Development of emodin analogs as ErbB2-targeting agents

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Target therapy has been demonstrated in clinic as a promising and feasible approach in cancer remedy and the ErbB2-targeting strategy remains a satisfactory medication in treating several types of cancer, including oral cancer. In order to develop *more efficient ErbB-targeted* agents, several series of emodin analogs with the computer-modeling validated ErbB2-binding core structure were synthesized, and evaluated the ErbB2 inhibitory ability in ErbB2-overespressing human oral cancer cell lines. Two emodin analogs, em08red and emacet displayed potent anti-proliferative and the inhibitory capabilities on ErbB2 activity against all tested ErbB2 overexpressing cancer cells. Therefore, both compounds were then chosen for further studies. Em08red-treatment significantly down-regulated the activation of ErbB2 as well as the expression level of ErbB2 protein *via* enhancing the ErbB2-proteasomal degradation and induced G2 phase arrest. The expression levels of anti-apoptosis proteins (Bcl-xl and Bcl-2) were also down-regulated while active caspase-3 and caspase-9 was detected in cells after em08red-treatment. Moreover, em08red treatment stimulated cytotoxic ROS production which could be partially reversed by *N*-acetyl cysteine pre-treatment. On the other hand, emacet treatment could significantly inhibit the growth of the ErbB2-expressing oral cancer cells. Our results also indicated that emacet treatment could arrest cancer cells in G0/G1 phase and several G0/G1 phase-associated markers (CDK4, cyclin D and cyclin E) were down-regulated in treated cells. Further experiment showed that emacet treatment could imped the DNA synthesis and exhibited dramatically cytostatic effects without noticeable cytotoxicity. Furthermore, emacet treatment completely diminished the heregulin-induced ErbB2 phosphorylation, but not EGF-mediated receptor 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 results clearly demonstrated that em08red could impede ErbB2 functions through inducing ROS in tumor cells that conduce to proliferative blockage and apoptotic cell death and emacet treatment could selectively block heregulin-stimulated ErbB2 activation, which might contribute to the cytostatic effect. As a result, em08red and emacet might serve as novel ErbB2-targeting drug leads, which imply a target therapeutic role of emodin analogs.