Discovery of anticancer drug candidate targeting the transcription factor STAT3

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Signal Transducers and Activators of Transcription 3 (STAT3) is hyperactivated in a wide variety of human tumors, thus STAT3 is believed to be an attractive molecular target for the development of anticancer therapy. Activity of STAT3 requires its own SH2 domain-mediated binding to phosphotyrosine-containing sequence. In this study, we developed a HTS system for identification of inhibitors of STAT3 dimerization and identified a potent hit compound by HTS.

At the beginning, we developed an *in vitro* high-throughput chemoluminescence-based assay by using ALPHAScreen system. Biotin-labeled recombinant human STAT3 protein and FITC-labeled phosphopeptide (VTQPLpYG-FITC) were employed in this system. The specific binding of these molecules are clearly detected by photosignal trunsduction with ALPHAScreen beads. We screened our chemical library with this system and identified several hit compounds for their ability to inhibit the STAT3 dimerization. Among them, compound A strongly inhibited the STAT3 dimerization without affecting to Grb2-phophopeptide interaction. SPR analysis revealed that compound A bind to SH2 domain of STAT3. We next examined antiproliferative activity of compound A with MTS assay. Compound A showed antiproliferative effect against MDA-MB-468 (IC_{50}=2.4 μM) and MDA-MB-435S (IC_{50}=7.9 μM) cells in which STAT3 is constitutively hyperactivated. In contrast, no antiproliferative effect was observed against STAT3-silent MCF7 cells (IC_{50}>20 μM).

In conclusion, we identified the compound that inhibits the STAT3 dimerization *in vitro* and showed antiproliferative activity against STAT3-activated cancer cells. Compound A is expected to have a potential of the lead compound for anticancer drug candidate.