Available online on 15.11.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Mini Review

Mini Review: Modulating cytotoxicity effects in Cancer Drug Delivery

Hao Wu[1, 2, 3, 4]

[1]School of pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, P. R. China
[2] Jiangsu Key Laboratory of Chinese Medicine Processing, Nanjing University of Chinese Medicine, Nanjing 210023, P. R. China
[3] Engineering Center of State Ministry of Education for Standardization of Chinese Medicine Processing, Nanjing 210023, P. R. China
[4] State Key Laboratory Cultivation Base for TCM Quality and Efficacy, Nanjing University of Chinese Medicine, Nanjing 210023, P. R. China

ABSTRACT

A review of cytotoxicity associated with cancer treatments as presented in literature was discussed. In all the studies, the research is aware of the cytotoxic effects of the cancer drug and the delivery form such as nanotechnology-based delivery. The scope of the review was limited to showing 1) the need for modulating cytotoxicity and 2) how cytotoxicity has been controlled in actual studies on treatment plans in vivo and in vitro.

Keywords: Cytotoxicity, *in vivo*, *in vitro*, nanotechnology, nanoparticles, apoptosis

Article Info: Received 04 Oct, 2018; Review Completed 10 Nov 2018; Accepted 12 Nov 2018; Available online 15 Nov 2018

Cite this article as:

Wu H, Mini Review: Modulating cytotoxicity effects in Cancer Drug Delivery, Journal of Drug Delivery and Therapeutics. 2018; 8(6):272-274 **DOI:** http://dx.doi.org/10.22270/jddt.v8i6.2054

Introduction

Cytotoxicity is the action of a cytotoxic compound on a cell that the cell will either undergo necrosis by the loss of the integrity of their membrane, followed by its rapid death, or is guided to the pathway of apoptosis or autophagy[1-5]. Cytotoxic drugs or cytostatics are used for the treatment of cancer where they destroy the cancer-causing cells. By inhibiting cell division, this process of cell destruction is started. While cytotoxic drugs used to reduce metastases help control the spread of cancer and effectively act upon primary and secondary tumors, the drugs also have an effect on surrounding healthy cells[6-12]. Effect on normal cells is less pronounced compared to cancer cells, and yet in the case of aggressive tumor conditions, the effect on normal cells is also higher, either killing them or necessitating more time for the healthy cells to recover. In this context, research works aim to identify how cancer can be treated by controlling cytotoxicity. This work reviews the effects of modulating cytotoxicity effects in cancer drug delivery by looking up research works on the same[13-19].

Cytotoxicity and Treatment Efficacy

The use of nano-technology based medication delivery has been heralded as an optimal solution for cancer treatment. However, cytotoxicity has to be banked against efficacy. The drug that cures should not be the drug that also induces a new issue. All nanomedicines have some amount of cytotoxicity associated with them and hence the therapeutic effect or treatment efficacy to toxicity should always be monitored and modulated[20-24]. In vitro and in vivo, studies have been conducted to asses this modulation. It was identified that larger surface areas of treatments with nanoparticles could result in heightened and severe cytotoxicity. Nanoparticles used in cancer treatment in rats showed that it caused lung tumors as a side effect-the cytotoxicity. Smaller nanoparticles hence are considered more toxic than an equivalent chemical compound. Hence cytotoxicity has to be managed.

Managing Cytotoxicity

Han et al., analyze combination cancer therapy in the form of multiple anticancer agents delivered via a nanomicelle amphiphilic dendrimer AmD. This combination cancer therapy with nanotechnology form of delivery was observed to offer reduced cytotoxicity in-vitro and synergistic results for the patient. In-vitro cancer activity was checked on MDA-MB-231 cells with 5-FU/DOX-DNM. The cells were treated with an application of the drug mixture in different amounts. The 5-Fu/DOX-DNM, DOX-DNM, 5 Fu-DNM, free dox, and free 5-Fu were used to stain the cells and absorbance was measured in order to understand cytotoxicity. The drug release time curves were mapped for all the drug forms used at different pH levels and it was identified that Dox and 5-Fu in standalone forms were pH dependent, and only around pH 5.0, the drug was rapid release. The cytotoxicity levels of different formulations are presented below.

