# Molecular Medicine – An Overview

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Advances in the fields of molecular genetics and cell biology are transforming medicine. Discoveries made today in the laboratory are translated at a rapid pace into new diagnostics and therapeutics. The aim of this series of reviews on different aspects of molecular medicine is to update physicians on new advances at the bench that are likely to impact bedside medicine.

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The twentieth century may rightfully be called "the century of the genome." It started with the discovery of George Mendel's forgotten nineteenth century papers, which launched the era of modern genetic research. Avery proved that DNA is the genetic material, and Watson and Crick demonstrated that the secret of life is embedded in a simple double-helix structure based on only four nucleotides. Nirenberg demonstrated that the genetic code is a simple combination of three letters. The progress recently culminated in the full elucidation of the human genome. The post-genomic era is here, promising leaps and advances in medicine. The aim of this short article is to give an overview of genomic-molecular medicine and to serve as an introduction to a series of reviews on different aspects of molecular medicine soon to appear on the pages of this journal.

Our blueprint is found within approximately 30,000 genes contained in the nucleus of each of our body cells. Each gene is composed of *exons* and *introns*. During the process of transcription the exons are joined together to form mature mRNA. The mRNA moves to the cytosol where it is translated into protein. The dogma that each gene codes for one protein has been proven wrong. It is now clear that genes may give rise to different mRNAs (through various combinations, or *splicing*, of exons) and proteins. Thus there are many more proteins than genes.

Alterations in the primary structure of a gene result in either the absence of a normal protein or the formation of an abnormal one. When such mutations or other genomic changes occur in the *germline* – a hereditary disease ensues. In some diseases, such as cancer, mutations occur only in the body, or *somatic*, cell.

Not all mutations are deleterious. Indeed *genomic instability* is essential for adaptation to changing environmental conditions and is the basis of evolution. Long before DNA was known, Mendel described *alleles*. Alleles are created by variations in the structure of proteins responsible for a particular phenotype – hair color, for example. Allelic proteins are the result of *polymorphisms* in the coding sequence of genes. One of the major challenges of the modern post-genomic era is to discover genetic polymorphisms that impact on the risk for complex diseases such as maturity-onset diabetes, hypertension, schizophrenia, etc.

## Genomic stability

During a human lifetime the DNA is copied faithfully many billions of times. Amazingly, very few mutations accumulate during this process. Our genetic information is extremely stable. This incredible achievement is the result of a very complex system that guards genomic stability. A large series of proteins sense mistakes in DNA copying or damage to DNA caused by other factors. These DNA-guarding proteins order the cell to stop cycling and to fix the damage. If the complex fixing machinery fails, an execution order is given to the cell to commit suicide through the process of *apoptosis*, or programmed cell death.

Mutations in these *caretaker* genes lead to genomic instability. When these mutations occur in the germline they predispose to development of cancer, radiation sensitivity, and other abnormalities of rapidly dividing tissues. Examples are ataxia telangiectasia, Fanconi anemia, Li-Fraumeni syndrome (caused by germline mutation in *p53*), familial breast cancer (mutations in *BRACA*1 or 2), hereditary non-polyposis colon cancer (caused by mutations in the mismatch-repair system), Bloom syndrome, xeroderma pigmentosum and many more.

