
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
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Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Reversing the tumor immune escape with Selenium

Claudia Lennicke

Institute of Medical Immunology, Halle, Germany

sitc

Society for Immunotherapy of Cancer

#SITC2017

Presenter Disclosure Information

Claudia Lennicke

The following relationships exist related to this presentation:

No Relationships to Disclose

Selenium, in brief

- ✓ an essential trace element

  RDI: 30 – 70 µg

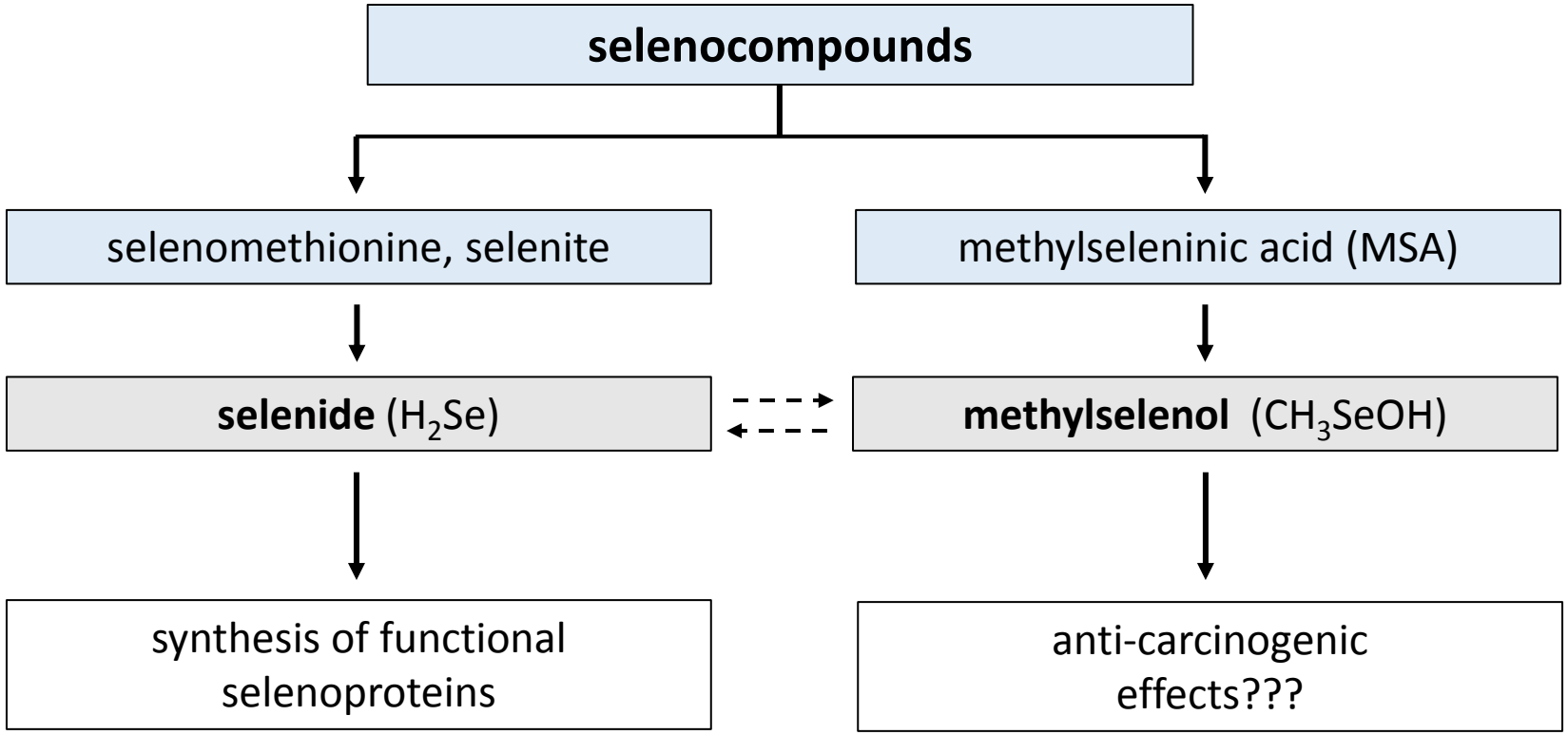
- ✓ an „anti-oxidant“ ✸

- ✓ cancer therapeutic potential?

Selene,
the goddess of the moon

Selenoprotein	Chromosomal location (number of exons)	Sec location in protein (length of protein)	Selenoprotein structure
15kDa	1p22.3 (5)	93 (162)	
DI1	1p32.3 (4)	126 (249)	
DI2	14q31.1 (2)	133 (265)	
DI3	14q32	144 (278)	
✸ GPx1	3p21.31 (2)	47 (201)	
✸ GPx2	14q23.3 (2)	40 (190)	
✸ GPx3	5q33.1 (5)	73 (226)	
✸ GPx4	19p13.3 (7)	73 (197)	
✸ **GPx6**	**6p22.1 (5)**	**73 (221)**	
H	**11q12.1 (4)**	**44 (122)**	
I	**2p23.3 (10)**	**387 (397)**	
K	**3p21.31 (5)**	**92 (94)**	
M	22q12.2 (5)	48 (145)	
N	1p36.11 (12)	428 (556)	
O	**22q13.33 (9)**	**667 (669)**	
✸ P	5p12 (4)	59, 300, 318, 330, 345, 352, 367, 369, 376, 378 (381)	
✸ R	16p13.3 (4)	95 (116)	
S	**15q26.3 (6)**	**188 (189)**	
SPS2	-	60 (448)	
T	3q24 (6)	36 (182)	
✸ TR1	12q23.3 (15)	498 (499)	
✸ TR2	3q21.2 (16)	655 (656)	
✸ TR3	22q11.21 (18)	522 (523)	
V	**19q13.13 (6)**	**273 (346)**	
W	19q13.32 (6)	13 (87)	

