Unravelling the biological mechanisms of normal tissue preservation in spatially fractionated minibeam radiation therapy

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Research theme / topic: Healthy tissue protection, novel radiotherapy approaches, immunomodulation

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Background
Radiotherapy (RT) is a cornerstone of cancer treatment. However, the dose tolerances of normal tissues continue to be the main limitation in RT. Finding novel approaches leading to healthy tissues protection is of utmost importance. This is the case of minibeam radiation therapy (MBRT), an innovative RT approach. MBRT employs strong spatial dose modulation: the irradiation is performed by means of an array of sub-millimetric beams. The distinct radiobiological mechanisms activated by MBRT results in a remarkable reduction of normal tissue radiation toxicities. Numerous preclinical experiments and the outcome of the two first patients' treatments indicate that MBRT offers promise for the treatment of hopeless cases today, such as some bulky and radioresistant tumours. To make future patients optimally profit from the healthy tissue preservation offered by MBRT, a deeper understanding of the underlying biology and its relationship with the complex dosimetry of MBRT is needed. Along this line, the BIOMBRT project aims at providing a deep understanding of the potential differential immune and vascular effects (major players) after MBRT with respect to conventional RT involved in normal tissue sparing. With that aim we will perform a series of preclinical experiments. We will investigate the effect of MBRT on two different (radiosensitive) organs (brain and lung), impacted in two oncological diseases associated with high mortality: gliomas and advanced lung cancer. Dose-escalation studies will be performed to assess the gain of normal tissue complication probability with respect to conventional RT. A longitudinal imaging study will be carried out to get an understanding on how different MBRT configurations impact on both normal vasculatures. An extensive -omics study including single cell RNA sequencing, spatial transcriptomics and proteomics would provide a holistic vision on the differential pathways being activated in MBRT. Finally, multiplexing immunochemistry evaluations would complement the previous evaluations. The knowledge acquired would allow unleashing the full potential of MBRT and optimally design future clinical trials. Investigating the effects of temporal and spatial variations in dose delivery on the risk of health effects.

Aims
1. Deep understanding of the differential role of the immune system in normal tissue response to MBRT
2. Data integration and studies on the interrelation of vascular and immune responses after MBRT

Experimental plan
Aim 1
A comparative study between several MBRT configurations will be performed as well as versus conventional RT considering:
1.1. scRNAseq spatial transcriptomic and proteomic analyses generated by the Consortium will be employed to assess potential differential pathways involved in the immune impact on normal tissue response.
1.2. Lymphopenia and HSPC analysis in skull bone marrow.
1.3 Inflammation analysis.
1.4 Complement activation analysis.
Aim 2.
2.1 Data integration: correlation between gene expression and protein translation. The investigation on cell to-cell communication will enable establishing a model of endothelial-immune cell dialog.
2.2 The multiplex IHC studies will allow characterizing the spatial distribution of the different immune, vascular cells and adhesion molecules, their co/localization as a function of irradiation mode, time, organ and configurations. It would allow evaluating the interactions between the immune and vascular systems in the different irradiation configurations

Techniques. Immune cell isolation. 2D cell co-cultures of irradiated cancer cells and immune cells. Molecular analysis: flow cytometry, sorting, ELISA test, interpretation of omic-analyses. *In vivo* studies.

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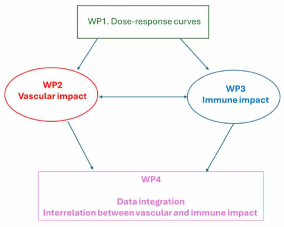

Project partner (6)
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