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Coupled ROS and Ca^{2+} Sustained Activation in Cancer Cells Induced by Near-Infrared Laser Pulse: Application for Cancer Therapy

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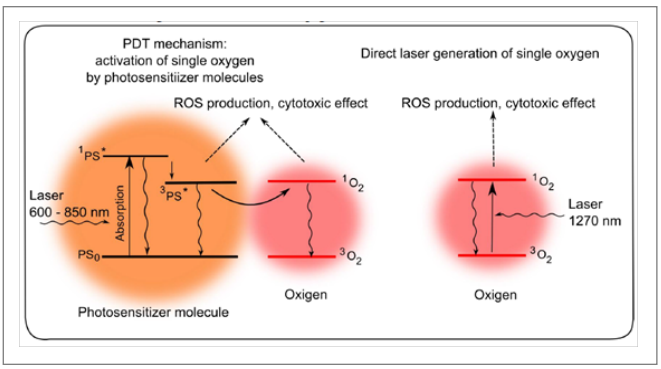
Abstract

Infrared quantum-dot laser diode irradiation (1268 nm) was observed to induce irreversible oxidative stress in cancer cells through direct triplet→singlet oxygen transition designating a novel cancer treatment equally with photodynamic therapy, PDT (Sokolovski, et al. Sci. Rep. 3:3484, 2013). A single laser pulse induction of reactive oxygen species (ROS) was attended with Ca2+ release and coupled ROS and Ca2+ sustained activation occurs far beyond the initial laser pulse exposure. Cancerous cells (HeLa) were observed to be more sensitive to laser-induced ROS generation then normal keratinocytes. The developed model of the laser-induced oxidative stress showed that the main impact on the cell oxidative state makes a cascade of secondary ROS triggered by primary laser-induced singlet oxygen and irreversible depletion of cellular antioxidant system in cancerous cells. We proposed the model of the amplification of laser-induced ROS generation due to the coupled ROS and Ca^{2+} activation through endoplasmic reticulum (ER) and mitochondria crosstalk.

Direct Laser-Induced Oxidative Stress vs. Photodynamic Therapy (Figure 1)

Kinetic model of redox homeostasis and its imbalance by laser-induced ROS generation in normal and cancerous cells



The model takes into account the following processes: (i) endogenous generation of primary ROS (O_2•, $^1O_2$,; (ii) their transformation into H_2O_2 by superoxide dismutase (SOD); (iii) generation of a secondary pool of ROS from H_2O_2 through the Fenton reactions (R2); and (iv) scavenging of H_2O_2 and its by-products by the cellular antioxidant system. In the enzymatic submodel of the H_2O_2 degradation is based on the redox cascade reactions which correspond to the key antioxidant cellular systems: thioredoxin peroxidase/thioredoxin/thioredoxin reductase (Tpx/Trx/TR) and glutathione peroxidase/glutathione/glutathione reductase (Gpx/GSS/GR) systems (Sokolovski, et al. Sci. Rep. 3: 3484, 2013) (Figures 2-10).

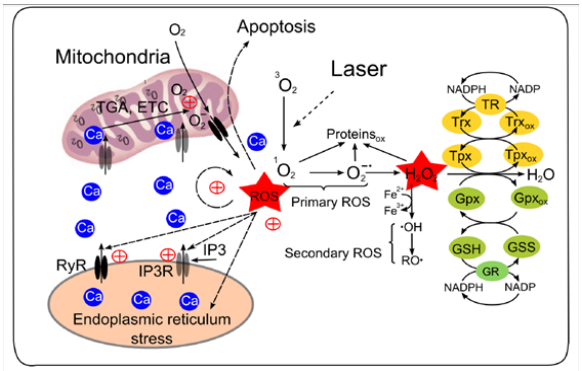
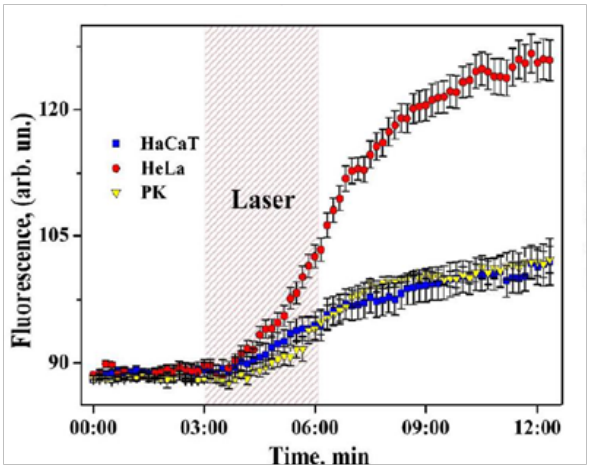


