Liposarcoma

Proliferation, senescence and the role of DDIT3

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i Patologens aula,
Ehrenströmsgatan 1 (Gula stråket 8),
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Av

Christina Kåbjörn Gustafsson

Fakultetsopponent:
Professor Marene Landström
Medicinsk Biovetenskap, Umeå universitet

Avhandlingen baseras på följande delarbeten:

I. Katarina Engström, Helena Willén, **Christina Kåbjörn Gustafsson**, Carola Andersson, Marita Olsson, Melker Göransson, Sofia Järnum, Anita Olofsson, Elisabeth Warnhammar and Pierre Åman. The myxoid/round cell liposarcoma fusion oncogene FUS-DDIT3 and the normal DDIT3 induce a liposarcoma phenotype in transfected human fibrosarcoma cells. *Am J Pathol 2006 168:5*

II. **Christina Kåbjörn Gustafsson**, Katarina Engström, Pierre Åman. DDIT3 expression in liposarcoma development. *In revision, Sarcoma 2013*

III. **Christina Kåbjörn Gustafsson**, Anders Ståhlberg, Katarina Engström, Anna Danielsson, Ingela Turesson and Pierre Åman. Cell senescence in myxoid/round cell liposarcoma. *In revision, Sarcoma 2014*

IV. Anders Ståhlberg, **Christina Kåbjörn Gustafsson**, Katarina Engström, Christer Thomsen, Soheila Dolatabadi, Emma Jonasson and Pierre Åman. Expression of normal and functional TP53 in myxoid liposarcoma/round cell liposarcoma. *Submitted 2014*

V. **Christina Kåbjörn Gustafsson**, Anders Ståhlberg, Pernilla Grundevik, Katarina Engström, Thoas Fioretos and Pierre Åman. Myxoid/round cell liposarcoma cell of origin and human muscle derived mesenchymal stem/precursor cells. *In manuscript*

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Lipomatous tumors comprise benign and malignant forms called lipomas and liposarcomas. Myxoid/round cell liposarcoma (MLS/RCLS) is the second most common liposarcoma and is characterized by the fusion oncogenes *FUS-DDIT3* or *EWSR1-DDIT3*.

To understand the morphology of MLS we investigated the role of the *FUS-DDIT3* fusion in the development of MLS/RCLS in *FUS-DDIT3*- and *DDIT3*-transfected human HT1080 sarcoma cells. Cells expressing FUS-DDIT3 and DDIT3 grew as liposarcomas in immune-deficient mice. Microarray-based comparison of HT1080, the transfected cells, and an MLS/RCLS-derived cell line showed that the *FUS-DDIT3*- and *DDIT3*-transfected variants shifted toward an MLS/RCLS-like expression pattern. *DDIT3*-transfected cells responded in vitro to adipogenic factors by accumulation of fat and transformation to a lipoblast-like morphology. In conclusion, the fusion gene and normal *DDIT3* induce a liposarcoma phenotype when expressed in a primitive sarcoma cell line.

MLS/RCLS may develop from cell types other than preadipocytes. In addition, development of lipoblasts and the typical MLS/RCLS capillary network could be an effect of the DDIT3 transcription factor partner of the fusion oncogene. Further immunohistochemical investigation of the expression of the DDIT3 protein showed that major cell subpopulations of well differentiated tumors and MLS/RCLS tumors were found to express DDIT3 or the derived fusion protein. Our results suggest a dual, promoting and limiting, role for DDIT3 in formation of lipoblasts and liposarcoma morphology.

Most liposarcoma types are characterized by genomic instability caused by impaired TP53 function. Further analysis of TP53 in MLS/RCLS with mass spectrometry, immunoblotting and immunohistochemistry show that a normal TP53 protein is produced in three of four MLS cell lines. This shows that the TP53 system is functional in the majority of MLS cases.

MLS/RCLS tumors express proteins involved in cell senescence. In a study of 17 MLS/RCLS cases, large subpopulations of tumor cells expressed the RBL2 pocket protein together with senescence-associated heterochromatin binding protein 1γ and IL8 receptor β. The expression pattern suggests that MLS/RCLS tumors contain large subpopulations of senescent cells compatible with the slow growth of this tumor type.

Keywords: Liposarcoma, *FUS-DDIT3*, *TP53*, senescence

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