



The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)

01-30 NOVEMBER 2022 | ONLINE

In the heart of cardio-oncology: the targets and biomarkers of anticancer drugs cardiotoxicity

Chaired by **DR. ALFREDO BERZAL-HERRANZ**;
Co-Chaired by **PROF. DR. MARIA EMÍLIA SOUSA**



pharmaceuticals



Vera M Costa^{1,2*}

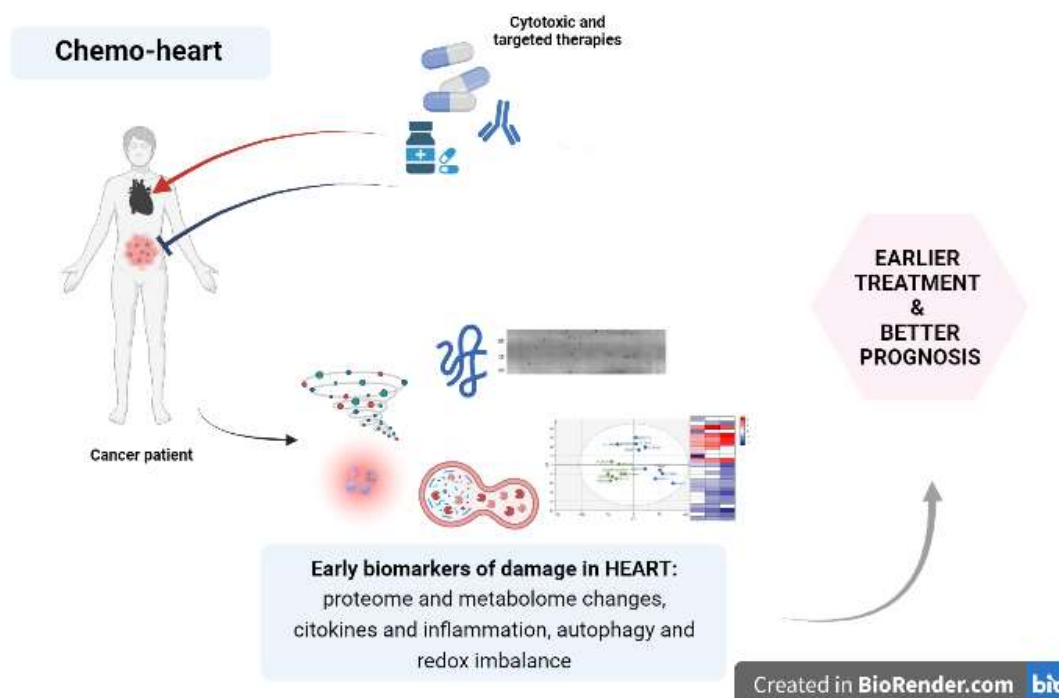
Associate Laboratory i4HB - Institute for Health and Bioeconomy, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal; UCIBIO - Applied Molecular Biosciences Unit, REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal.

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In the heart of cardio-oncology: the targets and biomarkers of anticancer drugs cardiotoxicity

Graphical Abstract



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Abstract:

The cardiotoxicity of anticancer drugs is the second leading cause of death in cancer patients. Among other adverse effects, left ventricular ejection fraction decrease or heart failure emerge after anticancer treatments comprising old or new targeted therapies. In the last few years, our group has been trying to unveil the cardiac adverse outcome pathways of classic chemotherapeutic agents, mainly focusing on two topoisomerase inhibitors, mitoxantrone and doxorubicin.

Mitoxantrone and doxorubicin both cause cumulative dose cardiotoxicity and were tested in *in vitro* and in pre-clinical models. Results obtained in mice and rats, following a clinical relevant dosing scheme, were mimicked *in vitro* and demonstrated that those drugs change cellular redox homeostasis and promote inflammation, although in different biomarkers. Moreover, autophagy and energetic pathways were affected, the first mainly after mitoxantrone treatments and the latter when doxorubicin was used. Thus, distinct cardiac fingerprints for these two drugs exist.

In conclusion, although their clinical cardiac effects are similar in humans, mitoxantrone and doxorubicin have different initiating cardiotoxic events. These were revealed taking into account the use of proper experimental models, clinical relevant concentrations and Omics methods. These data are of the essence to promote drug specific cardioprotective measures in the future, for patients treated with these drugs.

