants have been produced that are good models of human diseases, and can therefore be used to test candidate drugs. These include models of Alzheimer's disease, congenital heart disease, polycystic kidney disease and cancer.

The zebrafish (Danio reiro) is amenable to genetic analysis and has a generation interval of 2 to 3 months.

The Japanese medaka (Oryzias latipes) has similar properties to the zebrafish and is preferred in some laboratories.

Japanese pufferfish (Fugu rubripes)

The Japanese pufferfish has become a model organism because it has the shortest genome of any known vertebrate – just 400 million base pairs, representing about 25 per cent of the zebrafish genome or 10-15 per cent of the human genome. Despite its brevity, the pufferfish genome contains a similar number of genes to the human genome. However, the genes are organised differently, with smaller introns, less spacer DNA between the genes and an almost total absence of repetitive DNA. The compactness of the pufferfish genome simplifies the detection and analysis of genes and their regulatory elements.

The pufferfish genome sequence was published in 2002 and was only the second vertebrate genome to be completed (the human genome was the first). The entire genome was assembled using the shotgun sequencing method, over 30 000 genes were identified, and comparative genomics helped to reveal more than 1000 human genes that had not previously been recognised. As for the mouse and zebrafish genomes, there are large regions of synteny (conserved gene order) between pufferfish and human beings.