UNIVERSITÀ DEGLI STUDI DI UDINE
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CORSO DI DOTTORATO DI RICERCA IN:
Biomedical Sciences and Biotechnology

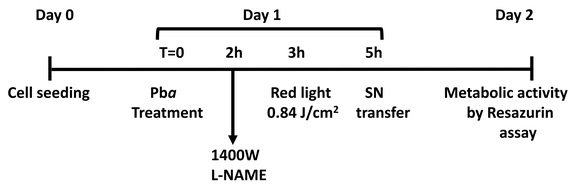
Can NO released by photooxidative stressed tumor cells affect the bystander cells?

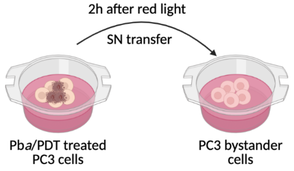
BACKGROUND: Photodynamic therapy (PDT) is a minimally invasive technique used in cancer treatment. It is based on the combination of a photosensitizer (PS), light and oxygen. This triad produces oxidative damage with the release of ROS and $^1O_2$. Not all cells in a given tumor are uniformly targeted by PDT. This situation depends on PS cellular uptake and on the light tissue penetration in the tumor, which may condition PDT efficacy. A high PDT insult leads to cell growth arrest, whereas a low PDT insult stimulates tumor cell growth, invasiveness and resistance.

AIM: Considering that low doses of NO, induced by Pb*a*/PDT in PC3 cells, play a cytoprotective role, we wanted to investigate whether this effect could be extended to «bystander» tumor cells.

RESULTS:

1. Low NO levels induced by Pba/PDT are able to stimulate «bystander» PC3 cancer cells





The supernatant (SN) of Pb*a*/PDT treated PC3 cells was transferred to untreated PC3 cells 2 h after irradiation.

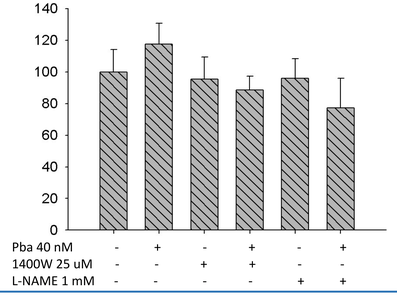


Fig. 1. Effect of NO derived from Pb*a*/PDT in stimulating untreated "bystander" cells using L-NAME and 1400W iNOS inhibitors. PC3 cells were treated in different ways as indicated in the x-axis. Values represent the mean ± SD obtained in two independent experiments.

2. The SN from PC3 cells treated with 40 nM Pb*a*/PDT is able to induce untreated «bystander» PC3 cells

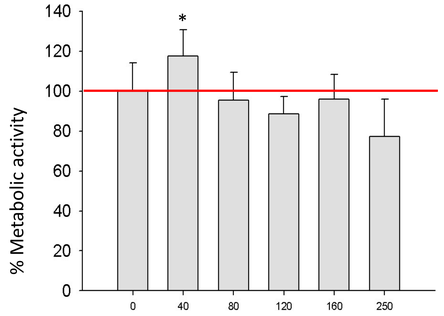


Fig. 2. Metabolic activity of Pb*a*/PDT-treated PC3 cells vs that of untreated "bystander" PC3 cells receiving the SN of PDT-treated cells. PC3 cells were treated in different ways as reported in the x-axis. Values represent the mean ± SD obtained in three independent experiments (Student's t-test; $P < 0.05$).

4. iNOS inhibition increases the efficacy of a low dose of Pb*a*/PDT, due to an increase in ROS production.

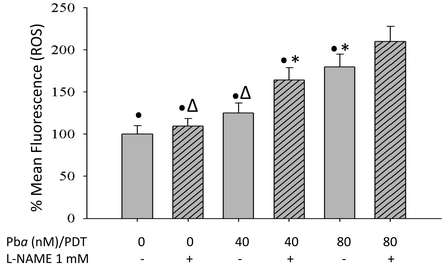


Fig. 4. ROS production in PC3 cells using Pb*a*/PDT and L-NAME iNOS inhibitor. PC3 cells were treated in different ways as indicated in the x-axis. Values represent the mean ± SD obtained in two independent experiments (Student's t-test; $P < 0.05$).

3. The SN derived from PC3 cells treated with 40 nM Pb*a*/PDT stimulates the migration of untreated «bystander» PC3 cells

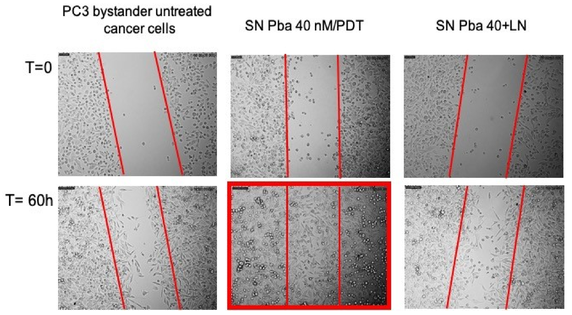


Fig. 3. PC3 cells vs untreated PC3 "bystander" cells receiving the SN of Pb*a*/PDT-treated cells. PC3 cells were treated with 40 nM Pb*a*/PDT. After the treatment a scratch wound was performed and the SN was transferred to untreated "bystander" PC3 cells. Images were taken every 6h.

CONCLUSIONS:

Our previous studies showed that a low dose of Pb*a*/PDT induces proliferation and survival of PC3 prostate cancer cells, while a high dose of Pb*a*/PDT inhibits cell growth.

A low dose of Pb*a*/PDT is able to stimulate the metabolic activity and migration of untreated «bystander» PC3 cancer cells, due to low NO levels that have cytoprotective and antioxidant properties.

FUTURE PERSPECTIVES:

To evaluate the molecular signaling pathways involved in «bystander» cancer cells stimulation.

To evaluate whether NO, induced by low Pb*a*/PDT, stimulates the tumor microenvironment (healthy prostate cells, macrophages,…).