Abstract

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Sorafenib inhibits endogenous and IL-6/S1P induced JAK2-STAT3 signaling in human neuroblastoma, associated with growth suppression and apoptosis.

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Abstract

Neuroblastoma is the most common extracranial solid tumor in the pediatric population. Sorafenib (Nexavar), a multikinase inhibitor, blocks cell proliferation and induces apoptosis in certain types of cancers. Here, we tested antitumor effects of sorafenib (≤ 10 μM) on four human neuroblastoma cell lines, CHLA255, CHLA171, CHLA90 and SK-N-AS. Sorafenib inhibited cell proliferation and induced apoptosis of neuroblastoma tumor cells in a dose-dependent manner. Sorafenib inhibited phosphorylation of Signal Transducer and Activator of Transcription 3 (STAT3) proteins at Tyr705 in these cells, associated with inhibition of phosphorylated JAK2, an upstream kinase that mediates STAT3 phosphorylation. Expression of a constitutively-activated STAT3 mutant (pSTAT3-C) partially blocked the antitumor effects of sorafenib on neuroblastoma cells. Sorafenib also inhibited the phosphorylation of STAT3 induced by IL-6 and sphingosine-1-phosphate (S1P), a recently identified regulator for STAT3, in these tumor cells. Moreover, sorafenib downregulated phosphorylation of MAPK (p44/42) in neuroblastoma cells, consistent with inhibition of their upstream regulators MEK1/2. Sorafenib inhibited expression of cyclin E, cyclin D1/D2/D3, key regulators for cell cycle, and the antiapoptotic proteins Mcl-1 and survivin. Finally, sorafenib suppressed the growth of human neuroblastoma cells in a mouse xenograft model. Taken together, these findings suggest the potential use of sorafenib for the treatment of pediatric neuroblastomas.

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