

GENETIC ENGINEERING OF MAMMALIAN CELLS

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Summary

This paper presents a perspective of genetic engineering of mammalian cells, including a summary of the methods, applications and ethical and social issues. Genetic engineering is the name of a group of artificial techniques used for direct genetic modification of organisms using recombination of DNA or other nucleic acid molecules. The procedures are used to indentify, replicate, modify and transfer the genetic material between organisms. Most techniques are related to the application of molecular genetics to the direct manipulation of DNA oriented to the expression of particular genes. In mammals, the genome is generally of larger size and have a more complex organization than in viruses, bacteria and plants. Consequently, genetic modification of superior animals, using molecular genetics and recombinant DNA technology is more difficult and costly than in simpler organisms. The interest in genetic engineering of mammalian cells is based in the idea of by example, to find a cure to genetic diseases such as cystic fibrosis by replacing the damaged copies of the gene by normal ones (gene therapy). Genetically engineered animals such as the “knockout mouse”, on which one specific gene is deleted, are used to model genetic diseases in humans and to discover the function of specific sites of the genome. Genetically modified animals such as pigs probably will be used to produce organs for transplant to humans (xenotransplantation). Other applications include production of specific therapeutic human proteins such as insulin in the mammary gland of genetically modified milking animals like goats (transgenic animals, bioreactors), to increase disease resistance and productivity in agriculturally important animals by increasing the frequency of the desired alleles in the populations used in food production by transfer of the best alleles or allele combinations by transgenesis or using marker assisted selection to speed up the results of ‘classical’ improvement methods (use of genetic engineering in animal breeding).

1. Introduction

Genetic engineering is the name of a group of artificial techniques used for direct genetic modification of organisms or population of organisms using recombination of DNA or other nucleic acid molecules. Many of these techniques were gradually developed beginning with the discovery of DNA structure in 1953. The procedures are used to indentify, replicate, modify and transfer the genetic material of cells, tissues or complete organisms. Most techniques are related to the application of molecular genetic to the direct manipulation of DNA oriented to the expression of particular genes. In a broader sense, genetic engineering involves as well the so called “traditional” methods of breeding, based on selection or crosses of individual evaluated on the basis of their phenotypes. The probably most accepted current meaning of genetic engineering is focused on methods for direct manipulation of DNA sequences with the process named recombinant DNA technology and gen cloning, which involve the capacity to isolate, cut and transfer specific DNA pieces, corresponding to specific functions in the organisms (genes).

In mammals, the genome is generally of larger size and has a more complex organization than in viruses, bacteria and plants. Consequently, genetic modification of superior animals, using molecular genetics and recombinant DNA technology is more difficult and costly than in simpler organisms.

In mammals, techniques for reproductive manipulation of gametes and embryos such as the obtention of a complete, new organism from of adult differentiated cells (cloning), and procedures for artificial reproduction such as in vitro fertilisation, embryo transfer and artificial insemination and eventually cloning, are frequently an important part of these processes.

Current research in genetic engineering of mammals is oriented toward a variety of possible medical, pharmaceutical and agricultural applications and to increase basic knowledge about mammalian genetics and physiology, including the genetic understanding of complex traits controlled by many genes such as many human and animal diseases. The interest in genetic engineering of mammalian cells is based in the idea of, for example, to find a cure to genetic diseases such as cystic fibrosis by replacing the damaged copies of the gene by normal ones (gene therapy). Genetically engineered animals such as the “knockout mouse”, on which one specific gene is deleted, are used to model genetic diseases in humans and to discover the function of specific sites of the genome.

Genetically modified animals such as pigs probably will be used to produce organs for transplant to humans (xenotransplantation). Other applications include production of specific therapeutic human proteins such as insulin in the mammary gland of genetically modified milking animals like goats (transgenic animals, bioreactors), to increase disease resistance and productivity in agriculturally important animals by increasing the frequency of the desired alleles in the populations used in food production by transfer of the best alleles or allele combinations by transgenesis or using marker assisted selection to speed up the results of ‘classical’ improvement methods (use of genetic engineering in animal breeding).

