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Implication of Plasmonic Photo Thermal Therapy in Treatment of Pet Animals Breast Cancers and Preventing Recurrence or Metastasis

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Abbreviations

PPTT: Plasmonic Photothermal Therapy; IFP: Interstitial Fluid Pressure; CTC: Circulatory Tumor Cells; TAMs: Tumor Associated Macrophages; CAFs: Carcinoma Associated Fibroblast Cells; MDSCs: Myeloid Derived Suppressor Cells; DTCs: Disseminated Tumor Cells; ADCC: Antibody Dependent Cytotoxic Cell Mechanism; BCSCs: Breast Cancer Stem Cells; TNT: Triple Negative Tumor Cells; TA: Tumor Antigens

Mini Review

The available conventional therapies (i.e. chemotherapy and radiation) for cancer treatment have poor specificity, dose sensitivity and bioavailability. Moreover, they do not sharply differentiate between cancerous and normal cells and also development of drug resistance may lead to further complications during course of treatment. At present, surgical resections are coupled with chemotherapy or radiotherapy to avoid tumor in situ recurrence or distal metastasis which might occur even after complete surgical resection. In light of the short comings of current treatment modalities for cancer, new approaches toward improving cancer therapy are designed to specifically target therapeutic agents to tumor cells while sparing healthy tissues from haram. This is one of the emerging interests in nanotechnology researches. Among the many experimented devices in treatment of therapy, plasmonic photothermal therapy (PPTT) went beyond in vitro and in vivo experiments to clinical application. Elsayed group is the first who applied PPTT as a treatment of naturally diseased pet animals with malignant mammary tumors as a model for human breast cancer PPTT. This treatment alone induced complete ablation of small (<10 cm^3) mammary gland tumors.

To avoid the obstacles in intravenous administration of gold nanorods (AuNRs) to the site of tumors, the researchers introduced AUNRs directly into the tumor in a dose of 50 µl/cm^3 of tumor mass, taking in consideration even distribution in tumor particularly the junction between tumor and bed of the tumor, followed by exposure of the inoculated tumor to near infrared (NIR) laser irradiation. NIR-Laser irradiation was tuned to induce intratumor heat (mild hyperthermia) with temp of 42 - 46 °C to avoid the burning of tissues and to kill target cells (cancer cells and cancer associated cells) while the normal cells surviving without any damage. Sparing of normal cells resulted from poor permeability of their cell membrane to AUNRs uptake and hence weak induction of hyperthermia. Moreover, normal cells are protected from heat via production of heat shock proteins which are lacking in cancer cells and render them more fragile and more sensitive to hyperthermia. All treated mammary tumors showed no in situ recurrence or distal metastasis *[1]*.

In large mammary (>10cm^3) congested and inflamed tumors, PPTT alone showed weak recovery response and this can be attributed to uneven distribution of AUNRs intratumor due to presence of interstitial fluid pressure (IFP) and over production of extracellular proteins by protumorigenic carcinoma associated fibroblast cells (CAFs). To solve this problem the group selected another approach, which was formed of a combination of surgery (mastectomy) followed by adjuvant therapy with PPTT. To inhibit the in situ recurrence of tumors, the whole wound margins tissues (fascia of the tumor) were inoculated with AUNRs in addition to spraying the whole wound surface (bed of tumor) with AUNRs to eradicate any occult cancer cells remained during surgery. After AUNRs application whole the wound margins and the wound surface were exposed to NIR-Laser irradiation followed by wound suturing. Complete wound healing without scar formation was noticed 2 weeks post operation.

It was interesting to notice that all treated animals with PPTT alone or in combination with surgery did not develop any in situ tumor recurrence or metastasis with long free survival reached to 4 years (equal to 24 years in human or more) *[2]*. This indicated that PPTT could eradicate cells encountered in tumor recurrence and distal metastasis. Elsayed group performed further investigations to elucidate the mechanism of PPTT tumor ablation and prevention of recurrence and metastasis. In the light of tumor hallmarks, we studied the PPTT killing of cancer cells and cancer associated cells and its effect on angiogenesis, tumor vasculature tumor immune systems cells, circulatory tumor cells (CTC) and disseminated tumor cells. The essence of PPTT is higher uptake of AUNRs because the highly proliferative cells having altered hyper

permeable cell membranes. These two phenotypic properties are accepted by fibroblast cells and macrophages in tumor microenvironment (TME). Breast cancer cells recruit fibroblast cells and macrophages through direct inter-relationship and by paracrine cytokines, chemokines and other growth and angiogenic factors produced by cancer cells thus producing what is called carcinoma associated fibroblast cells (CAFs) and tumor associated macrophages (TAMs). Moreover, this protumorigenic TME exerts its effect on other cells recruited from bone marrow to the site of tumor resulting in reprogramming of their genetic makeup inducing development of some cancerous properties such as high proliferation and altered cell membranes *[3]*. Of these cells are infiltrating tumor-T regulatory cells (iT-Tregs) and myeloid derived suppressor cells (MDSCs). These cells uptake AUNRs higher than their normal encounter cells. Immune system cells are suppressed by immune suppressive components in TME, and they remain in quiescent state during oncogenesis.

