ABC\textsubscript{B1} (ATP-binding cassette, sub-family B (MDR/TAP), member 1)

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**Identity**

Other names: MDR1 (multidrug resistance 1)

Location: 7q21.2

**DNA/RNA**

**Description**

Spans on a 120 kb genomic fragment; separated from MDR3 gene (which is transcribed in the same direction) by only 34 kb of intergenic DNA.

**Transcription**

5 kb mRNA.

**Protein**

**Description**

The protein is called P-glycoprotein; 170 kDa transmembrane glycoprotein which includes 10-15 kDa of N-term glycosylation; the N-term half of the molecule contains 6 transmembrane domains, followed by a large cytoplasmic domain with an ATP binding site, and then a second section with 6 transmembrane domains and an ATP binding site which shows over 65% of amino acid similarity with the first half of the polypeptide.

**Expression**

Normally expressed at secretory surface of a number of tissues, including biliary canaliculi, proximal tubules of the kidney, intestinal and colonic epithelium; hematopoietic stem cells express high levels of P-glycoprotein; overexpressed in many multidrug resistant cell lines and in tumour cells resistant to chemotherapy.

**Localisation**

Mainly at the cell membrane, with a secondary localisation at the Golgi apparatus.

**Function**

The P-glycoprotein is an energy-dependent efflux pump involved in extrusion of many types of lipophilic compounds; it may acts in normal tissues as a protective mechanism against noxious xenobiotics and as a transporter of endogenous substrates; in tumour cells, the drug efflux pump results in a decrease in intracellular drug concentration.

**Homology**

Closely related gene to MDR3 (also called PGY3), located at the same chromosomal site but not implicated in multidrug resistance; there are 3 murine homolog genes (mdr1, mdr2, mdr3) out of which only 2 (mdr1 and mdr3) are involved in multidrug resistance; member of a large superfamily of transmembrane transporter proteins named ATP Binding Cassette (ABC) transporters or Traffic ATPases; structural homology with other ABC transporter proteins (CFTR, MRP).

**Implicated in**

**Tumour cells resistance**

**Disease**

Tumour cells resistance to a wide variety of antineoplastic agents: doxorubicin, daunorubicin, vinblastine, vincristine, colchicine, actinomycine D, etoposide, teniposide, mitoxantrone, homoharringtonine; this phenomenon is named 'multidrug resistance' (MDR); P-glycoprotein is the main protein responsible for the MDR phenotype;
however, other agents may be involved in MDR, independently or in association with P-glycoprotein: "multidrug resistant associated protein" (MRP), "lung resistance protein" (LRP), 'anthracycline associated resistance protein" (ARX).

Leukemias

Disease
In leukemia, MDR1 overexpression is observed in patients with a lower complete remission rate and with a shortening of overall survival; frequently associated with intermediate and poor prognosis karyotype; in ANLL, approximately 50% of patients are MDR positive at diagnosis (range 22-70%) and the MDR phenotype is more frequently observed in CD34+ leukemias; in ALL, the average number of MDR-positive cases is 22% at diagnosis.

Tumour cell lines

Note
In numerous continuous tumour cell lines which acquired experimentally a MDR phenotype when cultured with progressively increasing drug concentration, the acquisition of MDR was associated with hyperexpression of P-glycoprotein; for the higher levels of expression, southern blots revealed an increase in the number of copies of the MDR1 gene per cell.

Cytogenetics
The genomic amplification of MDR1 appears as extrachromosomal 'double-minute chromosomes' (DM) or intrachromosomal 'homogeneous staining regions' (HSR).

Oncogenesis
Amplification.

References


Schoenlein PV, Shen DW, Barrett JT, Pastan I, Gottesman MM. Double minute chromosomes carrying the human multidrug resistance 1 and 2 genes are generated from the dimerization of submicroscopic circular DNAs in colchicine-selected KB carcinoma cells. Mol Biol Cell 1992 May;3(5):507-20.


