Magnetic hyperthemia and mechanical ablation induce an anti-tumour immune response in pancreatic adenocarcinoma

Angela Agaësse[1], Justine Journaux[1], Pascal Clerc[1], Megi Bejko[2], Julien Carrey[3], Auriane Bagur[2], Olivier Sandre[2], Stéphane Mornet[4], Mary Poupot[1], Véronique Gigoux[1]

[1]Centre de recherches en cancérologie de Toulouse (CRCT), INSERM U1037, Toulouse, France.
[2]Laboratoire de chimie des polymères organiques (LCPO), CNRS, Univ. Bordeaux, Bordeaux INP, Pessac, France.
[3] Laboratoire de physique et chimie des nano-objets (LPCNO), INSA, CNRS UMR5215, Toulouse, France.
[4]Institut de chimie de la matière condensée de Bordeaux (ICMCB), CNRS, Univ. Bordeaux, Bordeaux INP, Bordeaux, France.

angela.agaesse@inserm.fr

Pancreatic ductal adenocarcinoma (PDAC) is a cancer with a poor prognosis, resistant to conventional therapies, and characterized by a dense microenvironment, with a key role of CAFs (Cancer-Associated Fibroblast). This physical barrier not only limits the penetration and diffusion of therapies, but also the infiltration of immune cells restricting an effective anti-tumor immune response [1].

Magnetic iron oxide nanoparticles (IONPs) are innovative tools, exposed to a high-frequency alternating magnetic field they release thermal energy, causing cell death by magnetic hyperthermia (HM) [2]. Exposed to a low-frequency rotating magnetic field, IONPs generate mechanical forces causing cell death by magnetic-mechanical ablation (MMA) [3]. We developed IONPs, vectorized with gastrin, called NF@Gastrin, which specifically target pancreatic cancer cells and CAFs (Cancer-Associated Fibroblast) expressing the CCK2 receptor (MiaPaca2-CCK2 and CAF-CCK2) [4]. The aim of this project is to study whether local HM or MMA can stimulate immunogenic cell death and enhance an antitumor response in the PDAC.

We showed that NF@Gastrin internalize and accumulate in the lysosomes of MiaPaca2-CCK2 and CAF-CCK2 cells [4]. We demonstrated that HM and MMA specifically killed these cells in 2D culture model and 3D MiaPaca2-CCK2/CAF-CCK2 spheroids (Figure 1). Finally, we demonstrated that HM and MMA increased the expression of the Damage-Associated Molecular Pattern: calreticulin and HSP70 at the surface of the targeted cells in 2D and 3D models. This effect was associated with an increase in phagocytosis of these cells by human THP1 macrophages as well as an increase in the cytotoxic activity of Natural Killers (NK-92) when they were in contact with these cells in 2D model. Moreover, the infiltrations of THP1 macrophages and Natural Killers (NK-92) were observed within the MiaPaca2-CCK2/CAF-CCK2 spheroids (Figure 2). Taken together, these results strongly suggest that HM and MMA are two potential strategies capable of inducing immunogenic cell death and restoring an anti-tumor response in PDAC.

References

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Figures

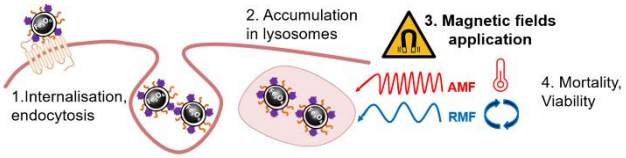

Figure 1. Cell death induce by targeted NF@Gastrin post magnetic fields (AMF: Alternating Magnetic Field; RMF: Rotating magnetic field).

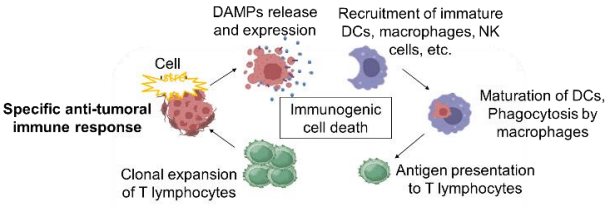

Figure 2. Immunogenic cell death mechanism triggered after treatment by magnetic hyperthermia or magnetic mechanical forces.