Keywords: Cardio-oncology; cardiotoxicity; doxorubicin; mitoxantrone.

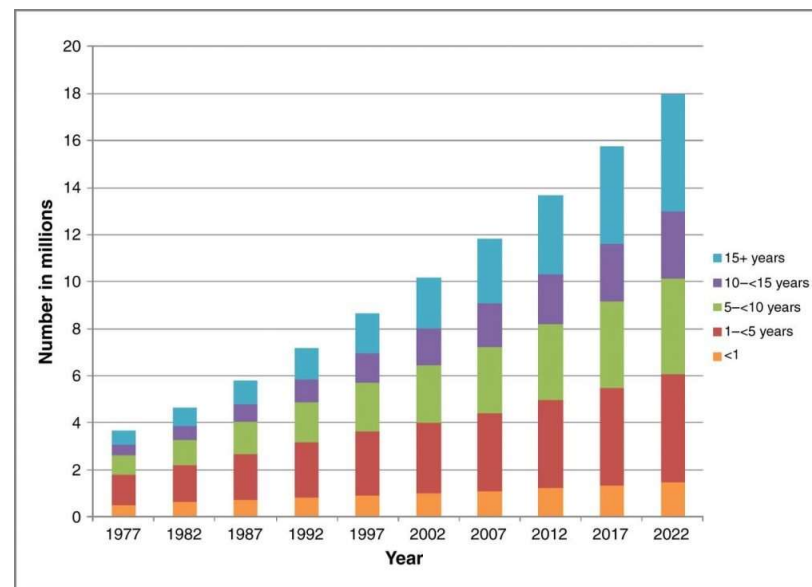
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Introduction

- Cancer is the second leading cause of death worldwide, following cardiovascular diseases.
- Still, and even though cancer incidence is increasing, the rate of survival among most cancers is steadily increasing too.
- **CANCER TREATMENT IS IN FACT A SUCCESS STORY.**



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Introduction

- NEW VISION TOWARDS CANCER



Managing late effects for pediatric cancer survivors.

400,000 pediatric cancer survivors in the United States.

73% will have a chronic health condition.

42% of those will likely experience severe, disabling or life-threatening condition or death.

 Cleveland Clinic Children's

Source: cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2014/special-section-cancer-in-children-and-adolescents-cancer-facts-and-figures-2014.pdf
ncbi.nlm.nih.gov/pmc/articles/PMC2653112/

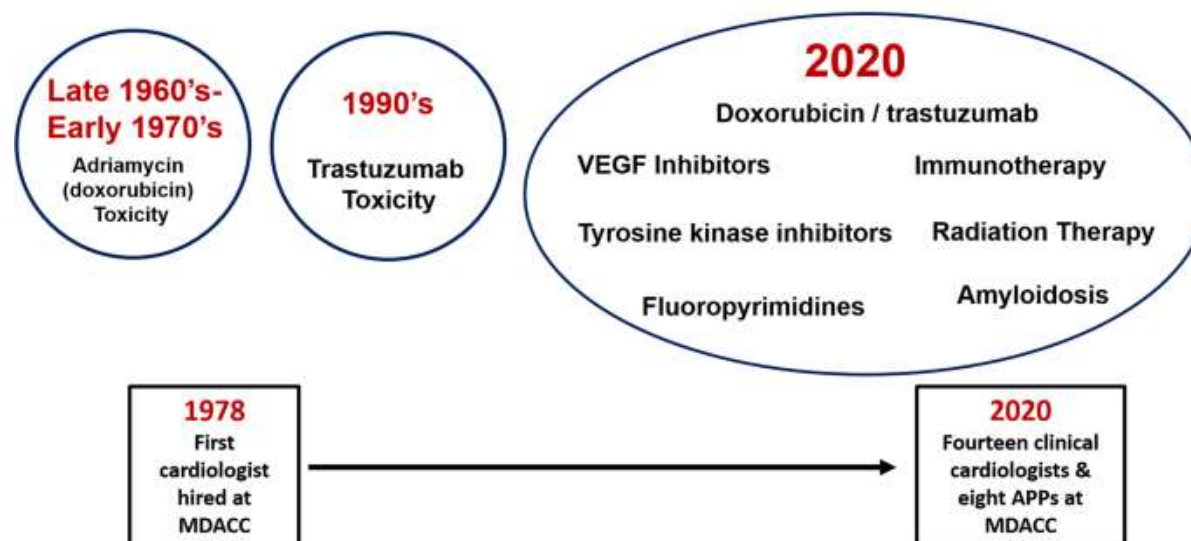
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Short term and long term side effects of cancer treatments: alopecia, myelosuppression, cardiotoxicity, neurotoxicity, recurrent cancer, hepatotoxicity and so on...