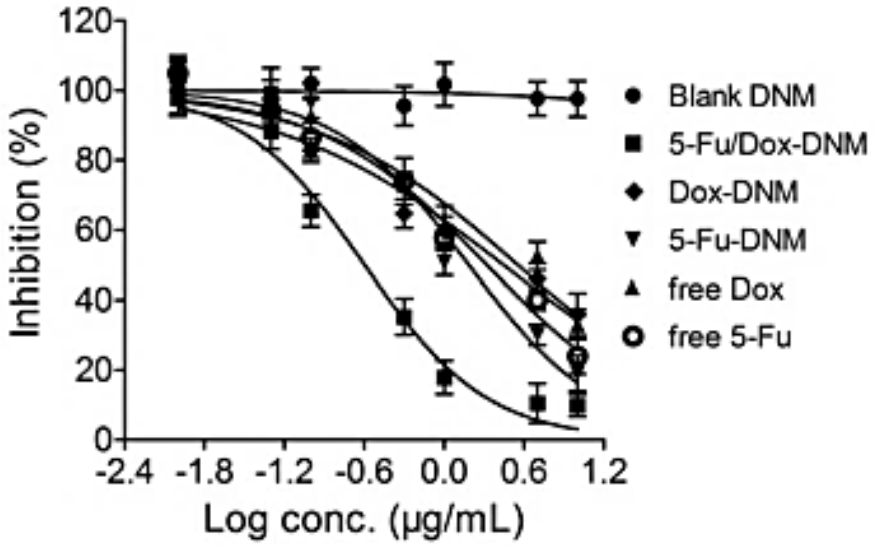

Figure 1: In vitro cytotoxicity of Different Formulations, (Han et al.,[2])

The micelle becomes positively charged at the same pH levels and electrostatic repulsion is created in the micelles as well, accelerating drug release. 5-Fu release was faster. The particle size of the 5-Fu/Dox was stable under normal pH conditions. In terms of cellular uptake after releasing it was identified that the 5-Fu/Dox-DNM, 5-Fu-DNM, and Dox-DNM showed a more rapid intake with appropriate intracellular concentrations compared to the free 5-Fu and Dox-DNM group[25-29]. The use of multiple dendrimeter enhanced cell adhesion and disruption. In-vitro cytotoxicity showed that there was a much lower dose of the free Dox and free 5-Fu as compared against non-combination methods of delivery. The use of the drug-loaded micelles resulted in negligible cytotoxicity because the cells in tested concentration were biocompatible. The cationic dendrimeters furthermore were higher than the anionic dendrimeters and they served to shield the positive charges on dendrimeter surface, hence contribution decreased cytotoxicity. Similar results were also observed in the analysis of acute in-vivo toxicity in dendrimeters in melamine-based vehicles of drug delivery[30-33].

Kang et al., argue the use of nanotechnology for reduction of cytotoxicity. "Cytotoxicity, distribution and the ability to cross the BBB are some of the most significant obstacles involved in chemotherapy for brain tumors. Nanotechnology has been widely exploited in drug delivery, with a tremendous potential for improving drug efficiency and efficacy". However, the researcher notes that the use of nano-technology could, in fact, result in more cytotoxicity, and hence nano-technology use has to be modulated in the following ways.

Firstly, it can be managed by managing its half-life, as this will decrease the amount of time that the nanoparticles spend in circulation or the short drug half-life can be extended in a targeted way to achieve treatment efficacy. Alternatively, cytotoxicity can be maintained by making use of only those compounds that are not cytotoxic. Elements like phospholipids, chitosan and dextran can be made use of in such situations.

Conclusion

Cytotoxicity is a serious concern when it comes to achieving efficient treatment plans. The very treatment plan for a cancer patient should not turn detrimental to their overall health. The issues in cytotoxicity are heightened in the case of aggressive concerns as well. Targeted deliveries and combination drug treatments are useful in controlling cytotoxic, but they carry a danger as well because all nanomedicines carry a certain amount of inherent toxicity. In this case, it is necessary to understanding how to control for cytotoxicity in treatment and this review focused on the different research evidence on modulation.

References

1. Kang, C., Qin, J., Osei, W. & Hu, K. Age-dependent Mitochondrial Targeting Of Protein Kinase C Epsilon In Cardioprotection. *The FASEB Journal* (2017).
2. Han, R., Sun, Y., Kang, C., Sun, H. & Wei, W. Amphiphilic dendritic nanomicelle-mediated co-delivery of 5-fluorouracil and doxorubicin for enhanced therapeutic efficacy. *Journal of Drug Targeting* 2017; **25**:140-148.
3. Sun, Y., *et al.* Co-delivery of dual-drugs with nanoparticle to overcome multidrug resistance. *European Journal of BioMedical Research* 2016; **2**:12-18.
4. Liu, F., Sun, Y. & Kang, C. Controlling Amphiphilic Functional Block Copolymers' Self-Assembly: From Structure to Size. (2016).
5. Song, L., *et al.* Crocetin inhibits lipopolysaccharide-induced inflammatory response in human umbilical vein endothelial cells. *Cellular Physiology and Biochemistry* 2016; **40**:443-452.
6. Sun, Y., Kang, C., Liu, F. & Song, L. Delivery of antipsychotics with nanoparticles. *Drug Development Research* 2016; **77**:393-399.
7. Kang, C., *et al.* Delivery of nanoparticles for treatment of brain tumor. *Current Drug Metabolism* 2016; **17**:745-754.
8. Xue, X., *et al.* Discovery of novel inhibitors disrupting HIF-1α/von Hippel–Lindau interaction through shape-based screening and cascade docking. *PeerJ* 2016; **4**:e2757.
9. Shuhong, X., *et al.* Dynamic expression of AQP4 in early stageof ischemia/reperfusion rats and cerebral edema. *Chinese Pharmacological Bulletin* 2016; **32**:1433-1441.

