Combining Biological and Physical Approaches to Cancer Treatment

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Introduction

Hyperthermia is the heating of a tumor using a variety of heat transfer methods continue to be an active area of cancer research. It is mostly used as an adjuvant therapy to radiotherapy or chemotherapy, however, hyperthermia has as much promise as a primary treatment without the possible side effects. The most common treatments are radiofrequency, microwave and magnetic nanoparticle hyperthermia, which uses the injection of nanoparticles and their local activation using alternating magnetic fields to heat the tumor. Heat affects the architecture of cellular cytoskeleton, the molecular transport across the cell membrane, and the function of receptors, in a dose and time-dependent manner. [1]

The primary focus of my undergraduate research project is to understand biological tools and cancer immunology, and exploit the immune system to benefit cancer treatments using magnetic nanoparticle hyperthermia.

Magnetic nanoparticle hyperthermia

During this hyperthermia treatment nanoparticles are injected, either systemically or non-systemically, and about a fraction of these particles will go to the tumor, the rest will eventually end up in the spleen or the liver. With further research, targeting the nanoparticles to the tumor can become more efficient.

The nanotechnology approach to hyperthermia treatments uses electro-magnetic fields as external source of energy, and magnetic nanoparticles (MNPs) as receiver and local heat transducer. While there are a number of effects occurring in MNPs, the heat generation mechanism can be attributed to two different phenomena: relaxation and hysteresis loss.

Specific absorption rate (SAR) or specific loss power (SLP) terms are generally used to define the transformation of magnetic energy into heat. Localized heating utilizing various iron-oxide superparamagnetic magnetic nanoparticle has been studied by our group [2].

Cancer immunology

The reason that malignant cells can develop into tumors in the first place, is due to a lack of the immune system to thoroughly remove the potential cancer cells. This results from the tumor cells using a variety of tools to hide from immune system as well as ways to survive harsh environments. Two of them are CD47 and PD-L1, proteins that are expressed on the surface of cancer cells to enable the escape of the immune-surveillance [3].

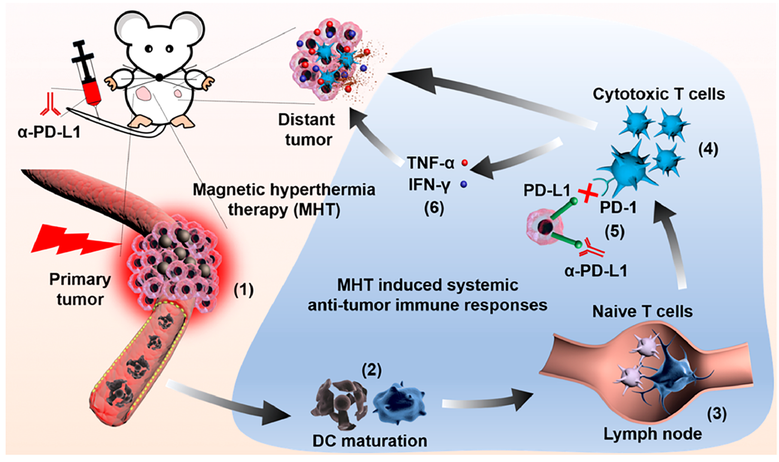
The way to counter the hiding qualities of CD47 and PD-L1 in tumor cells is use of calreticulin which is a calcium based enzyme that connects to outside of a cell that has gone through apoptosis (in this case it is induced by the heat from the hyperthermia treatment).

Although studies are unsure of how to increase the rate of calreticulin production, the binding of this chaperone is acidic region dependent [4].

Another way the tumor cells protect itself is the use of heat shock proteins, which are released when cancer cells are subjected to a stressful environment. The proteins used by the tumor are MTA1 and HIF1. MTA1 is used by cancer cells to cope with the constant stress environment that they are subjected to, such as hypoxia, lack of blood flow, lack of nutrition, and immune response attacks. MTA1 was tested to also inhibit protein breakdown which results in upregulation of proteins of HIF1, and both work together to promote antigenesis and improves the condition nourishment and oxygen supply to the tumor. When these heat shock proteins are released, this triggers an immune response in which the immune system interact with the HSP-antigens and then using these antigens to locate and destroy other potential future malignancies.