Introduction

- CARDIO-ONCOLOGY

Evolution of Needs for Cardio-Oncology



pharmaceuticals

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Special Issue "Current Frames on Cardiotoxicology of New and Old Anticancer Drugs"

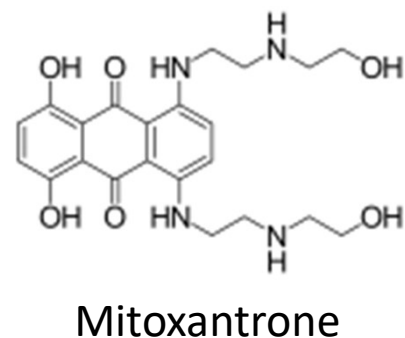
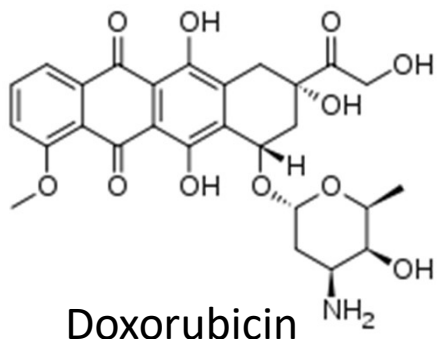
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AIMS

- To unveil the **cardiotoxic adverse outcome pathways (AOPs)** and the **early biomarkers of cardiotoxicity** that enable treatment or triage of patients before end stage heart failure, using both *in vitro* and *in vivo* models regarding 2 topoisomerase II inhibitors used in cancer: mitoxantrone and doxorubicin



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- Mitoxantrone *versus* doxorubicin

Pubmed entries (7th September 2022)

((doxorubicin OR adriamycin) AND (heart OR cardiac): 9,013 results

mitoxantrone AND (heart or cardiac): 534 entries

**Both have similar clinical
cardiotoxicity related to total
lifelong cumulative dose**

**BUT ARE THE MECHANISMS
SIMILAR?**

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Results and discussion

Oxidative stress and Redox homeostasis



Article

Inflammation as a Possible Trigger for Mitoxantrone-Induced Cardiotoxicity: An In Vivo Study in Adult and Infant Mice

Ana Reis-Mendes ^{1,*}, José Luís Soares-Sousa ¹, Ana Isabel Padrão ², Margarida Duarte-Araújo ^{3,4}, José Alberto Duarte ^{2,5}, Vítor Seabra ⁵, Salomé Gonçalves-Monteiro ^{6,7}, Fernando Remião ¹, Félix Carvalho ¹, Emília Sousa ^{8,9}, Maria Lourdes Bastos ¹ and Vera Marisa Costa ^{1,*}



biomolecules

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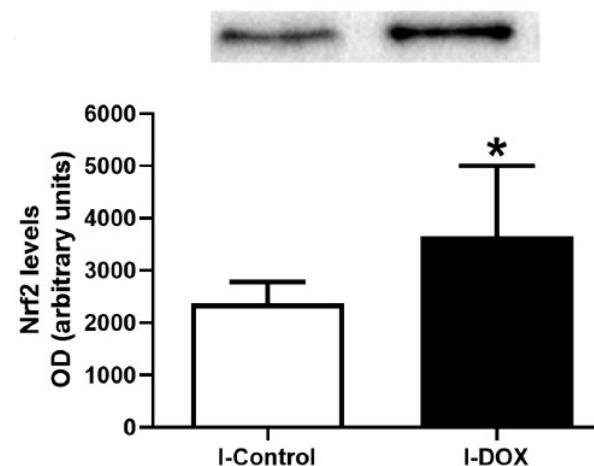
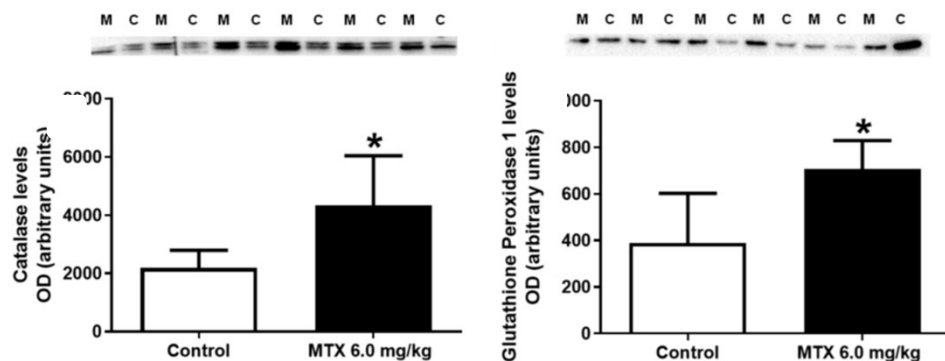
Role of Inflammation and Redox Status on Doxorubicin-Induced Cardiotoxicity in Infant and Adult CD-1 Male Mice

