| Project Details | |
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| Project Code | MRC21IIRBa Jungwirth |
| Title | How does the inflammatory microenvironment and therapy influence non-melanoma skin cancer initiation? |
| Research Theme | Infection, Immunity & Repair |
| Summary | Skin cancers can be the side effect of anticancer therapies originally aimed at a different tumour. In this PhD project the student will investigate the role of fibroblasts and immune cells in skin cancer initiation and develop in-vitro/ex-vivo models to mimic the human situation. The project will also address how healthy cells change due to the anticancer therapy and counter-intuitively promote the growth of skin cancers. |
| Description | Patients who have survived cancer have a 20% higher risk of developing a second cancer than the general public. These second primary cancers, also referred to as metachronous tumours, are defined as new cancers that are distinct from the initial disease and in some cases can be a side effect of the anticancer treatment against the original cancer. 18-30% of melanoma patients treated with a targeted anticancer therapy against the oncogene BRAF develop non-melanoma skin cancers, such as keratocanthomas and cutaneous squamous cell carcinoma (cSCC). cSCC is an aggressive cancer that is initiated and maintained by cancer stem cells, whose self-renewal strongly depends on an inflammatory microenvironment. Research on cancer progression and therapy resistance has historically focused on tumour cells. More recently, studies have started to address the impact of the tumour microenvironment, notably fibroblasts and immune cells. Recent single cell RNASeq data have shed some light on the inflammatory tumour microenvironment in cSCC, highlighting signalling networks between tumour and stromal cells as potential therapeutic targets. However, the link between the emergence of metachronous skin cancers and cancer therapy-induced phenotypic changes of normal fibroblasts and immune cells in healthy tissues has not been investigated in much detail. Besides the lack of studies in the field, a contributing limitation is the lack of a robust cell culture system to maintain and expand cSCC cancer stem cells ex vivo. In this PhD project, we will address the following: Aim 1: Re-constructing the pro-tumourigenic niche of cSCC Epidermal skin stem cells can be maintained ex-vivo in 2D in the presence of fibroblasts or on fibroblast-derived extracellular matrices. Recent technical advances have enabled long-term expansion of epidermal stem cells ex vivo in 3D organoid cultures. We will exploit this intrinsic ability of epidermal stem cells and apply it to establish cSCC cancer stem cell organoids. We will use established human cSCC cultures to setup the methodology and expand our studies to primary cSCCs. In vivo, macrophages, T cells and fibroblasts are predominant at the tumour-stroma interface, while B lymphocytes infiltrate the tumour. We will mimic this situation in vitro, by including purified immune cell types and fibroblasts in our 3D organoid cultures and test natural matrices and synthetic hydrogels. This will enable us to reconstruct the pro-tumourigenic cSCC niche in vitro and will allow us to study and dissect the signalling crosstalk between the cancer cells and the stromal cells. Aim 2: Investigate the impact of therapies on the pro-tumourigenic niche We will examine how targeted |

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| | anticancer therapies (e.g. BRAF inhibitors used to treat melanoma or non-small cell lung cancer) change the tumour microenvironment in the skin to promote the initiation of cSCC. We will compare and analyse the multicellular composition of healthy untreated and treated tissues in vivo and in vitro. Preliminary data have shown that fibroblasts change their secretome after therapy exposure. We will analyse how these changes impact the immune cell recruitment and their ability to promote cancer stem cell characteristics and the initiation of cSCC to identify factors which could be targeted to prevent disease progression. The student will receive training in cancer cell biology and a range of molecular & cell biology techniques, including 2D & 3D co-cultures in the Jungwirth (expertise in fibroblast research, Bath) and Walko (expertise in epidermal stem cells and cell signalling, Bath) labs. Wuelfing (Bristol) is an immunologist and imaging expert; he will consult on immunology questions and provide microscopy training. Turner (Bath) is also an immunologist and will provide training in specialised immunological techniques, such as flow cytometry. Patel, a consultant dermatologist in Cardiff (ECSCRI), is an expert in cSCC and in vivo models. |
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