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RECENT ADVANCES IN MEDICINE USING MOLECULAR GENETICS

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ABSTRACT

As researchers discover the role genes play in disease, more genetic tests become available to help doctors make diagnoses and pinpoint the cause of the disease. For example, heart disease, diabetes, cancer can all be caused either by a mutation in certain genes, or by environmental factors such as diet or exercise to name a few. The ultimate goal of is to identify the factors that are responsible for these diseases. This knowledge will facilitate the development of gene-specific therapies and cures and also methods for identify individuals at risk for these diseases.The recent evolution of molecular genetics techniques and their application in deciphering the molecular genetic basis of inherited diseases have facilitated the dawning of molecular medicine. A complete genetic map of the human genome, based on easily identifiable highly polymorphic DNA markers, has been developed. This achievement is a milestone in that it provides the foundation for genetic linkage analysis, a technique essential to the mapping of the chromosomal locus responsible for a disease. Before the development of multiple informative markers, identification of a disease-related gene required a priori knowledge of the defective protein, which was known for only a few diseases. The previous approach of "from a defective protein to a defective gene" has been replaced with the approach of "from a defective gene to a defective protein." It is anticipated that the emerging field of molecular biology will greatly aid in the future stratification and therapy for patients with malignant tumors. In this review, recent advances in the diagnosis, molecular genetics, and treatment of diseases

INTRODUCTION

The very origins of molecular biology and molecular genetics lie in Griffiths' experiments with mice in the late 1920s, showing that heat-killed pneumococci could transfer virulence to living non-virulent bacteria. This led to the discovery of transformation and so, through the work of Avery and his colleagues, to the demonstration that DNA was the chemical substance of the gene. Watson and Crick's discovery of the structure of DNA, the elucidation of the genetic code and the basic mechanisms of protein synthesis and gene expression, and the development of recombinant DNA techniques allowing any stretch of human DNA to be isolated, multiplied in the test-tube and have its sequence read.

ADVANCES IN CLINICAL RESEARCH USING MOLECULAR GENETICS

The recent availability of the highly informative STRP markers (short tandem repeat polymorphic) compared with previous markers based on RFLP (restriction fragment length polymorphism) has greatly accelerated chromosomal mapping by linkage analysis.[4] Furthermore, the RFLP markers detected by Southern blotting required 5 to 7 days, whereas STRP markers are detected by PCR and require as few as 1 to 2 days.[4 5] The loci for more than 400 disease-related genes have been mapped, and the responsible genes have been identified for more than 40 of these diseases.[1] Theoretically, it is possible to map the chromosomal locus of any disease-related gene if a family with 10 or more living affected individuals spanning two or more generations is available.[4 5] Subsequent to the chromosomal mapping of the locus by genetic linkage analysis, several techniques, such as positional cloning, are used to identify the responsible gene.[6 7] Positional cloning refers to cloning of a segment of DNA with only its chromosomal position in relation to a marker known. This process of identifying the genes, which may require years, has been accelerated recently through the development of two techniques:
YAC (yeast artificial chromosomes) and PFGE(pulsed-field gel electrophoresis).[8]

Before the availability of YAC, one could clone fragments of DNA only as large as 45 000 bp, whereas with YAC, it is possible to clone fragments as large as 1 to 2 million bp. Separation of DNA fragments by agarose gel electrophoresis was limited to those of 40 000 bp, whereas with PFGE, fragments as large as 2 million bp can be separated.

One dramatic advance in cancer research is the discovery of specific genetic changes in cancers cells, especially human cancers, and their functional significance, this has great promise for new approaches to prevention &

treatment.

The direct molecular evidence for the genetic basis for cancer comes from the transformation of cells in culture to a cancerous-like state by Rous' sarcoma and other oncogenic viruses.5. The transformed state, however, must first be established by the ability of the cells to cause tumours in suitable animal hosts.

Application of recombinant DNA techniques to the analysis of the genes and gene sequences of the oncogenic viruses showed which of their genes are responsible for their ability to cause a cancer. These are the oncogenes, which are altered or mutated forms of genes that occur in normal cells. Molecular genetics makes it easy to jump from one species to another, and so it could be shown that the viral oncogenes that cause cancers in mice and chickens were also oncogenes in human tumours. So now we have identified a class of genes whose particular role seems to be in the control of cell growth. There are two ways in which this can happen.

- The genes may trigger the production of growth factors or their receptors (molecules on the cell surface where growth factors attach).
- They may act indirectly, through the processes by which a growth signal is transmitted from the surface of a cell to the nucleus.