Ana Reis-Mendes; Ana Isabel Padrão; José Alberto Duarte; Salomé Gonçalves-Monteiro; Margarida Duarte-Araújo; Fernando Remião; Félix Carvalho; Emília Sousa; Maria Lourdes Bastos; Vera Marisa Costa

Biomolecules 2021, Volume 11, Issue 11, 1725



Infants



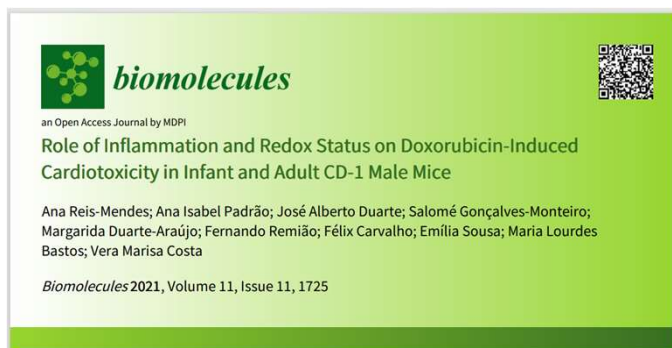
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Results and discussion

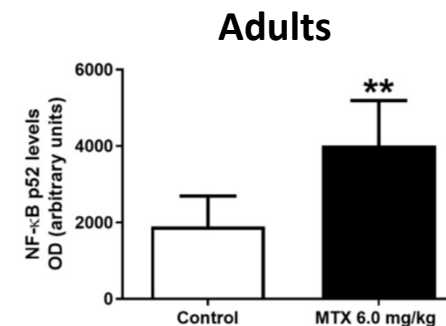
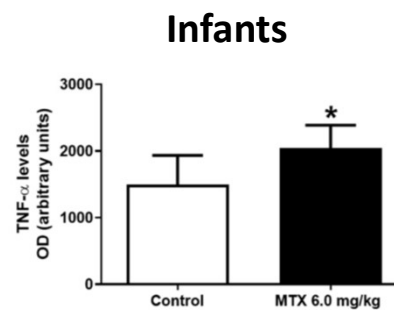
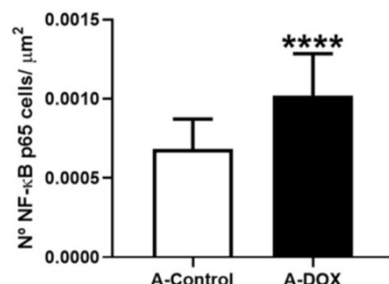
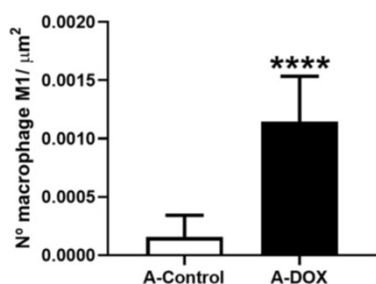
Inflammation



Article

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Results and discussion

Energetic pathways and mitochondrial homeostasis

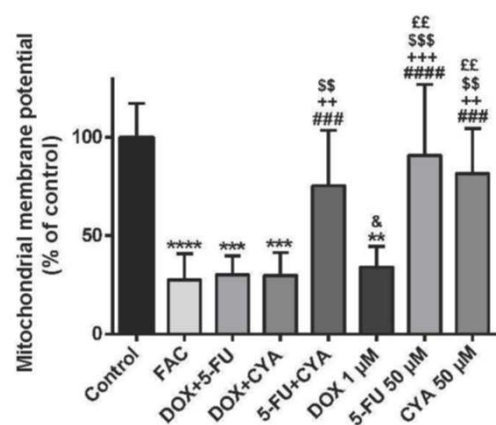
H9c2 cells



Article

Doxorubicin Is Key for the Cardiotoxicity of FAC (5-Fluorouracil + Adriamycin + Cyclophosphamide) Combination in Differentiated H9c2 Cells

