Grb10 is involved in BCR-ABL-positive leukemia in mice.

Abstract:
The SH2-containing adaptor protein Grb10 was first identified in a yeast screen as a new binding partner for BCR-ABL and associates with BCR-ABL in a tyrosine-dependent manner. However, its function in BCR-ABL-mediated leukemogenesis in vivo is still unknown. Here we describe an important role of Grb10 in BCR-ABL-induced leukemia by using a versatile system for efficient oncogene expression and simultaneous Grb10 knockdown from a single vector. Primary bone marrow (BM) cells coexpressing Grb10-miR/BCR-ABL showed a significant decrease in colony formation and cell cycle progression. Transplantation of Grb10-miR/BCR-ABL- or control-miR/BCR-ABL- transduced BM leads to a CML/B-ALL-like phenotype with significantly delayed disease onset and progression resulting in prolonged overall survival in Grb10-miR-transplanted mice. Methylcellulose experiments exhibit additive effects of imatinib treatment and Grb10 knockdown. Cell cycle analysis suggests an anti-proliferative effect of Grb10 knockdown in BCR-ABL(+) primary BM cells. However, Grb10 abrogation was not capable of completely abolishing the BCR-ABL-induced disease. Our findings were confirmed in the human BCR-ABL(+) cell line K562, where we demonstrate reduced viability, cell cycle progression and induction of apoptosis by stable Grb10 microRNA expression. Taken together, our
results suggest that Grb10 knockdown in vivo leads to impaired proliferation, longer survival and reduced colony formation, suggesting an important role of Grb10 in BCR-ABL-mediated leukemogenesis.