Identification of characteristic IGF2BP expression patterns in B-lineage neoplasms

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INTRODUCTION AND OBJECTIVES

Insulin-like growth factor 2 mRNA-binding proteins – IGF2BP1, IGF2BP2, and IGF2BP3 (also referred as IMPs, VICKZs) – are coded by different genes and belong to a family of regulatory RNA-binding proteins involved in localization, stability and translation control of their target RNAs (e.g., IGFR, c-myc, H19, TrCP1, CD24, CD44, beta-catenin, MDR1, and GL1) (reviewed in 1, 2). While growing body of data supports biological significance and even prognostic utility of these evolutionarily highly-conserved molecules in different types of epithelial and soft tissue tumors (reviewed in 3), so far few studies have focused on these targets in the context of normal and malignant hematopoiesis (4-6). The objective of this study was systematic analysis of IGF2BP expression in normal hematopoietic tissues and diverse hematopoietic neoplasms.

METHODS

In total 300 samples were analyzed of which 12 and 27 were bone marrow (BM) and peripheral blood (PB) from healthy donors, respectively, and diagnostic samples from acute myeloid leukemia (AML, n=84), chronic myeloproliferative neoplasms (MPN, n=31), acute lymphoblastic leukemia (ALL, n=97), chronic lymphocytic leukemia (CLL, n=31), and multiple myeloma (MM, n=16) patients. The expression of IGF2BP1, IGF2BP2, and IGF2BP3 was assayed at the mRNA level using reverse transcription quantitative PCR (RT-qPCR) with in-house designed IGF2BP isoform-specific primer and probe sets. GUSB gene transcript was used as a reference for normalization. The threshold for statistical significance in 1-way ANOVA analysis (non-parametric Kruskal-Wallis Dunn’s test) was set at P=0.01.

RESULTS

Quantitative assessment revealed that low IGF2BP1 and IGF2BP3, and high IGF2BP2 expression are characteristic to healthy donor BM and PB. Myeloid malignancies – AML and MPN – essentially retain the “normal” IGF2BP expression profile (Figure 1a). In contrast, ALL, CLL, and MM are associated with characteristic perturbations of IGF2BP expression pattern (Figure 1a). Namely, lymphoid lineage neoplasms tend to underexpress IGF2BP2 when compared to the normal corresponding tissue and myeloid lineage malignancies though it was statistically highly significant only in the case of CLL and MM (p<0.001, Table 1). In addition, CLL also shows a remarkable variation in IGF2BP3 expression levels while MM appears to be virtually negative for this transcript (Figure 1a).

The most prominent perturbations were identified in ALL where expression levels of IGF2BP1 and IGF2BP3 varied over five and four orders of magnitude, respectively. As ALL is comprised of biologically and clinically different disease entities IGF2BP profiles were further reanalyzed with respect to this (Figure 1b). We have identified significant associations of overexpressed IGF2BP1 with ETV6/RUNX1-positive (p<0.001), underepressed IGF2BP2 with EZ2/PEX1-positive (p<0.01), and overexpressed IGF2BP3 with MLL/AF4-positive (p<0.001) leukemias (7). In contrast to T-ALLs, B-ALLs negative for recurrent fusion genes underexpress IGF2BP2 (p<0.01) and overexpress IGF2BP3 (p<0.001) when compared to donor BM (Table 1).

CONCLUSIONS

Altogether, our results show that deregulation of normal IGF2BP expression pattern is associated with malignant B-lymphopoiesis. The potential utility of IGF2BP profiling in B-lymphoid neoplasms will emerge as the functions of IGF2BP are further delineated.

REFERENCES


ACKNOWLEDGEMENTS

This study was supported by the European Economic Area and Norwegian Financial Mechanism Grant No. 2004-LT0040-IP-1EEE.

Figure 1. Expression profiles of IGF2BP’s in normal hematopoietic tissues and leukemia.

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<td>Difference in rank sum</td>
<td>Significance (P=0.01)</td>
<td>Difference in rank sum</td>
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<tr>
<td>DONOR BM vs. Donor PB</td>
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Table 1. Summary of 1-way ANOVA analysis of IGF2BP1, IGF2BP2, and IGF2BP3 mRNA expression in samples from normal donor bone marrow, peripheral blood, different hematopoietic malignancies, and distinct ALL entities.

Poster presented at EHA 16 on 11th June 2011