Genes in this class are often found to be the genetic culprits in different human tumours. The first growth factor for cancer cells, epidermal growth factor (EGF), was found as a substance that led to the early opening of eye lids of new born mice.(ref). Oncogenes have been shown to be critical for the development of chronic myelogenous leukaemia (CML); raised epidermal growth factor receptors, or related receptors, are found in more aggressive breast and bladder tumours; and mutated rats oncogenes, involved somewhere in the signalling process, are found in many tumours including, for example, up to 70% of colorectal tumours: the commonest cancer in the Western World not due to cigarette smoking (), blocking the function of a growth factor which has been switched on inappropriately by the cancer cell, is one approach to specific therapy.

Sex hormones, particularly estrogens, are important for the growth of breast tumors in humans and in mice. One of the classic oncogenic viruses that cause breast cancers in mice was discovered by its transmission through the milk. (Ref) The virus inserts DNA next to a gene which it switches on as a key step in the production of a cancer. Studying this mechanism led to the discovery of a class of growth factor like substances that play an important role in the control of differentiation at early stages in embryogenesis (development of the embryo). Already it seems clear that changes in the level of production of these factors are important in some human tumors.

The growing ability to read and write in the language of the genes has already explained some of the once-mysterious basic concepts of genetics. The difference between dominant and recessive traits as causes of genetic disease used to be just an abstraction based on a great deal of observation. If a genetic defect expressed itself only in patients who inherited the trait from both parents, it was called recessive; both copies of the gene coding for the trait were presumably defective, resulting in disease. If the trait was dominant, on the other hand, it meant that one defective copy of the gene was sufficient to spell disaster.

But why should some disorders require two mistakes, while others resulted from only one? Molecular genetics has given a concrete and remarkably simple explanation.

"It now appears that these two categories [recessive and dominant] correspond pretty closely to the two fundamental categories of proteins: enzymatic and structural,

Recessive disorders tend to result from failures in genes that code for enzymes, the biological catalysts that do much of the body's chemical work. A person who has inherited the defective gene from only one parent often goes disease-free because the normal gene inherited from the other parent produces enough of the enzyme to serve the body's needs. The disorder appears only when the person inherits the same defect from both parents and therefore lacks any working copy of the normal gene.

If the genetic defect affects structural proteins, however, for example, collagen, a key component of connective tissues and bones, one copy of the faulty gene is usually enough to cause disease. It is easy to see why. A four-engine airplane can still fly even if one of its engines fails, as long as the other engines provide enough power, but a single faulty strut that makes a wing fall off will cause the plane to crash. Sometimes rather subtle differences in the defects of a single gene can make a profound difference in a patient's fate, as Louis Kunkel of the HHMI unit at Harvard University learned after he and his team discovered the gene for Duchenne muscular dystrophy (DMD).(). Major flaws in that huge gene result in the presently incurable DMD, a muscle-wasting disease that leaves young boys wheelchair-bound by age 12 and generally kills them by age 20, because the muscles that control breathing fail. By contrast, lesser defects in that same gene produce a much more benign disease, Becker's muscular dystrophy. (REF)

Genetic research has illuminate many disorders of single organs, such as the eye, teeth, skin, and cochlea (the hearing apparatus of the ear), Valle believes. The deafness of about two-thirds of patients with serious hearing problems has a genetic basis (Harold Schmeck & Pines Maya 1991).

Molecular biologists have found genes that are expressed only in the cochlea and therefore are probably important in hearing. Once such genes have been identified, several strategies exist for determining their functions and suggesting treatments.

The benefits of genetics research can be divided into two categories: those that generate knowledge and those that generate treatment, animal models as extremely important to both. Deliberately produced genetic diseases in animals will have pathologies like those of human diseases. "We will learn how to recognize them, treat them, and analyze them in animals.

In addition, many aspects of human development are being clarified by work with mice, flies, and worms. Scientists have discovered that genes which are developmentally active in both Drosophila, the fruit fly, and C. elegans, the nematode worm, have direct counterparts in mammals, although the functions of these genes in humans are not yet entirely clear. 7

When genes of species that separated from each other many millions of years ago show so much similarity, there is every reason to believe they are related. Many molecular biologists have noticed that nature is quite frugal

in preserving devices that have proved biologically effective, example the human enzyme ornithine delta aminotransferase, which is defective in gyrate atrophy, is 54 percent identical to the comparable enzyme that functions in yeast.

