Mistletoe viscotoxins increase natural killer cell-mediated cytotoxicity.

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Mistletoe extracts have immunomodulatory activity. We show that nontoxic concentrations of Viscum album extracts increase natural killer (NK) cell-mediated killing of tumor cells but spare nontarget cells from NK lysis. The compounds responsible for this bioactivity were isolated from mistletoe and characterized. They have low molecular mass and are thermostable and protease-resistant. After complete purification by HPLC, they were identified by tandem MS as viscotoxins A1, A2 and A3 (VTA1, VTA2 and VTA3, respectively). Whereas micromolar concentrations of these viscotoxins are cytotoxic to the targets, the bioactivity with respect to NK lysis is within the nanomolar range and differs between viscotoxin isoforms: VTA1 (85 nm), VTA2 (18 nm) and VTA3 (8 nm). Microphysiometry and assays of cell killing indicate that, within such nontoxic concentrations, viscotoxins do not activate NK cells, but act on cell conjugates to increase the resulting lysis.

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