2. Expression and Regulation of Eukaryotic Genes

A typical eukaryotic gene has three main components; (1) A promoter region in the 5' end, preceding the start of the transcription region, (2) the region that transcribe the genetic message to mRNA, including the exons and introns, and (3) the region of 3' end, following the mRNA region. The regions in the 5' and 3' ends control in a great extent the beginning and end of transcription. The promoter region 5' contains several regulation signals. There are several *transcription factors*. These factors regulate the transcription process.

3. Recombinant DNA Technology

The expression *recombinant DNA* refers to the creation of new artificial combinations of segments or DNA molecules. These new combinations are obtained by a series of steps,

- DNA fragments are obtained by cleaving DNA at particular, rather short nucleotide sequences using a group of restriction enzymes or endonucleases.
- The fragments obtained by digestion by restriction enzymes, bonds to other DNA molecules or cloning vectors.
- The recombinant molecule formed by the vector and the inserted DNA segment is transferred to a host cell. In this cell, the recombinant DNA molecule is replicated, producing many copies of identical copies known as clones.
- The replication of the host cells creates a new population of cloned cells containing the cloned sequence.
- The cloned DNA fragments from the host cells could be purified and analysed.
- Eventually, the cloned DNA could be transcribed and the resulting mRNA may be translated. The resulting genic product could be isolated and examined.

By obtaining large amounts of DNA containing specific cloned sequences, it is possible to study gene organization, structure and function. Some of the clones may be genes coding proteins of interest for the industry. This allows the development of the biotechnology industry. Cloning a specific gene requires the ability to identify or characterise particular regions of the genome. In practice we need a probe that will react with the target DNA.

3.1. Restriction Enzymes

Restriction enzymes or endonucleases are of paramount importance for DNA recombinant technology. These enzymes isolated from bacteria have this name, because they limit viral infections by degrading the DNA of the viruses. Restriction enzymes, cleave DNA at specific restriction sites, characterised by specific nucleotide sequences. Recognition frequency depends on the number of nucleotides of the *primer* or recognition nucleotide sequence. Until today, about 200 types of restriction enzymes have been discovered.

Restriction enzymes are named according to the organism from which they were obtained. There are at least three types of restriction enzymes. The enzymes of type I

cut both DNA strands at a position more than 1000 nucleotide apart from the recognition sequence. Enzymes type III are relatively rare and cut the DNA at a position 24 to 26 bp from the recognition sequence. Restriction enzymes types I and III are not very specific. Restriction enzymes type II are very well studied and are very useful in recombinant DNA technology because they are very specific and cut the DNA at the recognition sequence site.

Restriction enzymes are used in many applications of genetic engineering, including cloning of genes or genomes, PCR and sequencing. Fragmentation of the genome is used also in genetic fingerprinting and in the development of restriction maps based on genetic markers. Cloning, as an application of restriction enzymes, consist in to bring together DNA fragments of very diverse origin treated with the same, or compatible enzymes. The resulting recombinant DNA may became a self-replicating unit if it holds prokaryotic or eukaryotic elements allowing these properties.

3.2. DNA Vectors

After joining the DNA segment and the vector or cloning vehicle, a DNA segment could enter into a host cell to replicate or cloning itself. Vectors are essentially transporting DNA molecules. Characteristics for being a vector are,

- Should be self replicating together with the transported DNA segment.
- It should contain some cutting sites for restriction enzymes, present only used to insert DNA fragments that are cut with the same enzyme.
- Should have a selection marker (normally antibiotic resistance genes or genes from enzymes that the host cells do not have), in order to distinguish the host cells having the vector or not.
- The vector of the host cell should be easy to recover.

Bacterial cells are very useful for cloning, replicate and express genes of superior eukaryotic organisms. However, mammalian cells continue to be the more suitable to protein production such as human, in a biologically active form. Advances in genetic engineering are allowing massive production of proteins with pharmacological or biomedical interest in mammalian cells.

