Investigating The Role of JAK/STAT Pathway upon Dasatinib Induced Apoptosis for CML Cell Model K562

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AIM: STAT5A and STAT5B genes; members of JAK-STAT signaling pathway; are nuclear transcription factors that are responsible for activating the genes that exhibit increased expression in hematopoietic malignancies and signal transduction. Dasatinib prevents the gained imatinib resistance, responsible for MDR genes’ overexpression and BCR-ABL kinase region mutations by activating signalling ways of SRC kinase family (LYN, HCK) and by inhibiting BCR-ABL, SRC kinase family (SRC, LCK, YES, FYN), c-KIT,EPHA2,PDGFR kinases. Investigating the apoptotic case of leukemic cells and evaluating the transcriptional changes of STAT5A and STAT5B following dasatinib treatment on CML model cell line K562 was aimed.

METHODS: The cytotoxic effective dose IC_{50} of dasatinib upon K562 cells was determined via XTT method. The apoptotic case of the cells was assessed spectrophotometrically by ‘Cell Death Detecton Kit’ after applying of IC_{50} dose between 24–96 hours. Target genes’ expression levels were also determined by real time qRT-PCR following dasatinib treatment for the same time interval. Protein expression analyses were performed by Western Blot analysis according to ‘WesternBreeze Chromogenic Kit- Anti-Rabbit’ kit manual instructions. Statistical analyses were done by GraphPad prism software with a significance of p<0.05.

RESULTS: The IC_{50} dose of dasatinib was determined as 3.3 nM for 48th hour. When we compared the apoptosis rate of dasatinib treated/untreated cells; a 4.5 fold apoptosis induction was assessed at 96th hour in dasatinib applied group (p<0.0001). When we compared target genes’ mRNA expression levels, while STAT5A expression was decreased 1.5 fold (by %33.2 inhibition) at 96th hour (p=0.02), STAT5B exhibited a 4.7 fold downregulation (by %77.6 inhibition) for the same hour (p<0.001). STAT5A and STAT5B protein expression levels were significantly suppressed at 96th hour and these protein expression results were in the same line with mRNA expression results.

CONCLUSION: One possible reason of dasatinib induced leukemic cell apoptosis might be due to significant decrease in STAT5A and STAT5B expression levels that are transcription factors and exhibit upregulated expression in leukemia. Therefore, STAT5A and STAT5B are important molecular targets in the research of CML pathogenesis.