INHIBITION BY DEXAMETHASONE OF TRAIL-INDUCED APOPTOSIS OF THYROID CANCER CELLS

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Selective induction of apoptosis in malignant cells may represent an attractive mechanism to control neoplastic cell proliferation. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a member of the tumor necrosis factor (TNF) family of proteins including FasL, and TNF-α. Since TRAIL is able to induce apoptosis in many transformed and malignant cells, but not in normal cells it has raised strong interest as a new promising anti-cancer agent. Glucocorticoid hormones can either promote or inhibit apoptosis according to cell type. In a number of solid tumors glucocorticoids may inhibit apoptosis by different stimuli raising questions on the use of these compounds as adjuvant therapy in cancer. We have investigated the effect of dexamethasone (DEX) on the apoptosis induced by TRAIL in follicular undifferentiated thyroid (FRO) cancer cells. Apoptosis was measured by percent hypodiploid nuclei, caspase-3 activation, and mitochondrial membrane depolarization. DEX strongly inhibited the apoptotic changes induced by TRAIL. The DEX protective effect was almost abolished by the steroid receptor antagonist RU486 suggesting that the DEX action is mediated by receptor activation. The role of Bcl proteins in the DEX effect was then investigated. In FRO cells DEX stimulated in a time-dependent fashion the expression of Bcl-x_L, but not that of Bcl-2. The technique of small interference RNAs was utilized to investigate the role of Bcl-x_L in the effect of DEX. Transfection of the cells with siRNAs against Bcl-x_L inhibited both basal and DEX-stimulated Bcl-x_L expression. Furthermore, transfection of the cells with siRNAs against Bcl-x_L weakly stimulated control cell apoptosis and restored apoptosis in TRAIL-stimulated cells treated with DEX. The scrambled oligos had no effect. These results demonstrate that dexamethasone, a potent glucocorticoid agent, protects thyroid cancer cells from apoptosis induced by TRAIL. DEX acts through receptor activation and up-regulation of the expression of the anti-apoptotic protein Bcl-x_L. GC administration as adjuvant therapy in patients with carcinomas in other organs may contribute to development of thyroid metastases by inhibiting chemotherapy-induced apoptosis in the primary tumours as well as apoptosis of transformed cells migrated into the thyroid tissues.