Mapping of the Genes for Rat P-glycoprotein 1, 2, and 3 (Pgy1, Pgy2, and Pgy3) to Chromosome 4

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Species: Rat
Locus name: P-glycoprotein 1, 2, and 3
Locus symbol: Pgy1, Pgy2, and Pgy3
Map position: Chromosome (Chr) 4

Method of mapping: PCR analysis of somatic cell hybrids generated by fusion of Sprague-Dawley rat hepatocytes with the mouse hepatoma cell BWTG3 [14].

Molecular reagents: Primer sequences for Pgy1 used in PCR were 5'-ACTCTTTGGTCCATTGG-3' (nucleotide positions 40 to 58 of GenBank X61103 deposit) and 5'-ATCTCCGATGTCAGTATG-3' (nucleotide positions 289 to 271 of GenBank X61103 deposit). The primer sequences for Pgy2 were 5'-AGAACCCAGACCTTGATG-3' (nucleotide positions 141 to 158 of GenBank X61104 deposit) and 5'-GGTTACGGCCATGTTTGC-3' (nucleotide positions 326 to 309 of GenBank X61104 deposit). The primer sequences for Pgy3 were 5'-ACATTCAAGCTGGCACAC-3' (nucleotide positions 243 to 260 of GenBank X61105 deposit) and 5'-TGCTCATCACATTTCAAGC-3' (nucleotide positions 615 to 598 of GenBank X61105 deposit).

Discussion: P-glycoprotein is an ATP-dependent integral membrane glycoprotein which mediates the energy-dependent efflux of various antitumor agents from multidrug-resistant (MDR) cancer cells, with broad substrate specificity for a number of structurally diverse drugs [3, 5, 6, 8]. P-glycoprotein expression is increased in the rat liver following xenobiotic exposure, suggesting that P-glycoprotein may act to protect the liver from xenobiotic toxicity, based on its role in MDR cells [4]. P-glycoprotein is distributed in normal tissues, such as the gastrointestinal tract, the liver and the kidney, which are susceptible to drug deposition, and expression of P-glycoprotein in such tissues reduces drug absorption and increases drug elimination into the bile and urine [6]. In addition, the expression of P-glycoprotein at the blood-brain barrier has been shown to be a critical factor in preventing the entry of some drugs into the central nervous system [2, 15]. Therefore, targeted disruption of the P-glycoprotein gene may increase the availability of and sensitivity to different agents [13]. P-glycoprotein is encoded by a family of highly conserved genes. The sequence comparison of P-glycoprotein genes [11] has shown that mouse and rat have three classes of P-glyco-

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protein genes, termed I, II and III, whereas man has only classes I and III [4]. Several lines of evidence have suggested that the different P-glycoprotein isoforms are functionally distinct despite their great similarity [4]. Class I or II P-glycoprotein can confer MDR, but class III P-glycoprotein apparently cannot confer MDR.

We determined the chromosomal localization of three different P-glycoprotein genes in the rat by PCR analysis with rat × mouse somatic cell hybrids. The primer sets used in this study amplified specific 249-bp, 185-bp and 372-bp products of Pyg1, Pyg2 and Pyg3, respectively, from rat genomic DNA but not from mouse genomic DNA (Fig. 1). The rat specific PCR products demonstrated 100% concordance with markers on rat Chr 4. We therefore concluded that Pyg1, Pyg2 and Pyg3 are located on rat Chr 4. This result supports the previous report that mapped Pyg1 on 4q12 in the rat [12].

Rat Chr 4 share partial genetic homology with human Chrs 7 and 12, and mouse Chrs 5 and 6 [16]. The PGY1 and PGY2 genes in man are located on 7q21 [1, 9] and the Pyg1, Pyg2 and Pyg3 genes in the mouse on Chr 5 [7, 10]. Therefore, our present data are consistent with the idea that rat Chr 4 is partially homologous to human Chr 7 and mouse Chr 5.

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References