Small Molecules Affecting the Expression of Her2 Induce Apoptosis in Human Breast Cancer Cell Lines

Y-S. Lin, K. Taber, D. Davidson, R. Peoples, G. Johannes, T. Giordano, G. Powers
Message Pharmaceuticals, Inc., Malvern, PA 19355, USA

A growing number of genes are known to be regulated at the post-transcriptional level, generating multiple novel targets for drug discovery. Message Pharmaceuticals is developing small molecules capable of modulating these post-transcriptional processes. One target Message Pharmaceuticals has chosen to study is Her2. Her2 protein expression has been shown to be up-regulated in a significant percentage of breast and other types of carcinomas through both gene amplification and translational mechanisms. Inhibition of HER2 expression using antisense oligonucleotides or ribozymes has been demonstrated to lead to apoptosis of Her2-overexpressing tumor cells. In a cellular screen, Message has identified compounds that reduce the levels of Her2 expressed by cancer cell lines. One of these compounds induces apoptosis of Her2-expressing lines but is not toxic to primary cell cultures or human diploid cell lines. Cancer cells treated with this compound were blocked at the G2-M progression of the cell cycle. In addition, these cells were shown to differentially express genes involved in apoptotic cascades after short incubations with this compound. Studies on elucidating the precise molecular mechanism of action are now in progress.