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EDITORIAL

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Cells, disease, and genotypes: the revolution of molecular medicine

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Molecular medicine

Over the 20th century, the data set dealt with in all fields of medicine was based largely on physiological and pharmacological concepts. In the next 20 years, medicine will surely change more than it has in the past two thousand years. Molecular biology and information technology are the drivers of this change. Despite the explosion of literature in the field of molecular cell biology over the last two decades, many physicians have hardly understood the profound impact of molecular biology in the practice of their specialties. Nevertheless, molecular biology is essential to understand the mechanisms of life. A new generation of physicians will need both basic scientific laboratory training and clinical skills, not only to provide the transition from molecular biology advances to clinical application, but also to keep basic science research on track.

Molecular medicine, which is the application of molecular biology to elucidate the ultimate causes and potential cures of disease, has become a major focus of research at virtually every medical school. Incorporating molecular biology techniques into clinical research will help to identify and define reversible and irreversible intracellular processes behind disease. Whether they are hereditary or not, many diseases have a genetic background. Classic genetics states that the genotype is responsible for the phenotype. The pathogenesis of most diseases, however, might be the result of complex interactions among genotype, environment, and the nature of processes leading to cell, tissue, organ, or systemic injuries. As the molecular mechanisms of normal physiology and disease become clearer, we may be able not only to prevent disease, but also to design accurate genetic tests and individualized treatments.

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Genes, our destiny

A gene is a sequence of DNA that encodes a functional product, a protein. Protein production requires the induction of gene expression. Factors regulating gene transcription play a major role in modulating cell development and function. A typical cell may contain thousands of proteins, which play a variety of roles. Enzymes, a large class of proteins, are essential to catalyze all biochemical reactions. Other proteins play structural roles, help to form compartments, and bind with nucleic acids and other cellular elements. Some proteins also function as hormones, antibodies, or carriers. The development of recombinant DNA technology has made it possible to define the molecular structure of many physiological substances and to elucidate the molecular interactions responsible for their behavior in vivo.

In the early 1990s, little was known about how cells communicate or how they translate stimuli. Cellular events that mediate organ inflammation, tissue damage, and repair are ultimately controlled at the molecular level and cannot be fully understood without considering the functions of the relevant genes and their products. Various cellular stimuli induce complex intracellular signaling cascades that activate or induce particular genes or subsets of genes. Activation leads to the synthesis of particular sets of proteins and a consequent change in cellular behavior. Depending on

the nature of the physiological or pathological perturbation, these steps are potential targets for therapeutic strategies. The information resulting from the sequencing of the human genome, when combined with the sophisticated tools of molecular biology, will allow a more rapid identification of both genes responsible for disease susceptibility and genes encoding structural and functional proteins that make us what we are. Molecular changes seen in sick tissues and organs are either exaggerations of normal physiology or inappropriate expressions of repair patterns. By using standard biochemical techniques, DNA, mRNA and proteins can be extracted from any tissue or cell population. Combining such techniques with polymerase chain reaction (PCR) technology, we can assess the relevance of altered gene transcription and translation to given physiological and pathological states.

Microbes and human cells: encounter between two genomes

Microorganisms evolve to levels of virulence that maximize their transmission from one host to another. This requires that microbes balance the benefit of achieving high numbers with the risk of killing or incapacitating the host, thereby reducing the time available for transmission. The variables conducting that balance change with time and environmental conditions. As a consequence, different bacterial populations evolved from an original clone accumulate genetic variations that underlie their differences in ecological fitness and virulence. Although human populations are continuously exposed to pathogens, most people survive infection and develop immunity. This means that, besides genetic variations causing different bacterial virulence, there are also distinct host responses.

Acute-phase reactions consist of sudden changes of protein expression with either decreasing or increasing synthesis of specific cellular products. Morbidity and mortality associated with bacterial infections depend not only on the number of invading bacteria and expression of virulence factors, but also on host factors – mainly host immune responses. Apparently, multiple genes control resistance to bacterial infections; genetic differences explain different responses to infection. Children of individuals who died from an infectious disease before the age of 50 are at a higher risk of dying from infection. Various candidate genes have been identified either by clinical observations or by gene mapping. One of them is the mannose-binding lectin (MBL) gene, which is associated with susceptibility to develop meningococcal disease. Although 1% of the population carry pathogenic strains of *Neisseria meningitidis* in their nasopharynx, it is unknown why they cause fatal disease in a lower percentage. Differences in bacterial virulence and acquired immune response do not explain everything. In addition to adaptive responses, there is also an innate immune response, which does not involve the production of specific antibodies, but activates the alternative complement pathway via the MBL pathway. The amount of MBL in human plasma is genetically regulated; three alleles code for structurally different proteins. Those having variant alleles of MBL have higher susceptibility to various infections. Meningococcal disease is more frequent among children who are homozygous for these genes than in controls. Genetic variants of MBL could account for a third of all cases of meningococcal disease. This finding may explain why patients suffering the same disease may react differently to the same type of therapy.

Understanding microbial diseases

Highly sensitive, rapid, and specific molecular tools are now available to identify infectious agents by the direct detection of DNA or RNA sequences unique to a given organism. This allows analysis of any clinical sample for the presence of foreign, nonhuman DNA. On the other hand, antibiotic-resistant microorganisms have become a major concern in many medical centers. Several studies have identified outbreaks of methicillin-resistant *Staphylococcus aureus* among hospitalized patients by using DNA assay and pulsed field gel electrophoresis. Staff-to-patient transmission, and contamination of environmental surfaces are major sources of infection. Strains with amplified polymorphic DNA genetically identical to those found in infected patients have been isolated from the hands of health care givers.

Cytokines play a major role in the pathophysiology of local and systemic inflammatory reactions in response to infections or many inflammatory states. At present, sepsis is a major challenging problem in medicine. Despite the use of powerful antimicrobial agents, sepsis is the most common cause of respiratory failure, multiple system organ dysfunction, and death in hospitalized patients. Tumor necrosis factor (TNF) is a central mediator of sepsis; high levels of TNF correlate with mortality in several infections. Transcription of the TNF gene is regulated by various nuclear factors bound to sites in the TNF promoter region. Variations of the nucleotide at position –308 of the TNF promoter have been reported to be associated with the clinical outcome of malaria, severe septic states, and autoimmune disorders. Disease association to the promoter region of the gene might depend on altered control of TNF production.

We have introduced here some already identified factors. Nevertheless, molecular networks underlying infectious disease are controlled by multiple microbial and human genes, and follow complex inheritance patterns. Genomics will surely bring a deeper insight to help understand the mechanisms of infection disease.

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