In prokaryotic cells, most used vectors are plasmids, cosmids, phages and artificial bacterial chromosomes. Plasmids are pieces of DNA capable of auto-replication and are able to remain in stable state as extra-chromosomal circles in the cell. Cosmids are plasmids modified by insertion of the Cos region of the lambda phage, able to clone large DNA inserts. The most important phage used as a vector is lambda phage. There are currently many vectors derived from this phage. Phages are parasites capable of to replicate inside the bacterial cells. Another important prokariotic phage is M13. Many of these vectors contain genes for antibiotic resistance to test if the clone was integrated to the genome of the host cell. Bacterial artificial chromosomes (BAC) are vectors able to manage large between 100 and 300 kb and the inserts remain stable without rearrangements or elimination of internal material.

Unlike prokaryotic cells, there are no plasmids known able to remain in free form in mammalian cells. *Amplicones* are defective viruses used for cloning DNA in mammalian cells able to remain as cytoplasmic episomes for some time. They have some resemblance to plasmids. In this group is the simian virus (SV40 or *Herpes simplex*). Artificial chromosomes are also free and are expected to be useful to introduce *therapeutic* genes with regulating sequences to mammalian cells.

Genetic modification through gene transfer to mammalian cells is termed transfection. Characteristic vectors in mammalian cells are viruses. Most frequently, DNA viruses with two strands or with a phase of their life cycle with two strands are used. It is convenient that these vectors have an increased rate of replication of the cloned gene and allow an efficient and specific selection in the host cell. Most important limitations are the risk of obtaining an amplified vector possibly oncogenic, multiplied many times, related to the massive production of a substance obtained by genetic engineering. Among the more commonly used viruses in eukaryotic cells, are retroviruses, but when the manipulated cells are to be introduced in a living organism, there are risks related to mutation by insertion or the possibility to develop a lymphoma.

In cell culture it is possible to introduce naked DNA or DNA covered with liposomes without using any vector. Other vectors used in mammalian cells are adenoviruses, adeno-associated viruses, vectors derived from Herpes virus, vaccinia virus and plasmids and artificial mammalian chromosomes. These plasmids are introduced to the cell united to liposomes, in what is called mixed vectors. A small part of these recombinants integrates to the host genome as a permanent and stable genetic transfer. Vectors based on yeast artificial chromosome (YAC) are a vector allowing inserts of more than 1 Mb. This capacity to clone large DNA sequences of these vectors make them important tools to build up physical maps in the human genome project.

3.3. DNA Libraries

The collection of cloned segments of the genome of one organism is a library. Cloned libraries could contain genetic material of the whole genome, the DNA of one chromosome or from the genes that are transcriptionally active. A library made from a fraction of the genome such as a chromosome, may be very valuable to select specific genes and to examine the organization of the genes in the chromosome.

Technological improvements now make possible the cloning of large DNA pieces, using artificially constructed chromosome vectors that carry mammalian DNA fragments as large as 1 Mb. These vectors are maintained in yeast cells as artificial chromosomes (YACs). Before YACs were developed, the largest cloning vectors (cosmids) carried inserts of only 20 to 40 kb. YAC methodology drastically reduces the number of clones to be ordered; many YACs span entire mammalian genes. A more detailed map of a large YAC insert can be produced by subcloning, a process in which fragments of the original insert are cloned into smaller-insert vectors. Because some YAC regions are unstable, large-capacity bacterial vectors (i.e., those that can accommodate large inserts) are also being developed.

4. Genetic Maps

A primary goal of mapping is to make a series of descriptive diagrams and maps of each chromosome at increasingly finer resolutions. Mapping involves (1) dividing the chromosomes into smaller fragments that can be propagated and characterized and (2) ordering (mapping) them to correspond to their respective locations on the chromosomes. After mapping is completed, the next step is to determine the base sequence of each of the ordered DNA fragments. The ultimate goal of genome research is to find all the genes in the DNA sequence and to develop tools for using this information in the study of mammalian biology and medicine. A genome map describes the order of genes or other markers and the spacing between them on each chromosome. Genome maps are constructed on several different scales or levels of resolution. At the coarsest resolution are genetic linkage maps, which depict the relative chromosomal locations of DNA markers (genes and other identifiable DNA sequences) by their patterns of inheritance. Physical maps describe the chemical characteristics of the DNA molecule itself.

