The Role of Fusion Oncogenes and Cancer Stem cells in Myxoid Liposarcoma

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. Ståhlberg A, Kåbjörn Gustafsson C, Engtröm K, Thomsen C, **Dolatabadi S**, Jonasson E, Li CY, Ruff D, Chen SH, Åman P. Normal and Functional TP53 in Genetically Stable Myxoid/Round Cell Liposarcoma. *PLoS ONE*, 2014.

II. Åman P, **Dolatabadi S**, Svec D, Jonasson E, Safavi S, Andersson D, Grundevik P, Thomsen C, Ståhlberg A. Regulatory mechanisms, expression levels and proliferation effects of the FUS-DDIT3 fusion oncogene in liposarcoma. *J Pathol*, 2016.

III. **Dolatabadi S**, Candia J, Akrap N, Vannas C, Tomic T, Losert W, Landberg G, Åman P, Ståhlberg A. Cell cycle and cell size dependent gene expression reveals distinct subpopulation at single-cell level. *Frontiers in Genetics*, 2017.

IV. Svec D*, **Dolatabadi S***, Thomsen C, Cordes N, Shannon M, Fitzpatrick P, Landberg G, Åman P, Ståhlberg A. Identification of inhibitors regulating cell proliferation and FUS-DDIT3 expression in myxoid liposarcoma using combined DNA, mRNA and protein analyses. *Manuscript*.

*These authors contributed equally

V. **Dolatabadi S**, Jonasson E, Lindén M, Fereydouni B, Bäcksten K, Nilsson M, Martner A, Åman P, Ståhlberg A. JAK-STAT signalling controls cancer stem cell properties in myxoid liposarcoma. *Manuscript*.

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Abstract

Myxoid liposarcoma (MLS) is characterised by the *FUS-DDIT3*, or the less common *EWSR1-DDIT3* fusion oncogene and is the second most common type of liposarcoma. The fusion oncogenes encode chimeric transcription factors that are causal factors in tumourigenesis however, their functions are poorly known. Notwithstanding continuous progress in treating MLS patients, existing therapies suffer from a major flaw as they do not target the cancer stem cells (CSCs). Unique features of CSCs include self-renewal, tumour initiating capacity and increased resistance to radiotherapy- and chemotherapy-induced cell death. Thus, CSCs are crucial targets for successful therapy. The aims of this project were to define the role of fusion oncogenes in tumourigenesis and to define signalling pathways controlling CSC features in MLS. Here, we demonstrated that MLS has an intact TP53 system that may explain why this tumour entity is genetically stable. We investigated the regulatory mechanisms, expression levels and effects of *FUS-DDIT3* in detail, and showed that *FUS-DDIT3* was uniquely regulated at both transcriptional and post-translational level. We also screened 70 well-characterised kinase inhibitors and determined their effects on cell proliferation and *FUS-DDIT3* expression at mRNA and protein levels. To facilitate these studies, we developed a novel direct lysis approach that enables us to quantify, cell proliferation, mRNA and protein expression in the same sample. This method allowed us to identify a number of previously unknown signalling pathways that regulated the expression of *FUS-DDIT3*. To study cell division and growth in detail, we applied single-cell analysis on unsynchronized cells at different cell cycle phases and cell sizes. We found that the total transcript level per cell and the expression of most individual genes correlated with progression of the cell cycle, but not with cell size. Detailed studies of cell cycle predictive genes revealed a previously unknown G1 subpopulation. Finally, we showed that MLS contains cells with CSC features and that JAK-STAT signalling controls their numbers. Leukaemia inhibitory factor stimuli increased the number of CSCs, while JAK inhibition depleted the CSC pool. Inhibition of JAK-STAT also showed synergistic effects when combined with chemotherapy *in vitro*. Our findings concerning *FUS-DDIT3* function and CSCs have increased our molecular understanding of tumour development and therapy resistance in MLS that will facilitate development of specific treatment strategies.

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