Blockade of Her2/neu binding to Hsp90 by emodin azide methyl anthraquinone derivative induces proteasomal degradation of Her2/neu.


Source

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Abstract

Overexpression of HER2/neu, a transmembrane tyrosine kinase acting as a coreceptor for other EGFR family members, is well-known to be associated with a poor prognosis in cancer. In the present study, we observed that emodin AMAD, a novel emodin azide methyl anthraquinone derivative, extracted from nature's giant knotweed rhizome of traditional Chinese herbs, potently decreased Her2/neu protein in dose- and time-dependent manners and also inhibited the downstream MAPK and PI3K-Akt signaling pathway. Intriguingly, reverse transcription-PCR and protein turnover assay revealed that the decrease of Her2/neu was independent of mRNA level but primarily owing to its protein stability. Meanwhile, proteasome inhibitor MG132 but not lysosome inhibitor chloroquine could restore Her2/neu and polyubiquitination of Her2/neu was augmented during emodin AMAD treatment. Furthermore, immunofluorescence study with anti-Her2/neu antibody showed that emodin AMAD disturbed the subcellular distribution of Her2/neu, with decreased location in the plasma membrane. Molecular docking studies predicted that AMAD can interact with the ATP-binding pocket of both Hsp90 and Her2/neu. Importantly, coimmunoprecipitation and immunofluorescence study revealed that emodin AMAD markedly impaired the binding between Hsp90 and Her2/neu and could bind to both Hsp90 and Her2/neu as reinforced by molecular modeling studies. In addition, combination of emodin AMAD treatment and siRNA against Her2 synergistically inhibited proliferation and induced apoptosis. Taken together, these data suggest that blockade of Her2/neu binding to Hsp90 and following proteasomal degradation of Her2/neu were involved in emodin AMAD-induced apoptosis in Her2/neu-overexpressing cancer cells. Our results provide suggestions that emodin AMAD could be promising as a new targeting therapeutic strategy in the treatment of Her2/neu-overexpressing cancers.

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