To date, most of the progress in understanding the genetics of human disease has involved relatively rare conditions, such as cystic fibrosis or Duchenne muscular dystrophy, which are caused by errors in single genes. But science is also stalking the genes that contribute to heart disease, cancer, diabetes, obesity and mental illness - the big killers and cripplers of mankind.

It may soon be possible to tell some people that they have certain genetic predispositions to a specific major illness and suggest that they tailor their lifestyles accordingly. Similarly, the use of drugs to treat some of the important diseases could be tailored to the genetically varied needs of patients, with benefits for them and for the health care system in general: "Different strokes for different folks,"

On the other hand, some scientists fear that people might be stigmatized or become uninsurable because of genetic traits, such as carrier states, that don't in themselves have any appreciable effect on health.

Other scientists have forsaken the genes that reside in cell nuclei and are finding new clues to disease in the genes of what are probably our oldest and most entrenched "parasites" - the mitochondria - tiny, energy-generating organs inside every cell. Mitochondria are thought to be the descendants of ancient bacteria that not only found a home in animal cells, but also adapted so thoroughly that they became indispensable functional parts of those cells. We inherit mitochondria only from our mothers; sperm leave their mitochondria behind when they enter the egg. Flaws in mitochondrial genes have been found to lead to certain types of blindness and epilepsy and may also contribute to some degenerative disorders, such as dementia, which are associated with aging.

"Mitochondrial DNA gives us a whole new way to think about genetic transmission of diseases," says Douglas Wallace of Emory University, a specialist in those vital intracellular power stations. (2- 1991)

In even more fundamental ways, discoveries in genetics have led to novel strategies for treating disease. Decades ago, scientists learned that DNA is mainly the archive of genetic information. Its orders are translated into action by segments of ribonucleic acid (RNA), which serve as the working blueprints for all proteins. Today, chemists are beginning to create valuable new drugs by fabricating "anti-sense" segments of RNA, whose sequence is the exact opposite of an unwanted sequence, to combine with certain existing strands of RNA and thus block the action of specific genes.

The bottom line in any kind of biomedical research lies in the realm of treatment and prevention. The ultimate step in that direction is gene therapy - the deliberate transplantation of genes to treat or even prevent human disease. Many geneticists dismiss gene therapy as a distant prospect, but others disagree.

Gene therapy was actually tried in 1970 and again in 1980 without success, but the knowledge and techniques were primitive by today's standards. The first attempt in what might be called the modern era of gene therapy began in September 1990 at the National Institutes of Health (NIH), when doctors treated a 4-year-old girl. The child suffered from a grave immune deficiency because she lacked the enzyme adenosine deaminase. The doctors took her own white blood cells, altered them by adding the gene for the missing enzyme and transplanted the altered cells back into her.

Ultimately the same approach may be applied to other types of diseases like cancer or HIV, a possibility that may be tried as soon as techniques are sufficiently refined. E.g. Instead of treating an AIDS patient for the rest of his or her life with drugs drug to protect the immune system against the HIV virus, doctors might use gene transplants to render the patient's immune system permanently resistant to the virus.

The first gene therapy attempts used the patient's white blood cells as the target for gene insertion. In the future, scientists hope to perfect techniques for using bone marrow cells. Several research centers are making progress in animal experiments using liver cells and endothelial cells, such as those that line blood vessels, to deliver valuable genes to the tissues where they would be useful. Another strategy that would have seemed sheer fantasy a few years ago is being discussed seriously in the scientific world today, is the idea of using inhalant spray to deliver copies of a good gene to airway tissues of cystic fibrosis patients.4

The transplantation and manipulation of genes in other species has already proved valuable in genetics research and will probably play an even larger role in the future.

Mario Capecchi and his team at the University of Utah (REF) have recently used the method of gene manipulation known as homologous recombination to discover the function of a mouse gene. The gene first attracted notice because it produced breast cancer in the animals when it became activated abnormally. By developing mice in which that gene, and only that gene, had been knocked out, the scientists showed that the gene's normal function is crucial to the development of two regions of the animals' brain: the midbrain and cerebellum. The discovery opens an important door to studies of brain development and brain function.

To use homologous recombination, the scientists must be able to identify and grow embryonic stem (ES) cells, the unspecialized precursors of all other cells in an organism. In Capecchi's mouse experiments, ES cells are modified to alter the specific gene under study and then implanted in a very early mouse embryo and used to breed animals that have the desired trait or flaw. Some experts consider this technique among the most exciting recent advances in genetics research.

Another really exciting thing about modern molecular genetics is that we now have opportunities to make animal models of these diseases and to study what happens at the tissue level in a direct way.