To elucidate the killing effect of PPTT on cancer cells and cancer associated cells such as TAMs, CAFs, iT-Tregs and MDSCs, breast cancer cells were numbered before and after PPTT. The extent of biomarkers mRNA expression level is related to the number of expressing cells. Biomarker specific gene for each type of these cells was selected to be assayed before and after PPTT treatment by application of quantitative real time polymerase chain reaction (q RT-PCR). CD163 was selected as biomarker for proliferative TAMs, BRCA1, BRCA2, P53 and Ki67 for breast cancer cells, Nanog for breast cancer stem cells and VCAM-1 for endothelial cells lining tumor vasculature. IL-10 and IL-12 were used as biomarkers for assaying activity of the immune cells. It was reported that the level of mRNA expression decreased significantly after 5 minutes of PPTT and decreased to minimum through 2 weeks. These results indicated that PPTT kill almost all cells after 5 minutes exposure and decreased to minimum after 2 weeks. As specific biomarkers for some cells such as CAFs, iT-Tregs and MDSCs remain in confusion. But due to the high proliferation and altered cell membranes permeability, these cells uptake gold nanorods more than their normal counterpart cells. Therefore, they became more sensitive to PPTT effect lead to their killing. PPTT is also destructive to tumor vasculature which resulted in gradual shrinkage of tumor size during treatment. The tumor vasculature is eradicated through two mechanisms. The first is internalization of AUNRs by hyper permeable endothelial cell membrane and intravasation of AUNRs via gaps between endothelial cells lining the lumen of the vasculature. After NIR-Laser irradiation, the endothelial cells are destroyed by intracellular hyperthermia and the induced hyperthermia in intravascular lumen promotes the sluggish flow of blood.

The second mechanism is the prevention of new tumor vasculature synthesis due to eradication of cancer cells and cancer associated cells which are the source of the angiogonic factors. PPTT play a key role in restoring the immunological activity of local and systemic immune response. Mild hyperthermia kills tumor cells by apoptosis, but not necrosis releasing DAMPs (damaged associated molecular patterns) including tumor antigens (TA). Dendritic cells uptake DAMPs and present the tumor antigens to Th1 and CD8+ cells in the drainage lymph node. Macrophages also phagocytose DAMPs and present them to Th2 and B lymphocytes to activate humoral immune response. Effector T cytotoxic cells and antibodies enter circulation to reach the site of tumor and cytotoxic CD8 eradicate the present tumor cells in tumor site and in circulation where they induce cytotoxicity to circulatory tumor cells (CTCs) and disseminated tumor cells (DTCs). Antibodies against tumor antigens help the eradication of tumor cells in tumor site and other sites via the antibody dependent cytotoxic cell mechanism (ADCC). At the same time eradication of the source of immunosuppressive cytokines (BCSCs, CAFs, TAMs, Trigs and MDSCs) eliminate the immune suppressive effect on natural killer cells (NK) which restore their cytotoxic activity against cancer cells in tumor site and in circulation. Therefore, CTC and DTCs are eradiated by three cytotoxic mechanisms: cytotoxic T lymphocytes, ADCC and NK cells.

Another tumor hallmark is the invasion and metastasis of breast cancer stem cells (BCSCs) from the tumor site to enter circulation and from circulation to distal organs to persist as disseminated tumor cells. BCSCs encountered in recurrence and metastasis are eradicated by two mechanisms. The first mechanism is the eradication from tumor site by PPTT-direct killing. BCSCs and triple negative tumor cells (TNT) are highly sensitive to PPTT *[4]* and disappearance of NANOG mRNA confirmed the eradication of its source which is BCSCs. The second mechanism is elimination of CTCs and DTCs by cytotoxic T lymphocytes resulted by cell mediated immune response with a phenomena defined as abscopal effect.

It can be concluded that PPTT is a very promising treatment for breast cancer due to its high efficiency to eradicate cancer cells either alone (in case of small tumor) or in combination with surgery. Moreover, PPTT eradicates CTCs and DTCs which are the precursors of in situ recurrence or distal metastasis.

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