Drug resistance mechanisms in FGFR-driven cancers

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Introduction

Fibroblast growth factor (FGF) signalling regulates a plethora of cellular functions such as development, proliferation, survival, migration and differentiation. Due to its powerful effects on the cell, FGF signalling is often hijacked in cancer (Table 1). One relatively common aberration is activating mutation, seen in a variety of cancers. Many of these are highly sensitive to treatment with FGFR inhibitors. However, cancer cells are able to develop resistance to such therapies relatively easily – an Achilles heel of kinase inhibitors. Therefore, our aim is to delineate resistance mechanisms in cancer cells to ultimately improve treatment options.

In my project I focus on cancers harbouring FGFR1 and FGFR2 alterations (Table 1). I plan to investigate FGFR signalling in a 3D cell culture model of cancer (Alvetex – see Figure 1), to delineate resistance mechanisms in cancer cells. It is possible that resistance is caused by compensatory down regulation of other pathways, such as PI3K/AKT, PLC, MAPK, P3K/AKT, PLC and JAK/STAT, which has been shown in Figure 2.

Current therapies

There has been a large motivation to develop FGFR-targeted therapeutics. Kinase inhibitors to target FGF signalling have been developed as shown in Table 2.

3D Alvetex model

• Co-culture of resistant and parental cells with fibroblasts for a more physiological cell model system.
• Mimics the 3D structure of cancer cells and the interaction with stromal cells to create a more physiometric environment.

Table 3 – Benefits of Alvetex for 3D cell culture.

Future work & Ideas

• Generation of BCL-resistant MFE-296 and SNU-16 with and without stromal support, comparing the acquisition of resistance in cells cultured in Alvetex and conventional plasticware.
• Microarray: Generate RNA samples for microarray of co-culture model of cancer models in 2D and 3D with an without stromal support.
• qPCR to check for expression levels of downstream targets of FGF signalling in gastric cancer.
• Fluorescent labelling of further cancer cell lines (SNU-16, SNU-1, H1299, HS20) and fibroblasts (MRC-5).

Acknowledgments

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References


Fearon et al. submitted PHLD1A mediates drug resistance in receptor tyrosine kinase driven cancer.

Table 1 – Aberrant FGFR1 and FGFR2 signalling and associated neoplastic diseases.

Table 2 – FGFR-targeted therapies in clinical trials.

Figure 1 – FGFR signalling. Schematic representation of FGFR signalling. Upon ligand binding, four key pathways are induced: MAPK, PLCγ, JAK/STAT.

Figure 2 – Aberrant FGFR1 and FGFR2 signalling in cancer.

Figure 3 – Mechanisms of FGFR inhibition. Schematic representation of therapeutic options and their mechanism of action.

Figure 4 – PHLD1A levels of MFE-296 cells and resistant MFE-296 upon PD173074 treatment.

Figure 5 – PHLD1A knockdown. AKXDCA endometrial cells can be made resistant to FGFR inhibitors by knocking down PHLD1A.

Figure 6 – Electron microscopy image of an Alvetex scaffold.

Figure 7 – Coating methods of Alvetex scaffolds showing uncoated collagen and Matrigel-coated scaffolds.

Figure 8 – Cell signalling of FGFR2 amplified (SNU-1) and FGFR2 wild-type (SNU-1) gastric cancer upon treatment with FGFR inhibitors.

Figure 9 – SNU-16 cells are highly sensitive to FGFR inhibitor SU5402.

Figure 10 – A2O treatments of MFE-296 azurite, HRE-EGFP co-culture model reduces cell number over a time range of 7 days.

Figure 11 – BGJ treatments of MFE-296 azurite, HRE-EGFP co-culture model reduces cell number over a time range of 7 days.

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