RESEARCH ADVANCES IN HCM- HYPERTROPHIC CARDIOMYOPATHY

Recent advances in basic research have translated into clinical breakthroughs that have heralded exciting new ways to prevent, diagnose, treat and cure disease.

For over four decades many Laboratory have remained at the cutting edge of medical discovery in the field of molecular genetics. Much of this effort was devoted to delineation of the molecular characteristics of the new cardiac cell type and to defining the role of these cells in the

development of life-threatening abnormal rhythms of the heart.

All of our genetic information is stored in the DNA molecule, contained within the nucleus of each cell. Each DNA molecule is made of two individual strands paired together. and then twisted like a coiled ribbon into a shape called a double helix. A piece of DNA millions of base pairs long in conjunction with some proteins is called a chromosome.

Humans inherit 23 chromosomes from each of their parents for a total of 46 chromosomes. There are 44 chromosomes, known as autosomes that are identical in men and women. The remaining two chromosomes are called sex chromosomes, that are designated X and Y. Women inherit two X chromosomes, whereas men inherit one X chromosome from their mother and one Y chromosome from their father. Although some strands of DNA contain segments that account for only 2% of the entire DNA molecule, they are in charge of making the protein molecules that form the building blocks of the human body.

The manner in which we inherit our chromosomes provides each of us with two copies of every gene that is contained on the autosomes. The sequence of bases in each gene contains instructions for making a single protein each protein serving a particular function in the body. For example, enzymes help us digest food, structural elements give our cells shape, and signaling molecules help the cells communicate with each other. The human genome is estimated to contain 30,000 to 40,000 genes. Depending on the combination of the genes we inherit, we end up with some traits that resemble our mother and others that resemble our father. Unfortunately, we not only inherit the looks but also some abnormal genes that may cause disease

Many diseases occur as a result of mutations in certain genes. However, inheriting a gene with a mutation from only one parent does not mean that you are at risk for the disease. Everyone has two copies of most genes – one copy from each parent. Sometimes it only takes one damaged copy of a gene to cause disease while other times it takes two. In fact, there are many different ways to inherit diseases and other traits.

Familial HCM is inherited as an autosomal dominant disease that is characterized by hypertrophy, often of the left ventricle, with predominant involvement of the interventricular septum in the absence of other causes of hypertrophy, such as hypertension or valvular heart disease. The clinical manifestations of HCM are diverse, ranging from a benign asymptomatic course to severe heart failure and SCD.[1] SCD is a well-recognized outcome of HCM.

The true prevalence of HCM remains unknown. Clinical diagnostic criteria probably underestimate the prevalence of the disease as the phenotypic expression of the disease (ie, development of hypertrophy) is age dependent and [8] the presence of concomitant diseases such as hypertension and valvular heart disease also confounds the diagnosis of HCM.[1] Several investigators have estimated the prevalence of the disease to be approximately 0.1 to 1 per 1000 population.

The disease was first described in the 19th century, but it was not until 1958 that Teare described the familial inheritance of HCM.[2]Braunwald et al in 1964 and Frank et al in 1968[2] described several families with HCM, and they further delineated its familial nature. Clark et al[9] and van Dorp et al[3] performed routine echocardiography on all family members of patients with HCM and showed that the pattern of inheritance of HCM was autosomal dominant with a high but variable degree of penetrance. Echocardiographic screening of the families in their studies showed that cardiac hypertrophy was present in many asymptomatic relatives of the affected individuals.

Identification of the mutations responsible for HCM will provide an important diagnostic armamentarium. The present diagnosis of HCM occurs through echocardiographic detection of cardiac hypertrophy. This usually is not evident until puberty or later, whereas a genetic diagnosis is possible before or at any time after birth and requires only a blood sample. A characteristic of HCM is that the development of hypertrophy and its phenotypic expression are age dependent.

The recent availability of the highly informative STRP markers compared with previous markers based on RFLP has greatly accelerated chromosomal mapping by linkage analysis.— Theoretically, it is possible to map the chromosomal locus of any disease-related gene if a family with 10 or more living affected individuals spanning two or more generations is available [5] Subsequent to the chromosomal mapping of the locus by genetic linkage analysis, several techniques, such as positional cloning, are used to identify the responsible gene.[6] Positional cloning refers to cloning of a segment of DNA with only its chromosomal position in relation to a marker known. This process of identifying the genes, which may require years, has been accelerated recently through the development of two techniques: YAC and PFGE[5]

Before the availability of YAC, one could clone fragments of DNA only as large as 45 000 bp, whereas with YAC, it is possible to clone fragments as large as 1 to 2 million bp. Separation of DNA fragments by agarose gel electrophoresis was limited to those of 40 000 bp, whereas with PFGE, fragments as large as 2 million bp can be separated.

