In vivo investigation of inflammatory response of different doxorubicin formulations

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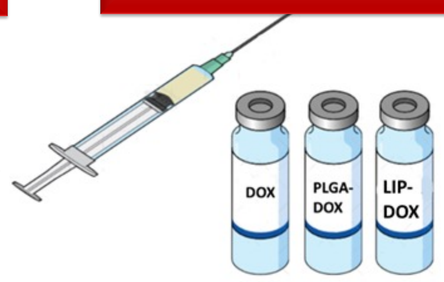
Introduction

Doxorubicin (DOX) is one of the most effective cytotoxic drugs against solid tumors and hematological malignant diseases. However, the clinical application of DOX is limited due to dose-related toxicity and inflammatory response [1]. Nanoformulation may significantly improve therapeutic outcomes by reducing the side effects and delivering DOX at tumor sites.[2].

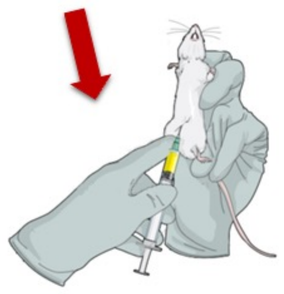
Aim of this study:

- evaluation of inflammatory response in rats administered intraperitoenally by three different DOX formulations – DOX as free compound solution, a novel delivery system based on poly(lactic-co-glycolic acid) (PLGA-DOX), and commercially available DOX encapsulated in liposomal nanoparticles (LIP-DOX)

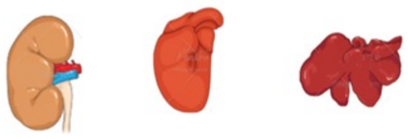
Methods



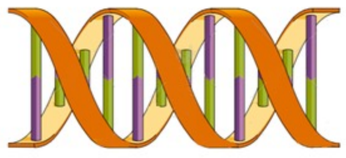
1 DOX administered in three different forms: DOX, PLGA-DOX and LIP-DOX



2 Different DOX formulations were injected intraperitoneally to male and female Wistar rats four times, once per week



3 Organs removed for analysis



4 RNA purification from isolated organs and reverse transcription to cDNA

5 Gene expression analyses of inflammation-related genes (IL-6, IL-8, TNFα and IL-1β) in tissues by Real-Time PCR

Primers used for PCR analysis:

IL-6	Forward	ATATGTTCTCAGGGAGATCTTGGAA
	Reverse	GTGCATCATCGCTGTTCATACA
IL-8	Forward	CTCCAGCCACACTCCAACAGA
	Reverse	CACCCTAACACAAAACACGAT
TNFa	Forward	GGCTGCCCCGACTATGTG
	Reverse	TGACTTTCTCCTGGTATGAAATGG
IL-1β	Forward	CCAGGATGAGGACCCAAGCA
	Reverse	TCCCGACCATTGCTGTTTCC

Results

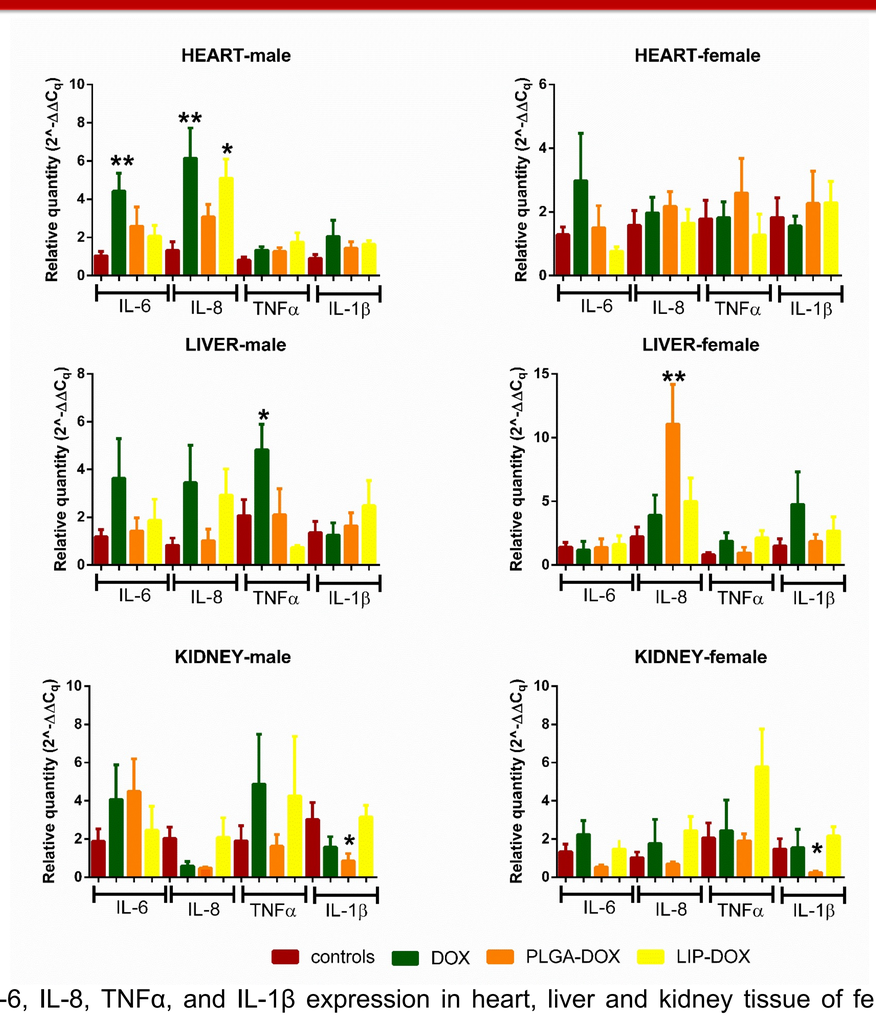


Figure 1. IL-6, IL-8, TNFα, and IL-1β expression in heart, liver and kidney tissue of female and male Wistar rats after the treatment with different DOX formulations. Relative quantification of expression was calculated using $2^{-\Delta\Delta Cq}$ method. Data are presented as means ± S.E.M. (N=8 for all treatment groups). Stastically significant differences between controls and treated animals ($p < 0.05$) are denoted with asterisks (*).

Conclusion

- Free DOX compound significantly increased expression of IL-6 and IL-8 in heart and liver tissue of male rats
- PLGA-DOX increased production of only IL-8 in liver tissue of female rats, but did not significantly elevate expression of other inflammation-related genes in other organs, which was similar to results obtained for LIP-DOX
- significant reduction of IL-1β expression in kidney tissue was noticed after administration of PLGA-DOX in both gender, as potential attenuation of inflammatory response
- novel PLGA-DOX formulation demonstrated lower inflammatory potential compared to commercially available and clinically used DOX and LIP-DOX

References

[1] Carvalho, C.; Santos, R.; Cardoso, S.; Correia, S.; Oliveira, P.; Santos, M.; Moreira, P. *Curr. Med. Chem.* **2009**, *16*, 3267–3285.
[2] Olusanya, T. O. B.; Ahmad, R. R. H.; Ibegbu, D. M.; Smith, J. R.; Elkordy, A. A. *Molecules* **2018**, *23*, 1–17.

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