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MAIN FIELDS OF RESEARCH; ABSTRACT

The tumour microenvironment is increasingly considered as one of the driving forces of cancer development. It is emerging more and more that cancer cells need collaborative interactions with their supporting stroma to survive and thrive. A major component of the tumour stroma consists of so-called cancer-associated fibroblasts (CAFs), which are activated fibroblasts that can stimulate growth and migration of cancer cells through the secretion of growth factors and cytokines. Recent work from our group demonstrates that a deficiency in base excision repair (BER), one of the major cellular pathways responsible for the maintenance of genome integrity, drives reprogramming of primary fibroblasts into CAFs[1]. Specifically, BER deficiency can be induced through siRNA-mediated knockdown of XRCC1, the main coordinator of BER. We observed that exhaustion of BER doesn't only lead to an accumulation of mutations, but it triggers the induction of a CAF-like signature in fibroblasts. Moreover, conditioned medium from fibroblasts with XRCC1 KD promotes the proliferation and migration of epithelial cancer cells via paracrine factors *in vitro*. Nevertheless, the mechanisms driving this reprogramming remain poorly understood. This prompted us to further analyse the process underlying this activation *in vitro*, and to investigate whether BER deficiency could trigger fibroblast reprogramming and support tumour growth and metastasis development *in vivo*.

To investigate the effects of BER deficiency *in vivo*, we generated a mouse model of stromal specific KO of XRCC1, inducible by Tamoxifen administration. Luciferase-labelled LLC cells are then injected subcutaneously in the lower back, and metastasis development is assessed upon surgical resection of primary tumours through non-invasive bioluminescence imaging (IVIS) and histopathological analyses.

In summary the goal of my project is to further understand how the modulation of DNA repair could have a key role in CAFs activation, shaping of tumour microenvironment, and consequently on cancer cell growth and migration both *in vitro* and *in vivo.*

1.Legrand, A. J. et al. Persistent DNA strand breaks induce a CAF-like phenotype in normal fibroblasts. Oncotarget 9, 13666 (2018).

SPECIAL TECHNIQUES AND EQUIPMENT

Cell culture, PCR and RT-PCR, Western Blot, fluorescent microscopy, *in vivo* experiments, non-invasive bioluminescence imaging (IVIS).