HCM was the first primary cardiomyopathy that was subjected to these techniques. During the short period of 4 years, three genes and a fourth locus responsible for this disease have been identified.[9] [10] [11] [12] In addition, structure-function analysis has shed significant light on the molecular basis of this disease. It is hoped that within the next few years the application of molecular genetics tools will not only facilitate the ability to diagnose HCM but also help to stratify and develop more definitive therapy.

The development of techniques for growing mammalian (including human) normal and cancerous cells in the laboratory - tissue culture - has had a great impact on clinical research. It has enabled experiments aimed at understanding single cells or defined mixed cell populations to be done in the laboratory rather than in animals. Tissue culture is the ultimate pioneer of so-called 'alternatives' to animal experiments and is now a much more fundamental part of clinical research than work with animals

GENE THERAPY

Since genetic syndromes are typically the result of alterations of the chromosomes or genes, there is no treatment currently available that can correct the genetic alterations in every cell of the body. Therefore, there is currently no "cure" for genetic disorders. However, for many genetic syndromes there is treatment available to manage the symptoms. In some cases, particularly the mechanism of disease is well understood and offers the

potential for dietary and medical management to prevent or reduce the long-term complications. In other cases, infusion therapy is used to replace the missing enzyme. Current research is actively seeking to use gene therapy or other new medications to treat specific genetic disorders.

For the first time, researchers have found a way to inject a precise dose of a gene therapy agent directly into a single living cell without a needle (L James lee et al 2011) The technique uses electricity to "shoot" bits of therapeutic biomolecules through a tiny channel and into a cell in a fraction of a second.

L. James Lee et al (2011) at Ohio State University describe the technique in the online edition of the journal Nature Nanotechnology, where they report successfully inserting specific doses of an anti-cancer gene into individual leukemia cells to kill them. They have dubbed the method "nanochannel electroporation," or NEP.

"NEP allows us to investigate how drugs and other biomolecules affect cell biology and genetic pathways at a level not chievable by any existing techniques. There have long been ways to insert random amounts of biomaterial into bulk quantities of cells for gene therapy. Fine needles can inject specific amounts of material into large cells. But most human cells are too small for even the smallest needles to be of any use.

NEP gets around the problem by suspending a cell inside an electronic device with a reservoir of therapeutic agent nearby. Electrical pulses push the agent out of the reservoir and through a nanometer- (billionth of a meter) scale channel in the device, through the cell wall, and into the cell. Researchers control the dose by adjusting the number of pulses and the width of the channel.

They explain how they constructed prototype devices using polymer stamps and individual strands of DNA as templates for the nanometer-sized channels.

Lee invented the technique for uncoiling strands of DNA and forming them into precise patterns so that they could work as wires in biologically based electronics and medical devices. But for the NEP, gold-coated DNA strands were stretched between two reservoirs and then etched away, in order to leave behind a nano-channel of precise dimensions connecting the reservoirs within the polymeric device.

Electrodes in the channels turn the device into a tiny circuit, and electrical pulses of a few hundred volts travel from the reservoir with the therapeutic agent through the nano-channel and into a second reservoir with the cell. This creates a strong electric field at the outlet of the nano-channel, which interacts with the cell's natural electric charge to force open a hole in the cell membrane - one large enough to deliver the agent, but small enough not to kill the cell.

Tests record showed, they were able to insert agents into cells in as though as little as a few milliseconds, or thousandths of a second. At the moment, the process is best suited for laboratory research, because it only works on one cell or several cells at a time. But teams are working on ways to inject many cells simultaneously. They are currently developing a mechanical cell-loading system that would inject up to 100,000 cells at once, which would potentially make clinical diagnostics and treatments possible. (1)

First, they tagged bits of synthetic DNA with fluorescent molecules, and used NEP to insert them into human immune cells. After a single 5-millisecond pulse, they began see spots of fluorescence scattered within the cells. They tested different pulse lengths up to 60 milliseconds - which filled the cells with fluorescence.

To test whether NEP could deliver active therapeutic agents, they inserted bits of therapeutic RNA into leukemia cells. Pulses as short as 5 milliseconds delivered enough RNA to kill some of the cells. Longer pulses - approaching 10 milliseconds - killed almost all of them. They also inserted some harmless RNA into other leukemia cells for comparison, and those cells lived.

