A TRAIL to Chinese herbal medicine

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With apoptosis–targeting therapies coming of age, the report by Li-Weber and colleagues provides a novel molecular rationale for the evaluation of substances derived from traditional medicinal herbs in combination with biologicals to achieve a better response in anticancer therapy.

Here, the anti-inflammatory flavonoid wogonin is demonstrated to overcome a central, NF-κB–mediated resistance mechanism in TRAIL (TNF-related apoptosis-inducing ligand)–induced apoptosis. Wogonin, derived from the traditional Chinese herbal medicine Huang-Qin (Baikal skullcap, Scutellaria baicalensis), strongly synergizes with TRAIL– or TNFα–induced apoptosis. This is achieved by shifting the cellular redox equilibrium to a more reduced state. Wogonin thereby attenuates NF-κB activity and interferes with antiapoptotic stress responses that follow death receptor ligation. Notably, wogonin spared nonmalignant cells, indicating promising perspectives for a clinical setting. This has important implications, as clinical trials targeting receptors for the death ligand TRAIL (Apo-2L) have been initiated. Whereas the natural ligand TRAIL (AMG-951) itself has only recently entered phase 1 trials, clinical development of agonistic TRAIL-mimicking antibodies is more advanced. Mapatumumab (HGS-ETR1) is an agonistic antibody against the TRAIL receptor I (death receptor 4, DR4). Phase 2 clinical trials of mapatumumab (HGS-ETR1) as monotherapy have been completed in patients with non–Hodgkin lymphoma, advanced colorectal cancer, and non–small cell lung cancer, and a randomized phase 2 study of HGS-ETR1 in combination with bortezomib in multiple myeloma is under way. Antibodies targeting TRAIL receptor II (DR5), HGS-ETR2, and HGS-TR2 are in phase 1. Results from these studies confirm a low toxicity profile but indicate at the same time that mono-therapy targeting TRAIL receptors has only limited efficacy. This was expected, given the high rate of TRAIL–resistant tumor cell lines. Nevertheless, a far better, synergistic tumor cell killing can be achieved by combinations of TRAIL or the agonistic anti-DR4 and -DR5 antibodies with conventional chemo- or radio-therapy or some of the novel, targeted therapies including bortezomib.1-3

NF-κB–driven, antiapoptotic signaling by death receptors has only recently been recognized. Ligation of death receptors by their natural ligands or agonistic antibodies triggers a death signal through formation of a death-inducing signaling complex consisting of the receptor itself, the adaptor FADD binding to the cytosolic death domain, and an inducer caspase (caspase-8 and/or –10) that is recruited via the death effector domain found in both FADD and the caspase. In parallel, recruitment of TRAF family proteins via the adaptor TRADD promotes activation of the NF-κB pathway that triggers survival signals by inducing expression of antiapoptotic factors. Whereas Bcl-2, Bcl-xL, and Bfl-1 interfere with the intrinsic, mitochondrial apoptosis machinery, induction of FLIP proteins blocks the extrinsic death pathway through interference with caspase-8 binding and activity. This allows cells with a dominant NF-κB signal to evade death receptor–triggered apo-

REFERENCES


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