International Journal of Pharmaceutics 533 (2017) 111–124

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Co-delivery strategies to overcome multidrug resistance in ovarian cancer

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ARTICLE INFO

Keywords:
Co-delivery
Drug efflux pump
Drug targeting
Multi-drug resistance
Multifunctional nanocarriers
Ovarian cancer

ABSTRACT

Cancer is one of the leading causes of death and equally strikes both genders. Among women, ovarian cancer is responsible for many deaths as it remains symptomless in the earlier stages and generally diagnosed in third stage. At this point it becomes difficult to carry out de-bulking surgery and treatment with different chemotherapeutic drugs has shown resistance, a phenomenon known as multidrug resistance (MDR). Different treatment choices are available for ovarian cancer; however, this article only focuses on various co-delivery strategies, where two different agents are encapsulated in a single carrier and act via different pathways to overcome cancer cell resistance. Ovarian cancer develops MDR via different pathways but majorly involving pump and the non-pump mechanisms in most cases. To overcome MDR it is imperative to strike malignant cells from various directions. Nanocarriers are known to strike the pump mechanism by avoiding the drug efflux pump located on cellular membrane. The efflux pump can also be blocked by blocking activity of ATP binding cassette (ABC) membrane transporters. To stop the non-pump mechanism one can use chemosensitizers, genes, apoptotic factor and others. Treatment of cancer cells could even more effective if the drug is combined with co-agents in a single carrier with targeting moiety. These co-agents along with nanocarriers, allow the drug to accumulate in high enough concentrations in ovarian cancer cells to kill them without affecting normal cells.

1. Introduction

Cancer remains as one of the most studied and deadliest disease worldwide. It is the second leading cause of death worldwide and it has been estimated that 1 in every 7th death is due to cancer (Torre et al., 2015). Cancer results from accumulation of serval irreparable mutations in otherwise normal cells. Thus, the control mechanisms that will prevent uncontrolled division and cell overgrowth are disabled (Weinberg, 2013). Since there are many types of cancers, various treatment approaches are available, those can be used stand alone or in combination (Urruticoechea et al., 2010).

Delivery of drug molecules at the site of action or their physiological targets (such as receptors) is necessary to achieve therapeutic effects in humans (Bae and Park, 2011; Khan et al., 2013; Petrak, 2005). However, reaching the target site is not often straightforward, and requires specialized delivery systems in order to localize and drop their load exactly where demanded. Furthermore, to be an effective drug delivery system, it is necessary to control certain attributes such as degradation of carrier system after delivering the active ingredient, releasing the drug at a specified rate, site of drug release and eventually expulsion from the body (Bae and Park, 2011). Such events are even more important when the host of a delivery system is an anticancer agent. The majority of anticancer drugs fail to destroy the malignant cells because of a number of reasons, the important one is the development of resistance against chemotherapeutic agents (Xavier et al., 2016). To date, different mechanisms are thought to be accountable for drug resistance against chemotherapy including, a) Multidrug efflux pumps: In 1976 it was discovered that MDR is related to over expression of a single protein encoded by the gene ATP binding cassette (ABC), subfamily B, member 1 (ABCB1/P-gp; also known as MDR1) and is involved in

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http://dx.doi.org/10.1016/j.ijpharm.2017.09.060
Received 3 August 2017; Received in revised form 20 September 2017; Accepted 21 September 2017
Available online 22 September 2017
0378-5173/

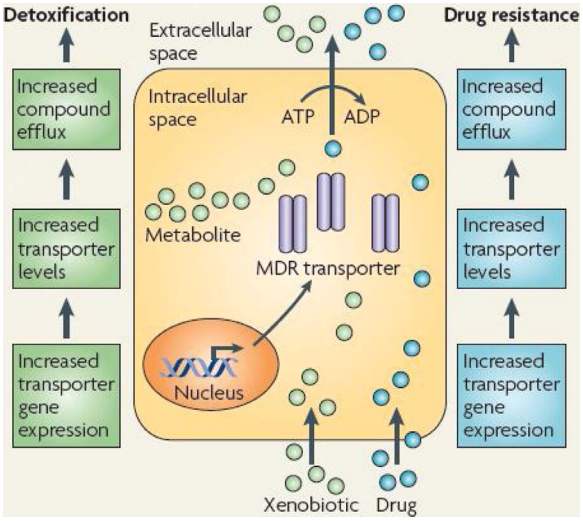

Fig. 1. ABC transporters in cells and are responsible for detoxification and cancer drug resistance in malignant diseases.
Reproduced with permission from Nature Publishing Group (Fletcher et al., 2010).

treatment failure of liver cancer, kidney cancer, colon cancer, lymphomas and leukaemia. Later on ABCC1/MRP1 (responsible for drug resistance in prostate, lung and breast cancer) and ABCG2 also known as BCRP (causes resistance in breast cancer and leukaemia) were discovered. A key role of ABC transporter is protection of cells from toxic molecules entering cell by diffusion or active uptake (Fig. 1). This protective mechanism is responsible for cancer cell resistance against chemotherapeutic agents (Fletcher et al., 2010). b) Changes in lipid metabolism (ceramide pathway), c) enhanced drug elimination by detoxification mechanism, d) decrease in drug influx by altered surface receptors/carriers, e) inactivation of drugs via glutathione mediated reduction, f) enhanced DNA repair capacity of cancer cells, induced by drugs, g) reduced ability to undergo apoptosis and over-expression of antiapoptotic genes in cancer cells due to chromosomal abnormalities, and h) altered drug targets such as topoisomerase II (Iyer et al., 2013; Jabr-Milane et al., 2008; Kapse-Mistry et al., 2014; Markman et al., 2013).