We hope that NEP could eventually become a tool for early cancer detection and treatment - for instance, inserting precise amounts of genes or proteins into stem cells or immune cells to guide their differentiation and changes - without the safety concerns caused by overdosing, and then placing the cells back in the body for cell-based therapy.

They are potential applications for diagnosing and treating leukemia, lung cancer, and other tumors.

TOMOSYN-2 THE DIABETES SUSCEPTIBILITY GENE REGULATES INSULIN SECRETION.

In a study published in the open-access journal of Genetics, a research team from the University of Wisconsin-Madison has identified a gene called tomosyn-2 that confers diabetes susceptibility in obese mice and acts as an inhibitor on insulin secretion from the pancreas.

Insulin is produced in the body in a constant proportion to maintain blood sugar levels at a safe level. If the body's insulin production is insufficient (type 1 diabetes) or resistant to insulin (type 2 diabetes) it develops high blood sugar and diabetes symptoms.

The researchers discovered tomosyn-2 during their search for genes that contribute to diabetes susceptibility in obese mice. They analyzed the genetics and compared them with obese diabetes-resistant and diabetes-susceptible mouse strains. They found a single amino acid difference that destabilizes the tomosyn-2 protein in the diabetes-resistant mice, which effectively released the inhibited secretion of insulin and enabled the animals to release sufficient insulin to avoid diabetes.

Although the likelihood of diabetes being caused by a single gene is extremely small, identifying important biological pathways can potentially lead to clinically useful information. The study shows the power of genetics to discover new mechanisms for even a complex disease like type 2 diabetes. Article Date: 09 Oct 2011

IMMUNIZATION WITH DNA VACCINE MAKES TRADITIONAL FLU VACCINE MORE EFFECTIVE AND MAY HELP FORTIFY AGAINST FUTURE PANDEMICS:

People with no pre-existing immunity against an emerging virus strain represent the biggest threat for a worldwide outbreak, making the development and distribution of effective vaccines a vital necessity for the prevention of future pandemics. The H5 antigen is ideal for testing unique approaches to improve the protection of influenza vaccines, as most of the general population is largely naïve to H5N1 influenza.

Findings published online first in The Lancet Infectious Diseases journal demonstrate that results from two new phase 1 human trials indicate that prime (initial) immunization with a DNA vaccine against H5N1 influenza followed by a booster dose of conventional influenza vaccine has a higher effect than administering two doses of

traditional influenza vaccines; a treatment strategy that could be used to fortify against future pandemics.

A human study carried out to evaluate safety and immunity responses of a prime-boost influenza vaccination strategy consisting of a vaccine made from DNA encoding the haemagglutinin (HA) from a H5N1 influenza virus before administering a booster dose of the H5N1 monovalent inactivated vaccine (MIV). A monovalent vaccine is designed to immunize against a single antigen or microorganism.

For the trial, researchers randomly administered 81 healthy adults who had no history of influenza vaccination with a dose of the DNA vaccine at day 0 or twice a day 0 and week 4. After this, participants received a MIV booster at 4 or 24 weeks, or a two-dose regimen of MIV with either a 4 or 24-week interval. (JE Ledgerwood et al. 2011)

Findings revealed that the prime-boost strategy was safe overall with great improvements to the immune response, particularly in those participants where the time between the prime and the boost was extended to 24 weeks.

Researchers also discovered that antibodies generated by DNA priming with a 24-week MIV boost interval achieved a protection level of 81% in individuals, whilst the increase in geometric mean antibody titer, a measure of immune response, was over four times higher compared with that of individuals who received only MIV at 4 or 24 weeks.(JE Ledgerwood et al. 2011)

They noted that the production of neutralizing antibodies that targeted the stem region of the HA protein was stimulated in several individuals administered with the prime-boost regimen(C.J Wei et al200); An important discovery because the stem only varies little across different strains of the virus, meaning that antibodies generated against the stem can neutralize multiple influenza virus strains. "A DNA-MIV vaccine regimen could enhance the efficacy of vaccines and shows that anti-stem antibodies can be elicited by vaccination in man.

"These findings are especially important because a major limiting factor in the preparation against pandemic influenza is the restricted manufacturing capacity to produce enough doses of vaccines in a short period of time to cover the population in need. If the vaccination strategy presented in this study was followed, the total amount of traditional vaccines against influenza would be reduced by half, which would allow more individuals to be vaccinated in a timely manner.