Cancer is a genetic disease of the somatic cell. Usually, multiple

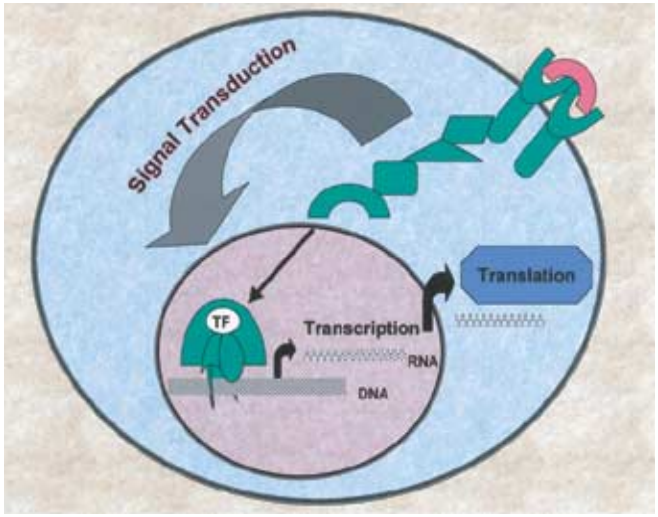


**Figure 1.** From the environment to gene regulation.
Environmental signals attach to receptors located at the cell membrane. The signal generated is transduced and amplified by a series of cytosolic proteins into the nucleus. There, complexes of proteins known as transcription factors (TF) bind to the DNA and regulate gene transcription. The mRNA moves to the cytosol where it is translated into new proteins.

mutations are needed to transform a normal cell into a malignant one. For this to occur a cancer cell has to acquire a *mutator phenotype* through mutations in one or more of the proteins, such as p53, that protect the genome from instability. The genetic instability of a cancer cell allows accumulation of many mutations and explains the typical malignant behavior and the fast emergence of resistance to therapy. The genomic instability of cancer cells is also their weakness. Cancer cells are more sensitive to DNA-damaging agents because, unlike normal cells, they lack the machinery that senses the DNA damage, orders them to stop dividing and fixes the damages.

## Regulation of gene expression

While most cells in the body have identical genes they differ in the genes that are actually *expressed*, i.e., the genes from which RNA and proteins are made. The enormous variety in body cells and tissues is explained by differential gene expression. Thus, regulation of gene expression is critical for cellular processes like growth, proliferation, differentiation, and survival.

To prevent uncontrolled expression the genes are normally inaccessible to the transcriptional machinery. Control of accessibility is achieved by chemical modifications, such as methylation or acetylation, of the DNA and of the histone proteins in which the DNA is packed. The nature and regulation of these *epigenetic* mechanisms is currently undergoing intensive research.

*Transcription factors* – proteins that regulate gene expression – bind to specific DNA regulatory sequences located in the proximity of genes. Each gene, or group of genes, has specific transcription factors that regulate its expression. Transcription factors commonly interact with each other and form protein complexes that regulate the formation of specific RNA molecules and proteins. The variability in the composition of these protein complexes introduces another layer of diversity to the control of gene expression. Mutations in transcription factors are common causes of disease. For example, in most leukemias the inactivation of lineage-specific transcription factors results in block of differentiation and accumulation of undifferentiated proliferating progenitors with the typical blast morphology.

The question of environment versus genetics has been debated for decades. It is now accepted that the two are tightly connected. Cues from the environment bind, or activate, receptors on the surface of cells. Signals from these receptors are transduced into the cells and are amplified further by a series of intracellular proteins. This process of *signal transduction* ends in the nucleus where specific transcription factors activate or suppress the expression of downstream genes. In many types of cancers, mutated signaling proteins, such as Ras, generate environmental-independent signals for growth and proliferation. Blocking of these abnormal signals is a major target of future cancer therapy.

## Molecular medicine

The major advances in genome research have opened a new era in modern diagnostics and therapeutics. The Nobel Prize-winning technique of *polymerase chain reaction* and modern DNA sequencing techniques enable the detection and characterization of DNA alterations in a variety of diseases from minute amounts of DNA. Specific multicolored probes are used for *in situ* visualization of structural anomalies of chromosomes. Gene expression can now be followed using micro-arrays popularly known as "DNA chips" on which probes for all known genes are assembled. Thus, using a relatively small amount of RNA, a whole gene expression profile can be documented. Large studies are underway to establish the *transcriptome* of each type of cancer. This new tool is expected to assist not only in diagnosis but also in identification of new, specific targets for cancer therapy. The same tool can be used for screening for mutations in various genes. Perhaps in the not too distant future a genetic disease chip will be used for routine blood testing in the same way that a biochemical profile is done today. Not surprisingly, the ease of screening for genetic diseases or traits and the progress in genetic prenatal diagnosis are raising serious medical, social and ethical dilemmas.

