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Molecular Enhancement of Thermal Ablation Therapies Using TNF-α-Coated Gold Nanoparticles in a Translational Model of Renal Tumors

R. Pedro, K. Thekke-Adiyat, M. Shenoi, R. Goel, S. Schmechel, J. Slaton, J. Bischof, and K. Anderson
University of Minnesota, Minneapolis, USA

Thermal ablation therapies are currently used for the treatment of select renal masses. Such treatments are limited to tumors that are small (<3 cm diameter), exophytic, and away from vital structures such as ureter or intestine. Novel treatment approaches are geared towards increasing the size of the thermal lesion created, limiting damage to collateral normal tissues, reducing local recurrence and distant metastases as well as improving the imaging potential of the therapy. Previous studies have demonstrated the enhancement of thermal therapies in pre-clinical murine models of solid tumors by intravenously infusing 33 nm TNF-α and PEG coated gold nanoparticles (CYT-6091, Cytimmune Sciences Inc.) prior to ablation. This study investigates the enhancement of thermal ablation therapy by CYT-6091 in a translational animal model of renal tumors. New Zealand White rabbits (37 for radiofrequency ablation (RFA), 20 for cryoablation) had VX-2 tumors implanted into their bilateral kidneys. The tumors were allowed to grow for 14 days to a size of ~1 cm. For RFA, the rabbits were split into 3 treatment groups of 10 rabbits each and a sham group of 7 rabbits. The groups were treated with CYT-6091 (200 μg/kg) only, RFA only, or CYT-6091 (200 μg/kg) followed 4 hours later by RFA. For cryoablation, 2 treatment groups of 10 rabbits each were used. The groups were treated with cryoablation only or CYT-6091 (200 μg/kg) followed 4 hours later by cryoablation. The kidneys were harvested 3 days later for RFA and 7 days later for cryoablation. Gross and microscopic measurements of the ablation size as well as histological analysis using H&E staining were performed. The RFA plus CYT-6091 group had a larger zone of complete cell death than the RFA only group when measured both on gross sectioning (0.32 ± 0.03 vs. 0.22 ± 0.07 cm^3, $p = 0.015$) and on microscopic examination (0.30 ± 0.07 vs. 0.23 ± 0.03 cm^3, $p = 0.03$). Overall this was a 23% increase in ablation volume. This difference in ablation size was due to a replacement of partially ablated tissue at the periphery in the RFA only group by completely ablated tissue in the RFA plus CYT-6091 group. Thus this zone of partially ablated tissue was smaller in the RFA plus CYT-6091 group than the RFA only group (0.08 ± 0.02 cm^3 vs. 0.13 ± 0.05 cm^3, $p = 0.01$). Excessive tumor growth into the ablation lesion at day 7 following cryoablation prevented accurate measurements in these groups; however, a significant decrease in the rate of peritoneal carcinomatosis (metastases) was obtained in the cryo plus CYT-6091 group compared to the cryoablation alone group (1/10 vs. 8/10, $p = 0.04$). We have shown that use of CYT-6091 prior to thermal ablation therapy in a rabbit kidney tumor model can minimize the zone of partial treatment at the periphery of the thermal lesion and thus maximize the complete kill zone in RFA while significantly decreasing the rate of metastases in cryoablation. These data provide preliminary evidence for the efficacy of adjuvant use of CYT-6091 for thermal ablation therapies in a large animal translational tumor model.

Cell Motion in a Two-Stream Microfluidic Channel

J. Hanna, T. B. Darr, and A. Hubel
Department of Mechanical Engineering, University of Minnesota, 111 Church St. SE, Minneapolis, MN 55455

C. Mata and E. K. Longmire
Department of Aerospace Engineering and Mechanics, University of Minnesota, 110 Union St. SE, Minneapolis, MN 55455

D. H. McKenna
Department of Laboratory Medicine and Pathology, University of Minnesota, 420 Delaware, Minneapolis, MN 55455

Microfluidic channels have been proposed as a method for removal of cryoprotective agents from cell suspensions [Fleming, Longmire, and Hubel, J. Biomech. Eng. 129, 703 (2007)]. The device tested consists of a rectangular cross section channel of 500 μm depth, 25 mm width, and 160 mm length, through which a cell suspension and wash stream flow in parallel. Cryoprotective agents diffuse from the cell stream to the wash stream and the wash stream is discarded. The washed cell stream is then ready for use. This device must be capable of removing 95% of the dimethyl sulfoxide (DMSO) from the cell stream with minimal cell losses. Our previous studies have demonstrated our ability to remove DMSO [Mata, Longmire, McKenna, Glass, and Hubel, Microfluid. Nanofluid. 5, 529 (2008)]. The next phase of the investigation involves characterizing the influence of flow conditions on cell motion through the device. To that end, Jurkat cells (lymphoblasts) in a 10% DMSO solution were flowed through the microfluidic channel in parallel with a wash stream composed of phosphate buffered saline solution (PBS). Average cell stream velocities were varied from 0.94 to 8.5 mm/s (Re 1.7 to 6.0). Cell viability at the outlet was high, indicating that cells are not damaged during their passage through the device. Gravitational settling caused an accumulation of cells near the bottom of the channel, where flow velocities are low. Cell settling leads results in an initial transient period for cell motion through the device. For the initial portion of cells flowing through the device, cells tend to accumulate in the device until a critical device population time is reached. Cell recovery (number of cells out of the device divided by the number of cells input to the device) is high (90–100%) after the device has been fully populated. For a single stage device with average cell stream velocities of $\geqslant$6 mm/s, cell recovery was 90–100%. As more stages are added to the device, the population time for the device increases. Gravitational settling of cells also leads to a time-varying cell concentration from the input syringe to the inlet of the channel, as well as cell losses due to cells remaining in the horizontally-oriented syringe. Reorienting the syringes to a vertical position eliminates these losses. Cell motion within the channel can be modulated by the flow conditions used. For sufficiently high Reynolds numbers, the Segre-Silberberg effect [Segre and Silberberg, J. Fluid Mech. 14, 115 (1962)] can be used to move cells from the low velocity region of the cell stream to a higher velocity region thereby reducing the transient portion of processing the cells and improving overall recovery of cells through the device.

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