Selenium, in brief



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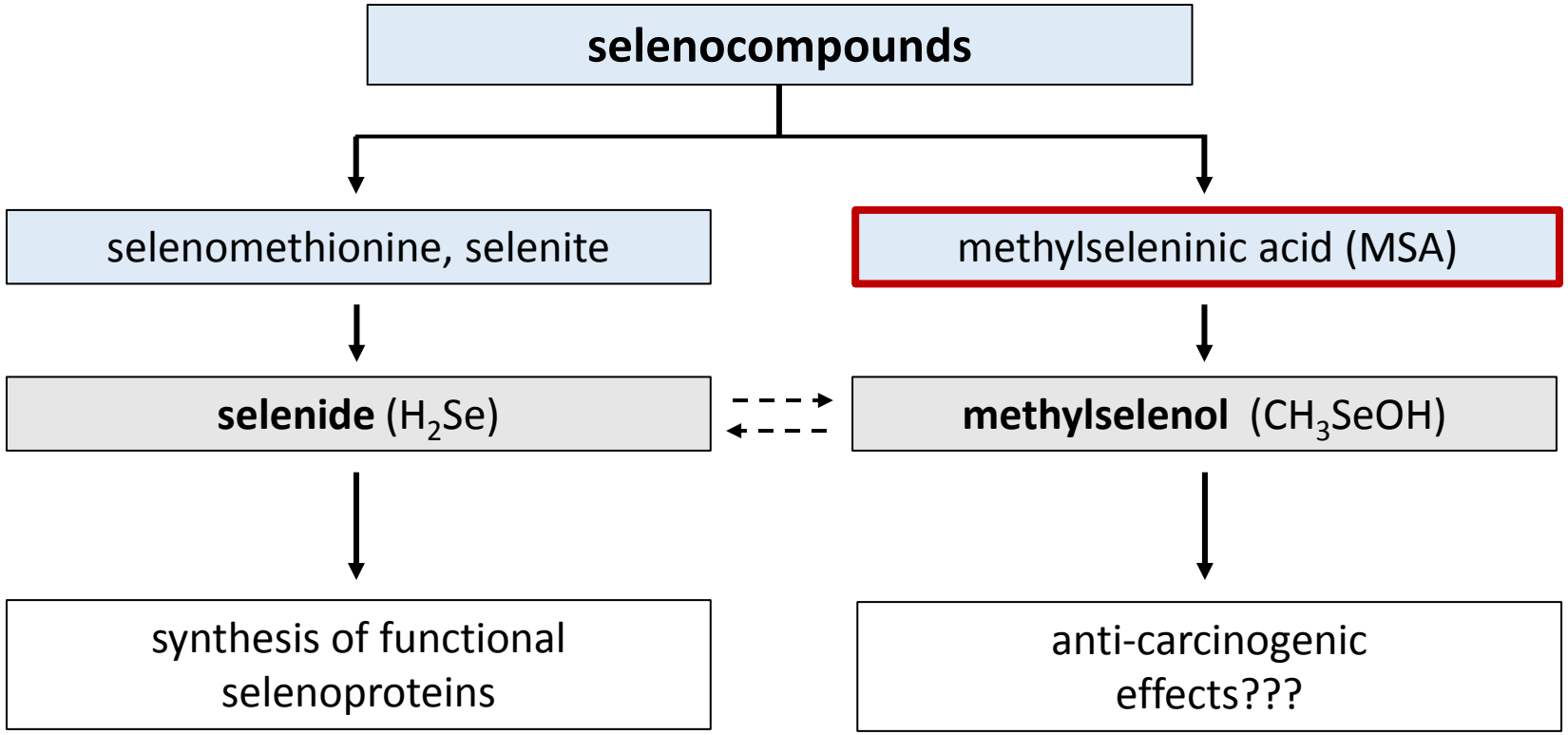
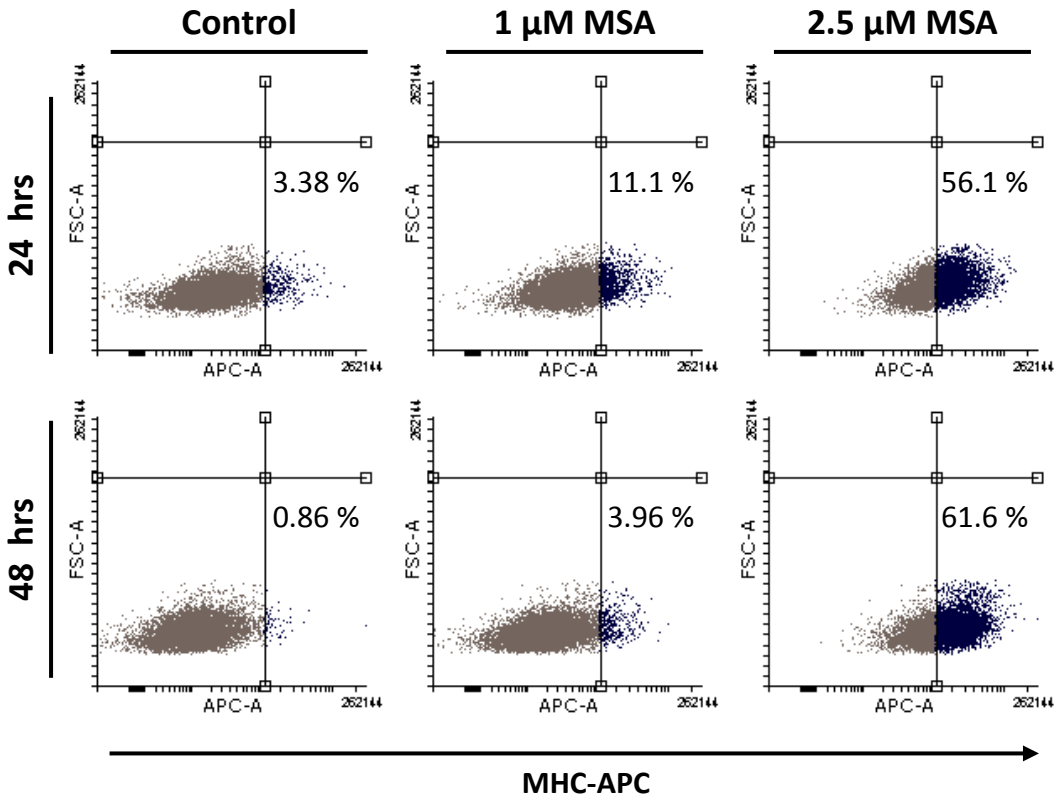


MSA upregulates MHC class I



Flow cytometry analysis of B16F10 cells exposed to MSA

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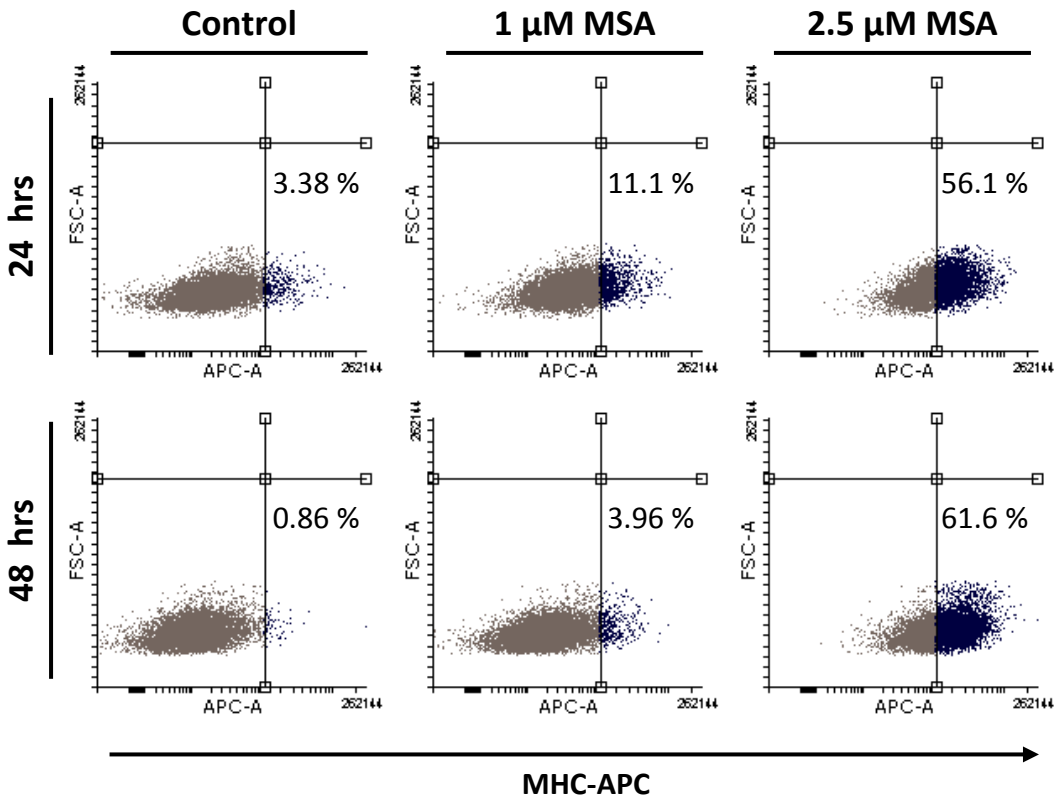

