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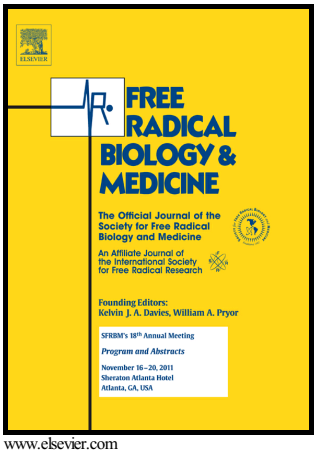


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# Enhanced Aggressiveness of Bystander Cells in an Anti-tumor Photodynamic Therapy Model: Role of Nitric Oxide Produced by Targeted Cells

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## ABSTRACT

The bystander effects of anti-cancer ionizing radiation have been widely studied, but far less is known about such effects in the case of non-ionizing photodynamic therapy (PDT). In the present study, we tested the hypothesis that photodynamically-stressed prostate cancer PC3 cells can elicit nitric oxide (NO)-mediated pro-growth/migration responses in non-stressed bystander cells. A novel approach was used whereby both cell populations existed on a culture dish, but made no physical contact with one other. Visible light irradiation of target cells sensitized with 5-aminolevulinic acid-induced protoporphyrin IX resulted in a striking upregulation of inducible nitric oxide synthase (iNOS) along with NO, the level of which increased after irradiation. Slower and less pronounced iNOS/NO upregulation was also observed in bystander cells. Activation of transcription factor NF-κB was implicated in iNOS induction in both targeted and bystander cells. Like surviving targeted cells, bystanders exhibited a significant increase in growth and migration rate, both responses being strongly attenuated by an iNOS inhibitor (1400W), a NO scavenger (cPTIO), or iNOS knockdown. Incubating bystander cells with conditioned medium from targeted cells failed to stimulate