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The Translocation t(7;12)(q36;p13) in Childhood Acute Myeloid Leukemia

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i sal 2119, Hus 2 Entré F, Hälsovetarbacken, Arvid Wallgrens backe 4, den 26 april 2024, klockan 9.00

Av: Anders Östlund

Fakultetsopponent: Professor Kajsa Paulsson, Lunds universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. **An induced pluripotent stem cell t(7;12)(q36;p13) acute myeloid leukemia model shows high expression of MNX1 and a block in differentiation of the erythroid and megakaryocytic lineages.**
Nilsson T., Waraky A., Östlund A., Li S., Staffas A., Asp J., Fogelstrand L., Abrahamsson J., and Palmqvist L. Int J Cancer, 2022. **151**(5): p. 770-782

II. **Aberrant MNX1 expression associated with t(7;12)(q36;p13) pediatric acute myeloid leukemia induces the disease through altering histone methylation.**
Waraky A., Östlund A., Nilsson T., Weichenhan D., Lutsik P., Bähr M., Hey J., Adamsson J., Morsy M.H.A., Li S., Fogelstrand L., Plass C., and Palmqvist L. Haematologica, 2024. **109**(3): p. 725-739

III. **Characterization of Pediatric Acute Myeloid Leukemia with t(7;12)(q36;p13).**
Östlund A., Waraky A., Staffas A., De Moerloose B., Arad-Cohen N., Cheuk D., Fernandez Navarro J.M., Jahnukainen K., Kaspers G.J.L., Kovalova Z., Pasauliene R., Saks K., Zeller B., Norén-Nyström U., Hasle H., Fogelstrand L., Abrahamsson J., and Palmqvist L. Manuscript

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Abstract

The reciprocal translocation t(7;12)(q36;p13) gives rise to acute myeloid leukemia (AML) in infants and very young children. A fusion transcript *MNX1*::*ETV6* is sometimes detected and an aberrant expression of *MNX1* is detected in 100% of patients but the mechanism of transformation has previously not been identified. In earlier studies the frequency and outcome for t(7;12) AML has varied widely and remain contested leading to most treatment protocols stratifying t(7;12) to a high-risk group, however, the NOPHO-DBH-AML-2012 protocol used in Sweden does not. The aims of this project were to determine the frequency, event-free survival and overall survival of t(7;12) in childhood AML, and identify molecular mechanisms involved in the development of AML with t(7;12). In Paper I an iPSC model of t(7;12) was developed. Using this model, a high ectopic expression of *MNX1* and the long noncoding RNAs *MNX1-AS1* and *MNX1-AS2* from the same gene locus was observed. The t(7;12) translocation gave rise to a differentiation block and the model matched the gene expression signature from t(7;12) AML patient material. In Paper II a murine model was used. High expression of MNX1 did induce leukemia, however only in transduced fetal liver cells and not bone marrow cells and primarily in immunocompromised recipient mice. In Paper III patient data and patient material was investigated. AML with t(7;12) was associated with trisomy 19 and with CNS involvement. The expression of fusion transcripts in t(7;12) AML patients was heterogenous, giving rise to several fusion transcripts involving *ETV6*. All t(7;12) AML patients had a high expression of *MNX1*, *MNX1-AS1* and *MNX1-AS2*. The frequency of t(7;12) AML was 7% in AML patients 0-2 years old. Patients with t(7;12) AML often suffers relapse but allogeneic hematopoietic stem cell transplantation (HSCT) was an effective treatment.

The work presented in this thesis has led to the conclusions that the t(7;12) translocation drives high expression of *MNX1*, that the high expression of *MNX1* is the transforming event and that AML with t(7:12) likely has a fetal cell of origin. The frequency of t(7;12) AML was relatively low at 7% in AML patients under 2 years old in this study and patients often relapsed but allogeneic HSCT was an effective treatment.

Keywords: Acute myeloid leukemia, t(7;12)(q36;p13), MNX1, ETV6, Fusion transcripts, NOPHO.

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