[14:00～14:10]

RECENT TOPICS OF GENETIC POLYMORPHISM IN DRUG THERAPY

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Advances in molecular biology have shown that genetic diversity is the rule rather than the exception with all proteins, including enzymes that catalyze drug-metabolism reactions. For an increasing number of such enzymes, allelic variants with different catalytic activities from that of the wild-type form have been identified. The differences involve a variety of molecular mechanisms leading to a complete lack of activity, a reduction in catalytic ability, or, in the case of gene duplication, enhanced activity. Furthermore, these traits are generally inherited in an autosomal, Mendelian recessive fashion and, if sufficiently prevalent, result in subpopulations with different drug-metabolizing abilities, i.e., *genetic polymorphism*. In addition, the frequency of specific allelic variants often varies according to the racial ancestry of the individual. It is possible to phenotype or genotype a person with respect to a particular genetic variant, and it is likely that such characterization will become increasingly useful in individualizing drug therapy, especially for drugs with a narrow therapeutic index. Accumulating evidence also suggests that individual susceptibility to diseases associated with environmental chemicals, such as cancer, may reflect genetic variability in drug-metabolizing enzymes.

A number of genetic polymorphisms are present in the drug metabolizing enzymes. Cytochrome P450s lead to alter drug metabolizing ability. The best characterized of these is that associated with CYP2D6. About 70 *single nucleotide polymorphisms* (SNPs) and other genetic variants of functional importance have been identified in the CYP2D6 gene, many of which result in an inactive enzyme while others reduce catalytic activity; gene duplication also occurs. As a result, four phenotypic subpopulations of metabolizers exist: poor(PM), intermediate(IM), extensive(EM), and ultrarapid(UM). Some of the variants are relatively rare, whereas others are more common, and importantly, their frequency varies according to racial background. For example, 5% to 10% of Caucasians of European ancestry are PMs, whereas the frequency of this homozygous phenotype in individuals of Southeast Asian origin is

only about 1% to 2%. More than 65 commonly used drugs are metabolized by CYP2D6, including tricyclic antidepressants, neuroleptic agents, selective serotonin reuptake inhibitors, some antiarrhythmic agents, adrenergic receptor antagonists, and certain opiates. The clinical importance of the CYP2D6 polymorphism is mainly in the greater likelihood of the adverse reaction in PMs when the affected metabolic pathway is a major contributor to the drug's overall elimination. Also, in UMs, usual drug doses may be inefficacious, or inthe case where an active metabolite is formed, for example, the CYP2D6-catalyzed formation of morphine from codeine, an exaggerated response occurs. Inhibitors of CYP2D6, such as quinidine and selective serotonin reuptake inhibitors, may convert a genotypic EM into a phenotytic PM, a phenomenon termed *phenocopying* that is an important aspect of drug interactions with this particular CYP isoform.

A polymorphism in a conjugating drug-metabolizing enzyme, namely that in NAT2(N-acetyltransferase2), was one of the first to be found to have a genetic basis some 50 years ago. This isoform is involved in the metabolism of about 16 common drugs including isoniazid, procainamide, dapsone, and caffeine. About 15 allelic variants have been identified, some of which are without functional effect, but others are associated with either reduced or absent catalytic activity. Considerable heterogeneity is present int he worldwide population frequency of these alleles, so that the slow-acetylator phenotype frequency is about 50% in American whites and blacks, 60% to 70% in North Europeans, but only 5% to 10% in Southeast Asians. It has been speculated that acetylator phenotype may be associated with environmental agent-induced disease such as bladder and colorectal cancer; however, definitive evidence is not yet available. Similarly, genetic variability in the catalytic activity of glutathione S-transferases may be linked to individual susceptibility to such diseases. Thiopurine methyltransferase(TPMT) is clinically important in the metabolism of 6-mercaptopurine, the active metabolite of azathioprine. As a results, homozygotes for alleles encoding inactive TPMT(0.3% to 1% of the population) predictably exhibit severe pancytopenia if given standard doses of azathioprine; such patients typically can be treated with 10% to 15% of the usual dose.

In the present meeting, the importance of the genetic polymorphism of drug metabolizing enzymes in term of individual and racial variations in drug therapy will be described.