Proposal N° : **12**

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Title
3D spheroids for the study of magneto-mechanical cancer cells destruction

Keywords
3D spheroids, cancer cells destruction, magnetic nanoparticles

Summary
The objective of this internship is to develop a 3D spheroid model of cancer cells, in gel, to study the destruction of cancer cells by application of magneto-mechanical vibrations. Cell death is achieved by mixing cells with magnetic nanoparticles, which vibrates when a rotating magnetic field is applied. These effects were first studied in vitro, on 2D cultures of cancer cells. The transition to in vivo studies on mice allows to realize that the differences in the mechanical properties of the liquid medium (in vitro) and the in vivo medium could lead to significant differences in the vibration of the particles. The internship that we propose is to develop a spheroidal model of cancer cells with mechanical properties closer to those of a real tumor. It will thus be possible to study in a more realistic way the mechanisms that allow the triggering of cell death by mechanical vibrations.

Full description of the subject
The CEA INAC /SPINTEC and BIG/ Biology of Cancer and Infection/ Invasion Mechanisms in Angiogenesis and Cancer research labs offer an internship opportunity on the development of a 3D spheroid model for the study of mechanically-induced cancer cells death.

Identification of the anti-tumor effect associated with the magnetic-field induced mechanical vibrations of nanometric magnetic particles has been achieved in 2010. Since then, several studies have demonstrated the likely applicability of this approach for cancer therapy, with both in vitro and in vivo experiments. The INAC /SPINTEC lab has been involved in these studies with the development of suitable magnetic nanoparticles, using optical lithography or powder technology. Our past and present activities are also devoted to the application of this technique for the development of a therapy for glioblastoma, an aggressive form of brain cancer.

Up to now, for the in vitro studies, magnetic particles were incubated with 2D cell culture in a liquid medium. Depending on the case, the particles may either attach to the cell membrane or undergo endocytosis. The application of a rotating external magnetic field induces mechanical vibration of the nanoparticles, leading to cell death in a matter of minutes. One important observation is that under these experimental conditions, a significant rate of apoptotic cell death is often detected. In vivo studies with mice proceed in a similar way, with the magnetic particles injected in a tumor.

From a physical point of view, one key parameter for the understanding of this effect is the efficiency of the mechanical energy transfer, from the particle, to the cell. Among other things, this depends on the viscosity of the liquid growth medium (for a 2D cell culture) or the stiffness of the cell tissue (for in vivo experiments). Because they differ significantly, it is difficult to extrapolate, to in vivo case, the observation collected from in vitro experiment.

The internship we propose consists in the development of a 3D spheroid model of breast cancer cells, with mechanical properties closer to that of a real tumor. Organoid cultures in 3D matrices are relevant models to mimic the complex in vivo environment that supports cell physiological and pathological behaviors. While traditional 2D cultures on rigid surfaces fail to reproduce in vivo cell behavior, 3D matrices are becoming increasingly popular supports for cell cultures because they allow mimicking the complex environment that supports cell physiological functions to better predict in vivo responses and thus to limit the need for animal models.

For this study, we will use spheroids generated from highly metastatic MDA-MB-231 breast cancer cells. Spheroids grown in gels will be incubated with magnetic nanoparticles and the impact of their mechanical vibration, as a function of the magnetic field intensity and duration, will be assessed by fluorescence imaging using cell viability, apoptosis assays (time lapse confocal microscopy). This internship is intended to be followed by a PhD thesis where a more detailed study on the effect of magneto-mechanical vibration on breast cancer cells will be undertaken, including in vivo studies with animal.

Requested skills

Cell biology, cell culture and testing, microscopy. Hepatitis B vaccination is required.

Possibility to follow with a PhD Yes, according to funding.