

Targeted nanotherapy of endocrine tumors by magnetic intra-lysosomal hyperthermia (MILH).

Veronique Gigoux

Team INSERM ERL1226: Receptology and Targeted Therapy of Cancers
Laboratory LPCNO, CNRS UMR5215-INSA, University of Toulouse, Toulouse, France
Contact : veronique.gigoux@inserm.fr

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 (LMP) causing lysosomal cell death (LCD) which displays necrotic or apoptotic features. To date, LCD has been obtained using lysosomotropic agents which could not selectively target lysosomes of tumoral cells. Thus, the development of an efficient LCD-targeting therapy constitutes a promising challenge as a new targeted anti-tumoral therapeutic approach. Magnetic intra-lysosomal hyperthermia (MILH) represents an effective way to trigger LCD specifically in cancer cells. Indeed, magnetic nanoparticles (MNPs) offer the potential to be driven into the lysosomes of cancer cells by grafting them with ligands or antibodies recognizing receptors overexpressed in tumors and able to internalize after activation. Moreover, targeted MNPs eradicate cancer cells by MILH upon application of a high frequency alternating magnetic field (AMF).

As a proof-of-concept, we showed that minute amounts of iron oxide MNPs targeting gastrin receptor (CCK2R) are internalized by tumoral cells through CCK2R-dependent physiological process, accumulated into their lysosomes and killed tumoral cells through LCD upon AMF application (275 kHz, 40 mT) [1,2]. Moreover, no perceptible temperature rise in the cell medium occurred during AMF application {Sanchez, 2014 #60; Domenech, 2013 #51; Creixell, 2011 #56}. We thus termed this approach: magnetic intra-lysosomal hyperthermia (MILH) which differs from magnetic fluid hyperthermia whereby tumor eradication is achieved with large doses of MNPs which cause temperature elevation of the whole tumor. We investigated the mechanism of cell death and demonstrated that MILH induced reactive oxygen species production, lysosomal damage leading to the leakage of lysosomal enzymes into the cytoplasmic compartment and to cell death. Moreover, ROS production and lysosome membrane permeabilization were detected only 30 minutes after AMF application, demonstrating that they occur at an early stage in the cascade of events leading eventually to cell death. We are currently seeking to clarify the mechanisms involved in cell death in MILH condition, especially the signaling pathway activated downstream of lysosomal damage.

In conclusion, our results strongly support the potential of lysosomal damage induced by MILH as a therapeutic strategy to eradicate specifically tumoral cells by using lysosome-targeting MNP. These data are very promising in light of the recent concept that induction of LMP has widely appeared as an efficient way to eliminate apoptosis-resistant cancer cells and that some lysosome-targeting drugs can also re-sensitize multi-drug resistant cancer cells to classical chemotherapy.

References

- [1] Sanchez C et al. (2014) Targeting a G-Protein-Coupled Receptor Overexpressed in Endocrine Tumors by Magnetic Nanoparticles To Induce Cell Death. *ACS Nano* 8(2):1350-63.
- [2] Connord V et al. (2015) Real-time Analysis of Magnetic Hyperthermia Experiments on Living Cells under Confocal Microscope. *Small* 11(20):2437-45.