10. Peng, J., *et al.* Enhanced Liver Regeneration After Partial Hepatectomy in Sterol Regulatory Element-Binding Protein (SREBP)-1c-Null Mice is Associated with Increased Hepatocellular Cholesterol Availability. *Cellular Physiology and Biochemistry* 2018; **47**:784-799.
11. Yang, Z., *et al.* Functional exosome-mimic for delivery of siRNA to cancer: in vitro and in vivo evaluation. *Journal of Controlled Release* 2016; **243**:160-171.
12. Kang, C., Hernandez, V.A. & Hu, K. Functional interaction of the two-pore domain potassium channel TASK-1 and caveolin-3. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 2017; **1864**:1537-1544.
13. Waller, A.P., *et al.* GLUT12 functions as a basal and insulin-independent glucose transporter in the heart. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 2013; **1832**:121-127.
14. Li, Q., *et al.* Identification by shape-based virtual screening and evaluation of new tyrosinase inhibitors. *PeerJ* 2018; **6**:e4206.
15. Chen, Y., *et al.* Identification of 4-aminoquinoline core for the design of new cholinesterase inhibitors. *PeerJ* 2016; **4**:e2140.
16. Kang, C. & Hu, K. Impact of hypoxia in the expression and regulation of the TASK-1 potassium channel in cardiac myocytes. *The FASEB Journal* 2016; **30**:lb598-lb598.
17. Kang, C. *Ion channels, protein kinase C and caveolae in cardioprotection*, (The Ohio State University, 2015).
18. Yung, B.C., *et al.* Lipid nanoparticles composed of quaternary amine–tertiary amine cationic lipid combination (QTsome) for therapeutic delivery of AntimiR-21 for lung cancer. *Molecular pharmaceutics* 2016; **13**:653-662.
19. Cheng, X., *et al.* Lipid Nanoparticles Loaded with an Antisense Oligonucleotide Gapmer Against Bcl-2 for Treatment of Lung Cancer. *Pharmaceutical research* 2017; **34**:310-320.
20. Kang, C. & Hu, K. Modulation of the two-pore domain potassium channel TASK-1 by caveolin-3. *The FASEB Journal* 2015; **29**:845.814.
21. Kang, C., Sun, Y., Wang, M. & Cheng, X. Nanosized camptothecin conjugates for single and combined drug delivery. *European Journal of BioMedical Research* 2016; **2**:8-14.
22. Qiao, H., *et al.* Orally delivered polycurcumin responsive to bacterial reduction for targeted therapy of inflammatory bowel disease. *Drug Delivery* 2017; **24**:233-242.
23. Liu, F., Sun, Y., Kang, C. & Zhu, H. Pegylated Drug Delivery Systems: From Design to Biomedical Applications. *Nano LIFE* 2016; **6**:1642002.
24. Sun, Y., Kang, C., Yao, Z., Liu, F. & Zhou, Y. Peptide-Based Ligand for Active Delivery of Liposomal Doxorubicin. *Nano Life* 2016; **6**:1642004.
25. Qiao, H., *et al.* Redox-triggered mitoxantrone prodrug micelles for overcoming multidrug-resistant breast cancer. *Journal of drug targeting* 2018; **26**:75-85.
26. Kang, C., Qin, J., Osei, W. & Hu, K. Regulation of protein kinase C-epsilon and its age-dependence. *Biochemical and Biophysical Research Communications* 2017; **482**:1201-1206.
27. Sun, Y., *et al.* RGD Peptide-Based Target Drug Delivery of Doxorubicin Nanomedicine. *Drug development research* 2017; **78**:283-291.
28. Kang, C. & Hu, K. Role of caveolin-3 in adenosine-induced increase in mitochondrial PKCε. *The FASEB Journal* 2013; **27**:1191.1197-1191.1197.
29. Cheng, X. & Lee, R.J. The role of helper lipids in lipid nanoparticles (LNPs) designed for oligonucleotide delivery. *Adv Drug Deliv Rev* 2016; **99**:129-137.
30. Sun, Y. & Kang, C. Self-Assembly of Peptides into Hydrogel. *Journal of Organic & Inorganic Chemistry* 2016; **2**:5.
31. Yao, Z., Sun, Y. & Kang, C. Structure and self-assembly of multicolored Naphthalene Diimides Semiconductor. *Nano LIFE* 2016; **6**:1642007.
32. Cheng, X., *et al.* T7 Peptide-Conjugated Lipid Nanoparticles for Dual Modulation of Bcl-2 and Akt-1 in Lung and Cervical Carcinomas. *Molecular pharmaceutics* 2018; **15**:4722-4732.
33. Zhong, X., Sun, Y., Kang, C. & Wan, G. The theory of dielectrophoresis and its applications on medical and materials research. *European Journal of BioMedical Research* 2017; **2**:7-11.