

Biology and Biophysics of cell damage

Mitochondria, the cell powerhouse, are essential in cellular bioenergetics. these organelles are Organized as individual components or as tight network in the whole cytoplasm and play a central role in life and death processes, mainly through regulations of energy supply, ions fluxes control, production of essential metabolites. beside the nuclear DNA, mitochondria possess their own DNA, maternally inherited. This mitochondrial DNA (mtDNA) is crucial for mitochondrial functions since it encodes most of the respiratory chain subunits. Damages within mtDNA could result into large pathological consequences in Human. This has been thoroughly documented in several phenomena such as mitochondrial dysfunctions, ageing, cancer. Some of the causes of these damages have been characterized ranging from dysfunctions during replication processes, to deleterious effects of reactive oxygen species. Many questions related to mtDNA stability are still under investigations:

- How do cells deal with mtDNA disorders such as double strand breaks (DSB)?
- How are mtDNA proteins involved in DSB formation?
- What is the mitochondrial behavior following X-rays exposure?

In this context, 2 main fields are explored on human cellular models

- mtDNA maintenance following double-strand breaks
- organo-metallic and/or metallic compounds and radiosensitization

MTDNA MAINTENANCE

This thematic is focused on mtDNA response following double-strand breaks. We are using in human cells a specific inducible tool using restriction enzyme (PstI) to target mitochondria and to cut selectively mtDNA. with this approach, we have shown that mtDNA is quickly degraded upon DSB induction (less than 10% remaining 8 hours post induction). This rapid loss is followed by a slow recovery in 2 to 3 weeks. No evidence of DSB repair was observed. These results showed that:

- mtDNA repair processes are limited for DSB recovery in human
- mtDNA DSB are mainly removed through degradation
- Current experiments are focused on the characterization of the degradation process.

RADIOSENSITIZATION

Cancer cells show various features. Among all of them, cell energetics is essential for tumor progression. In the meantime, the great energetic demand is provided by a shift between mitochondrial respiration and glycolysis, in favor of the 2nd metabolism pathways. Moreover, cancer cells display various mutations in mtDNA sequence, some of them being associated with tumor aggressiveness. In parallel, cancer treatments such as radiotherapy induce changes in mitochondrial behavior (i.e number, metabolism...).

To summarize, mitochondrial metabolism is strongly involved in tumorigenesis but also in response to irradiations.

Radiotherapy, used in cancer therapeutics, is based on the facts that cellular DNA repair mechanisms are overtaken by irradiation induced cell damages and as consequence cells undergo apoptosis. The current challenge in radiotherapy treatment is to counteract radio-resistance that generally occurs following irradiation procedure. Most of these strategies are focused on the main cellular target that is the nucleus. In our project, we investigate the ability to target other cell compartments to increase radiosensitisation processes.

The whole action constitutes an integrated field of research between fundamental biology approach and physics. All the state of the art for equipment is present on site with the PAVIRMA platform including a TIRF microscope and a X-Rad 320.

RADIOPROTECTION

This recent aspect is developed in collaboration with Human Nutrition Unit ([Proteostasis\(https://www6.clermont.inrae.fr/unh/Recherche/Equipes/PROTEOSTASIS\)](https://www6.clermont.inrae.fr/unh/Recherche/Equipes/PROTEOSTASIS) group) and [IPHC \(https://iphc.cnrs.fr\)](https://iphc.cnrs.fr). The projet focuses on the understanding of physiological, biochemical mechanisms that could induce radio-resistance.

<https://see.lpc.uca.fr/health/biology-and-biophysics-of-cell-damage-1> (<https://see.lpc.uca.fr/health/biology-and-biophysics-of-cell-damage-1>)