Maria Pereira-Oliveira, Ana Reis-Mendes, Félix Carvalho, Fernando Remião, Maria de Lourdes Bastos and Vera Marisa Costa *



HL-1 cardiomyocytes

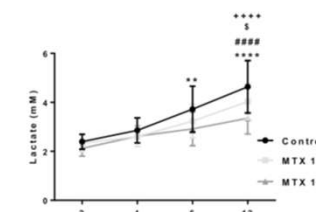
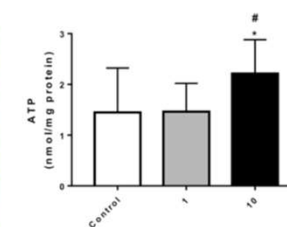
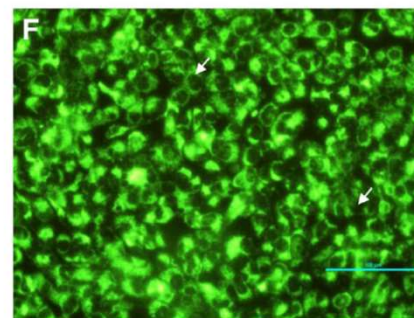
Archives of Toxicology
<https://doi.org/10.1007/s00204-020-02874-4>

ORGAN TOXICITY AND MECHANISMS



Mitoxantrone impairs proteasome activity and prompts early energetic and proteomic changes in HL-1 cardiomyocytes at clinically relevant concentrations

Vera Marisa Costa¹ · João Paulo Capela^{1,2} · Joana R. Sousa³ · Rute P. Eleutério³ · Patrícia R. S. Rodrigues³ · José Luís Soares-Sousa^{1,4} · Rui A. Carvalho⁵ · Maria Lourdes Bastos¹ · José Alberto Duarte⁶ · Fernando Remião¹ · M. Gabriela Almeida^{3,7} · Kurt J. Varner⁸ · Félix Carvalho¹



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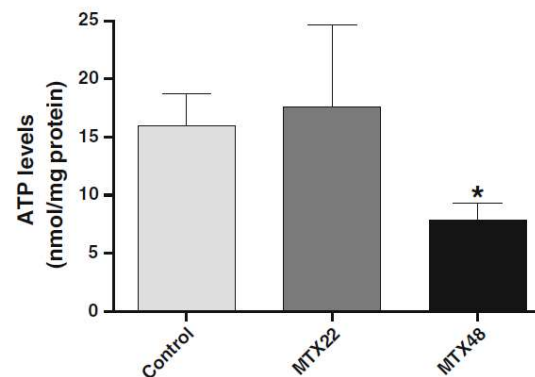
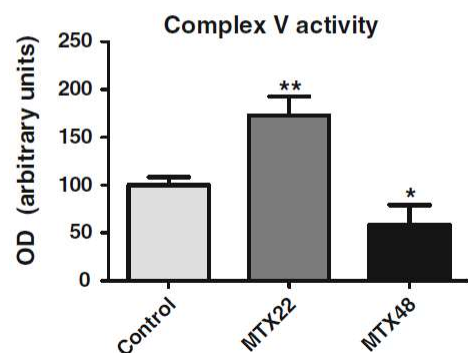
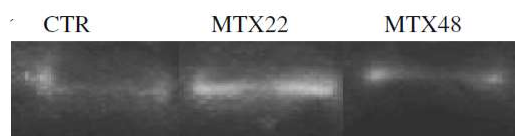
Results and discussion

Energetic pathways and mitochondrial homeostasis



Rat with 7.5mg/kg cumulative dose MTX

Sacrificed at 2 time-points



Rossato *et al.* 2013 Cardiovascular Toxicology

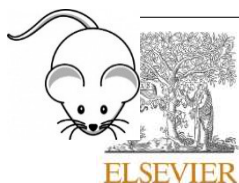
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Results and discussion