The report also supports the idea of a pre-pandemic vaccination, since various DNA vaccines can easily be mixed together to provide broad coverage against several potential pandemic influenza viruses (even across different subtypes), long before any outbreak. Hosts primed with DNA vaccines are very likely to have reduced morbidity and mortality, even without a boost.

OBESITY MASTER SWITCH GENE FOUND:

Fat plays a key role in our susceptibility to obesity, heart disease and diabetes - otherwise known as metabolic diseases. A master regulator gene which causes obesity and is linked to diabetes and cholesterol and controls the behavior of distant genes that exist inside fat cells has been identified (journal of Nature Genetics.) Researchers already knew about KLF14, a gene that is linked to cholesterol levels and diabetes type 2 - however, nobody knew what role it played until now. The authors say their discovery may help toward developing more effective treatments for obesity-related illnesses, such as diabetes and heart disease.

Tim Spector et al biopsied subcutaneous fat and found that the KLF14 is like a controller - it influences the behavior of distant genes inside fat tissue[7]. The KLF14 gene is inherited from the mother. We inherit a set of all genes from both our mother and father. But in the case of KLF14, the father's copy is switched off, making the copy from the mother the active gene - this is called imprinting. KFL14's ability to control other genes depends entirely on the KFL14 copy inherited from the mother - the father's copy has no effect. If medications could be developed to target KLF14, treatments for several metabolic diseases could be much more effective.

This is the first major study that shows how small changes in one master regulator gene can cause a cascade of other metabolic effects in other genes.

The KLF14 seems to act as a master switch controlling processes that connect changes in the behaviour of subcutaneous fat to disturbances in muscle and liver that contribute to diabetes and other conditions. KLF14 appears to regulate the behaviour of distant genes that influence BMI (body mass index), glucose levels, insulin levels, cholesterol and obesity.

ALTERING MESSENGER RNA HOLDS PROMISE FOR TREATING CYSTIC FIBROSIS, MUSCULAR DYSTROPHY, CANCER

The genetic code is the set of instructions in a gene that tell a cell how to make a specific protein. Central to the body's protein production process is messenger RNA, or mRNA, which takes these instructions from DNA and directs the steps necessary to build a protein. Protein production is not a perfect process - far from it. Frequent mutations or mistakes in DNA and messenger RNA can lead to flawed proteins that have the potential to cause serious harm.

The ability to manipulate the production of a protein from a particular gene is the new miracle of modern medicine. This is a really powerful concept that can be used to try to suppress the tendency of individuals to get certain debilitating, and sometimes fatal genetic diseases that will forever change their lives."

Researchers have found a common type of mutation that occurs when an mRNA molecule contains a pre-mature "stop" signal, known as a pre-mature stop codon. A premature stop codon orders a cell to stop reading the genetic instructions partway through the process, resulting in the creation of an incomplete, shortened protein.

In a new study published in the journal Nature, scientists discovered an entirely new way to change the genetic code. The findings, though early, are significant because they may ultimately help researchers alter the course of devastating genetic disorders, such as cystic fibrosis, muscular dystrophy and many forms of cancer.

Researchers were able to alter mRNA in a way that turned a stop signal into a "go" signal. As a result, the cell could read the genetic instructions all the way through and create a normal, full-length protein. These results have been shown both in vitro and in live yeast cells.

These findings are important because current estimates suggest that approximately one third of genetic diseases are caused by the presence of pre-mature stop codons that result in shortened proteins (Emily Boynton, 2011). The results could aid the development of treatment

strategies designed to help the body override stop codons and produce adequate amounts of full-length proteins, whose absence causes diseases like cystic fibrosis and contributes to different types of cancer.

Another type of RNA (- guide RNA -) was used to modify messenger RNA. Guide RNAs are short RNAs that bind to specific sequences in RNA and allow just one particular site to be modified. "Guide RNAs have tremendous power to zero in on one spot in the genome and make targeted changes. Artificial guide RNAs were programmed to target and change a specific stop codon in an mRNA.

The guide RNA found its way to its target, the stop codon, and directed the desired structure change. This breakthrough is remarkable as Guide RNAs were not thought to have access to messenger RNA, so no one believed they could target messenger RNA for modification. It allowed for the modification of a stop codon in way that allows translation to continue uninterrupted like it was never there in the first place. (J .Karijolich & Yi-Tao Yu. June 2011)

"Previous research has presented other ways to modify the genetic code, but what is really unique about this method is that it is at the RNA level and it is site specific.

