

MECHANISMS OF RESISTANCE TO ANTI-TUMOR THERAPY

Chemotherapy is one of the most widely used treatments for neoplasias, but genomic instability in cancer cells leads to treatment resistance and tumor progression.

OBJECTIVES

Review the **molecular routes** through which tumor cells become resistant to chemotherapy, **classify** mechanisms in multi-drug or specific and **contribute** to the knowledge in veterinary oncology to improve antitumor treatments.

METHODOLOGY

Keywords: Chemotherapy, Drug, Resistance, Mechanisms, Cancer.

Inclusion criteria: Reviews, systematic reviews, scientific articles and books of thematic relevance.

Sources: PubMed, UAB Virtual Library.

MECHANISMS OF RESISTANCE TO ANTI-TUMOR THERAPY

Multi-drug resistance (MDR) mechanisms

1. Reduction of entry through the cell membrane
due to a rigid membrane and mutations or decreased expression of receptors and transporters.

2. Expulsion of drug through the cell membrane
due to ABC transporters, which expel xenobiotics through ATP hidrolisis.

3. Diminished activation of prodrug or increased metabolism of drug
due to decreased or increased expression of phase I and II enzymes, respectively.

4. Apoptosis inhibition
due to increased antiapoptotic and decreased proapoptotic proteins, caspase inactivation or mutation of p53.

Specific mechanisms

5. Drug target alteration
mutations or decreased expression.

6. Increased DNA repair
due to increased expression of rate limiting proteins.

7. Compensation of inhibited pathways
due to constitutive activation of proteins of the inhibited survival pathway or activation of redundant pathways.

Other mechanisms

8. Epigenetics determine the expression of genes involved in resistance mechanisms.

9. Tumor microenvironment (TME) acts as a physical barrier, contains cytokines and GF that induce resistant mechanisms and promotes angiogenesis.

10. Cancer Stem Cells (CSCs) have MDR phenotype and ilimited self-renewal, giving place to recurrences of the tumor.

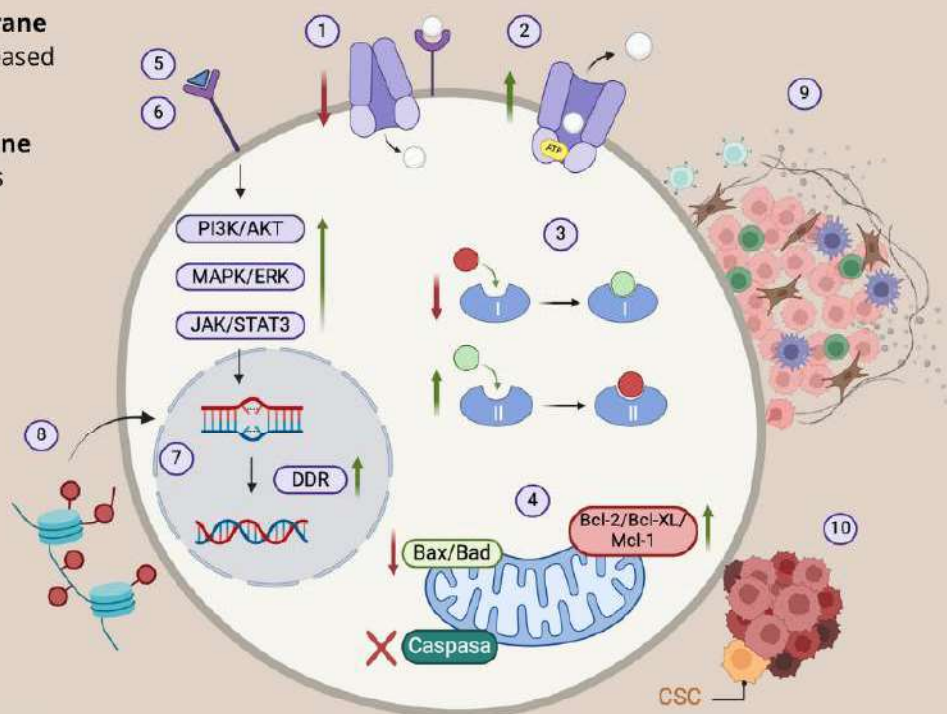


Fig 1. Overview of chemotherapy resistance mechanisms.
(Own creation with BioRender)

Most of this methods have also been described in companion animals

CONCLUSIONS

- Due to the increase in the prevalence of resistant cancers, **more research** of the molecular basis of resistance is required in order to help the pharmaceutical industry to develop new antitumor treatments.
- Combination of cytotoxic drugs** with different mechanisms of action is the most effective chemotherapeutic approach, as it minimizes resistance appearance.
- Lack of information of resistance to antitumor therapy in companion animals makes it difficult to understand resistance in these species.

BIBLIOGRAPHY

- Lei, Z. et al. (2023) 'Understanding and targeting resistance mechanisms in cancer', MedComm, 4(3), p. e265. Available at: <https://doi.org/10.1002/mco2.265>.
- Vaidya, F.U. et al. (2022) 'Molecular and cellular paradigms of multidrug resistance in cancer', Cancer Reports, 5(12), p. e1291. Available at: <https://doi.org/10.1002/cnr2.1291>.
- Weinberg, R.A. (2014) The Biology of cancer / Robert A. Weinberg. 2nd ed. New York: Garland Science.