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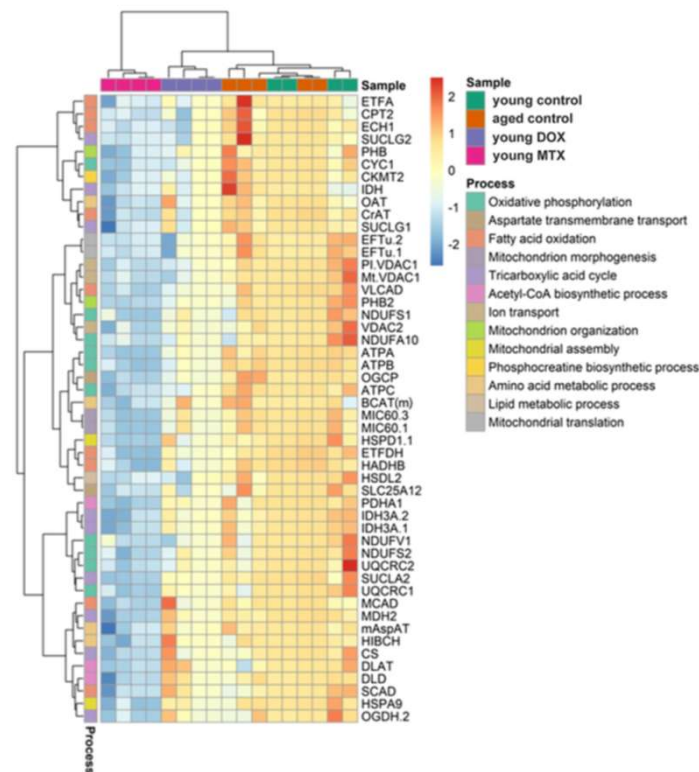
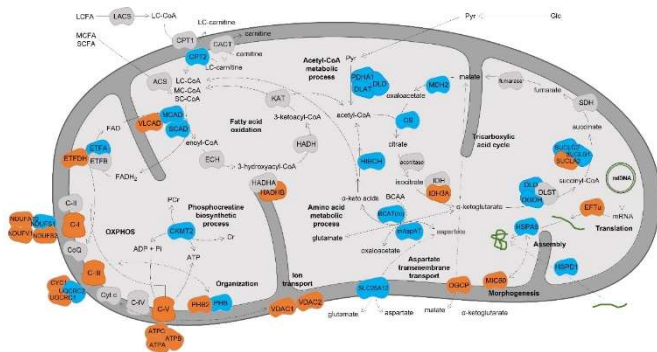
Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Toxicology

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

Exploring the aging effect of the anticancer drugs doxorubicin and mitoxantrone on cardiac mitochondrial proteome using a murine model

Sofia Reis Brandão ^{a,b,c}, Ana Reis-Mendes ^{a,c}, Pedro Domingues ^b, José Alberto Duarte ^{d,e}, Maria Lourdes Bastos ^{a,c}, Félix Carvalho ^{a,c}, Rita Ferreira ^b, Vera Marisa Costa ^{a,c,*}