4.1. Genetic Linkage Maps

A genetic linkage map shows the relative locations of specific DNA markers along the chromosome. Any inherited physical or molecular characteristic that differs among individuals and is easily detectable in the laboratory is a potential genetic marker. Markers can be expressing DNA regions (genes) or DNA segments that have no known coding function but whose inheritance pattern can be followed. DNA sequence differences are especially useful markers because they are plentiful and easy to characterize precisely.

Markers must be polymorphic to be useful in mapping; that is, alternative forms must exist among individuals so that they are detectable among different members in family studies. Polymorphisms are variations in DNA sequence that occur on average once every 300 to 500 bp. Variations within exon sequences can lead to observable changes, such as differences in eye color, blood type, and disease susceptibility. Most variations occur within introns and have little or no effect on an organism's appearance or function, yet they are detectable at the DNA level and can be used as markers. Examples of these types of markers include (1) restriction fragment length polymorphisms (RFLPs), which reflect sequence variations in DNA sites that can be cleaved by DNA restriction enzymes, (2) variable number of tandem repeat sequences such as microsatellites, which are short repeated sequences that vary in the number of repeated units and, therefore, in length (a characteristic easily measured) and (3) single nucleotide polymorphisms (SNP). Linkage maps are constructed by observing how frequently two markers are inherited together. Two markers located near each other on the same chromosome will tend to be passed together from parent to progeny. During the normal production of sperm and egg cells, DNA strands occasionally break and rejoin in different places on the same chromosome or on the other copy of the same chromosome (i.e., the homologous chromosome). On the genetic map, distances between markers are measured in terms of centimorgans (cM). Two markers are said to be 1 cM apart if they are separated by recombination 1 percent of the time. A genetic distance of 1 cM is roughly equal to a physical distance of 1 million bp (1 Mb). The value of the genetic map is that an inherited disease or a quantitative trait loci (QTL)

can be located on the map by following the inheritance of a DNA marker present in affected individuals (but absent in unaffected individuals), or when differences exist for performance of a quantitative trait between individuals with different markers, even though the molecular basis of the disease may not yet be understood nor the responsible gene identified. Care is required to follow the inheritance of the markers (usually a group of markers or *haplotype*), in a way the relationships found are not simply based on random associations among certain haplotypes and the observed traits or diseases.

Genetic mapping resolution has been increased through the application of recombinant DNA technology, including in vitro radiation-induced chromosome fragmentation and cell fusions (joining human cells with those of other species to form hybrid cells) to create panels of cells with specific and varied human chromosomal components. Assessing the frequency of marker sites remaining together after radiation-induced DNA fragmentation can establish the order and distance between the markers. Because only a single copy of a chromosome is required for analysis, even nonpolymorphic markers are useful in radiation hybrid mapping. In meiotic mapping (described above), two copies of a chromosome must be distinguished from each other by polymorphic markers.

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Biographical Sketch

Hugo H. Montaldo was born in Santiago, Chile in 1954. He did in Santiago his elementary and high school education. In 1980 he obtained a degree on Veterinary Medicine and Animal Husbandry from the National Autonomous University of Mexico. In 1989 he obtained an M.S. degree in animal husbandry (genetics) from the same University with an honorable mention. In 1996, he obtained a Ph.D. degree in Animal Science (breeding and genetics) from the University of Nebraska at Lincoln. From 1997 to 1998 he was Research Fellow at the University of New England in Armidale, NSW, Australia. He has worked as a researcher and professor in animal genetics since 1981 in several research and education organizations in Mexico. From 1992 he was appointed as associate professor of the State University of Guanajuato, Mexico. Since 1999, he is professor. Since 2001 he is professor of the department of genetics and biostatistics of the Faculty of Veterinary Medicine and Animal Husbandry of the National Autonomous University of Mexico. He has published more than 30 research papers in scientific journals, contributed with chapters to 5 books, and have more than 60 participations in seminars and congresses, including 10 invited lectures in several countries. He has participated in several committees for grant and project evaluation in Mexico and as a referee of several international journals. His major research interests includes animal genetics and biotechnology. Since 1989 he is a member of the National Researchers System of Mexico. He has received several awards, including the Gabino Barreda silver medal from the National Autonomous University of Mexico and the Young Scientist Research Award from the Canadian Government.