Synthesis and Mechanism Study of Emodin-derivatives as ErbB2-signaling Inhibitors

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Clinically, cancer patient with ErbB2 tyrosine kinase overactivation has been strong associated with poor prognosis and down-regulate the activity of ErbB2 strategy has been proven be a satisfactory approach to treat ErbB2-overexpression cancer. Recently, several reports have shown that the ErbB2-signaling could be interfered by emodin and its derivatives. In order to develop more efficient ErbB2-targeted agents, series of emodin analogs were synthesized and evaluated the ErbB2 inhibitory ability. Among them, two emodin analogs, Em08red and emacet, displayed potent ErbB2 inhibitory function and anti-proliferative activity against all three ErbB2 overexpressing oral cancer cell lines. Further experiments showed that Em08red-treatment could induce G2 arrested and apoptosis. Results showed the ErbB2-signaling pathway down-regulation and cytotoxic ROS production in the Em08red-treated cells might contribute the cytotoxic effect of Em08red. On the other hand, emacet treatment could significantly inhibit the growth of the ErbB2-ovrexpressed cancer cells through impeded the DNA synthesis. Furthermore, emacet treatment completely diminished the heregulin-induced ErbB2 phosphorylation, but not EGF-mediated activation. In addition, heregulin-triggered Erk1/2 activation was obviously hindered in emacet-treated cells. Cell mobility and phosphorylation of FAK protein were also reduced after emacet treatment. Collectively, our study identified two potent ErbB2-tyrosine kinase inhibitors emodin-derivatives, em08red and emacet, which through different mechanism to block ErbB2-signaling and might serve as novel ErbB2-targeting drug lead for further development.