Toxicology

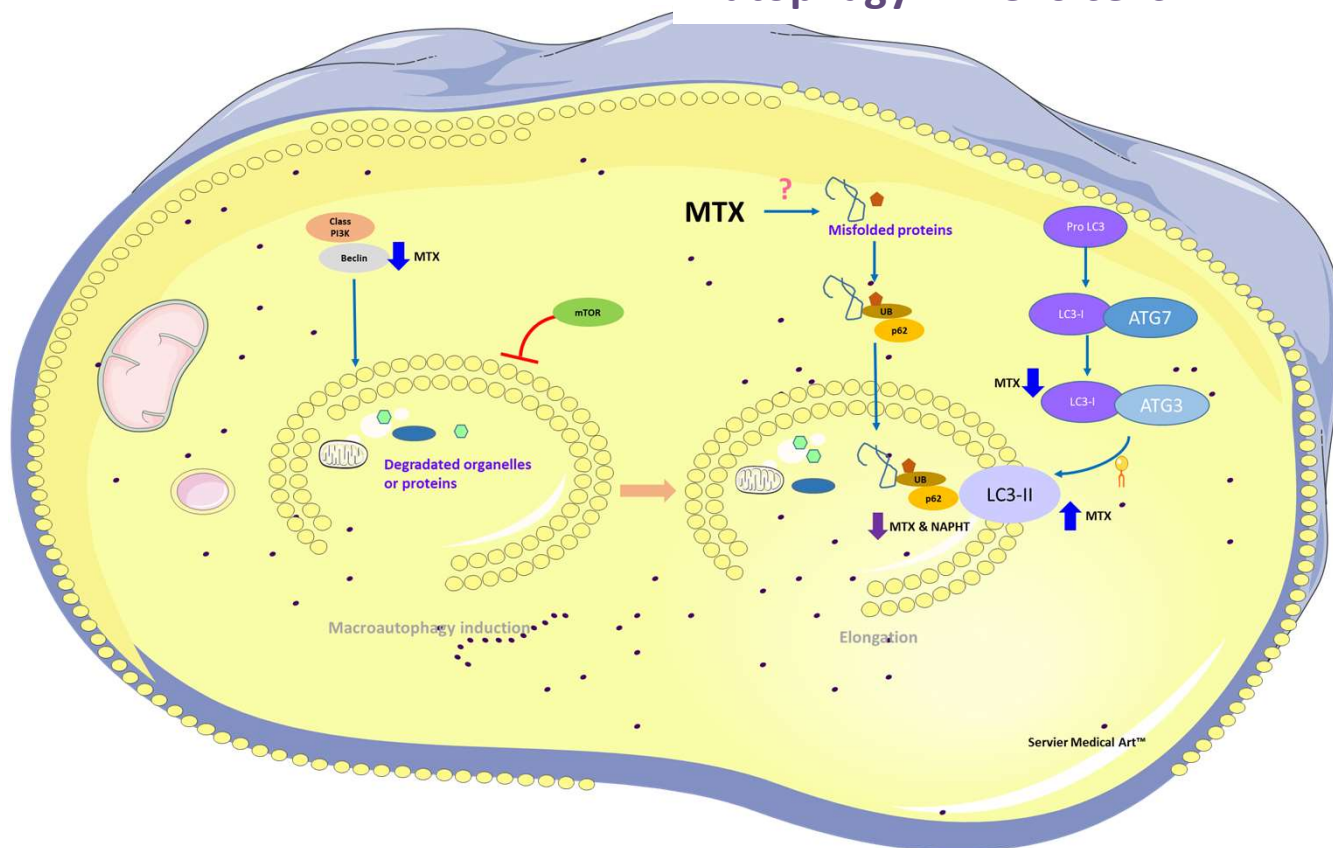
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Results and discussion

Autophagy in AC16 cells



Reis-Mendes *et al.* Archives in Toxicology In press

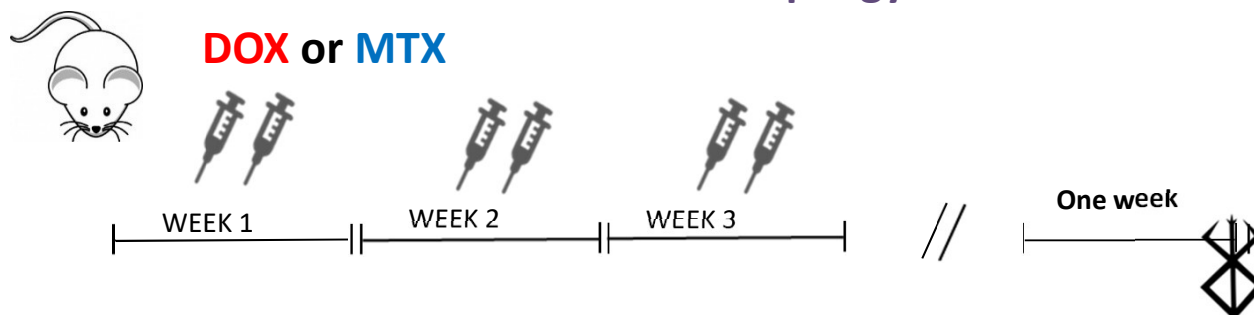
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Results and discussion