2. Strategies to overcome MDR in cancer

In chemotherapy one of the major issues is multidrug resistance against different anticancer drugs such as the taxanes (docetaxel and paclitaxel), vinca alkaloids (vinorelbine, vincristine, and vinblastine), anthracyclines (doxorubicin, epirubicin, and daunorubicin), epipodophyllotoxins (etoposide and teniposide), antimetabolites (methorexate, fluorouracil, cytosar, 5-azacytosine, 6-mercaptopurine, and gemcitabine), dactinomycin, topotecan, and mitomycin C (Ozben, 2006). MDR is generally defined as a state of cancer cells where they become simultaneously resistant to different antineoplastic drugs with different molecular structures and targets. MDR could be due to multiple causes as described previously but largely divided into two different classes, namely pump and non-pump mechanisms. Non-pump resistance is mainly caused by cellular antiapoptotic defense mechanism involving Bcl-2 protein (Chen et al., 2009). This protein prevents, cytochrome *c* release from mitochondria and is required to trigger caspase cascade for execution of apoptosis (Pakunlu et al., 2004).

The prime cause of pump resistance is an overexpression of ATP-binding cassette membrane transporters and is considered as the major contributor for MDR. So far, scientists have identified 48 MDR genes from ABC transporter super family (Chen et al., 2009; Ozben, 2006; Saraswathy and Gong, 2013). Therefore, one strategy is modulation of multidrug resistance efflux pump by using MDR inhibitors or MDR

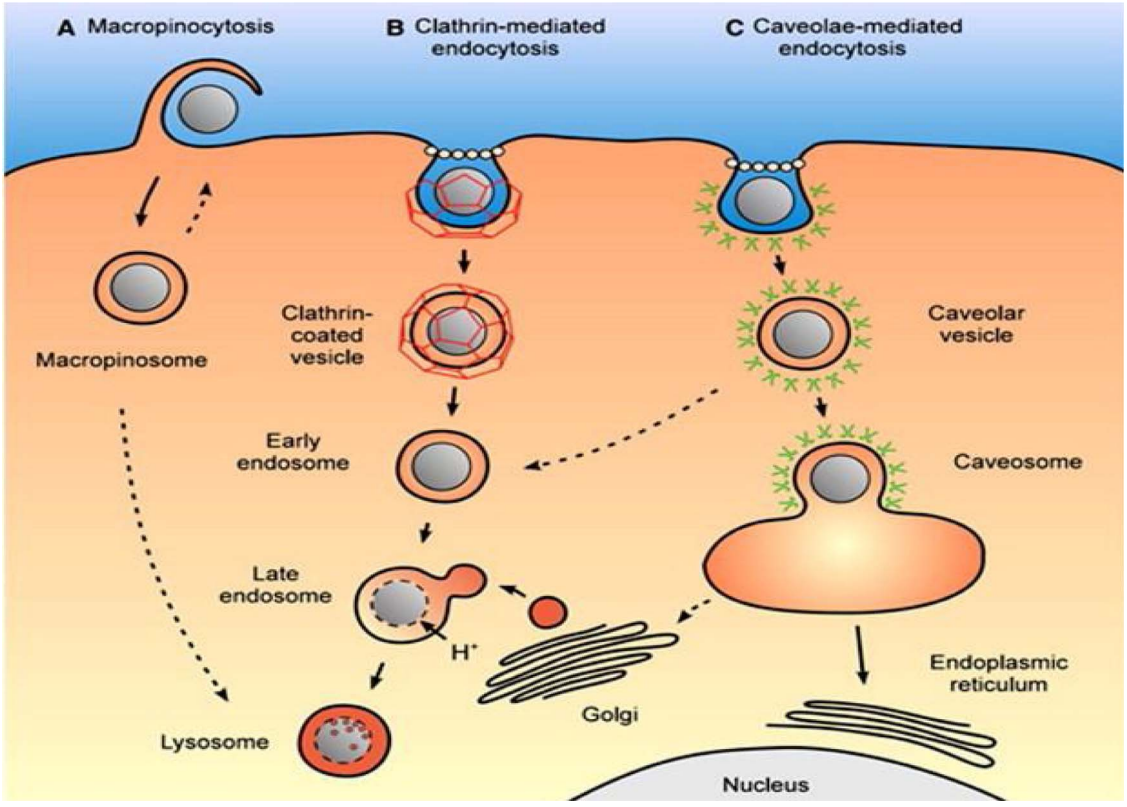

Fig. 2. Intracellular uptake of various nanocarriers via four different endocytosis mechanisms a) macropinocytosis, b) clathrin-mediated endocytosis, c) caveolae-mediated endocytosis, and d) clathrin- and caveolae-independent endocytosis (d is not shown in Figure).
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