ITD- and FL-induced FLT3 signal transduction leads to increased C/EBPbeta-LIP expression and LIP/LAP ratio by different signalling modules.

Abstract:

FLT3 receptor-associated signalling plays a role in proliferation and leukaemia. The transcription factor C/EBPbeta may be involved in malignancy with its alternative translation product C/EBPbeta-LIP. We investigated a potential connection between FLT3 signalling and the C/EBPbeta system in FLT3-internal tandem duplication (ITD)-positive leukaemia cells and FLT3-ITD- or FLT3-wild type (WT)-transfected 32D cells. In FLT3-ITD-positive cells or when ITD sequences were inserted into the FLT3-WT receptor, significant LIP levels, increased LIP/LAP ratios, and enhanced proliferation rates were detected, which were reduced by FLT3 inhibition. In FLT3-WT cells, incubation with FLT3 receptor ligand (FL) also elevated LIP, LIP/LAP, and proliferation, albeit to a lesser extent. CEBPB-directed siRNA decreased both LIP and proliferation rates in FLT3-ITD-positive and FL-stimulated FLT3-WT-positive cells. PI3K inhibition affected ITD-associated and FL-induced LIP levels. Rapamycin, an inhibitor of mTOR involved in CEBPB translation, completely blocked the increase in LIP in FL-stimulated FLT3-WT- but not FLT3-ITD-positive cells. In contrast, the ITD-associated LIP elevation was mediated by p(90)-ribosomal-S6-kinase. This is the first report showing a LIP increase in the presence of ITD or following FL exposure. Our data suggest
fundamental differences in the signalling cascades activated via ITD mutations or following FL stimulation, indicating the need for adapted molecular therapy.