Targeted Magnetic Intra-Lysosomal Hyperthermia produces lysosomal reactive oxygen species and causes Caspase-1 dependent cell death of cancer cells.

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Purpose: Cancer is a leading cause of death with millions of new people diagnosed with cancer every year. One major difficulty in anti-cancer therapy is the multidrug resistance which appears during treatments. Recently, studies have shown that cancer cells resistant to traditional therapies are sensitive to agents that induce lysosome membrane permeabilization causing lysosomal cell death. To date, lysosomal cell death has been obtained using lysosomotropic agents which could not selectively target lysosomes of tumoral cells. In this context, nanotherapy based on Magnetic Intra-Lysosomal Hyperthermia (MILH) generated by magnetic nanoparticles (MNPs) that are grafted with ligands of receptors overexpressed in tumors appears to be a very promising therapeutic option. Strikingly, in such approach, no perceptible temperature rise in the cell medium occurred during high frequency alternating magnetic field (AMF) exposure. Thus, MILH differs from standard magnetic hyperthermia whereby tumor eradication is achieved with large doses of MNPs which cause a temperature elevation of the whole tumor. As a proof-of-concept, we previously showed that minute amounts of iron oxide MNPs targeting gastrin receptor (CCK2R) are internalized by tumoral cells through a CCK2R-dependent physiological process, accumulated into their lysosomes and killed tumoral cells upon AMF application through lysosomal cell death [1,2]. However, mechanisms whereby MILH induces cell death are still elusive. Herein, we provide evidences that MILH causes cell death through a non-apoptotic signaling pathway.

Experimental Design: Cancer cells having internalized and accumulated gastrin-grafted MNPs in their lysosomes were exposed to alternating magnetic field (AMF: 40mT, 275kHz). Then, the different biological effects involved in cell death were analyzed following AMF exposure.

Results: The mechanism of cell death involves temperature elevation at the nanoparticle periphery which enhances the production of reactive oxygen species through the lysosomal Fenton reaction. Subsequently, MILH induces the lipid peroxidation of the lysosome membrane, lysosomal membrane permeabilization and the leakage of lysosomal enzymes into the cytosol, including Cathepsin-B which activates Caspase-1 but not the apoptotic Caspase-3 [3]. Moreover, the combination of MILH with doxorubicine decreased tumoral cell survival with an efficiency near to the additivity of individual treatments which respectively activate Casp1 and Casp-3 dependent cell death.

Conclusion: These data highlight the clear potential of MILH for the eradication of tumors overexpressing receptors which can be adapted to eradicate all cancer cell types including apoptosis-resistant cancer cells.

References: