Photothermal ablation of tumor vasculature via VEGFr targeted nanoshells

Amanda R. Lowery[1], Naomi J. Halas[2], and Jennifer L. West[1]
Department of [1]Bioengineering, [2]Electrical and Computer Engineering, Rice University, Houston, TX, USA

Introduction: Photothermal cancer therapy using targeted nanoshells may enable the preferential destruction of cancer cells while minimizing damage to healthy tissue. Nanoshells possess an optical tunability that spans the visible to the near infrared (NIR) region [1]—a region where light penetrates tissues deeply. Conjugated with tumor-specific antibodies, NIR absorbing nanoshells could be systemically injected and preferentially bound to tumor sites. NIR light heats the tumor-bound nanoshells, thus destroying the tumor. *In vitro* and *in vivo* studies have confirmed the ability to selectively induce cell death with the photothermal interaction of nanoshells and NIR light. Previous studies have demonstrated the ability of PEG-coated nanoshells to passively accumulate at a tumor site through the leaky vasculature that is characteristic of neoplastic tumors [2] Complete regression of tumors has been observed in animals receiving systemic injections of nanoshells prior to NIR laser treatment [2]. Furthermore, the tissue damage from the NIR laser therapy is confined to the tissue region receiving both NIR absorbing nanoshells and laser irradiation [3]. Nanoshells can be targeted to cancer cells or the tumor vasculature by the conjugation of tumor-specific antibodies to the gold surface. The ligand vasculature endothelial growth factor (VEGF) is used here to target the VEGF receptors and demonstrate the feasibility of an anti-angiogenic strategy.

Methods: Gold nanoshells were manufactured as previously described [1,4]. Briefly, silica cores were fabricated by the Stöber method in which tetraethoxysilane is reduced in basic ethanol [5]. Following amine functionalization, gold colloid (~ 3 nm) was adsorbed to silica surface. Reduction of additional gold completes the shell. Nanoshells were evaluated by their optical absorption profiles and SEM. The nanoshells used in the following study had a 110 nm core diameter with a 10 nm thick gold shell and a peak extinction at ~800 nm. VEGF was conjugated to the gold nanoshells through a bi-functional PEG linker, with an N-hydroxysuccinimide terminus for antibody coupling and a disulfide terminus for attachment to the gold surface.

In vitro, targeted nanoshells were incubated with the mouse endothelial Miles Sven 1 (MS1) cells. Unbound nanoshells were rinsed from the surface with PBS. Control cells were incubated with PEG-coated nanoshells. After exposure to NIR light (820 nm, 1.55 W, 1.5 mm diameter spot, 7 min), the cells were incubated overnight at 37°C. Cell viability was assessed with calcein AM and ethidium homodimer staining. Nanoshells were visualized by silver staining.

In vivo, targeted nanoshells were injected into the tail vein of mice bearing small CT-26 tumors. Nanoshells were allowed to circulate and bind to the tumor. Then tumors were irradiated with the NIR light (4 W/cm^2, 3 min) and monitored for growth and regression.

Results / Discussion: *In vitro*, cell death was confined within regions receiving targeted nanoshells and laser irradiation (Fig. 1). Silver staining verified the presences of nanoshells. Control nanoshells did not bind to the cells, as indicated by silver staining, and cells continued to be viable after irradiation. *In vivo*, tumors receiving the PEGylated and VEGF-nanoshells before irradiation regressed while tumors receiving irradiation without nanoshells continued to grow.

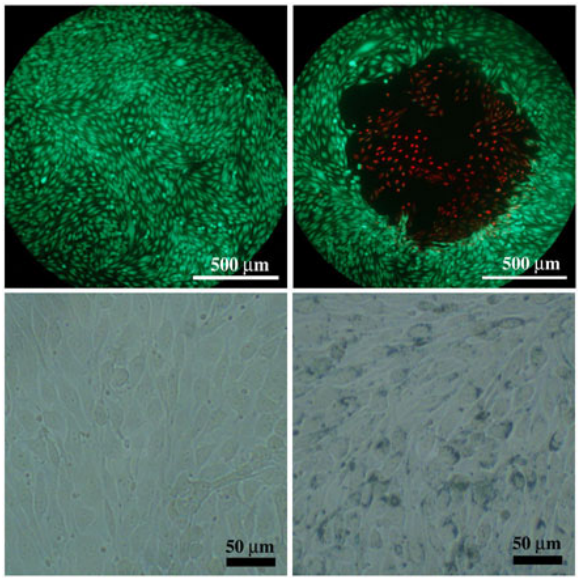

Figure 1. Left: PEGylated nanoshells did not bind to cells (bottom) and cell continued to be viable after laser exposure (top). Right: The angiogenic MS1 cells bound VEGF-nanoshells (bottom) and within the laser spot, cells were ablated (seen in red, top).

Conclusions: Nanoshells show promise as a minimally invasive cancer therapy. Nanoshells are biocompatible and display selective photothermal destruction of tissue by absorption of NIR light. Targeting may improve the cellular specificity of the nanoshell therapy.

References:

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