Nanotechnology to Overcome Cancer Drug Resistance

Muriel Freixanet Gustà[1]

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide and it is expected to become the leading cause of death in the coming decades. Although major advances have been achieved in the field of cancer treatment, multi-drug resistance (MDR) and relapse are still frequent. Initially, MDR was related only to efflux transporters, drug kinetics and regulation of drug targets; however, more recent studies revealed that tumor heterogeneity is a major driver.

Current anticancer therapies mainly include chemotherapy, radiotherapy or surgery, and so far alone or in combination fail to eradicate MDR-cells, which ultimately leads to relapse. Nanotechnology offers a novel set of smart drug delivery systems with unique physcochemical properties that enable to actively target MDR-cells and overcome drug resistance with combination therapy.

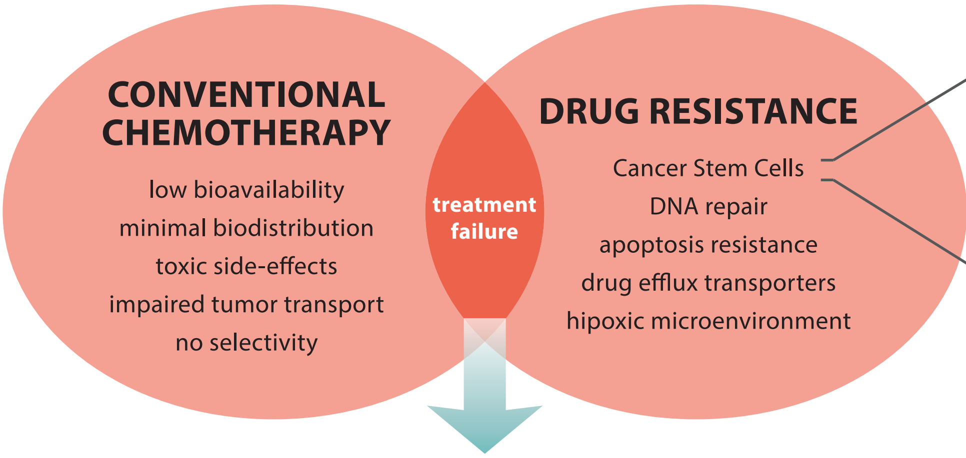
Aims

- Present the burden of cancer therapy failure due to drug resistance.
- Analyse the main factors triggering drug resistance in conventional chemotherapy.
- Expose the novel alternative nanotechnology-based approaches and their key role in overcoming drug chemoresistance.

Material and Methods

- Scientific literature searched using Pubmed and Scopus platforms, based on impact factor 6 or higher and published from 2005.
- Additional information was extracted from assitance to conferences, interviews with researchers, meeting reports or PhD thesis.

Results



The **Cancer Stem Cells** (CSC) hypothesis assumes a hierarchial tumor organization, where only a small subset of cells has tumorigenic capacity and is the responsible to maintain tumor heterogeneity. CSC share some properties with normal stem cells, like intrinsic resistance, and they have also been related to tumor initiation, progression, metastases and relapse.

CANCER NANOTECHNOLOGY

Drug nanocarriers

The use of nanovehicles in drug delivery provides a new approach that offers solutions to some of the problems associated to the systemic delivery of the conventional chemotherapy. Nanocarriers can protect a drug from degradation by evading the reticuloendothelial system (RES) and, thus, a high blood circulation profile enables transport through biological barriers, increasing the availability of drug at the targeted site and reducing the toxicity and other side effects.

Many types of nanoparticles are suitable to be used as nanocarriers when they have been properly functionalized and made biocompatible to perform drug delivery, depicted in Figure 1.

These drug delivery systems can be tuned at the nano scale and rationally designed to achieve personalized features as: specific targeting, controlled release of the payload and co-delivery of two or more therapeutic agents, and theranostics.

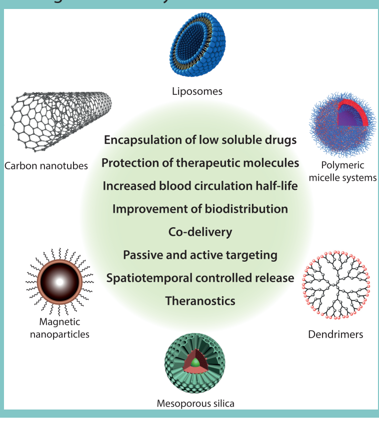


Figure 1. Examples of some of the main classes of nanoparticles that can be used for drug delivery.

Combination therapy

Combination therapy is usually defined as the use of two or more agents co-delivered simultaneously or a combination of different therapies. Since drugs differ in pharmacokinetic and pharmacodynamics properties, the target cells or tissues might not synchronously receive the optimal levels of each therapeutic agent if administrated systemically. However, the use of a nanocarrier to deliver them simultaneously allows for a better spatiotemporal control. These smart delivery systems enable to: (i) effectively combine the main therapeutic agent with another molecule that can block any level of MDR, and (ii) target selectively CSC. Acting on the signalling pathways and the factors of the microenvironment that induce MDR makes possible to overcome either intrinsic CSC or acquired resistance and would significantly improve the treatment outcome.

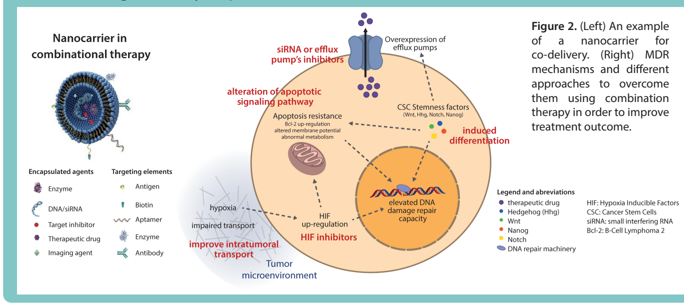


Figure 2. (Left) An example of a nanocarrier for co-delivery. (Right) MDR mechanisms and different approaches to overcome them using combination therapy in order to improve treatment outcome.

Conclusions

- Despite remarkable progress made in prevention, diagnosis and treatment, efficient cancer therapies remain elusive.
- The major causes that lead to treatment failure are: late stage diagnosis, and the lack of adequate approaches to treat metastases and tumor resistance.
- Tumor heterogeneity is the major trigger to cancer multi-drug resistance; where cancer stem cells play a major role in cancer initiation and progression, resistance, recurrence and metastases.
- Novel approaches based on nanotechnology provide great advances and offer new perspective into early diagnosis, therapies and cancer resistance.
- Nanocarriers have unique features that significantly improve drug delivery.
- Combinational nano-based therapies enable to overcome any level of drug resistance and effective targeting to cancer stem cells.

[1]Universitat Autonoma de Barcelona
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