Autophagy in mice



	DOX	MTX
Beclin 1	=	=
ATG5	↓	↓
LC3	↓	↓

Brandão *et al.* in preparation

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Results and discussion

Protein turnover and modification

HL-1 cardiomyocytes

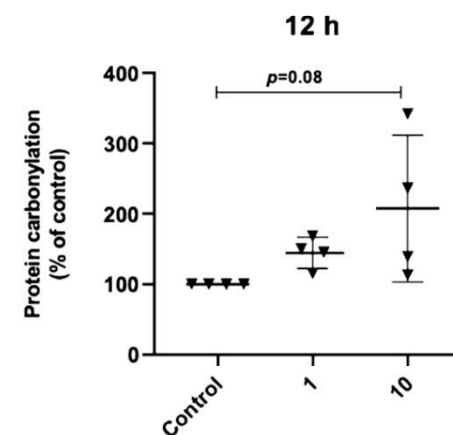
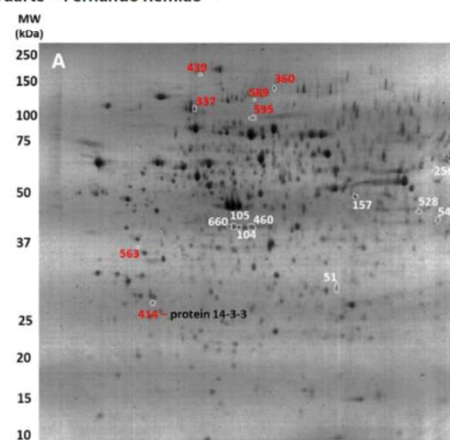
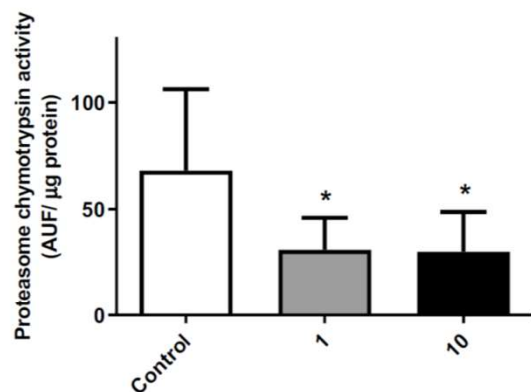
Archives of Toxicology
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ORGAN TOXICITY AND MECHANISMS



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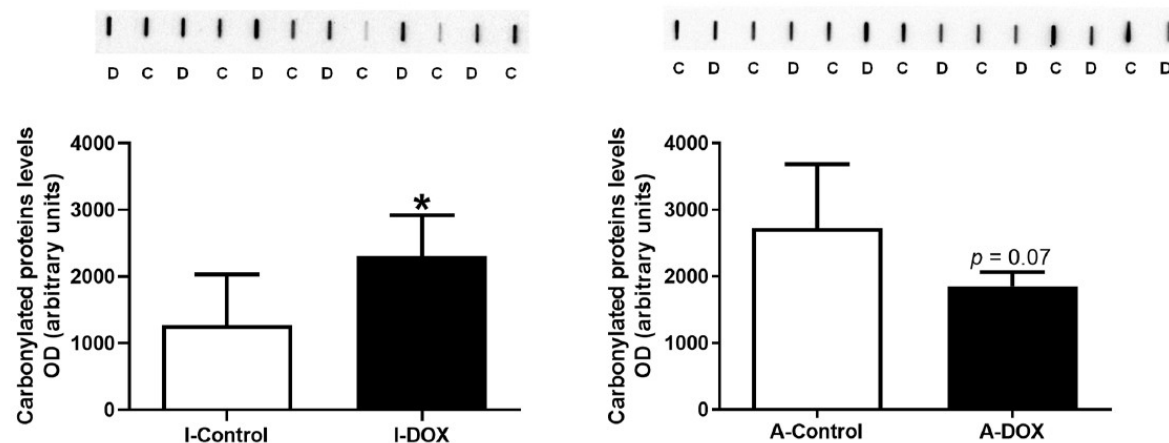
Protein turnover and modification



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Conclusions

Although both drugs have similar anti-cancer mechanisms and clinical signs of cardiotoxicity, they have different underlying adverse outcome cardiac pathways:

- **Redox homeostasis**
- **Energetic and mitochondrial homeostasis**
- **Inflammation**
- **Autophagy**
- **Protein turnover and modifications**

Thus, biomarkers of cardiotoxicity should be addressed in a DRUG by DRUG context using in vitro and in vivo models to identify susceptible patients and discover new pharmacological treatments

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Acknowledgments

FCT Fundação para a Ciência e a Tecnologia
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A special issue of *Pharmaceuticals* (ISSN 1424-8247). This special issue belongs to the section "Pharmacology".

Deadline for manuscript submissions: **20 December 2022** | Viewed by 62