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IDENTIFICATION AND ANALYSIS OF CYTOCHROME P450S IN CYNOMOLGUS MACAQUE

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Macaques, especially cynomolgus and rhesus macaques, are used in drug metabolism studies during drug development owing to their evolutionary closeness to humans. Due to scarce genetic information on drug-metabolizing enzymes in macaques, attempts have been made to isolate cytochrome P450 (CYP) cDNAs in cynomolgus macaque. In this presentation, I will give an overview of the outcomes of these attempts. More than 21 CYP cDNAs have been identified, most of which showed high sequence identities (~95%) and similar drug-metabolizing properties to their homologous CYP cDNAs of human in the same subfamilies, at least partly indicating the resemblance of functional characteristics for CYP enzymes between macaques and humans. In contrast, CYP2C76 cDNA isolated from cynomolgus macaque liver was not orthologous to any human CYP2C cDNAs, since the CYP2C76 gene was located in the genome region, which corresponded to the intergenic region in the human genome. Moreover, CYP2C76 partly accounted for difference of drug metabolism occasionally seen between macaques and humans, indicating the importance of lineage-specific CYPs in drug metabolism. Novel CYP2C93 that is not orthologous but paralogous to human CYP2Cs, similar to CYP2C76, and other novel CYPs that are orthologous to CYPs pseudogenized in human, have been identified and characterized in cynomolgus macaque, the results of which will be also presented and discussed. Investigation of these CYPs, regardless of the orthologous relationship to human CYPs, will provide essential information to understand drug metabolism in macaques.

Keywords: CYP, macaque, species difference, drug metabolism