The role of *MDR1* polymorphisms in multidrug resistance

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Introduction

Multidrug resistance:

- Many tumors show initial resistance to chemotherapy or acquired in the course of treatment, which is the major obstacle in curing these cases.
- Chemotherapy is widely used as a treatment modality in oncology, but their effectiveness has been limited due to the existence of multidrug resistance.
- Although there are several genes involved in this phenomenon, one of the most important genes in pharmacogenetics and chemotherapy is *MDR1* gene because many drugs used as antitumor agents are substrates for P-Glycoprotein (P-gp), *MDR1* encoded protein.

General goals:

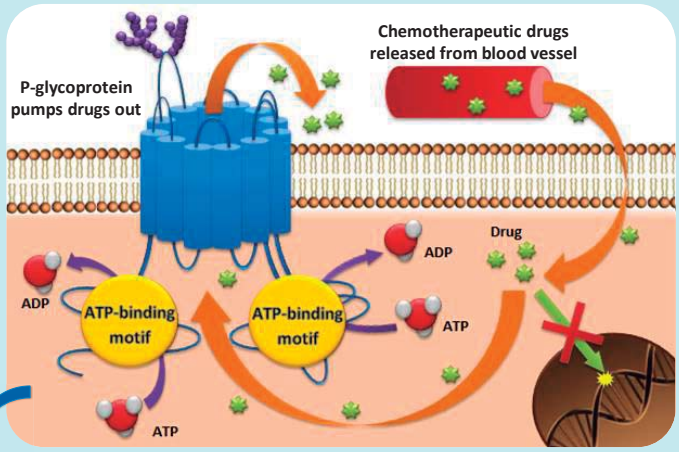
- Develop a bibliographical research about *MDR1* gene, involved in multiresistance phenomenon, and polymorphisms that generate variations in response to chemotherapy.

Specific goals:

- Determine the structure and clinically relevant substrates of P-glycoprotein (P-gp).
- Determine the polymorphisms that have been identified in the coding sequence of *MDR1* gene.
- Relate the presence of the most studied polymorphisms with the expression and function pf P-gp, and his clinical behavior en patients with leukemia, specifically in acute lymphocytic leukemia (ALL).
- Identify an additional treatment for leukemia that avoids multiresistance and toxicity.

MDR1 encoded protein

P-glycoprotein:

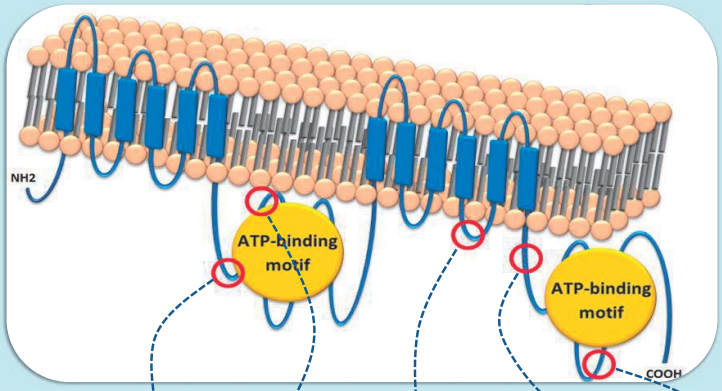


ATP-dependent efflux pump with broad substrate specificity that is capable of removing cytotoxic agents from inside the cell, allowing resistance to chemotherapy.

Genetic variants

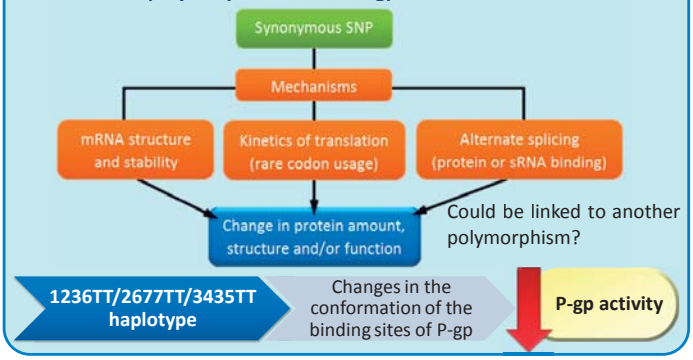
SNPs associated with altered P-gp functionality and expression:

- Genetic variations affect the interindividual variability of drug pharmacokinetics. For that reason, *MDR1* has been extensively studied, with at least 50 SNPs identified



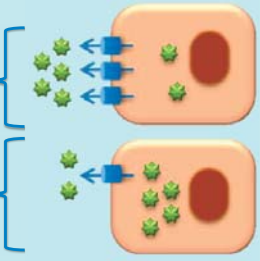
SNP	G1199A	C1236T	G2677T/A	G2995A	C3435T
Exon	11	12	21	24	26
Position	400	412	893	999	1145
Change	Ser to Asn	Ser to Ala	Ala to Ser/Thr	Ala to Thr	Ile to Ile
Clinical association	AA lower activity	CC lower prognosis	GG, GA, AA lower prognosis	No significant effect	TT lower level of expression

How C3435T polymorphism affects P-gp?



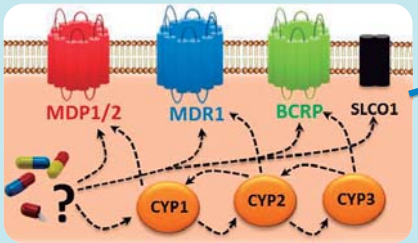
Clinical relevance of C3435T variants:

3435CC	Eliminates substrates with **high** efficiency
	Poor prognosis and lower event-free survival (EFS)
3435TT	Eliminates substrates with **low** efficiency
	Better prognosis
	Higher risk of developing ALL



Conclusion

- The final phenotype is defined by the whole drug efflux transporters, in conjunction with metabolism enzymes like CYPs.



These interactions could explain the variability of response

- Despite some conflicting results in clinical trials and the interindividual differences between ethnic groups, the importance of the *MDR1* gene in chemotherapy response is undeniable.

P-gp expression
P-gp activity
P-gp amplification

Prognosis

Identified problems:

- ✕ Despite the survival of patients affected by hematological malignancies being improved in the last years by chemotherapy, a significant amount of patients still relapse.
- ✕ Treatment is limited by toxicity and is constrained by the plateau of efficacy, while the pipeline of new chemotherapeutic drugs is running short.

We need second-line treatments more specific and less toxic for the patient

Proposed solutions:

PERSONAL TERAPHY BASED ON BIOMARKERS

✓ Detect polymorphisms associated with cell toxicity to develop personalized therapies according to the patient genotype to avoid toxicity.

GENE THERAPY AND IMMUNOTHERAPY

✓ T cells with Chimeric Antigen Receptors (CARs) can eradicate leukemic cells and perform a CD19-specific immune response in blood and bone marrow, showing a complete remission in the majority of patients.