Altering messenger RNA in this way may be another mechanism human cells use to create many different types of proteins. Given our complexity, humans have surprisingly few genes. While it is well established that the majority of human genes code for more than one protein, mRNA modification may be an unrealized way that humans are able to do this.

ANIMAL MODELS

One of the really exciting things about modern molecular genetics is that we now have opportunities to make animal models of diseases and to study what happens at the tissue level in a direct way. Cancer is not a single disease. It can affect any organ of the body to different extents and with different frequencies. This complexity means that cancer research encompasses virtually all aspects of fundamental cellular and molecular biology.

Patterns of cancer incidence, and other types of epidemiological studies, indicate that as much as 80% of cancer is in some sense caused by environmental factors. In principle, this much may therefore be preventable if the factors can be identified and controlled. However, the length of time it took to identify cigarette smoking as a major cause of lung cancer in implementing a truly effective anti-smoking policy, shows that preventability and actual prevention are far from equivalent.

Apart from cigarette smoking, the other major presumed environmental factors lie in the diet. But the relationship is complex, and hardly ever is a particular feature of the diet clearly linked to a particular difference in cancer incidence. Epidemiological studies have not resolved this issue and, undoubtedly, ideas based on our fundamental understanding of the cancer process are needed.

Viruses are increasingly recognized as significant causes of human cancer, especially the papilloma virus as a critical cause of cervical cancer, and the hepatitis B virus in the case of liver cancer. In the case of the papilloma viruses, this recognition has come entirely from modem techniques of molecular biology, which have also been the entire basis for the discovery of the HIV viruses as the cause of AIDS. New techniques also hold great potential for effective vaccination against these and other cancer causing viruses, as well as for the successful differential treatment and eventual cure of AIDS, and other diseases caused by related viruses.

Basic theories on the mechanisms of cancer causation have been known for some time: carcinogens, de-differentiation (the loss of key specific characteristics in a cell), the immune system, viruses, changes in the chromosomes that carry the genes and (the bottom line) gene changes in somatic (non-germ) cells. These ideas can all be combined into the one main notion that cancer is a series of changes in gene expression, usually genetic mutations, that lead progressively from the normal to the malignant cancer cell.

The development of most of these ideas depended on work with animals models. Peyton Rous showed that a fowl sarcoma could be propagated by means of a cell free preparation; a classic demonstration of a virus. The idea was slowly accepted, and it was work with the cancer-causing oncogenic viruses in animals that provided some of the most striking evidence - through the discovery of the oncogenes - for the genetic basis of cancer. This finding also advanced the discovery of HIV.5. The direct molecular evidence for the genetic basis for cancer comes from the transformation of cells in culture to a cancerous-like state, however its cancerous nature must be established by the ability of the cells to cause tumours in suitable animal hosts.

The discovery of antibodies by Behring, showing that acquired resistance to bacterial infection resided in blood serum, was the first of many animal experiments which formed the basis of our understanding of the immune system. This is the system which normally protects us from infections and is the basis for vaccination.

SUMMARY

Major advances in molecular genetics over the last decade have made it possible to identify the genes responsible for human diseases using purly genetic approaches eg the development of techniques for growing mammalian (including human) normal and cancerous cells in the laboratory - tissue culture – which has had a great impact on cancer research.

This has enabled experiments aimed at understanding single cells or defined mixed cell populations to be done in the laboratory rather than in animals. Tissue culture is the ultimate pioneer of so-called 'alternatives' to animal experiments and is now a much more fundamental part of cancer research than work with animals. Experts see many more insights such as these in the future, as research in molecular genetics opens some of the "black boxes" of biology.

Molecular biology has augmented traditional histopathologic and clinical classification schemes by providing further insight into the biological diversity of diseases. This emerging field is expected to have a great impact on the diagnosis, classification, and prognosis of diseases such as cancer, as well as aid in the rational development of innovative molecularly targeted therapies.

Cancer is not a single disease. It can affect any organ of the body to different extents and with different frequencies. This complexity means that cancer research encompasses virtually all aspects of fundamental cellular and molecular biology. The discovery of specific genetic changes in cancers, especially human cancers, and their functional significance, is one of the most dramatic

advances in cancer research in this century and has great promise for new approaches to prevention and treatment.

The delivery and transfer of foreign genes into tumor cells, a process known as gene therapy, has broad implications for the treatment of neoplastic diseases. As a result of addition of nanotechnology to molecular research, with existing knowledge in molecular and cellular biology, it seems that new and more personalized, more accurate and more rapid diagnosistiq tools will be devised in the future. As well as new treatments and also more personalised therapy.

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