Figure 2: Model of laser- induced oxidative stress and mechanism of ROS amplification due to the coupled ROS and Ca^{2+} activation



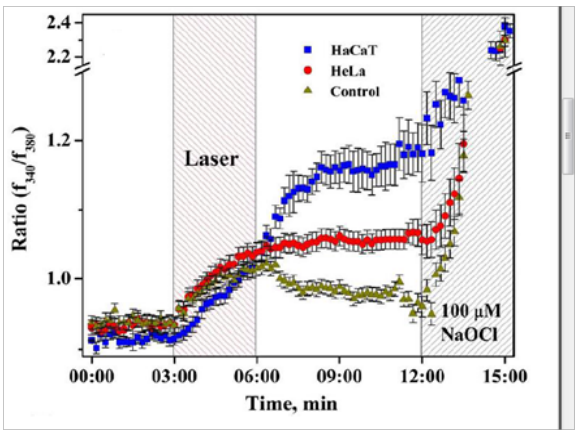


Figure 3,4: Coupled ROS (left) and Ca2+ (right) sustained activation induced by low energy near-infrared continuous wave laser pulse (1265 nm, 3 min, <200 J/cm2) in HaCaT (epidermal keratinocytes), HeLa (cervical cancer cells), and PK (primary keratinocytes) (Sokolovski, et al. Sci. Rep. 3 : 3484, 2013).

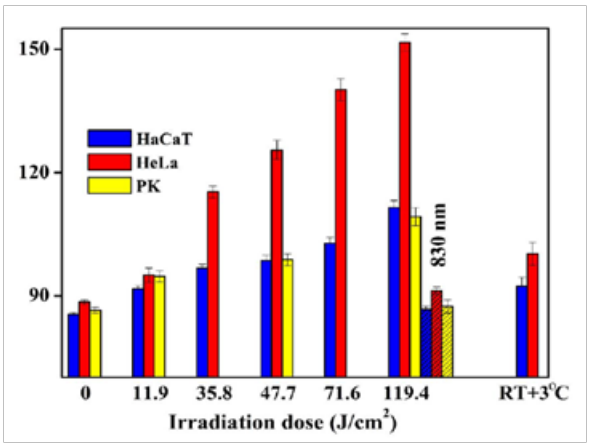


Figure 5: Dose-dependency of ROS concentration (fluorescence) in cell lines (12th min). 830 nm laser irradiation taken as a negative control.

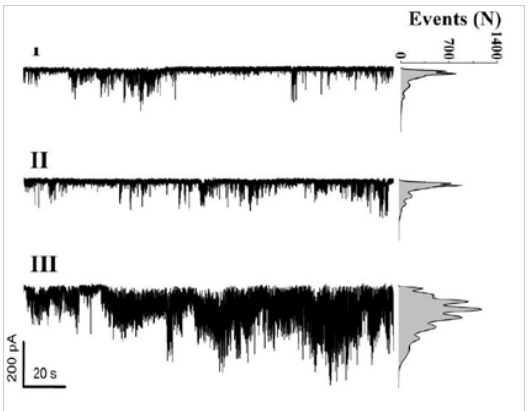


Figure 6: Single Ca^{2+} channel currents recorded before (I), during (II), and after (III) 1268 nm laser irradiation of 47.7 J/cm^2. Right: opened channel events amplitude.

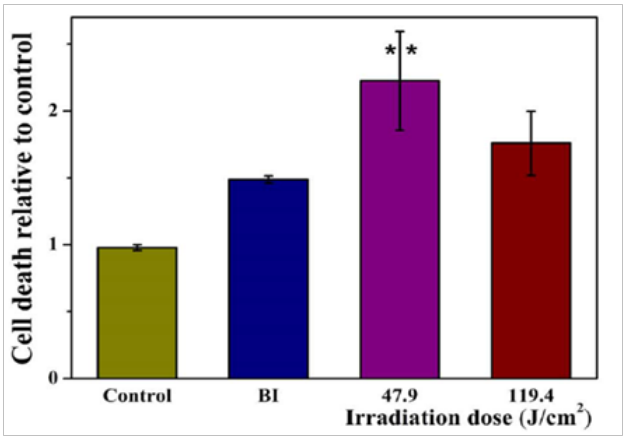


Figure 7: Laser-triggered cancer cell death. HeLa cell death rate measured by an enzymatic assay of LDH release.