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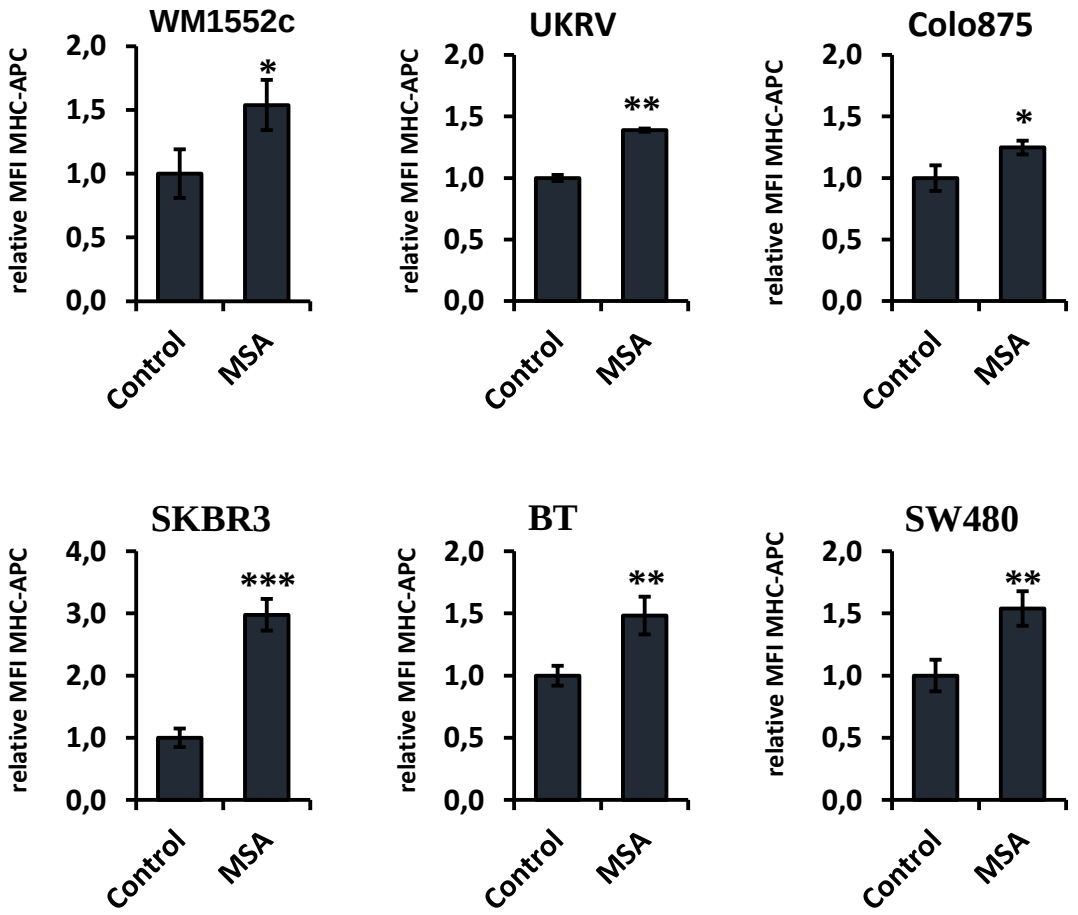

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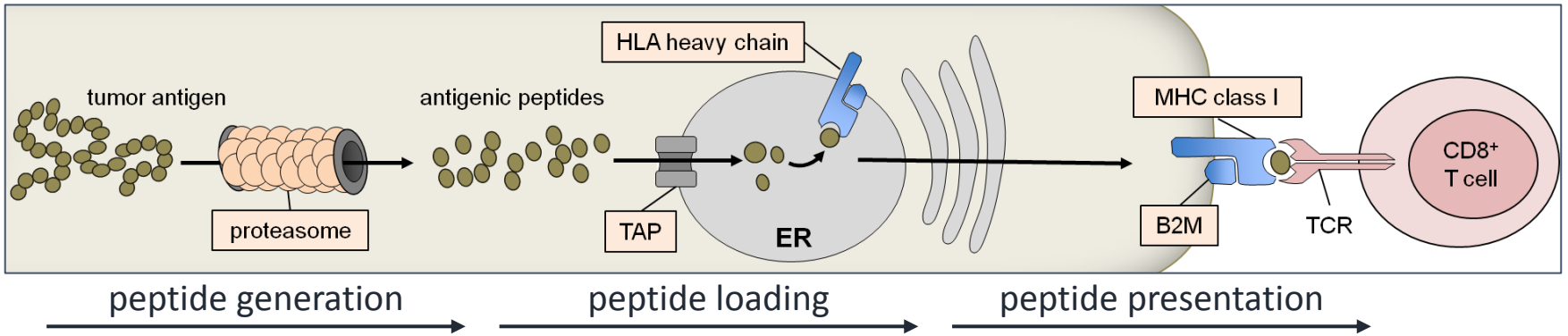

