Targeted therapy resistance

- Biomimetic extracellular vesicles derived from chimeric antigen receptor monocytes to treat glioblastoma: An efficient and safe intranasal drug delivery nanoplatform
- Protein lactylation and immunotherapy in gliomas: A novel regulatory axis in tumor metabolism (Review)
- NRF2 pathway activation predicts poor prognosis in lung cancer: a cautionary note on antioxidant interventions
- Striatal interdependencies in focal seizures: Insights from stereoelectroencephalographic functional connectivity analysis
- Asymmetric Cingulum Bundle Connectivity Is Modulated by Paracingulate Sulcus Morphology
- Radio-chemotherapy and metformin selectively modulate the heterogeneous landscape of glioma with ribosome biogenesis, long non coding RNA and immune-escape markers as major player
- Liquid biopsy in early detection and monitoring of CNS metastases
- Deep brain stimulation for epilepsy: A systematic review and meta-analysis of randomized and non-randomized studies of thalamic targeting

Targeted Therapy Resistance refers to the phenomenon where cancer cells that initially respond to targeted therapy (drugs designed to inhibit specific molecular pathways or mutations driving the cancer) become unresponsive or less responsive over time. This is a major challenge in oncology.

Here’s a structured breakdown:

 Mechanisms of Targeted Therapy Resistance Genetic Alterations

Secondary mutations: New mutations in the drug target that prevent binding (e.g., T790M mutation in EGFR in NSCLC).

Gene amplification: Overexpression of the target or alternate pathways (e.g., MET amplification after EGFR inhibition).

Bypass Signaling Pathways

Cancer activates alternative growth pathways (e.g., PI3K/AKT/mTOR, MAPK) to maintain proliferation.

Phenotypic Changes

Epithelial-to-mesenchymal transition (EMT): Cells become more invasive and less sensitive.

Histologic transformation: Example—NSCLC transforming into small cell lung cancer.

Tumor Microenvironment (TME)

Stromal cells, immune cells, and cytokines in the TME can protect tumor cells from drugs.

Drug Efflux and Metabolism

Increased expression of efflux pumps (e.g., P-glycoprotein) reduces intracellular drug concentration.

 Examples in Clinical Practice EGFR inhibitors in lung cancer → Resistance via T790M or MET amplification.

BRAF inhibitors in melanoma → Reactivation of MAPK pathway.

ALK inhibitors → Resistance via ALK mutations or bypass tracks like EGFR or KIT.

 Strategies to Overcome Resistance Next-generation inhibitors

E.g., Osimertinib for EGFR T790M mutations.

Combination therapies

Targeting primary and bypass pathways simultaneously.

Immunotherapy

Can be used when targeted options are exhausted.

Biopsy and molecular profiling at progression

Essential for understanding mechanisms and adapting treatment.