

Accepted Manuscript

Title: Oxidative stress and inhibition of nitric oxide generation underlie methotrexate-induced senescence in human colon cancer cells

Authors: Magdalena Dabrowska, Lukasz Uram, Zbigniew Zielinski, Wojciech Rode, Ewa Sikora



PII: S0047-6374(17)30068-4
DOI: <http://dx.doi.org/doi:10.1016/j.mad.2017.07.006>
Reference: MAD 10971

To appear in: *Mechanisms of Ageing and Development*

Received date: 30-3-2017
Revised date: 10-6-2017
Accepted date: 19-7-2017

Please cite this article as: Dabrowska, Magdalena, Uram, Lukasz, Zielinski, Zbigniew, Rode, Wojciech, Sikora, Ewa, Oxidative stress and inhibition of nitric oxide generation underlie methotrexate-induced senescence in human colon cancer cells. *Mechanisms of Ageing and Development* <http://dx.doi.org/10.1016/j.mad.2017.07.006>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Oxidative stress and inhibition of nitric oxide generation underlie methotrexate-induced senescence in human colon cancer cells

Magdalena Dabrowska^{a*}, Lukasz Uram^b, Zbigniew Zielinski^c, Wojciech Rode^d, Ewa Sikora^a

^a Laboratory of Molecular Basis of Ageing, Department of Biochemistry, Nencki Institute of Experimental Biology, Polish Academy of Sciences; 3 Pasteur St., 02-093 Warszawa, Poland

^b Faculty of Chemistry, Rzeszow University of Technology; 6 Powstancow Warszawy Ave., 35-959 Rzeszow, Poland

^c Laboratory of Molecular Basis of Cell Motility, Department of Biochemistry, Nencki Institute of Experimental Biology, Polish Academy of Sciences; 3 Pasteur St., 02-093 Warszawa, Poland

^d Nencki Institute of Experimental Biology, Polish Academy of Sciences; 3 Pasteur St., 02-093 Warszawa, Poland

* Corresponding author: Tel.: +48225892472; fax: +48228225342.

E-mail address: m.dabrowska@nencki.gov.pl

Highlights

- • Methotrexate induces premature senescence in human colon cancer C85 cells
- • The drug caused dihydrofolate reductase protein stabilization
- • DNA damage occurred predominantly at the senescence initiation phase
- • ROS generation reached the highest level at the senescence maintenance phase
- • NO generation declined at the senescence maintenance phase

ABSTRACT

The response of human colon cancer C85 cells to methotrexate takes the form of reversible growth arrest of the type of stress-induced senescence. In the present study it is shown that during C85 cell progression into methotrexate-induced senescence, dihydrofolate reductase, the primary intracellular target for the drug, is stabilized at the protein level and its enzymatic activity, assayed in crude cellular extracts, decreases by 2-fold. Dihydrofolate reductase inhibition results in an increase in dihydrobiopterin level and an ultimate decrease in the tetrahydrobiopterin : dihydrobiopterin ratio in senescent cells. Endothelial nitric oxide synthase expression declines. Despite concomitant upregulation of inducible nitric oxide synthase

Download English Version:

<https://daneshyari.com/en/article/8284707>

Download Persian Version:

<https://daneshyari.com/article/8284707>

[Daneshyari.com](https://daneshyari.com)