Summary

Apoptosis deficiency seems to be involved in the high resistance of melanoma to therapeutic treatment. This has come into focus because the cytotoxic effects of chemotherapeutic agents via apoptosis are known. Extensive investigations have been made analyzing the role of alterations in the apoptotic pathway in melanoma. The molecular changes affect antiapoptotic, as well as proapoptotic, processes and survival signals and involve various molecules. These mechanisms are also discussed in light of their use in further therapeutical strategies. Actually, a number of these findings have already been employed to test their therapeutical applicability in melanoma treatment. Furthermore, two concepts have been translated from the cell system via animal models into clinical trials.

Key Words: Melanoma; apoptosis; apoptosis deficiency; death receptors; caspases; Bcl-2-family; p53.

INTRODUCTION

Most chemotherapeutic drugs act through induction of apoptosis (programmed cell death). In 1972, Kerr et al. described an experimentally induced killing of tumor cells that involved a coordinated cell disintegration following typical morphological changes, coining the term apoptosis (1). The cytotoxic effect of chemotherapeutic agents appears mainly contributed by apoptosis (2,3). The weak response of metastatic melanoma to anticancer agents gives rise to the hypothesis that the chemoresistance of this malignancy is caused by raising its apoptotic threshold (2). Inactivation of apoptosis is a “hallmark of cancer,” an obligate ritual in the malignant transformation of benign cells (4). As a result, these cells enhance their chances of survival and increase their resistance to chemotherapy (3). Indeed, Staunton et al. (5) demonstrated a constitutive low level of spontaneous apoptosis in melanoma cells compared with other malignant cell types. An intensive search for cell death factors altered in melanoma has been made. It has been
shown that, indeed, various molecular changes in cell-death control in melanoma are present, and three types can be distinguished: activation of antiapoptotic processes, inactivation of proapoptotic effectors, and reinforcement of survival signals.

PROGRAMMED CELL-DEATH PATHWAYS

Apoptosis (programmed cell death) represents a complex genetic program consisting of several pathways that are summarized in Fig. 1. Tremendous efforts have been made to discover and describe the molecular mechanisms of apoptosis, which are discussed elsewhere in detail (6). Briefly, depending on cell type and stimulus, a complex net of sensor and regulator proteins is activated and balanced and there is no unique linear or defined pathway. However, to simplify, two main well-characterized caspase-activating cascades that regulate apoptosis are currently known.

One cascade is triggered from the cell surface by death receptors and the other is initiated by changes of mitochondrial membrane integrity (7). Oligomerization of surface receptors is followed by recruitment of adapter molecules, such as Fas-associated protein with death domain (FADD) and the initiator caspases-8 and -10 (8) into the death-inducing signaling complex (DISC). The subsequent autocatalytic cleavage of procaspase-8 or -10 is followed by activation of effector caspases (e.g., caspase-3) (9) and induction of specific endonucleases, resulting in DNA fragmentation (10,11). These two pathways converge with the activation of effector caspases and induction of specific endonucleases, resulting in DNA fragmentation and cleavage of nuclear proteins essential for nuclear and cellular structure, DNA-repair, and DNA-replication (12,13).

The family of death receptors include CD95 (Fas/APO-1), tumor necrosis factor (TNF)-R1, TNF-receptor apoptosis-inducing ligand receptor (TRAIL-R)1 and TRAIL-R2, DR3 (death receptor 3), and DR6 (reviewed in Locksley et al., ref. 14). Among them, the CD95 receptor, TRAIL-R1 and TRAIL-R2 are the most efficient mediators of apoptosis. Several studies suggest that death receptor–ligand interaction is involved in tumor sensitivity toward chemotherapeutic drugs (15–17). The extrinsic pathway is regulated on multiple levels, whereas the death-inducing signaling complex can also recruit negative and positive regulators of caspase-8 (18,19). Furthermore, in type II cells, the initial activation of caspase-8 is not sufficient. Here, caspase-8 cleaves the Bcl-2 family member, BID, which translocates to the mitochondrial membrane and activates the intrinsic pathway (20). By this mechanism, the death receptor and the mitochondrial pathway is connected.

The intrinsic pathway involves mitochondrial release of cytochrome-c, which binds apoptotic protease activating factor (Apaf)-1, and, in the presence of adenosine triphosphate (ATP), coordinates a series of conformational changes that allow the oligomerization of Apaf-1 into a ring-like complex, referred to as the “apoptosome” (21). The apoptosome binds and activates caspase-9 into the complex (9,22,23), which, in turn, recruits and activates effector caspases (e.g., caspase-3). These are considered as executors of apoptosis.

There are various additional points of control that can modulate apoptosis after cytochrome-c release. The family of inhibitors of apoptosis (IAP), containing X-chromosome-linked IAP (XIAP), neuronal IAP (NIAP), melanoma (ML)-IAP, and survivin, can interfere with the formation of the apoptosome and activation of the downstream caspases (Figs. 1 and 2). IAPs are inhibited by other proapoptotic factors released by the