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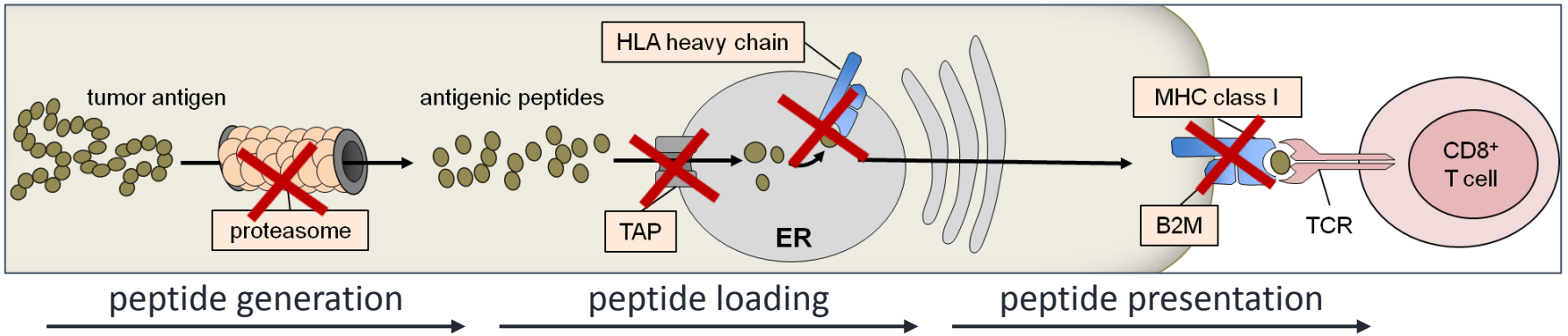
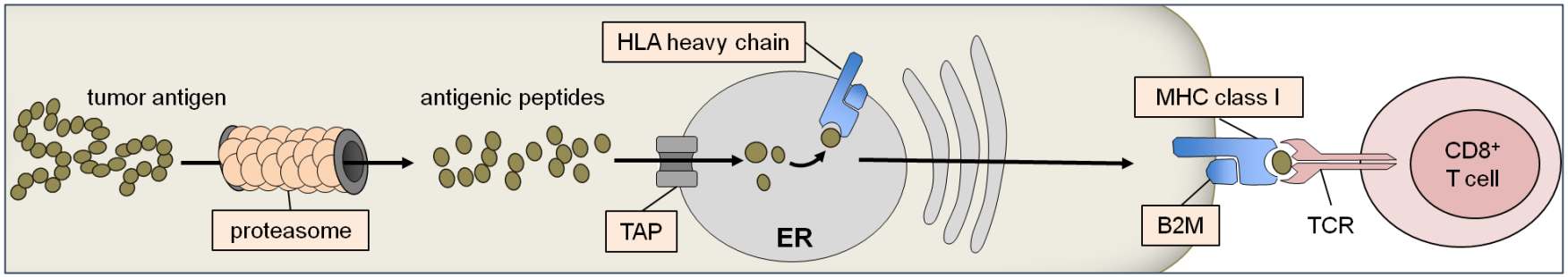
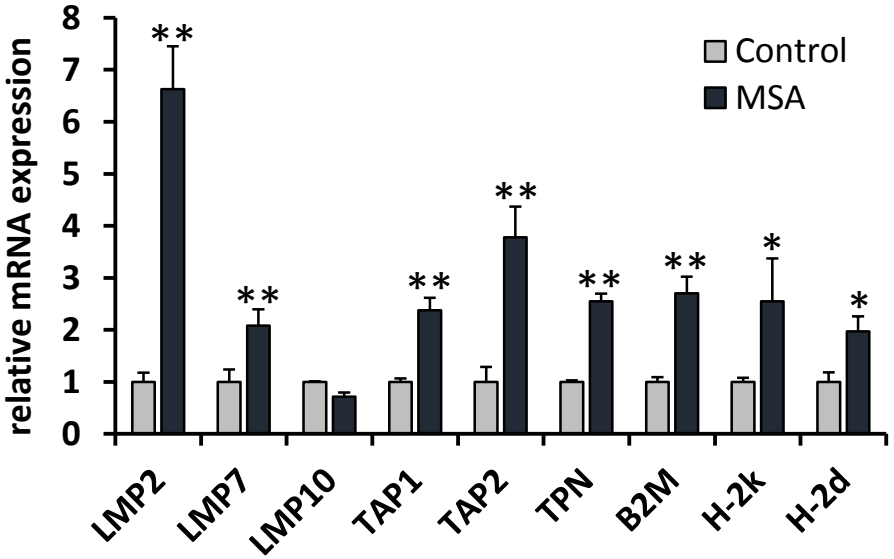
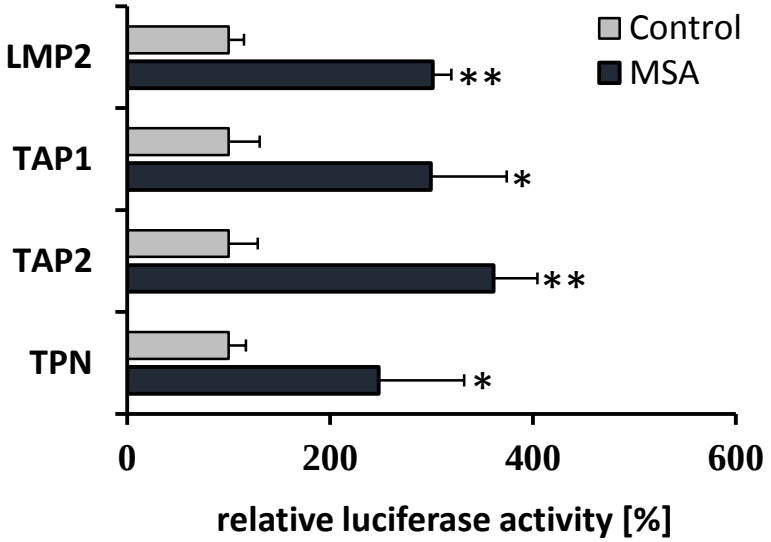


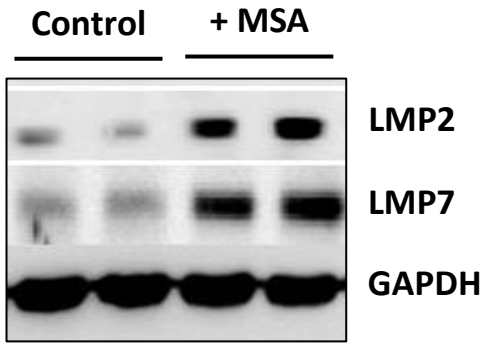
Abnormalities of APM components and MHC class I surface antigens are often associated with an immune escape of tumor cells

MSA upregulates MHC class I









B16F10 melanoma cells, treatment 2.5 µM MSA for 24 hrs, *p<0.05, **p<0.01 (student´s t test)

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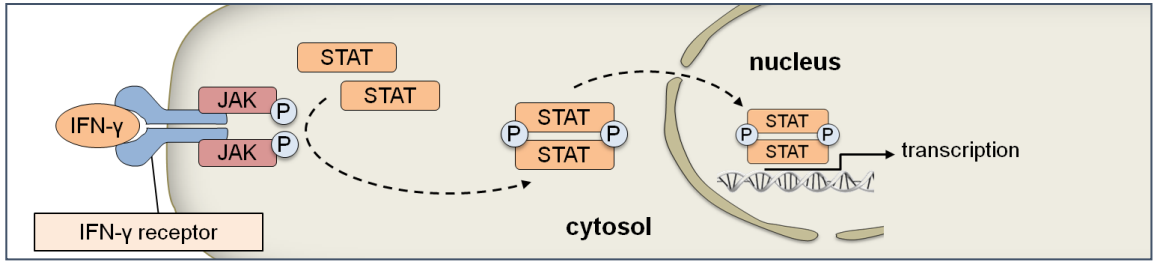
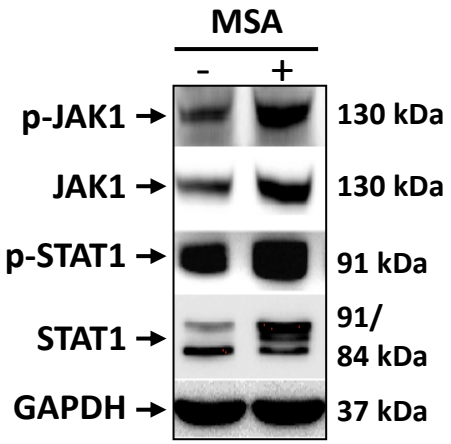
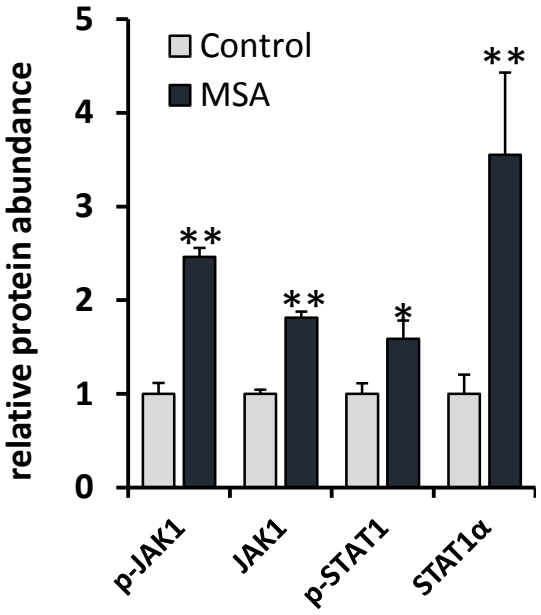
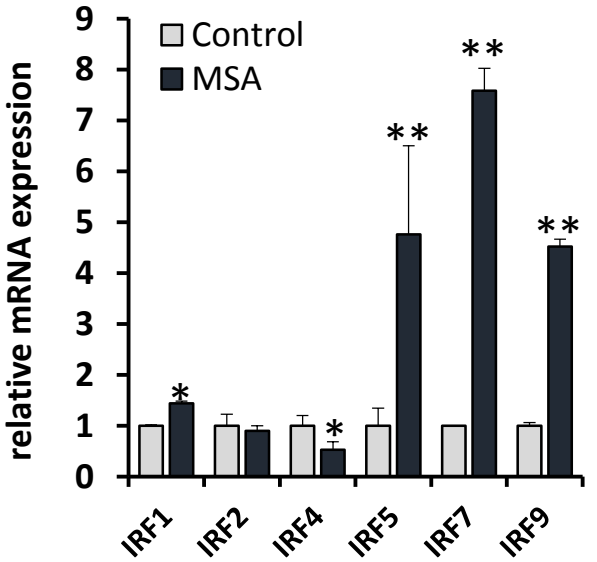
MSA activates JAK/STAT signaling