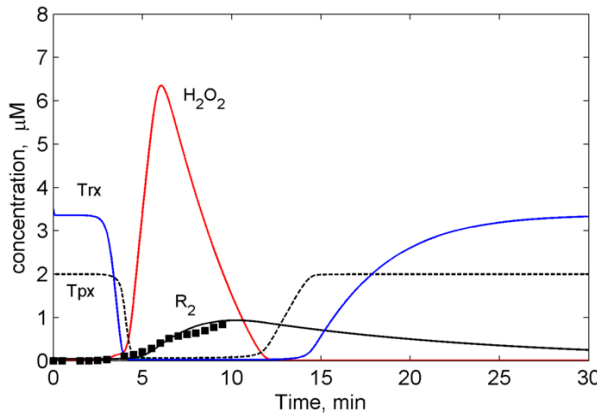


Figure 8: Results of the computational modelling: Suppression of laser-induced oxygen radicals (RO•) in normal cells by antioxidant cellular system (Tpx/Trx). Points – experimental data.

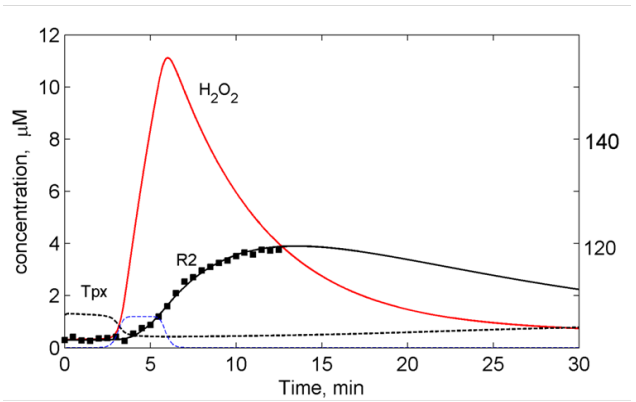


Figure 9: Results of the computational modelling: Sustained oxygen radical (RO•) induced by laser. Depletion of the antioxidant cellular system (Tpx/Trx) by laser-induced ROS. Points – experimental data.

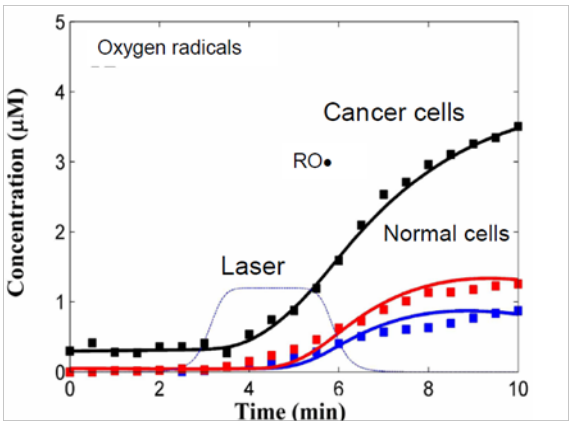


Figure 10: Sensitivity of cancer cells to laser-induced oxidative stress. Computational modelling of ROS generation by laser-induced single oxygen in normal cells (red, blue) and cancerous cell (black) at the different rate of single oxygen generation V1 (blue, black) and V2>V1 (red). Points – experimental data.

Conclusions

The joint *in vitro* and *in silico* investigation revealed hypersensitivity of cancer cells to 1268 nm laser-induced oxidative stress. The proposed amplification mechanism of laser-induced ROS due to the coupled ROS and Ca^{2+} activation through ER and mitochondria crosstalk is suggested to cause apoptosis in cancerous cells not damaging normal cells. The obtain results may propose a novel therapeutic approach based on direct laser photoactivation of molecular oxygen in the tumour without the need for exogenous drugs and gain opportunity to develop PS-free cancer phototherapy.

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