Prognostic markers in pediatric leukemia and mechanisms of KRAS induced leukemogenesis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 24 januari 2014, kl 9.00 av

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Avhandlingen är baserad på följande delarbeten:

I. Presence of FLT3-ITD and high BAALC expression are independent prognostic markers in childhood acute myeloid leukemia


Blood. 2011, 118:5905-5913

Response letter: High ERG gene expression is an unfavorable prognostic marker in pediatric acute myeloid leukemia


II. Prognostic implications of mutations in NOTCH1 and FBXW7 in childhood T-ALL treated according to the NOPHO ALL-1992 and ALL-2000 protocols


Accepted for publication: Pediatric Blood & Cancer, 2013

III. KRASG12D-initiated acute T-cell leukemia in mice is accompanied by loss of the wild-type Kras2 allele

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ABSTRACT

Leukemia results from uncontrolled growth of genetically altered blood cells. Depending on the cell type of origin, the leukemia is defined as T-cell, B-cell, or myeloid and as acute or chronic depending on its characteristics.

However, patients with a certain subtype of leukemia (e.g. acute myeloid leukemia (AML) or acute T-cell leukemia (T-ALL)) still exhibit great heterogeneity in response to treatment and clinical outcome. For optimal survival it is therefore necessary to identify high-risk patients who benefit from more intense treatment and stem cell transplantation as well as patients with lower risk that benefit from less intense treatment. The treatment response is influenced by the genetic alterations that drive the leukemia and mutation status may therefore be used as a prognostic marker for risk stratification. In Paper I and II we focused on genetic markers previously identified as relevant for risk stratification of adult patients with the aim to evaluate them in pediatric patients with acute leukemia. Our results identified presence of FLT3-ITD and high BAALC expression as independent markers for adverse prognosis in pediatric AML. In addition, we found that high ERG expression was predictive for an adverse prognosis in pediatric AML with MLL-rearrangement. We also identified that high expression of the NOTCH1 target gene HES1 was associated with better survival rates in children with T-ALL. This indicates that the level of NOTCH1-activity is predictive for prognosis in pediatric T-ALL.

Paper III focuses on mechanisms of KRAS-induced myeloproliferative neoplasm (MPN) and T-ALL in mice. The mechanistic role of hyperactive RAS is well understood in myeloid malignancies while its role in T-cell leukemogenesis is less clear. We used LSL-Kras2G12D;Mx1-Cre mice that models both MPN and T-ALL induced by hyperactive RAS and found that expression of KRASG12D had differential effects on the myeloid and T-lymphoid lineages. While increased proliferation of myeloid cells induced MPN by expansion of mature myeloid cells, increased proliferation and partial block in T-cell differentiation led to an expansion of early T-cell progenitors. With time, secondary genetic events resulted in T-ALL transformation and we identified loss of heterozygosity at the Kras2 locus as a cooperating genetic event in T-ALL induced by KRASG12D.

Keywords: Prognostic markers, AML, T-ALL, leukemia, FLT3, NPM1, ERG, BAALC, KRAS