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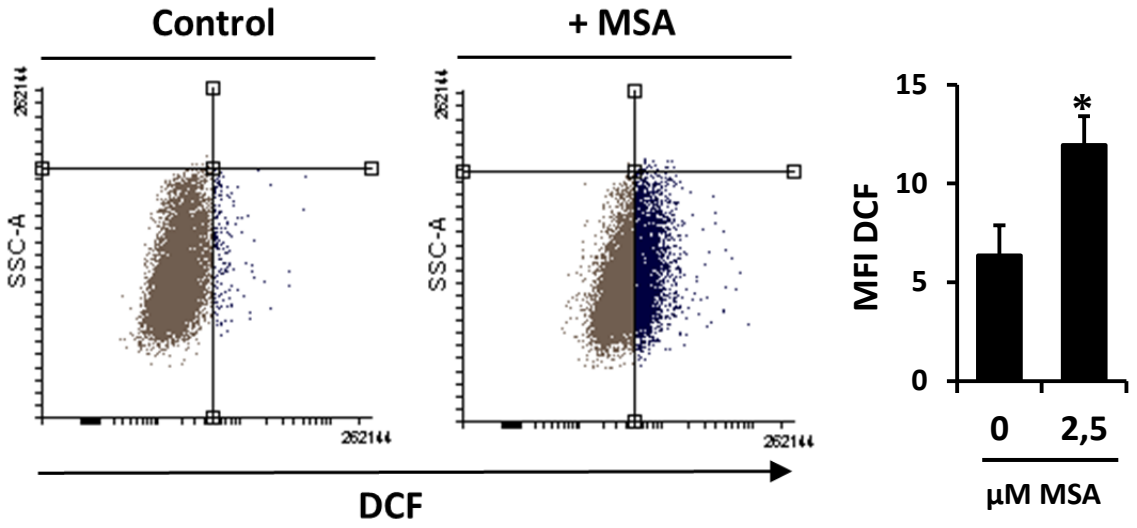
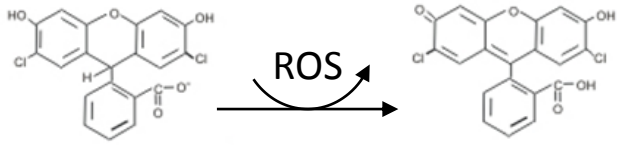
MSA is redox active





H_2DCF-DA (non-fluorescent)

DCF (fluorescent)

ROS, reactive oxygen species;
DCF, 2', 7' –dichlorofluorescin

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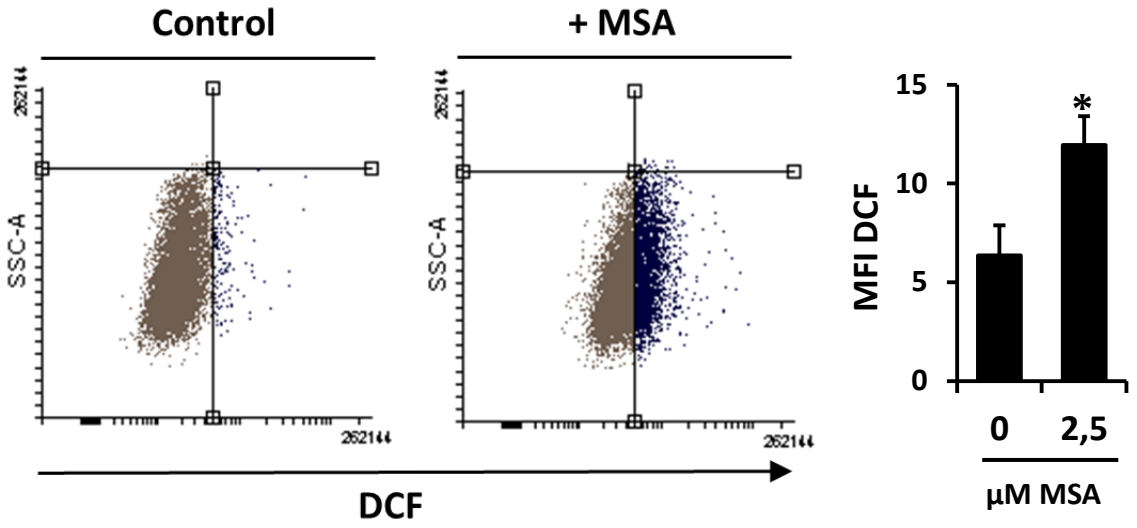
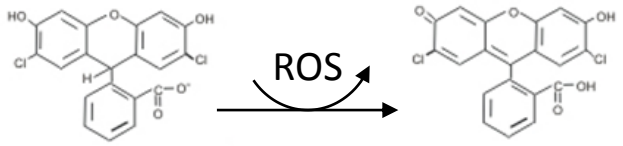
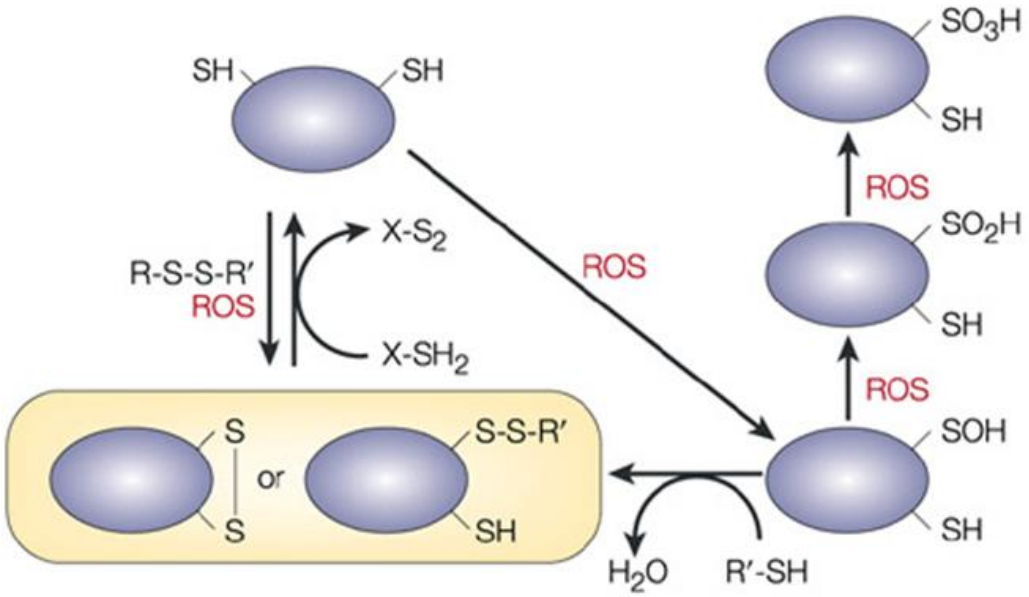




H_2DCF-DA (non-fluorescent)

DCF (fluorescent)