Because every protein, even the most complex, can be traced to a simple DNA structure of a string of repeated four nucleotides arranged in a three-letter code, it is possible to produce human proteins *in vitro* or in bacteria or yeast by simply constructing the specific coding sequence of DNA. The majority of proteins used in the clinic today, from insulin to erythropoietin, are produced by this method of *recombinant DNA technology*. There is no better illustration of the benefit of this technology than in the case of hemophilia. Almost all patients with hemophilia in the Western Hemisphere who received clotting factors in the 1980s died from AIDS. Since clotting factor concentrates were purified from pools of many thousands of plasma units, human immunodeficiency virus infection was inevitable. Had recombinant DNA technology existed then, many deaths could have been prevented.

Recombinant DNA technology enables gene delivery into cells and human beings. Nonetheless, *gene therapy* is not yet a part of current medicine. The main obstacles revolve around the

difficulties of delivering genes into primary "stem cells," and, in the tools cells have developed to protect their genome. Thus, cells use epigenetic mechanisms to silence foreign genes. Notwithstanding the difficulties, it is likely that several diseases such as hemophilia and immune deficiency will be treated with gene therapy in the near future. Artificial genes are also being used as *DNA vaccines*. Thus, instead of vaccinating with a viral protein it is possible to use its DNA. This may be a cheaper and safer approach to vaccination.

## Targeting the genome

Gene therapy is not the only way in which gene expression can be modified. Short antisense oligonucleotides can inhibit the RNA transcription of a target gene. Several therapeutic trials are currently underway. A promising trial is using the antisense approach to inhibit BCL-2, an anti-apoptotic molecule that inhibits apoptosis of cancer cells. Another approach is to target the mechanisms regulating gene transcription. One striking example is the use of all-trans-retinoic-acid (ATRA), a derivative of vitamin A in promyelocytic leukemia. In this leukemia, a translocation between chromosomes 15 and 17 fuses the retinoic acid receptor to a nuclear protein, PML. The resultant abnormal transcription factor inhibits the normal expression of genes involved in myeloid differentiation. ATRA binds to this abnormal fusion protein and relieves the inhibition. This leads to differentiation of the leukemic blasts into short-lived granulocytes. Retinoic acid therapy in leukemia is the prototype of *transcription therapy* – namely, drugs that repair the abnormal gene expression induced by cancer-specific transcription factors.

## Targeting signaling

This is perhaps the most active area in drug development that is driven by molecular medicine. Genetically engineered antibodies against growth factor receptors are already being used in cancer therapy as "magic bullets." The recombinant humanized antibodies can be used either alone or conjugated to radioisotopes or toxins. Herceptin is such an antibody, directed against the growth factor receptor that drives the proliferation of breast cancer cells. Many such antibodies are in advanced stages of introduction into the clinic.

Many new drugs are small molecules designed to alter specific intracellular signaling pathways. STI-571 (Gleevec) is one such wonder drug. It was designed to inhibit the protein kinase BCR/ABL, which is constitutively activated by a chromosomal translocation t(9;22) in chronic myeloid leukemia. This orally taken drug induces complete remission in most patients with this disease and has only minimal side effects. It is the most striking example of the yield of years of basic cancer research.

The best known and the most commercially successful drug targeting a specific signaling pathway is sildenafil, known better as Viagra. It enables erection by targeting the penile-specific nitric oxide signaling cascade.

Undoubtedly, we are at the beginning of the post-genomic molecular revolution. Molecular medicine is changing the way diseases are diagnosed and treated. Its impact will reach beyond the traditional medical field. Issues like screening for genetic traits and the availability of medications that affect lifestyle are already being elicited by the progress achieved in molecular biomedical sciences.

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