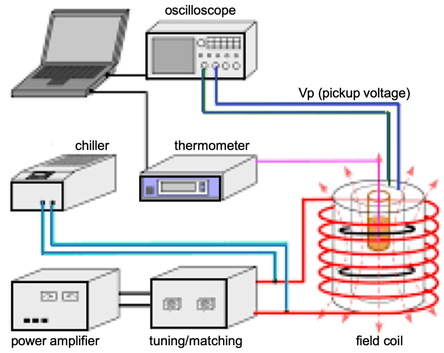
Despite these immunities utilized by the tumor cells, hyperthermia has a away to counteract these effects. For the calreticulin, although studies are unsure of how to increase the rate of production, calreticulin binding is dependent upon acidic regions, and hyperthermia treatment increases the acidity of the both the environment inside the tumor and around the tumor, therefore increasing the rate of binding. For the induction of heat shock protein release, the magnetic nanoparticle hyperthermia rapidly heats up the tumor, which causes a surge of the proteins to be released. Which will then activate the immune response that will kill future cancer cells, this process is represented in the graphic below.

Novel immunotherapy approach

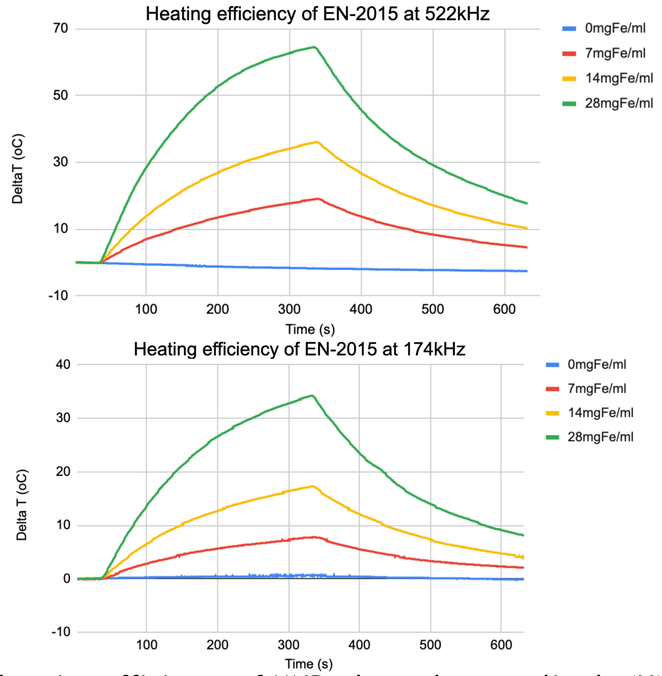


The tumor (1) is being exposed to Iron nanoparticles which releases the heat shock proteins which are then picked up by naive dendritic cells. The dendritic cells (2) then proceed to the lymph nodes where the Naive T cells (3) are exposed to the now mature dendritic cells. The mature dendritic cells (4) leave the lymph node to find and eliminate any other cells (5) that exhibit the TNF-alpha and INF-gamma proteins (6) [5].

Initial Experimental Results



A laboratory hyperthermia system was employed to generate an alternating magnetic field (AMF) at a discrete frequencies of 174 kHz and 522 kHz with a field amplitude of 5 kA/m. A thermoelectric solid state recirculating chiller (ThermoCube 400, Solid State Cooling Systems Inc.) is used to remove the heat by the field coil. The temperature of the sample suspension was measured every 1s using a fiber optic GaAs temperature sensor (T1, Neoptix, Inc.) with a resolution of 0.1°C digitized via RS232 In Labview (National Instruments). The MNPs used were magnetite (Fe_3O_4) magnetite/dextran core-shell nanoparticles of 60 nm (hydrodynamic diameter) - EM-2015 [Endomag UK]



The heating efficiency of MNPs depend on amplitude (H) and frequency (f) of AMF but also change with surrounding environment e.g. for those particles internalized within the cells – my future experiments will study heating efficiency of cell cultures.

References

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