**Editorial**

**Reflections and Perspectives on the Study of Xenobiotic-metabolizing Enzymes: What do we have to do?**

Since the discovery of cytochrome P450 (CYP), a huge number of scientific articles have been published on this enzyme. However, the focus of much of the research has changed over the last few decades. Until the early 1970s, no one could have answered a question about how many CYPs animals have, and it was then believed that no one would be able to purify CYP from animal tissue. However, since purification procedures have become well established, our knowledge of this enzyme has increased tremendously. The subsequent development of cDNA sequencing gave us information about the CYP superfamily and, now, commercial CYPs and their antibodies are widely available. These are routinely used to investigate the metabolism of drug candidates in the early stages of their development.

The annual number of scientific papers describing CYP studies has been around 2,500 in recent years. Figure 1 shows the current areas of interest for CYP, which were derived from publications cited in Medline in 2007. One of the major interests is the mechanism whereby CYP genes are regulated. This seems to be based on the fact that many CYP forms involved in drug metabolism are inducible. In matching needs for the development of 'tailor-made chemotherapy', inter-individual and inter-racial differences in drug metabolizing capability are the most attractive areas of interest. Although Figure 1 distinguishes between drug interactions and polymorphism, both of these are closely associated with inter-individual/racial differences. Although the basic characterization of eukaryotic CYPs including human enzymes may have been already established, those in lower eukaryotes, such as plants and insects, appear to be of interest and should be studied in more detail (Fig. 1).

Single nucleotide polymorphism (SNP) analysis of genes coding CYPs and other drug metabolizing enzymes greatly contributes to our understanding of why inter-individual differences in drug sensitivity exist. However, in many cases, it would be also true that SNP cannot rationalize all individual cases of sensitivity. Epigenetic control or regulation by micro RNA in CYP expression is expected to be an alternative mechanism. However, we may have to examine factors other than SNP resulting in non-synonymous amino acid alterations and those contributing to gene expression. One of the candidates appears to be a mechanism which governs the degradation of CYPs and other drug metabolizing enzymes, together with individual factors altering such processes. For example, in early studies, starved animals were often used to obtain enriched CYP in the sub-cellular fraction obtained from the tissues. However, it is now recognized that starvation results in cellular stress and induces autophagy. More importantly, only a limited number of studies have focused on the cellular and dietary components affecting the function of drug metabolizing enzymes. As has been established, fruit ingredients markedly inhibit CYP3A function. Recent evidence has suggested that cellular components, such as fatty acids and nucleotides, the levels of which are changed under physiological conditions, greatly affect UDP-glucuronosyltransferase function. Such evidence strongly suggests that dietary components and cellular metabolomes can explain individual differences in drug sensitivity. Thus, we may have to take more interest in lifestyle-related factors affecting the catalytic function and expression of drug metabolizing enzymes.

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