Unbalance Between Apoptosis and Proliferation in Female Genital Tract Malignancies

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Cancer is the worldwide leading cause of death and inspires extensive research on its prevention, early diagnosis, and treatment. While cell proliferation is important for the regeneration of damaged tissue, apoptosis is crucial for the maintenance of tissue homeostasis. An imbalance between these 2 components can lead to the development of cancer.

Molecular Pathways of Apoptosis Underlying Cancer Development

Apoptosis is initiated via the mitochondrial or the death receptor pathway. Central to the mitochondrial pathway is the release of cytochrome c from the mitochondria, leading to activation of the caspase cascade and execution of apoptosis.[1] The mitochondrial pathway is regulated by the BCL-2 family of proteins, i.e. proapoptotic BAX and BAK as well as antiapoptotic BCL-2 and BCL-xL. The death receptor pathway is activated when the cell surface death receptor—Fas—is bound by its ligand—Fas ligand, resulting in recruitment of the adaptor protein FADD and procaspase 8 to the intracellular domain of the death receptor and subsequent caspase activation. Inhibitors of apoptosis have been shown to play a role in oncogenesis through direct caspase and procaspase inhibition (primarily caspases 3 and 7) and transcription factor NF-κB signaling.[2] In addition, some proapoptotic molecules are downregulated or inactivated in cancer cells, such as Fas, p53, Bax or Bid.[3]

Deregulated Apoptosis in Female Genital Tract Cancer

Several lines of evidence showing deregulated apoptosis in female genital tract cancer have been reported. Genetic polymorphisms of p53 and p21, a downstream mediator of p53, have been found to be associated with the development of endometrial cancer.[4] Statistically significant higher nuclear p53 levels were found in malignant compared to normal human endometrial specimens by the Western blot technique.[5] Higher expression of BAG-1, an antiapoptotic molecule that binds BCL-2, was also found in high-grade endometrial cancer compared with normal endometrium.[6] Moreover, the BAX gene frameshift mutation was frequently detected in endometrial carcinoma, leading to a loss of BAX expression and resistance to apoptosis.[7] In primary Fallopian tube carcinoma, a high incidence of p53, HER-2/neu and c-myc overexpression was also found.[8] In cases of cervical squamous cell carcinoma treated with radiotherapy, BAX expression was associated with good survival while BCL-2 expression was associated with poor survival.[9] There have been limited reports on apoptosis marker analysis of female genital tract sarcoma because of the low incidence. Uterine leiomyosarcoma has been found to be associated with a higher positive rate of p21, p53, and BAX compared with uterine leiomyoma, and BCL-2-positive leiomyosarcoma was shown to be associated with a longer time to recurrence.[10] In a case of sarcoma botryoides of the uterine cervix, a point mutation of the p53

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gene was found, with overexpression of p53 protein in more than half of the neoplastic cells.[11] Liu et al showed that p53, BCL-2, BAX, and c-myc were frequently expressed in female genital tract sarcomas.[12] A significant positive association was detected between BAX and c-myc. In both univariate and multivariate analyses, they found that overexpression of p53 was associated with poorer survival.

Roles of p53 in Pathogenesis and Prognosis of Cancer

Somatic p53 mutations are found in approximately 50% of human cancers, but in the remaining wild-type p53-carrying tumors, the p53 pathway may also be inactivated via indirect mechanisms, such as interaction with the human murine double minute 2 (MDM2) oncoprotein, that lead to p53 destabilization.[13] In female genital tract sarcomas, Liu et al found that 44% of the 54 cases were positive for p53.[12] In response to cellular exposure to exogenous or endogenous carcinogens, the p53 proteins, as transcription factors, integrate multiple cellular stress signals to trigger transcription of genes involved in either cell cycle arrest or apoptosis. In addition, p53 also interacts with BCL-xL to induce transcription-independent apoptosis. The p53 family also includes p63 and p73, and intimate interactions exist among these 3 proteins. While p63 is essential for proliferation and differentiation, p73 promotes apoptosis in response to DNA damage. Some mutant p53 proteins, but not wild-type p53 proteins, bind to p73 to inhibit its apoptotic activity, which may be one of the causes of poor prognosis in cancer patients with p53 mutation. In these p53-positive cancer patients, the tumors may have a poor response to chemotherapeutic agents due to the aforementioned inhibitory effects of mutant p53 on apoptosis. In fact, p53 alone or in combination with other factors, such as hypoxia-inducible factor 1α and BCL-2, significantly predicts poor prognosis in many types of cancer. In the study on female genital tract sarcomas presented by Liu et al, 5-year survival was shown to drop from 55% in patients with p53-negative tumors to 30% in patients with p53-positive tumors.[12]

Therapeutic Implications of Apoptosis-related Markers

Since p53 is either mutated or inactivated in almost all cancer cells, restoration of p53 to inhibit tumor growth is a promising cancer therapy strategy. Molecules have been developed to either restore wild-type conformation to mutant p53 or induce mutant p53-dependent cell death. Moreover, because of a pivotal role of MDM2 in restraining p53, blocking the MDM2–p53 interaction to reactivate p53 function is a promising approach for cancer therapy in patients with wild-type p53. Recently, potent and selective small-molecule MDM2 inhibitors have been identified, but the cancer-therapeutic effects of these MDM2 inhibitors remain to be studied. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was also demonstrated to induce apoptosis in cancerous cells, but not normal cells, from human endometrium, ovary, cervix or Fallopian tube. Therefore, TRAIL may be an effective treatment for endometrial cancer and other female reproductive cancers, with minimal secondary effects on healthy tissue.[14]

Future Prospects

Female genital tract sarcomas are frequently associated with highly aggressive behavior and poor prognosis. Since the expression of apoptosis-related markers were found by Liu et al to be deregulated in these sarcomas,[12] further studies are required to explore the genetic mutations of apoptosis-related markers in these tumors and the upstream and downstream pathways. In this way, the mechanisms underlying the highly malignant nature of female genital tract sarcomas may be unraveled, thereby facilitating the design of targeted therapy that may improve the therapeutic effect of radiotherapy and chemotherapy.

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