Redox sensitive cysteine residues can be oxidized by ROS



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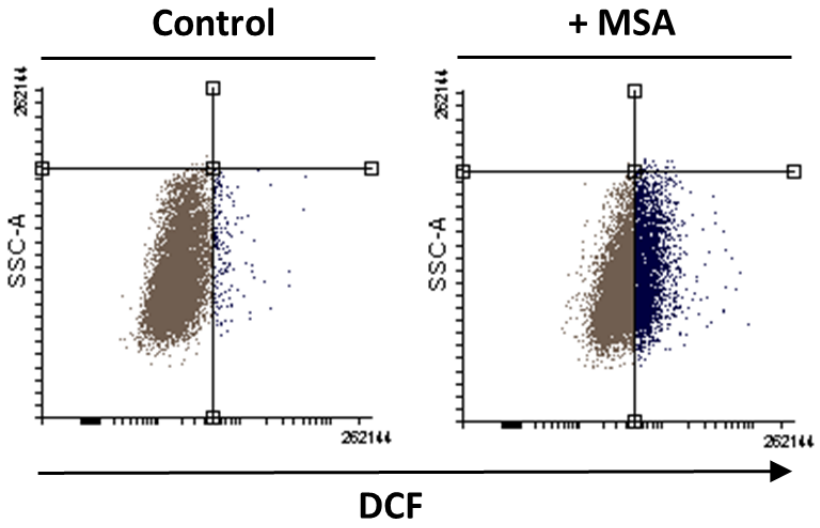

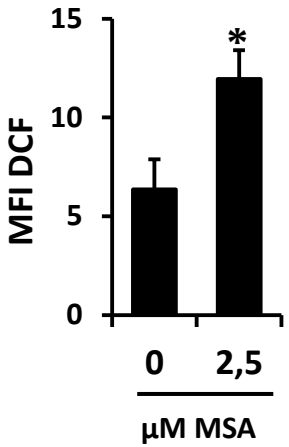

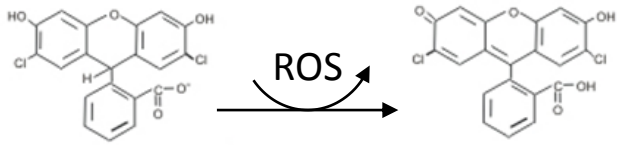

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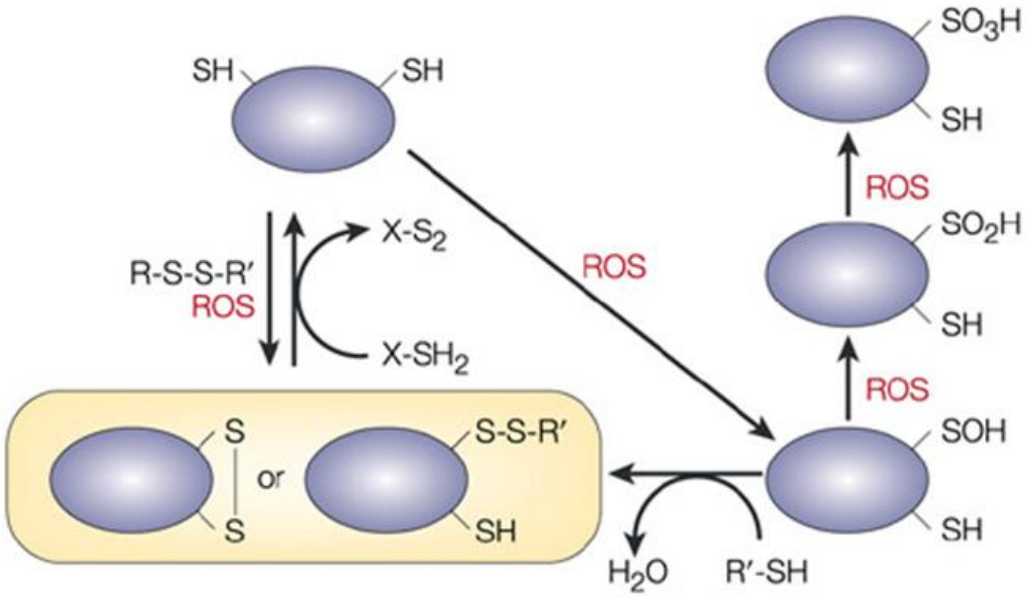

Are redox switches involved in the MSA mediated upregulation of MHC class I????

ROS, reactive oxygen species;
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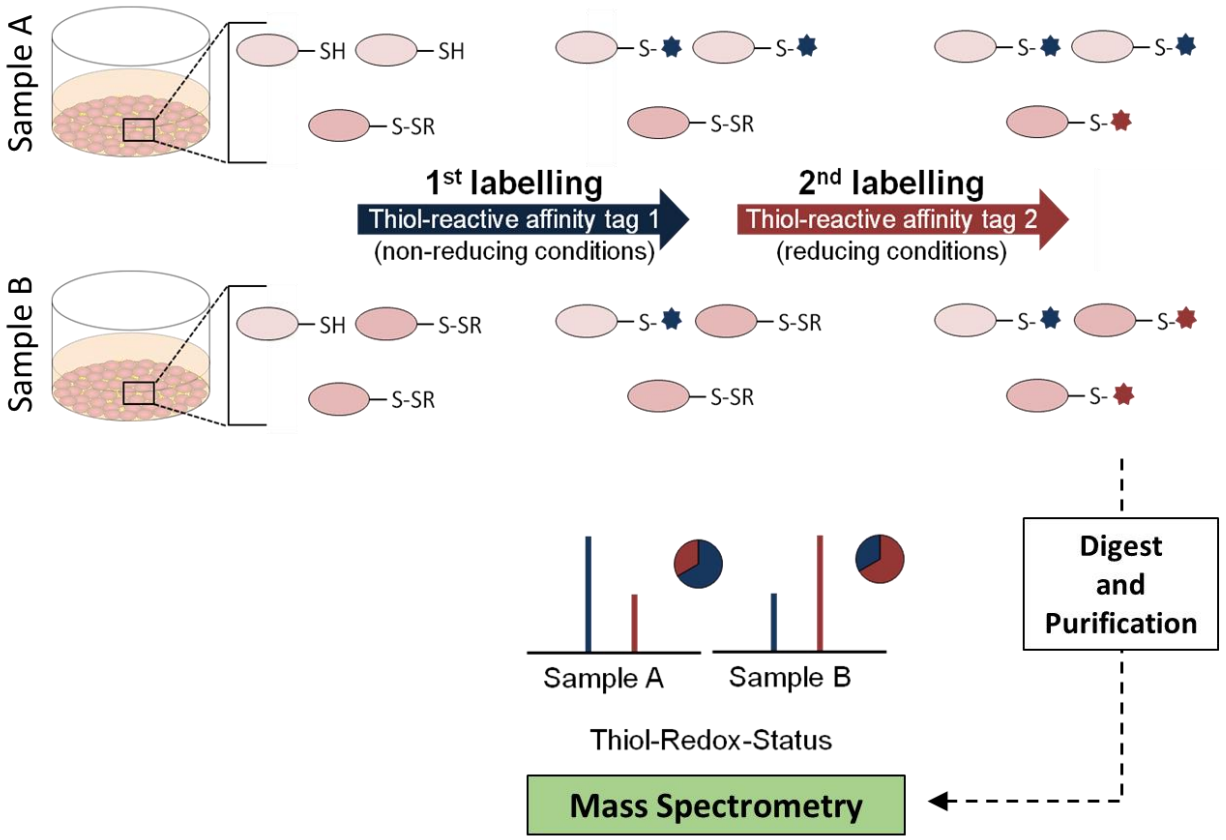
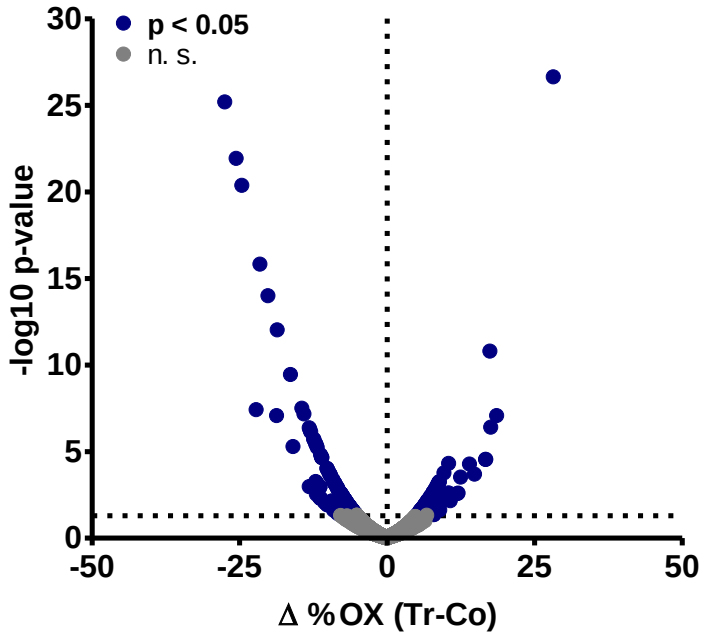
The iodoTMT technology

