The challenge of multiple drug resistance (MDR) in the successful treatment of cancer

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Background

- Cancer is a major problem today due to its ever-changing dynamics (heterogeneity). What adds to this complication is the phenomenon of multiple drug resistance (MDR). MDR is the phenomenon where the complex mechanisms involved in cancer results in resistance against structurally unrelated compounds.
- The overall aim of this study is to explore how MDR and the mechanisms/ factors leading to this phenomenon play a role in preventing the successful treatment of cancer.
- Lung cancer represents a highly heterogenous disease displaying an MDR phenotype, hence we look at the development of *in vitro* drug resistant lung cancer models used to study MDR in this cancer type. New /novel approaches under investigation for overcoming MDR are also explored.

Key Findings

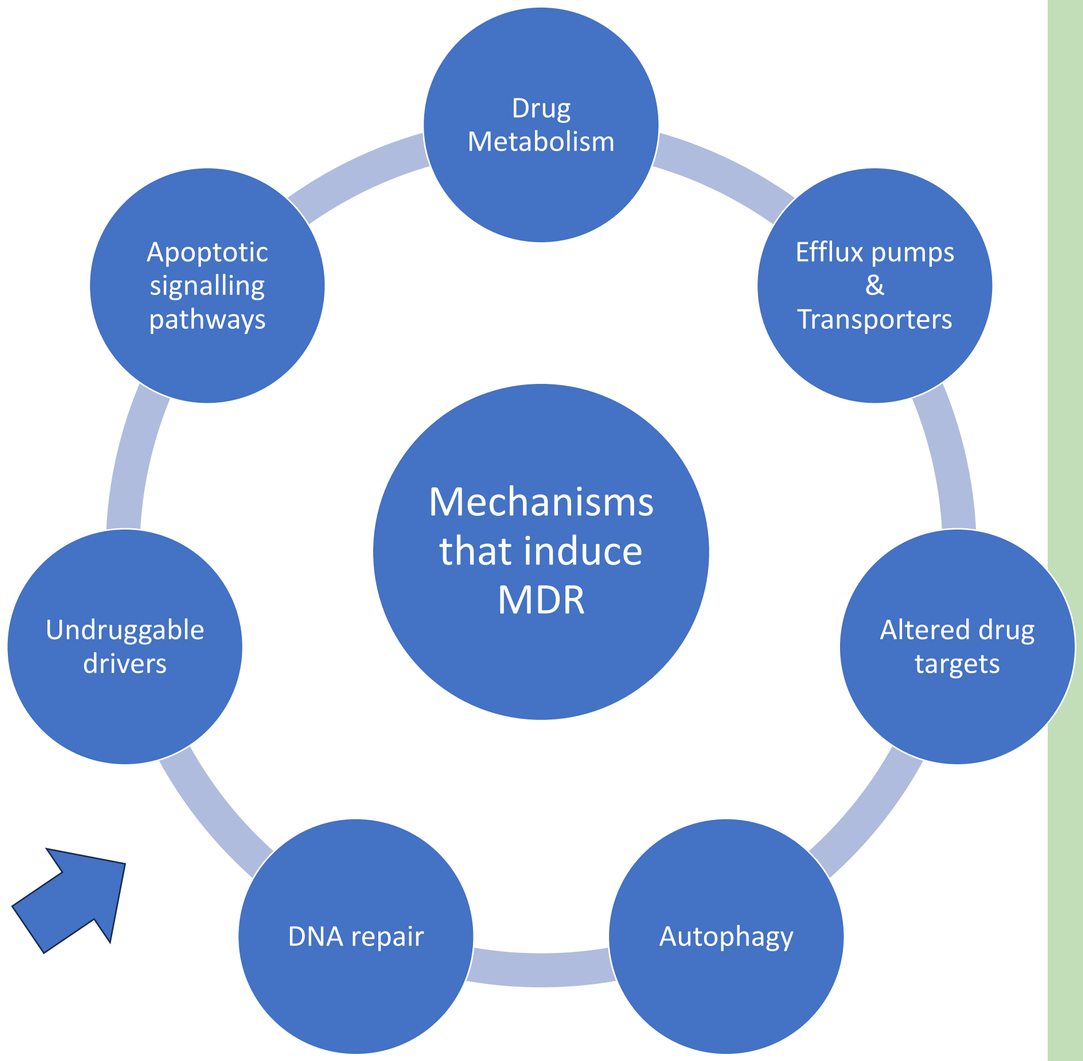
1. Mechanisms that induce MDR are summarized in Figure 1
2. It is also observed that inter/intra tumoral heterogeneity being a major challenge in the successful treatment of cancer (Lung cancer models used please see table 1).
3. The use of *in vitro* models along with *in vivo* models can greatly help in exploring for treatment options.

Research Methodology

- This study was conducted by extracting relevant datasets and recent research papers using the advanced filters/search options on PubMed. Key words for each section such as "cancer, *in vitro* models, multiple drug resistance, and mechanisms" where utilized to find the most relevant information.

Cancer heterogeneity refers to differences within cancer cells and tumour microenvironment, which contributes to treatment failure. Tumours exhibit genetic, epigenetic, transcriptomic, and proteomic diversity, making it challenging to predict drug response and choose effective therapies.

- **Intrinsic resistance**: e.g., low HER2 amplification & high P-glycoprotein expression (pumps out).
- **Acquired resistance:** e.g., overuse of chemotherapeutics.
- **Intra tumour heterogeneity** varies within a tumour.
- **Inter tumour heterogeneity** varies among different tumours.



Lung Cancer *In Vitro* Models

- Drug Selection strategy : pulsed or continuous.
- Cell line examples: A549, H460, SBC-3.
- Chemotherapy agents' example: cisplatin, mitoxantrone, taxol.
- There are 31 different chemoresistant lung cancer cell lines that have been developed using 17 different chemotherapy drugs at dose ranges of 2ng/ml-2000ng/ml, 1ug/ml-250ug/ml from both pulsed/continuous selection strategies.

Table 1: Published research on PubMed for Lung Cancer cell line models along with the type of chemotherapy drugs used, dosage, and treatment intervals to examine resistance.

Cell line name	Chemotherapy Drugs used	Dosage	Treatment Intervals
A549	Cisplatin (CDDP).	5-20μM	6-24 hours
A549	Paclitaxel (Taxol)	5-20μM	6-24 hours
H460	Cisplatin (CDDP)	5-20μM	6-24 hours
H460	Paclitaxel (Taxol)	5-20μM	6-24 hours
SBC-3	NB-506	2.5-250μg/ml	24 hours
SBC-3	SN-38	0.1-10nM	2-4 weeks
SBC-3	Adriamycin	10^{-10}M-5x10^{-8}M	NA
SBC-3	Adriamycin	0.05uM-5μM	NA
H69	Okadaic acid	NA	NA
A549	Taxol	175nm, 11.7nM, 175nM, 58.3nM	4hours once a week for 10 weeks

Conclusion & Future Directions

- *In vitro* models represent excellent models to study drug resistance mechanisms across different cancer types.
- Many challenges arise with heterogeneity being a major problem. Therefore, personalized medicine approaches along with potential biomarker identification could offer prognostic/ therapeutic potential.
- New/ current approaches aimed at overcoming MDR should include combination therapy and nanomedicine approaches.

References

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