EDHS-206, an Exquisitely Selective Inhibitor of TAK1, Targets Pro Survival TNFα-Dependent Signaling, Inducing Apoptosis in Rheumatoid Arthritis and Breast Cancer Models

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Abstract

Tumor necrosis factor alpha (TNFα) administration has shown limited therapeutic utility in cancer and inflammatory disorders due to dose-limiting side effects. We propose an alternative approach to targeting TNFα-mediated diseases by selectively inducing the TNFα apoptotic response in TNFα-rich microenvironments. TAK1 acts as a key mediator between survival and cell death in TNFα signaling. We report a novel potent and exquisitely selective TAK1 inhibitor (EDHS-206, IC50 9.5nM) that induces apoptosis in a TNFα-dependent manner in models of metastatic breast cancer and rheumatoid arthritis. Co-crystallization studies demonstrated that EDHS-206 inhibits the kinase in a DFG-in conformation. Kinetic analysis of EDHS-206-TAK1 interactions revealed a substrate-like intermolecular autophosphorylation mechanism for TAK1 activation, during which EDHS-206 delays the proceedings of the rate-limiting step. EDHS-206 represents an attractive starting point for the development of a novel generation of inhibitors that greatly sensitize cells to TNFα-induced cell death, potentially broadening the therapeutic efficacy of TNFα.

Suggested Citation