- ✓Identification of redox-modified proteins
- ✓Identification of redox-modified cysteine residues
- ✓Multiplex analysis



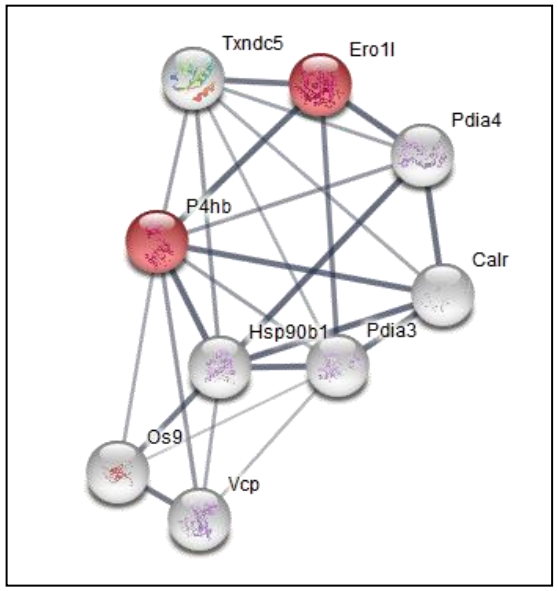
The MSA redoxome



##Databases: PANTHER, KEGG PATHWAY
##Statistical test method: hypergeometric test / Fisher's exact test
##FDR correction method: Benjamini and Hochberg

Term	No. of proteins	Corrected P-Value
Protein processing in endoplasmic reticulum	**9**	1,75E-03
Lysosome	**9**	3,72E-04
Response to elevated platelet cytosolic Ca2+	**6**	3,85E-03
Detoxification of reactive oxygen species	**5**	3,50E-04
trans-Golgi network vesicle budding	**5**	6,87E-03
Golgi associated vesicle biogenesis	**4**	1,56E-02
Selenocompound metabolism	**3**	1,73E-02
Calnexin/calreticulin cycle	**3**	1,39E-02

The MSA redoxome



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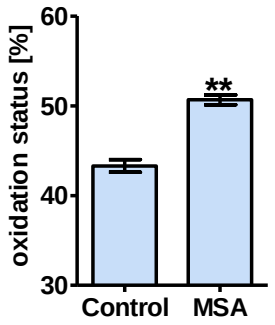
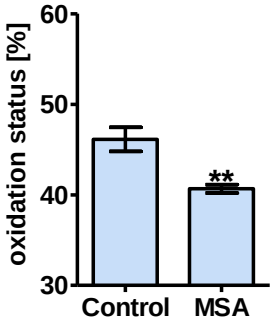
"**ERO1A** together with **P4hb (PDI)** regulates the expression of MHC class I via oxidative folding"(Kukita et al. *J Immunol* 194, 4988–96 (2015))

MSA activates ERO1a

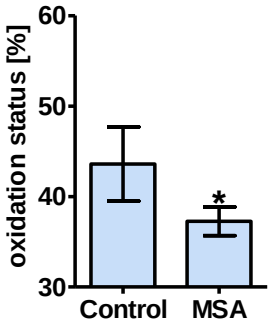
ERO1α:
DC$_{99}$AVKPCHSDEVPDGIK

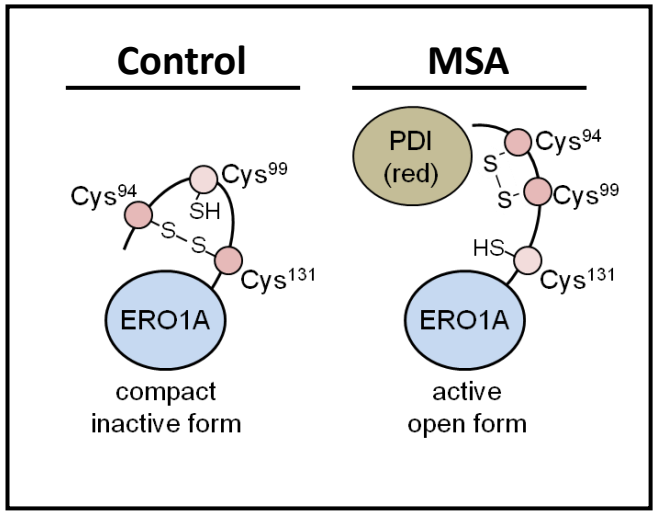


ERO1α:
YSEEANRIEEC$_{130}$EQAER



PDI:
YLLVEFYAPWC$_{55}$GHC$_{58}$K





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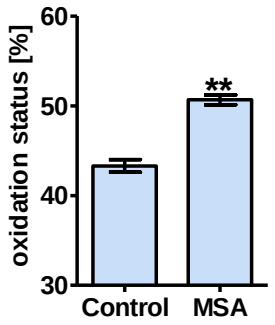

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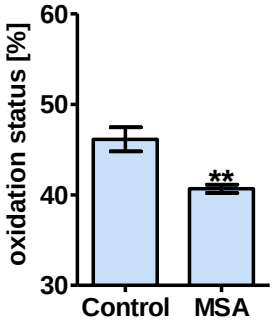

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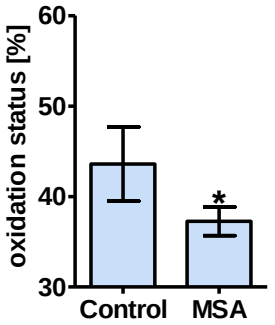

