small molecule inhibitor of Hsp70 has cytotoxicity against various cancers

Injae Shin
Yonsei University, Korea

Hsp70 acts as an anti-apoptotic factor and protects cells from various apoptotic stresses. Hsp70 is highly expressed in many cancer cells and its overexpression correlates with tumor development and resistance to chemotherapy. By using cell-based, high-throughput screening of an imidazole library and target identification with affinity chromatography, a small molecule named apoptozole (Az) that inhibits Hsp70 activity was discovered. This substance inhibits Hsp70 activity by binding to its ATPase domain but does not affect other heat shock proteins such as Hsp40, Hsp60, and Hsp90. We also conducted structure-activity relationship study. Treatment of cells with Az induces an array of apoptotic phenotypes in various cancer cell lines. The inhibitor blocks the interaction of Hsp70 with Apaf-1 but does not affect the interaction of Hsp70 with ASK1, JNK, Bax, and AIF, thereby inducing caspase-dependent apoptosis. In addition, the inhibitor remarkably reduces tumors in nude mouse models xenografted with cancer cells without affecting the viability. Interestingly, treatment of cancer cells and tumor-xenografted mice with a combination of a Hsp70 inhibitor and doxorubicin enhances apoptosis in comparison with a single treatment with either doxorubicin or the inhibitor. I will discuss the current progress made in Az-induced cancer cell death.

Biography

Injae Shin received his BS degree in 1985 and MS degree in Chemistry from Seoul National University, Korea in 1987. His PhD research was performed at University of Minnesota from 1991-1995 and his Postdoctoral studies at University of California at Berkeley from 1995-1998. He is a Director of Center for Biofunctional Molecules and an Underwood Distinguished Professor at Yonsei University. His research interests include the synthesis of biologically and chemically interesting compounds, the development of bioactive molecules that can be used for biological and biomedical studies, and functional studies of glycans using chemical tools including glycan microarrays.

injae@yonsei. ac.

Notes: