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Editorial

EDITORIAL

Personalized medicine: a new horizon for medical therapy

The development of low-cost high-throughput nucleic acid sequencing has had transformative effects on multiple aspects of biological science and medicine. Prominent among these is an enormous impact on human genetics. We are close to a time when the birthright of each individual, at least in more prosperous countries, will be a complete knowledge of their genomic DNA sequence. Every patient with a diagnosed malignancy may well have a genomic sequence of cells from their neoplasm. A challenge for modern medicine is to convert this information into guides to predict the incidence and consequences of disease with more individual precision than previously possible, and to use these data to design optimal approaches for therapy of disorders including cancer and autoimmune diseases. Glimmerings of such an approach have been around for decades, in pharmacogenetics.[1] Single mutations in a number of genes have been associated with abnormal reactions to drugs, inherited as simple Mendelian disorders. Similarly, specific single gene mutations have been known for some time to predispose to serious reactions to environmental influences. Perhaps the most striking of these are mutations that predispose to development of sudden, potentially fatal, cardiac arrhythmias.[2]

Increasingly massive whole genome disease association studies have shown that the occurrence of common diseases such as diabetes, inflammatory bowel disease and other autoimmune disorders, psychiatric disorders, and perhaps even aging itself, is influenced by variation in multiple genomic loci, probably at least hundreds. Very few genes are entirely redundant, and one might expect that aspects of each disorder vary with the particular blend of predisposing genetic variations in each individual. Deciphering of such complex interactions based on unguided association studies is a daunting task. Although multiple genetic interactions have emerged from studies on model organisms, there is a paucity of such interactions derived from Genome-wide association studies (GWAS). Detection of such interactions might require unrealistic numbers of observations, and it may be that these effects will become evident only by genetic studies guided by *in vitro* studies and a detailed knowledge of the physiologic and biochemical functions of the participating genes. This area represents a large domain that remains to be explored.

Oncology is a field in which precision medicine based on detailed genomic analysis is likely to become of increasing therapeutic significance in the near future. There has been remarkable success in treating certain malignancies by enhancing the immune response to common antigens through cell-mediated therapy or by preventing inhibition of the immune response by tumor cells. The former approach is limited by the lack of safely targetable surface antigens on many types of solid tumor, and the latter approach, facilitating the body's immune response, is strikingly successful in a small fraction of tumors but remarkably unsuccessful in many tumors, including those that are histologically similar to the responding tumors. Nevertheless, many tumors contain multiple carrier mutations that are potentially immunogenic, as well as driver mutations that often result in the production of "abnormal" proteins that could potentially be immunologically distinguishable from proteins of normal cells. Already success has been reported in targeting individual tumor-specific mutations,[3,4] and rapid sequencing methods should permit identification of such potential targets in most patients. Knowledge of the immune system is advanced to the place where there are multiple approaches imaginable to enhance immune response to specific antigens, and the

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application of a variety of methods to exploit knowledge about individual tumors potential antigens is an ongoing challenge of major importance for medicine. Also, it is not inconceivable that methods may be developed to directly attack cells expressing abnormal RNAs, or harboring specific mutations in DNA, offering yet another vista for precision medicine. Autoimmune disorders are yet another area where patient-specific knowledge of the structure of damaging antibodies and immune receptors might be exploited to control such reactions.

In summary, new molecular methods have provided an immense trove of information potentially specific for each patient, and a major challenge for the future is to develop methods to use this information for specifically targeted therapy, to bring the concept of precision medicine into clinical practice.

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