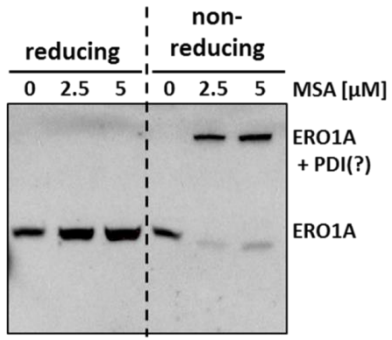

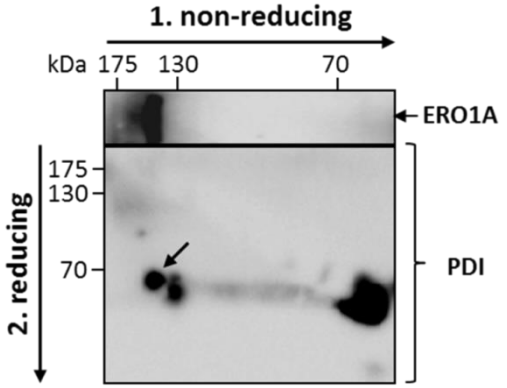

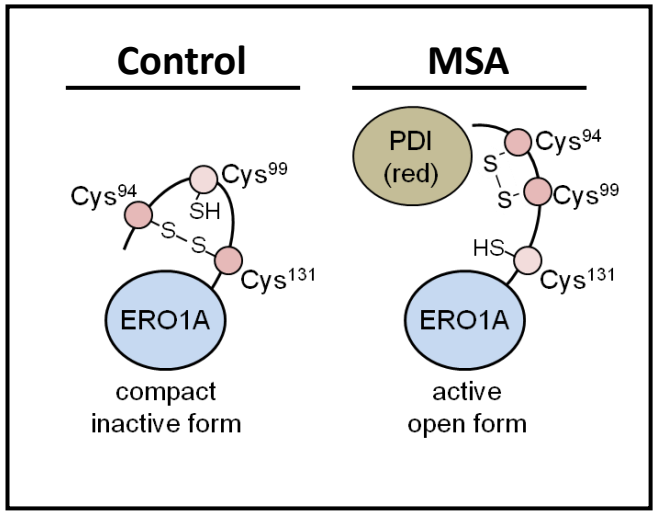

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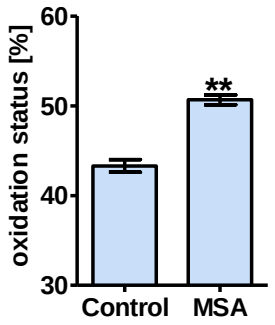

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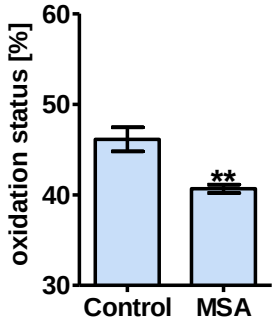

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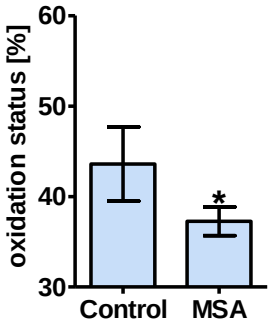

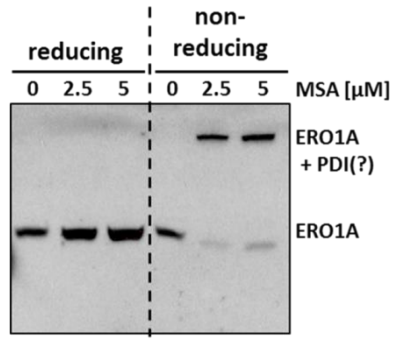

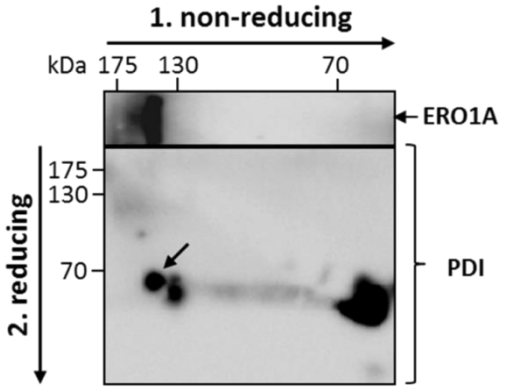

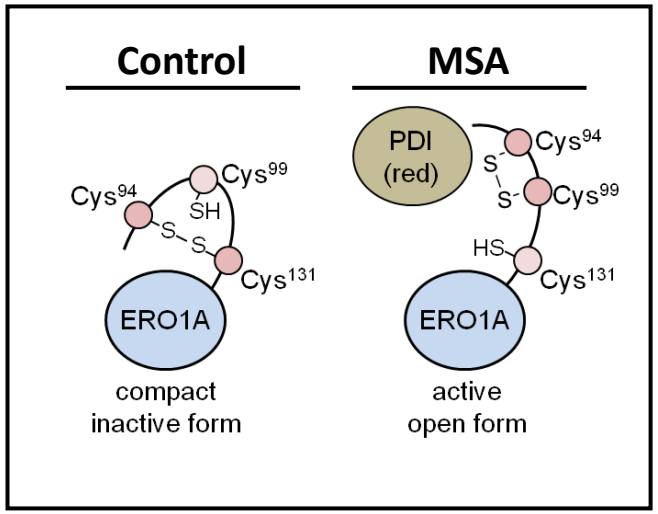

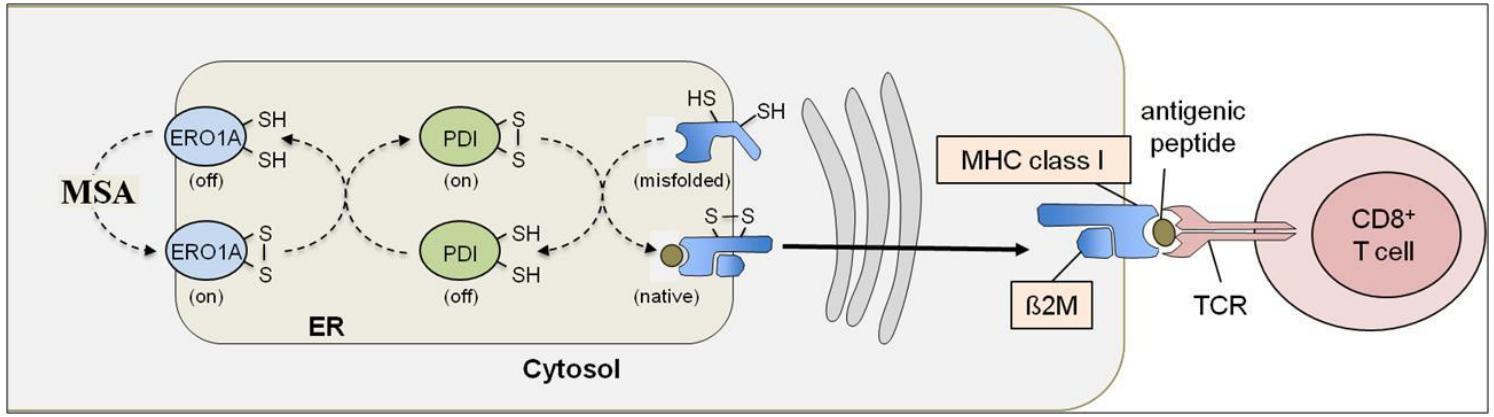

Methylseleninic acid (MSA)

- modulation of the MHC class I surface expression in tumor cells by
  - ✓ enhanced expression of IFN-γ signaling components
  - ✓ an upregulation of APM components
  - ✓ modulation the activity status of proteins involved in oxidative folding of MHC class I molecules
- Manipulation of the cellular redox status with redox active selenocompounds might reverse the tumor immune escape
- Adding of redox active selenocompounds might enhance the efficacy of immunotherapies

→ **Please visit Poster No. 460**

Acknowledgement

Seliger Lab

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Khleif Lab

Prof. Dr. Samir Khleif
Dr. Shamim Ahmad
Dr. Vivek Verma
Dr. Seema Gupta
Dr. Pankaj Gaur

Universitätsmedizin GREIFSWALD

Falko Hochgräfe
Prof. Christopher Lillig
Manuela Gellert

Thank you for your attention